Executive Function and Contingency Management for Methamphetamine Use Disorder in South Africa: A Comparison Pre- and Post-Treatment

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Date 15/03/2021

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Abstract

Background: Methamphetamine dependence is associated with impairment in executive function, as well as brain functional and structural alterations, findings on the relationship between executive function impairment and brain alterations seem inconsistent. Methamphetamine dependence may respond to contingency management, yet it is unclear if the treatment response is predicted by these neuropsychological, and brain functional and structural changes, and whether treatment alters neuropsychological impairment. I first conducted a systematic review to rigorously assess available findings on the relationship between executive function impairment and brain functional changes. I then explored data from a study of contingency management in methamphetamine dependence with the aims of determining 1) whether treatment response was predicted by executive function impairment and brain functional and structural alterations, and 2) whether treatment led to changes in executive function and brain functional and structural impairment in treatment responders and non-responders.

Methods: The systematic review involved a rigorous search and assessment of articles on the association of stimulant use and resting state functional connectivity. In the empirical study, 33 subjects underwent executive function testing, resting state-fMRI, and structural neuroimaging prior to contingency management treatment. Executive function was assessed with the trail making task, the Stroop-word task, and the Connors continuous performance task. Seed-based analysis was used for functional MRI, with a focus on brain regions associated with executive function, and brain structural alterations were assessed using measures of cortical thickness and surface area. In the statistical analysis, first associations of baseline executive function, rs-fMRI, and brain structural alterations with treatment outcome were assessed using linear regression, and second, comparison of executive function, rs-fMRI, and brain structural parameters at baseline versus at treatment end in treatment responders and non-responders was undertaken using linear regression, Cohen's d and a change score.

Results: The systematic review noted specific associations between executive function impairment and resting state-fMRI. While in the study, treatment responders had improved executive function at baseline as assessed by two measures (faster completion times on the trail making, and greater accuracy on the Connors continuous performance task), but worse executive function on a third measure (lower accuracy on the Stroop word task) when compared with non-responders. No statistically significant differences between groups was found with regards to rsFC, however greater cortical thickness was found in responders brain regions associated with executive function, in comparison to non-responders. Analysis of pre vs post treatment findings showed that in treatment responders there was better executive function after treatment, in comparison to non-responders (as assessed by greater accuracy on the Connors continuous performance task). Furthermore, in treatment responders there was greater increase in cortical volume in regions associated with executive function, than in non-responders.

Conclusion: These findings support the hypothesis that better executive function at baseline (task switching and selective attention) is associated with better outcomes in a contingency management trial of 8-weeks. There is also evidence of improved executive function post trial (in selective attention and cortical thickness findings support improved executive function) implying that abstinence as a consequence of a contingency management trial of 8-weeks may improve executive function, a larger sample size would be needed to determine if improvements extend to other regions of executive function.

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Abbreviations

Anterior Cingulate Cortex	ACC	Motivational Interviewing	MI
Antisocial Personality Disorder	ASPD	Neuro-Psychological	NP
Blood Oxygen Level Dependent	BOLD	Orbitofrontal Cortex	OFC
Cognitive Behavioural Therapy	CBT	Posterior Cingulate	PCC
Contingency Management	CM	Reaction Time	RT
Continuous Performance Task	CPT	Resting-state functional connectivity	rsFC
Default Mode Network	DMN	Resting-State Functional Magnetic Resonance Imaging	rs-fMRI
Dopamine	DA	Salience Network	SN
Dorso-lateral Prefrontal Cortex	dlPFC	Substance Use Disorder	SUD
Executive Control Network	ECN	Trail Making Task	TMT
Groote Schuur Hospital	GSH	Treatment Effectiveness Scores	TES
Independent Component Analysis	ICA	Wechsler Abbreviated Scale of Intelligence	WASI
Medial Prefrontal Cortex	mPFC	Western Cape	WC
Methamphetamine	MA	Working Memory	WM
Montreal Cognitive Assessment	MoCA		

Key Words

Contingency Management; Methamphetamine; Executive Function, Executive function; Resting-State Functional Magnetic Resonance Imaging; resting-state functional connectivity.

Chapter One: Introduction

1.1. Rationale

The abuse of narcotics results in damage not only to the individual but also to entire communities. In Cape Town, South Africa (SA), a study exploring wastewater-based epidemiology in 2017 revealed that methamphetamine (MA) is the primary drug of use based on the wastewater metabolites found in urine [5]. The use of MA outweighed the use of cocaine and methylenedioxymethamphetamine (MDMA) and registered at between 181.9 and 1184.8 mg per day [5]. Globally, parental and community substance abuse together with low socioeconomic status and perceptions of neighbourhood disorganisation, have been shown to increase the probability of offspring substance abuse [5, 6,7] . Approximately one in six individuals with substance use disorder (SUD) have access to treatment facilities [8], which highlights the need for a treatment regime that can reach more inaccessible areas.

According to the World Drug Report for 2017, South Africa has one of the greatest usages of MA in low income countries, rivalled only by Nigeria and South East Asia. More recently East Africa, the Middle East and South America have shown increasing usage and production [5]. Globally MA use is expanding, including in Asia (largely East and South East Asia), Australia, Near and Middle East, Western and Central Europe and the America's [5]. MA can be taken orally, smoked, snorted or injected, and purity of the product varies greatly, with toxic substances mixed into the sold product which can have deadly consequences [5]. Internationally MA is often used recreationally, but this can leads to addiction with extensive availability of the different types of MA [9].

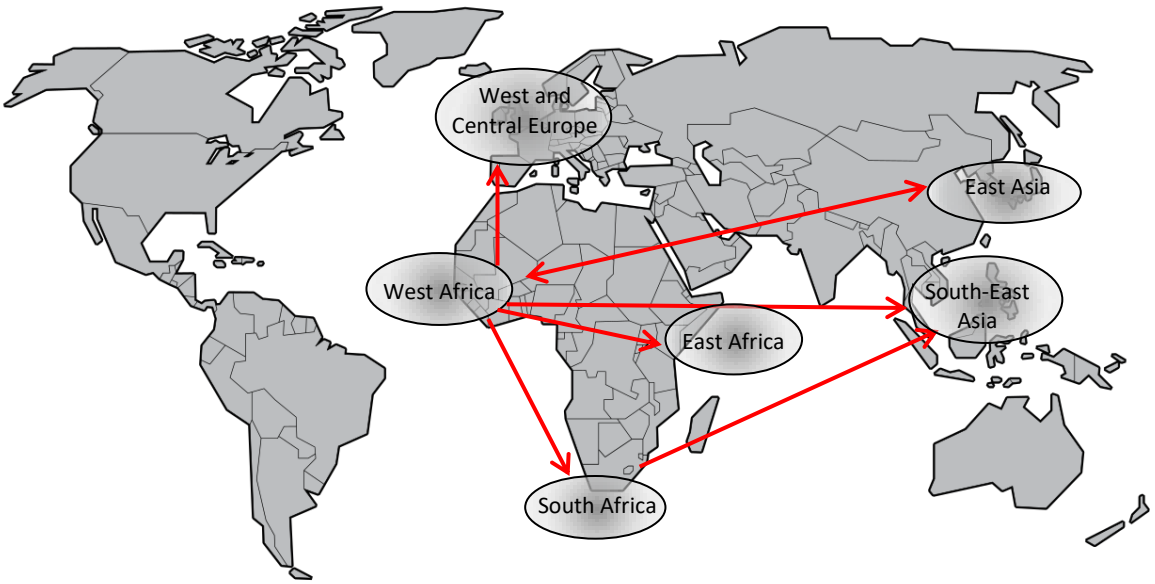

Figure 1: Drug production areas pertaining to Africa

Climate plays a major role in production of drugs such as opioids, cocaine and cannabis, but plays no role in the production of MA. Manufacture is cheap and easy and profits are huge [5]. Nigeria is a dynamic

production zone due to weak control on imports of MA ingredients, which are imported for manufacture for cold and asthma medicine [5]. According to Obasanjo who heads the West African Commission on Drugs, drug lords are sponsoring politicians in Nigeria which exacerbates the problem.
Asia on the other hand has generally been dominated by heroin production and use as a result of its climate, but due to economic growth and increasingly interlinked markets coupled with rapid and cheap production, MA is now increasing in popularity [5, 6]. Globally, most MA supplies are mass produced in China and then shipped from there [5].

Treatment options for Methamphetamine Use Disorder (MUD) have been focused on counselling , and South African rehabilitation centres tend to employ Motivational Interviewing (MI) or Cognitive Behaviour Therapy (CBT), both of which have both produced positive results in stimulant treatment [7]. Contingency management (CM) is a form of operant conditioning whereby rewards for certain behaviour (drug-negative urine tests) are given to enforce the desired behaviour. A study that included CM with CBT showed significantly improved results and reduction of stimulant use during treatment [8]. Globally treatment for MUD is twofold, that which includes psychosocial behavioural therapies as outlined above as well as pharmacological treatment using buproprion, modafinil, naltrexone, mirtazapine and topiramate [10] amongst other agents, none of which have been identified as completely effective in treating MUD.

Broadly, the fronto-striatal circuitry is my main area of interest and functional, as they play an important role with regards to attention and reward in methamphetamine use, with the dorsal attention network and reward network also playing major roles. Connectivity and structural changes within executive function regions should correspond to improved measures (self-report and neuropsychological) of impulse control, executive function performance and self-regulation. The dorso-lateral Prefrontal Cortex (dlPFC) and Anterior Cingulate Cortex (ACC) are both directly involved in executive function as well as sustained attention and are further associated with cognitive inhibition and self-regulation.

MA dependent individuals in the Western Cape tend to use MA on a daily basis, and due to the chemical effects of MA in the human brain, these results in a large amount of dopamine release and overstimulation of dopaminergic pathways [11] specifically in the mesolimbic reward networks (striatum). CM encourages deliberative thought and future goal setting (e.g. what to spend the vouchers on in the future), and therefore might be expected to further potentiate recovery of the PFC resulting from abstinence. One possible mechanism through which CM might facilitate neuroplasticity is through upregulation of D_2/ D_3 receptors in the PFC as a result of rewards obtained during CM, acting in parallel to reductions in stimulation of the D_1 receptors in the mesolimbic reward system as a result of abstinence from methamphetamine [11-13].

We don't know if baseline executive function predicts worse outcomes in CM, nor do we know if the abstinence achieved through the treatment of CM has a positive effect on executive function.
The effectiveness of CM, in which MA users favour the redemption of vouchers for prosocial goods over the consumption of MA, will be strongly associated with alterations in connectivity of the brain's reward system and executive control networks. We further predict that by modifying actual behaviour via the purchasing of prosocial goods, participants will present with corresponding changes in their fronto-striatal circuitry. Consequentially we expect to find the reward system altered at baseline and that fronto-striatal connectivity will emerge as being sensitive to adherence of treatment. Specifically we expect to find greater connectivity in the cognitive control networks as well as reduced connectivity in the striatum that may correlate with structural changes.

We predict that there will be greater volume and resting-state functional connectivity (rsFC) of the fronto-striatal networks following an 8 week CM intervention. This hypothesis is based both on the role of these regions in increased cognitive control as a result of the intervention [12, 14] as well as evidence that the prefrontal cortex (PFC) suffers down regulation of D2 receptors as a result of exposure to MA [13]. Abstinence from the drug following CM will likely result in dendritic growth, upregulation of D2 receptors as well as an influx of inflammatory glial cells [11]. It is noteworthy that inflammation is associated with repair, yet elevated volume of inflammatory cytokines in these brain regions may be indicative of withdrawal prior to regeneration.

I will now present a literature review that explores the role MA plays in a South African context, and brain regions and neurotransmitters most affected by stimulant misuse. Finally I will discuss behavioural changes associated with MA misuse.

1.2. Literature Review

Methamphetamine use disorder (MUD) according to the DSM-5 is no longer classified as 'abuse' or 'dependence', there is a single diagnosis and severity is based on the number of symptoms the individual presents with [15]. Two out of 11 possible symptoms in a 12 month period need to be met to be considered a disorder [15]. The possible symptoms include: (1) use of more MA than originally planned, or for a longer time period than planned, (2) the individual is unsuccessful in cutting down or stopping usage, (3) notable time is taken to obtain MA or recover from its effects, (4) there are cravings to use MA, (5) Social and work commitments have been negatively impacted by use of MA, (6) there is continued use even though there are persistent social or interpersonal problems caused by use of MA, (7) important social, occupational or recreational activities have been forsaken in order to use MA, (8) using MA in particularly dangerous situations like whilst driving, (9) use of MA even though the individual is aware that it is having a negative effect on them, (10) the individuals body has developed a tolerance to MA, and more of the substance is required to achieve the same effect they initially experienced when first using, (11) there are withdrawal effects when not using MA.

Not only is manufacture of MA particularly hazardous to individuals and communities [5], MA use also affects those who have no immediate contact with the substance including the quality of life of the children of MA users, and their local environments [16]. People affected extend to law enforcement and emergency services, family and relatives as well as the economy of the close-knit community due to theft [16].

1.2.1. Methamphetamine Use in South Africa

In South Africa MA misuse is highly prevalent in the Western Cape (WC), specifically in the Cape Flats, and is largely associated with gangsterism [17]. According to Pluddermann and colleagues these communities have the most rapid rate of adolescent addiction in the world [17, 18]. Adolescence is a key age in which self- control and regulation is developed [19]. Socioeconomic challenges in low income countries like South Africa can result in risks to this development [20], which is especially important as MA use targets the brain areas (PFC and striatum) that are involved in normal brain development during this age, thus impeding the development of the required self-control and regulation [19].

One of the biggest background obstacles that SA faces in combating the growing trend of MA use is poverty, insufficient transport systems for doctors and specialists to attend to the growing population, together with few, inadequately trained medical and counselling staff [21]. Studies exploring the effects of environmental exposures on the nervous system have discovered that settings that are limited in resources, such as those in the MA using communities of the WC, are associated with a higher risk for neurological illness directly related to the socio-economic environment [22, 23]. These studies identify illicit

drug taking as an important and likely result of poor socio-economic environments [22, 23]. In a South African setting and more specifically the Western Cape, MA use has been historically associated with conduct disorder; adolescents with conduct disorder have presented with weaker rsFC in the anterior DMN (social cognition) [24], which may exacerbate the use of MA.

1.2.2. Current interventions for MA

Although drug dependence has been largely viewed as a social problem, the physiological changes associated with it, including neuronal changes and its accompanying inflammatory responses, has led some to argue that it be classified as a chronic inflammatory illness instead [25, 26]. Nevertheless counselling is the main form of therapy for this disorder.

Motivational Interviewing (MI) is a brief counselling therapy employed in MA recovery, used at a number of clinics in SA. There are mixed reports of significant success in the literature regarding the effectiveness of MI [27]. Studies exploring the effectiveness of standard MI (1-3 sessions) and Intensive MI (9 session) over a 6 month time period show significant improvement in Addiction Severity Index (ASI) psychiatric scores in intensive MI treatment and none with standard MI [28]. No statistically significant differences in other measures of the ASI were found between groups, however intensive MI did have improved abstinence results [27, 28].

Cognitive behaviour therapy (CBT) is another widely used form of therapy for MA use. CBT therapy coupled with MI has been demonstrated to produce a significant increase in abstinence and a reduction in depression [7]. Yet when exploring the effectiveness of a variety of combinations of treatment (CBT with MI and CM), the groups receiving CM alone as well as CM coupled with CBT showed the highest treatment retention and highest treatment effectiveness scores (TES) [8, 29]. When exploring the effectiveness of CM, it is noteworthy that inclusion of the CBT did not appear to augment treatment results [7].

1.2.3. Contingency Management (CM)

CM has been shown to be effective for stimulant dependant individuals who are seeking treatment [30-34]. 42 Subjects in a CM trial for MA dependence in Los Angeles County responded positively and consistently with the rewards associated with CM, moreover they outperformed those not receiving CM [30]. When CM is coupled with a positive affect regulation program, participants reported increased self-awareness which assisted them to engage more fully with the rehabilitation process [35]. Abstinence in treatment seeking MA users has been shown to be more obtainable for those with a limited lifetime history of substance use [36], as well as a lower frequency of use [37], yet CM still shows improved outcomes in long-term, heavy users over other treatment options alone [38]. Moreover, participants engaged in a CM

study remained abstinent 9- to 12- months post treatment as assessed by follow-up evaluations [39]. Further, CM has been shown to significantly improve treatment attendance [40].

It can be argued that the reason for the success of CM is in the monetary value of an alternate reward system which results in dopamine release. This alternate source of dopamine may act in a tempering fashion, reducing the craving for MA. Reiger et al. (2015) suggest that the success may rather be as a result of a deliberate decision making process, which acts as an immediate alternative to drug use [41]. They argue that the monetary value of vouchers in early stages of MA abstinence, a critical period for success, are so minimal that the reward alone is unlikely to affect success to the same extent as deliberate decision making [41]. It is possible that the initial monetary reward of CM is too minimal to produce outcomes on its own in first world countries, yet in a South African context, where average monthly household earnings for MA users can range between R0 and R20,000 it is possible that the vouchers may be considered substantial and as such may add to the potency of the treatment.

1.2.4. Brain areas and neurochemistry in MA use

To place the impact of MA use in context it is helpful to understand the brain areas involved as well as to understand the role of the key neurotransmitter, dopamine (DA), in MA addiction.

1.2.4.1. Dopamine (DA) receptors and Neurotoxicity

MA misuse, like other narcotics, is associated with molecular changes in the brain, which in turn may reinforce their continued use [42]. There are two main DA receptor types in the striatum and nucleus accumbens, D_1 (direct) and D_2 (indirect through G protein coupled receptors) [42]. The PFC has mostly D_1 receptors on the other hand [42].

D_1 and D_2 DA receptors have been known to contribute to the neurotoxic effects of MA [43]. The upregulation of D_1 receptors in the striatum has been linked to the positive reinforcement of MA use and greater use resulting in elevated neurotoxicity [43]. D_2 type receptor signalling in the cortex is associated with an increase in potential therapeutic value in MA recovery and response inhibition, as it has been seen to reduce the neurotoxic effects of MA use [44, 45]. D_2 receptors are downregulated in this MA dependence and present with lower binding potential [45, 46]. Moreover reduced number of D2/D3 receptors in MUD within the striatum has been associated with below average executive functioning [47].

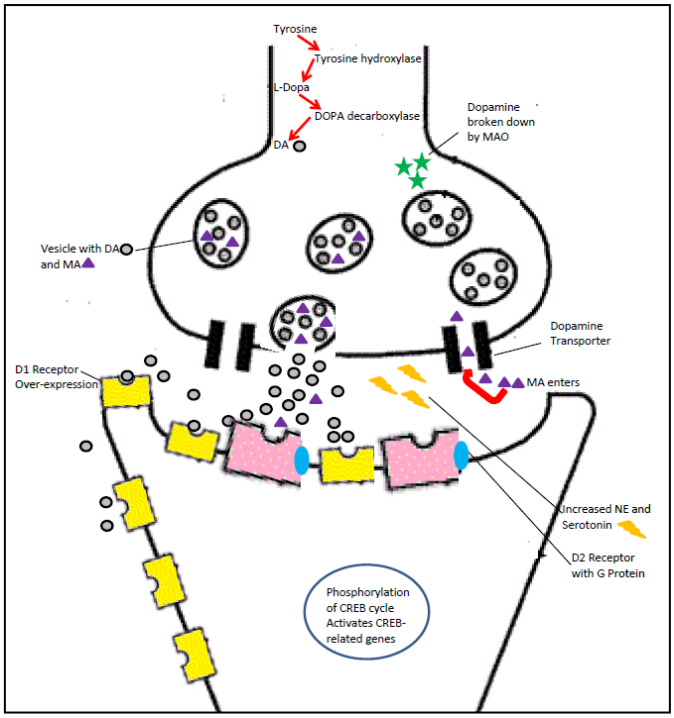

Figure 2: The effect of MA on DA receptors

MA enters presynaptic terminals of dopaminergic neurons through the DA transporter (DAT) and liberates the transport of DA out of storage vesicles and into the synapses through the membrane transporter [42]. MA also indirectly elevates extracellular levels of norepinephrine (NE) and serotonin due to its effect on DA release [42]. After a period of time, if a reward is presented at regular intervals, DA starts to be secreted in response to the predictive cues associated with anticipation [42]. This together with the release of DA in response to the use of the drug makes the cessation of the drug more difficult.

Neurotoxicity (physical damage to neurons) due to MUD focuses mainly on oxidative stress, excitotoxicity and neuroinflammation [48]. MA use results in the production of reactive oxygen species (ROS), through the increase in oxidation of DA, these ROS largely attack the mitochondria of the cells, which affects energy production in the cell, while MA also increases oxygen leakage which creates a positive feedback loop [48]. Excitotocicity is caused by calcium damage to neurons due to elevated levels of glutamate caused by the presence of MA, which in turn causes endoplasmic reticulum damage resulting in mis/ unfolded protein production [48]. Neuroinflammation as a result of MA usage, largely affects DA dominant regions, where excess DA in the synapses stimulates the local microglia to put in action a neurotoxic signal cascade [48].

Long term effects of MUD results in both cognitive and physical problems, these include greater risk of infection with Human Immunodeficiency Virus (HIV) and other communicable diseases, periodontal problems, hypertension, stroke, kidney failure as well as a propensity to develop Parkinson's disease, depression and psychosis [48].

Cognitive impairments have been linked to neurotoxicity involving cytokine and chemokine inflammatory changes in the brain, which create persisting neuronal injury [13, 49, 50]. Increased cognitive deficits, mainly in attention and memory [51], cognitive inflexibility and maladaptive decision making [52] may act together making rehabilitation difficult for those with MUD. Poor cognitive control and difficulty in applying goal directed decision making have been suggested to result in negative reinforcement of MA use [53]. It stands to reason that cognitive training or superior cognitive function could act as a valuable tool to assist in abstinence in MA rehabilitation.

1.2.4.2. Prefrontal Cortex (PFC)

The mass of the cellular grey matter of the cortex when compared with the mass of the cells in the precentral gyrus increased over the course of human evolution [54]. Humans have more than double the brain mass than that of higher primates [54]. This implies that impulses generated by the neurons in the primary motor cortex become more controlled as the mass of the cortex increases [54]. MA use has been associated with a reduction in global cortical thickness, [55] which may affect cortical functioning and its associated executive functioning.

The PFC is pivotal for the formation of intentions as well as for regulating and verifying complex behaviour [54]. It receives afferent impulses from all parts of the brain for regulation thereof, and is very well connected with the reticular formation resulting in a modulating effect on arousal and consciousness [54]. The PFC is one of the last areas of the brain to develop, which continues well into adolescence and early adulthood [54], as such its development is particularly affected by adolescent MA use.

The PFC is essential in the inhibition of immediate responses to irrelevant stimuli, thus allowing for complex behaviour including; creating plans and goal orientated behaviour [54], as well as executive functions [42]. Moreover, together with the hippocampus it is essential for the encoding and storage of explicit memories. The dlPFC is largely associated with mediating working memory, while the hippocampus stores declarative information for a period of time before it is moved to the cerebral cortex [42]. Reduced PFC control that can occur with MA use has been linked to increased compulsivity associated with drug taking, which in turn may be positively correlated with length of use [56, 57]. MA use is associated with a reduction in neuronal integrity and elevation in active neurodegeneration in the right dlPFC in adults [58].

1.2.4.3. *Striatum*

The striatum, composed of the caudate nucleus and putamen, is the region for the main input to the basal ganglia [42]. It has both direct and indirect connections with the cerebral cortex, brain stem and thalamus [42]. Although it is largely populated with GABAergic spiny neurons, these are modulated by dopaminergic

neurons in the substantia nigra pars compacta and ventral tegmental area which in turn influences corticostriatal transmission [42].

DA in the striatum has been implicated in the reinforcement of motor learning (creation of habits) and reward signalling through strengthening synapses. More specifically it is thought to provide information about the behavioural value of a stimulus [42]. The caudate in particular has been associated with habituation to repeated stimuli [54]. It is worth noting that there is a large influence of cholinergic interneurons in the striatum which also function in reward based behaviour and they are suspected to alert the spiny neurons in the area to the presence of salient stimuli [42]. The shape of nicotine closely mimics that of acetylcholine and thus cigarette smoking plays a part in activating these neurons. A large majority of MA users smoke cigarettes which contribute to the reward driven behaviour [59]. Striatal volumes have been shown to increase in MA use with a knock on effect of increased more impulsive reward driven behaviour [56].

1.2.4.4. The Default Mode Network (DMN), Salience Network (SN) and Central Control Network (CCN)

The brain has a variety of networks or regions that work in unison. Certain areas present with reduced activation during cognitive tasks, which are negatively correlated with task load [60], while others increase in activation [61]. The DMN, is composed of regions falling in the former category, and is active in self-reflection, episodic memory, metallisation and autobiographical reminiscing. The DMN encompasses the posterior cingulate (PCC), precuneus, medial prefrontal cortex (mPFC) and the inferior parietal lobe [60-64]. The CCN, engages in cognitive tasks like working memory and decision making, and comprises the dorsolateral frontal and parietal neocortices [61]. Thus in healthy individuals when the CCN is activated the DMN becomes less active, while activation of the DMN has the opposite effect [61, 65, 66]. The right anterior insula have recently been identified as playing a role in the switching from the DMN to the CCN in certain tasks [67, 68], consistent with its conceptualisation as part of the salience network [67].

A rs-fMRI study using 46 MA dependent individuals conducted in South Africa revealed that there was greater connectivity between the anterior (frontal medial cortex) and posterior (precuneus and posterior cingulate cortex) DMN which positively correlated with MA use [69]. This connectivity decreased in intensity with increased time of abstinence [69]. The frontal medial cortex has been associated with memory and decision making [70], the precuneus with episodic memory [71] and the posterior cingulate cortex with internally directed cognition [72] which could imply that the MA users are ruminating on past events that dictate decision making. Alternately greater connectivitybetween regions reflects less dynamic co-activation of these regions in MUD (possibly because this network is less responsive to task demands), which is seen as greater average connectivity over the entire rsFC scan sequence. Furthermore, current MA users displayed hyper-connectivity between right fronto-parietal cognitive networks and posterior

DMN, which again decreased with increased time of abstinence [69]. This may suggest rumination dictate d to by recent memory, possibly a form a craving that decreases with abstinence. Moreover, greater rsFC in the DMN has been associated with weaker recorded levels of happiness; this is especially true when rsFC is greater within the anterior and posterior mPFC, posterior parietal cortex, which positively correlate with the inclination to ruminate [73].

1.2.5. Behavioural Changes Associated with MA Misuse

1.2.5.1. Cognitive Control

MA use results in severe cognitive impairments with lasting effects into abstinence in mice, which, in turn can negatively affect recovery [10]. Although these may extend to human subjects[13, 74], the degree of impairment suffered is likely to be moderated by a number of individual differences such as genetic predisposition, impulsivity and risky decision making [75]. A review by Dean et al. (2013) suggests that cognitive impairments caused by MA use is of a yet to be determined duration, with impairments being mild in early-to-middle adulthood, further, the authors implicate moderator variables that seem to affect severity in an individual [76]. A fMRI study utilising the Stroop word task showed that MA users made more errors and had a slower response speed than controls [77, 78], this was coupled with weaker activation in the right inferior frontal gyrus, supplementary motor cortex/ ACC and anterior insular during the incongruent condition [77]. These data suggests that hypo-functioning in cortical areas contribute to poor executive function which is associated with MA use [56, 77]. Moreover, the reduction in reaction time suggests that MA users may be deficient in the ability to adapt a new behavioural response based on prior experience [78]. This in turn implies that MA users may have a disadvantage in situations that require executive control.

Iudicello et al. (2010) conducted a longitudinal study exploring effects of abstinence in MA over a 1 year period, using the Trail Making Task (TMT) part B and the Stroop task to measure executive functions [79]. At baseline the abstinent and currently using groups performed significantly more poorly than HC, while at follow up the abstinent group could no longer be distinguished from HC with regards to cognitive performance [79]. The abstinent group exhibited disproportionate improvement over time, and poorer baseline performance was correlated with greater improvement [79].

An fMRI study using a two-choice prediction task and two-point response task showed that MA users were more influenced by immediately preceding outcomes and had weaker dlPFC and orbitofrontal cortex (OFC) functioning than controls, which again confirms cognitive deficits in decision making in MA users [80]. Further, rat studies have shown that MA intoxication leads to deficits in reversal learning as well as distortions in temporal memory which is consistent with damage to the PFC and corticostriatal circuity [81]. It is not clear whether cognition is a predictive variable in positive outcomes in MA abstinence.

Although reaction time and working memory variables have previously been linked to treatment outcomes [37], more research is required on this subject.

Prior research also revealed that although MA users performed more poorly than healthy controls (HC) at baseline in cognitive functioning tasks, after a 13 month period of abstinence these cognitive impairments are no longer distinguishable from HC [79]. Other studies exploring attention and processing speed showed that MA users preformed significantly worse that HC in cognitive battery of tests, which became nonsignificant when the participants education was controlled for [82]. The MA group did show poorer performance than HC in early abstinence (4 days abstinent) [82]. After 1 month of abstinence MA participants showed no statistically significant improvement in any cognitive domain, however a trend towards improvement was revealed, suggesting that length of time of abstinence may play an important role in cognitive improvements [82].

1.2.6. Relapse vs Abstinence

Success of treatment can be defined as the number of months of continuous abstinence post discharge/ treatment. According to Walton et al. (1994) one of the key reasons for relapse is societal acceptability and availability [83]. This point is particularly pertinent for a South African context where in certain areas in the WC, MA is easily available and widely used.

In a longitudinal study conducted in the US on 350 in-patients participants diagnosed with SUD, participants with a maintained state of abstinence were assessed [84]. 23% maintained abstinence during the time period of 3 years, and 13% achieved abstinence for 5 years post treatment [84]. The highest risk period appeared to be within the first year post treatment with 61% relapsing within that time, 36% having no months of abstinence, 14% relapsing within 2-6 months and 11% in 7-12 months [84]. A total of 7% relapsed in the second year, 3% in each of their 3rd and 4th years, 2% in year 5 and 1% in year 6-7 [84]. The most significant indicator of relapse was parental drug use, and ever having sold drugs for cash [84], while the most significant protective factors against relapse included experiencing paranoia, hallucinations and violent behaviour while the participant was still actively using, as well as longer time spent in treatment and participation in a self-help or treatment post discharge [84]. It is likely that these factors are not independent of one another, and treatment duration would likely depend on severity of symptoms.

Another fMRI study using the rock, paper scissors task showed greater FC in the right inferior frontal gyrus in relapsers as well as higher left middle temporal gyrus and right caudate, thalamus, hippocampal gyrus and hippocampal activation compared with those that responded to treatment [85]. Moreover relapsers to treatment had lower bilateral insula, striatum, thalamus, posterior cingulate and precuneus activation than abstainers [85].

Stewart et al. (2019) conducted a neuroimaging review to determine the effects of abstinence on the brains of people who ceased to misuse opioids and stimulants [86]. They revealed that although the majority of research was conducted on chronic cocaine misuse, it was still evident in all narcotics that intervention showed improvements in brain functionality [86]. Brain regions identified to have greater grey matter volume in abstinence (30-35 weeks) included the insula, cingulate cortex, superior frontal, middle and tempular regions as well as the cerebellum, with greatest effect found in the frontal regions and lower insula and striatal volumes [86]. fMRI studies show that with increased abstinence there is weaker functional activity in the striatum, thalamus, cingulate, frontal (medial PFC) and insula (to name but a few) related with drug cues in people who abstained from abusing stimulants [86].

In a longitudinal study conducted over 1 year, 51% of the initially abstinent (multiple treatment programs) participant's relapsed within 2-3 months [87]. The only discernible demographic feature between responders to treatment and relapsers was that relapsers had 2.13 more years of education than those who remained abstinent, with years of education for the entire group ranging from 8-16 years [87]. Relapsers also performed more poorly on the Wisconsin Card Sorting test (an executive function measure with domains of attention, flexibility, working memory and visual processing) [87]. Reaction time for relapsers in the selective attention task (Oddball Task) was slower than the abstinent group, and relapsers responded to fewer targets [87]. With regards to fMRI analysis, signal alterations in the right lateralised posterior cingulate, right insula and adjacent precentral cortex together when combined with lifetime manic episodes correctly classified 88.9% of relapsers and 90.9% of abstainers [87]. Those with antisocial personality disorder/ conduct disorder (ASPD) had a 65.9% relapse rate and if ASPD was used as a covariate in place of mania in fMRI predictions of relapse, then the accuracy of predicting relapse changed to 81.8% [87]. We hypothesised that an 8 week period of CM treatment would show structural and functional changes in regions which are utilised in executive function and attention, and that these changes would an increase in executive function as measured by neurocognitive tasks.

Having explored the brain regions affected by MA and associated cognitive changes, I will now conduct an exhaustive systematic review on stimulant use disorder and resting state MRI, which will be covered in the next chapter. I will explore studies that have been conducted where the SUD group is compared with healthy controls, and I used the gaps in the literature to shape the main aims and hypotheses for the study we conducted into MA misuse and CM as a treatment.

Chapter Two

Stimulant Misuse and Resting State Functional Connectivity: a Systematic Review

2.1. Introduction

Misuse of psychostimulants is a prevalent global problem with amphetamines being the second most misused class of illicit substances after opioids, and cocaine being the fourth [88]. Psychostimulants promote striatal dopamine release, which reinforces drug self-administration [89]. Psychostimulants have different modes of action, cocaine blocks the dopamine reuptake and amphetamines promote monoamine release leading to elevated extracellular dopamine (DA) in the striatum [89]. There have been advances in understanding the effects of stimulant misuse in the brain in recent years, largely attributable to MRI studies. Research has revealed abnormal functioning in stimulant use disorder within the corticostriatal circuit in cocaine [90-92] and methamphetamine [93] dependence. Moreover, the neural correlates of relapse [92, 94-97] and impulsivity [96, 98, 99] have been a focal point in stimulant misuse research using rsfMRI. This growing body of work may help identify potential treatment opportunities for cocaine [95, 100, 101] and methamphetamine dependence [69, 93, 102, 103].

Functional magnetic resonance imaging (fMRI), based on a blood-oxygen-level-dependent (BOLD) contrast mechanism [104], can provide information about task-related brain function and the intrinsic activity within brain circuits at rest [105]. Measurements in the resting state, when a participant is lying still but awake and not conducting a task can identify anatomically separate regions that act in a coordinated fashion to maintain various behavioural states, including those related to addiction [106, 107]. Known as resting-state functional connectivity (rsFC), such measures have high test-retest reliability [108-110], and have revealed abnormalities related to neuropsychiatric disorders [108].

The focus of resting state fMRI studies is primarily large amplitude, low frequency fluctuations (typically < 0.1Hz) in BOLD signal [108, 109, 111]. These have been used to identify large-scale brain networks, such as the default mode network (DMN), the salience network (SN) and the executive control network (ECN) [111]. It is important to note that only a few of the functions of the listed brain regions are described below, and these regions are not limited to the listed functions.

The DMN is active when an individual engages in introspective thought, mind wandering, or recalling autobiographical memories [112]. The DMN is composed of sub-networks that include the medial temporal lobe subsystem (posterior cingulate cortex/ precuneus [100, 113, 114]) which facilitates reflection on previous memories, and the medial prefrontal subsystem[94, 100] which manipulates past experience into self-relevance [112] as well as the hippocampus [115-117] (transference of memory to long-term storage). These subsystems structurally interact at various points with the posterior cingulate cortex [112], being a brain region of relevance in stimulant misuse [100].

The ECN is active while an individual is performing a task and as such activity within the ECN is typically anti-correlated with activation of the DMN [90]. The ECN includes the dorso-lateral prefrontal cortex (dlPFC) [93, 101, 114] (executive function, working memory and planning [118]) and in some classification systems the orbito-frontal cortex (OFC) [98, 114] (control and organisation of behaviour and decision making [119]). Many descriptions of the ECN include parietal regions, which we included into both the ECN and the dorsal attention network, with posterior parietal lobule and visual areas comprising the dorsal attention network [120]. Even though we have included the parietal region into two networks, it is important to note that neither work in isolation of the other [120]. Further it is worth noting that parietal regions subserving the ECN and DAN (as well as DMN) can be spatially diassociated [121].

According to Menon et al. (2010), the salience network (SN) toggles between the DMN and the ECN [122], and its primary nodes are the dorsal anterior cingulate cortex [114, 123] (error detection [124, 125], inhibition [126] and appraisal of social processing [127]) and the anterior insula [94, 113, 128, 129] (which may be essential in awareness and subsequently consciousness [130] this would include craving [131] and introspection [132]). The modulation between the DMN and ECN by the SN is consistent with the notion of competing neural networks within the brain [133] that can be detected in rsFC data.

Current research suggests that the dorsal attention network, like the ECN is anti-correlated with the DMN as well as being active in top-down attention-demanding tasks [134]. It comprises prefrontal (dlPFC) and superior parietal cortices (spatial orientation, somatosensory processing and visual processing) as well as the frontal eye fields and middle temporal motion complex [135]. The dorsal attention network exerts a top-down influence over vision whilst attention is being spatially orientated, although this network is also activated even when attention is not specifically directed [120].

The concept of rsFC between brain networks arose from the findings of interactions between anatomically defined, spatially remote brain regions [106, 136]. Despite individual variability, rs-fMRI has provided a universal map of canonical resting-state networks that are co-activated to varying degrees [108, 109]. Various factors such as sex and age [108] are often used as covariates in analysis, as they influence rsFC within and between networks. Further, rsFC is modulated by arousal, emotion and cognitive states [108] such as interoception or problem solving.

The most commonly used methods to compare intrinsic rsFC in patients are independent component analysis (ICA) and seed-based analysis. Seed-based analyses typically identify regions of interest and correlate the average BOLD time course of voxels within the region of interest and between all other voxels in the brain, or with the mean signal from other regions of interest [111, 136]. In contrast ICA is a model-free, data-driven source-detection method [111, 136]. Other analytical methods include graph theory,

which is a type of seed-based analysis (incorporating global efficiency), classifying networks as collections of nodes that are connected by edges in order to compute connectional characteristics [111]. Graph analysis allows researchers to make inferences about the energy allocation and information transfer (global efficiency) of the brain as well as identifying brain clusters that work in unison (clustering coefficient or the degree to which nodes cluster together) [111]. The clusters/ nodes in the brain create a small-world network in which direct and indirect interconnectivity of nodes within the brain with a configuration of multiple short-range connections and a few long-range ones[137]. Regions that have larger energy allocation and greater clustering coefficient (greater number of mutual connections between nodes) are less dynamic and more robust [138].

Clustering algorithms are also used to group all items that are alike based on characteristics relevant to the area under investigation [111]. Finally multivariate pattern classification explores spatial and temporal patterns across the brain and has been used to distinguish between population groups as well as to tell apart different cognitive tasks. These data can be used in attempts to recreate a participant's perceptual experience and bootstrap how the brain will react to novel stimuli [139].

In much the same way that there are multiple means of analysing data, there are also multiple models of addiction. Various models regarding the process of addiction have been proposed, yet no one theory has been accepted as the standard model, although certain models are more influential than others. Koob and Volkow have defined a three-stage cycle in addiction, the 'Opponent process model'. The stages in this cycle consist of "binge/ intoxication, withdrawal/ negative effect and preoccupation/ anticipation" with corresponding dysregulation of incentive salience, negative emotional state and disruptions of executive function respectively [140]. Incentive salience involves the basal ganglia, while adverse emotional states implicate the amygdala (specifically the central nucleus of the amygdala), bed nucleus of stria terminalis and the shell of the nucleus accumbens [140]. Further, dysfunctional executive control largely implicates the prefrontal cortex [140].

Motivational circuits become dysregulated in drug addiction, as the individual focuses more pronouncedly on incentives and fulfilment of drug seeking habits in a binge/ intoxication stage which results in surges of dopamine in the basal ganglia [141]. The withdrawal/ negative affect stage is associated with elevated stress (measured by release of peptides like corticotropin-releasing factor and dynorphin in the amygdala) and a marked decline in dopamine function within the reward system (which includes, but is not limited to, the ventral tegemental area, ventral striatum including the nucleus accumbens, the dorsal striatum including the caudate nucleus and putamen as well as the substantia nigra) [141]. The preoccupation/ anticipation stage is dominated by cravings and deficiencies in executive function, and is marked by elevated glutamatergic neuronal activity from the prefrontal cortex and insula to the basal ganglia and amygdala [141]. Consistent with this model, neuroimaging research has uncovered corticostriatal dysfunction

in people who misuse MA, evident by poor neuronal integrity, atypical neurotransmitter function, abnormal neuronal connectivity and neuro-inflammation [52]. Moreover, these abnormalities have been linked with certain adverse behaviours such as risky decision making, limited self-control and cognitive inflexibility [52].

There are long-term negative consequences to drug taking, and the continued use of drugs in the setting of losses and/or negative consequences implies that decision-making and associated brain regions involved in executive function may be dysfunctional [142]. Koob characterised the decision making process as consisting of three stages: determining of preferences, choice implementation and feedback processing [142]. Establishing preferences requires gathering of information and assigning values based on risk and reward, and involves the ventral striatum, medial PFC, cingulate cortex and OFC [142]. In the choice stage, competitive desires are inhibited and motivational anticipation of the choice is focused upon [142]. Feedback processing involves evaluation of potential gains versus losses, and assessing possible changes in outcomes and consistency between previous feedback and more recent choices [142].

Motivation, reward and brain areas involved in decision-making show dysfunction in stimulant use disorder, rendering the risk of relapse as a potential threat [142]. Key brain regions involved in addiction within the reward circuit are the amygdala and nucleus accumbens. Together with the dorsal striatum they promote drug seeking behaviour in addiction, yet these deep grey matter regions do not act in isolation, as the OFC also plays a part in the compulsive drug seeking behaviour [143]. Volkow et al (2000) found that OFC function is correlated with dopamine D2 receptor availability in the striatum [143]. Notably, recently abstinent cocaine users exhibit a hypermetabolic state in the OFC which is proportional to levels of D2 receptors in the striatum and the intensity of cocaine craving [143]. Bonson et al. (2002), using positron emission tomography (PET), extended this line of research and revealed that in response to cocaine cues in actively using participants there was strong left hemisphere activation of the lateral OFC, lateral amygdala and rhinal cortex as well as strong activation in the right dlPFC and cerebellum [144].

Volkow and Koob identified a desensitised reward circuit in substance use disorder. This circuit when depressed has been associated with an anhedonic, demotivated response to every-day activities, an increase in stress reactivity and a conditioned response which exacerbates cravings as well as depressed executive control [26]. In turn, this state facilitates impulsivity and poor decision making [26]. Changes detected in rsFC of the OFC and reward circuit of people who misuse substances play an important role in relapse by increasing cravings and compulsive behaviour [145]. Understanding such regional changes in brain function is likely to improve treatment opportunities for individuals with Stimulant Use Disorder.

Cognitive-affective abnormalities as a consequence of stimulant use disorder are common. These include impairments in impulse control [99, 102] and compulsive behaviours [98], poor goal directed behaviour [92] and

inadequate reversal learning [146] as well as flawed moral judgement [123]. It is important to bear in mind the differences between impulsivity and compulsivity. While impulsivity is associated with spontaneous and poorly thought through decisions which may lead to risky behaviour, compulsivity refers to behaviours that have a more repetitive quality which the individual finds difficult to resist [147].

Stimulant misuse has been associated with abnormal executive function, yet it is not yet known whether the cognitive deficits result from stimulant misuse or predates it. As Dean et al (2013) point out, longitudinal studies have identified cognitive difficulties as a predictor for drug misuse [76]. Moreover, in a more recent study (2018) in which they examined childhood academic transcripts, T1 fMRI scans and cognitive battery scores for 37 MA dependent subjects compared with 41 controls, they found that academic transcripts acted as a predictor for MA use, while MA use itself contributed to greater cognitive decline [148]. In support of MA misuse leading to cognitive decline, animal studies have shown deterioration of cognitive abilities one week post binge doses of MA, where the MA was administered in a pattern that mimicked the use of human stimulant misusers [76].

The hypothalamus has been characterised as a bridge between the endocrine and nervous system. In healthy subjects it releases a multitude of hormones including oxytocin, which is important in attachment [149], and receives signals from peripheral circulation, including cues from the peptide leptin that reduces appetite [150]. Further, in healthy subjects the hypothalamus plays a role in circadian rhythms [151] and body temperature as well as in stress, (hypothalamus, pituitary, adrenal axis or HPA-axis) [152]. Stimulant Use Disorder has been shown to affect alexithymia [113], appetite and sleep patterns, which indicates that the hypothalamus may be implicated in stimulant misuse.

The literature yields no published findings of the neural correlates of treatment of MA with CM. Moreover, the cursory examination of the literature indicates that studies of rs-fMRI in Stimulant Use Disorder (SUD) have reported inconsistent findings. Accordingly we undertook a systematic review of rs-fMRI findings in SUD, collating all data that has addressed this issue.

The studies included in this review conducted research on cohorts of individuals who misuse stimulants (amphetamines and cocaine). The aims of this review include (1) to combine the current resting-state fMRI research comparing individuals with stimulant used disorder with a non-drug using sample. (2) To analyse the current body of literature together in order to benchmark agreement between studies and identify potential areas for future research. In this review we were particularly interested in the dynamism of rsFC within and between networks, as well as the association between the rsFC and behaviour.

2.2. Methods

2.2.1. Design

Three databases were systematically searched by LvN for relevant literature, including PubMed, Scopus and Medline databases. These databases were chosen so as to cover as large a range of research as possible [153]. The following key words were used for PubMed: (methamphetamine OR amphetamine OR cocaine OR central nervous stimulants [MH:exp]) AND (network* OR connectivity OR circuit* OR connectome [mh:exp]) AND (MRI OR fMRI OR magnetic resonance imaging [MH:exp]). The keywords used for Scopus and Medline were: (methamphetamine OR amphetamine OR cocaine OR central nervous stimulants AND network OR connectivity OR circuit OR connectome AND MRI OR fMRI OR magnetic resonance imaging) see outcomes for search in appendix R. After collating the results of the database searches two researchers (LvN and JI) independently performed thorough screening of both the titles/ abstracts and the full-text articles, where applicable.

The respective databases were searched for relevant papers from inception date till September 18, 2018. Out of the initial 606 articles found from the first search, the first screening used abstracts to determine suitability and yielded 174 studies (see diagram 1). The second screening used full papers to determine suitability and yielded 35 papers that met all inclusion criteria. Any discrepancies regarding inclusion between the reviewers selections were resolved through discussion and full agreement was achieved between the reviewers (Cohen's Kappa Index of 100%) before a decision was made. The review was also registered with the PROSPERO registry (https://www.crd.york.ac.uk/prospero/) which is an international database whereby reviews based on health and social care can be registered not only to prevent duplication, but also to allow researchers to compare review methodology.

2.2.2. Eligibility

Studies were included if they involved rsfMRI, were conducted on adults (18-64 years, inclusive), diagnosed using standardized criteria (ICD 9+ or DSM III, IV or 5) as having primary dependence on stimulants including cocaine, methamphetamine (MA) or amphetamines. Further, studies were required to include a control group of participants without a diagnosed substance use disorder and no psychological comorbidities. Studies were restricted to those with a minimum sample size of 10 subjects in each group to help ensure that study effect size estimates were reliable. Finally, research that used brain imaging methods other than rsfMRI were excluded, as were review articles, animal studies, case reports and those employing samples with medical comorbidities (e.g. cardiomyopathy, diabetes, non-drug related mental disorders etc.) but not drug related comorbidities (e.g. drug related depression, drug related psychosis, etc.). Publication in English was not an eligibility criterion, yet all selected reports were available in English.

The STROBE Checklist (Strengthening the Reporting of Observational Studies in Epidemiology) (Appendix A) was used to ensure consistent and relevant information was extracted from each of the study reports, and to determine the quality of the study reports [154]. The STROBE Checklist consists of 22 items relating to each section of a scientific paper [154]. Using this checklist we assigned a rating for each item, whereby a rating of 2 was assigned if the paper had included all aspects relevant to that item, a rating of 1 was assigned if there was only partial information, and 0 if no information was provided (see Table 1). As part of the quality rating, we classified studies with a sample size of 20-30 as adequate, with <20 as low and >30 as high, in line with recommended guidelines for power in MRI research [155].

	Title & abstract	Introduction	Methods	Results	Discussion	Other Information	Total possible score
Highest score	4	4	28	20	10	2	68

Table 1: Strobe scoring

2.2.3. Quality Control

Study information was entered into a customised electronic data extraction form by one assessor (LvN), with a random subset of 25% of the eligible papers checked independently by a second rater to confirm fidelity of data entry (JI).

2.3. Results

The full search identified 606 potentially relevant studies, with 211 from PubMed, 62 from Scopus and 333 from Medline (flow chart 1). Duplicate papers (n = 432) were removed and post screening, 35 eligible papers remained, of which two papers were unavailable despite multiple attempts to acquire these from the authors. Moreover, many of the papers that were excluded had more than one reason for exclusion.

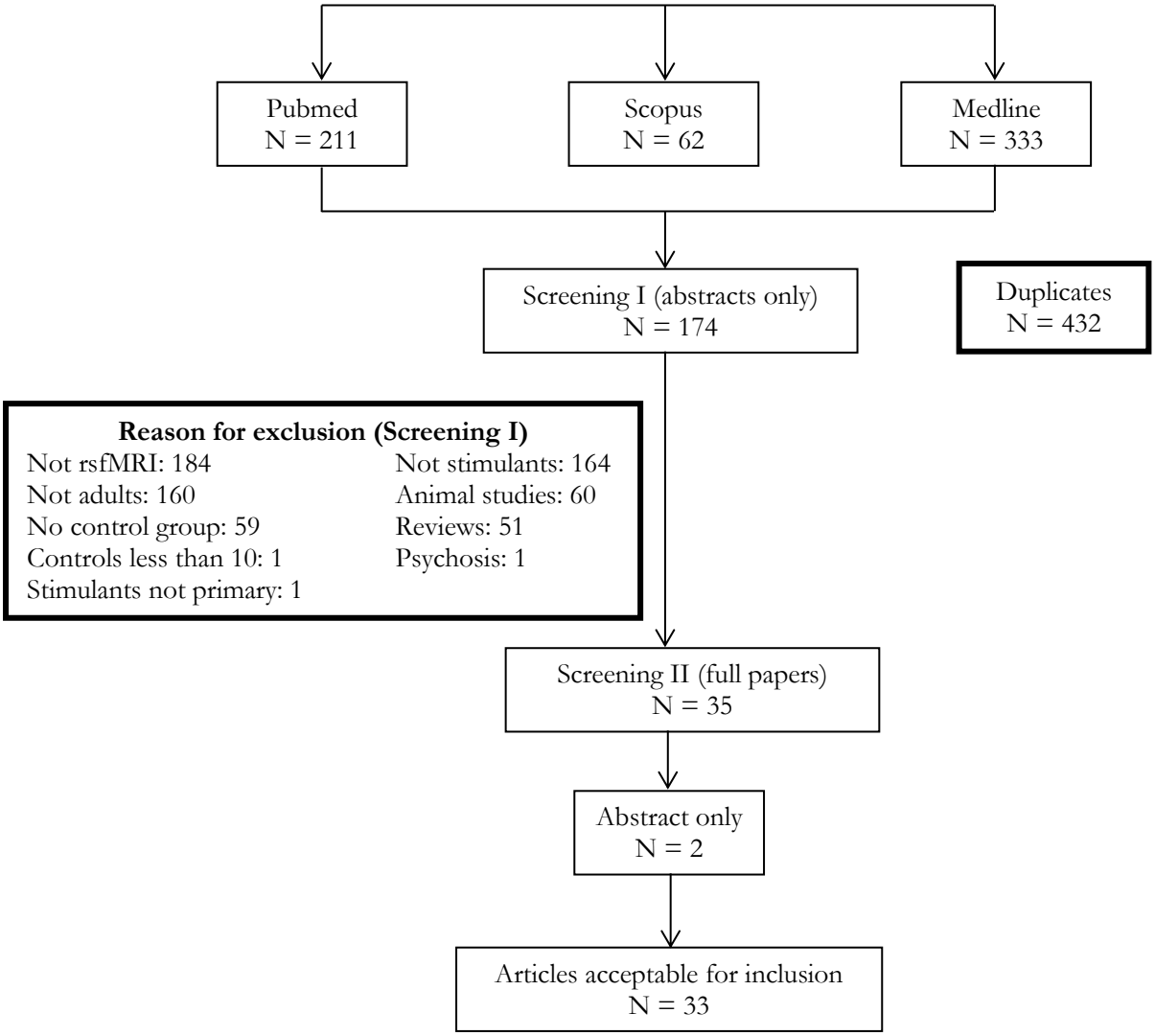

Diagram 1: Flow chart of data assimilation

When exploring differences and similarities between studies we isolated rs-fMRI acquisition, processing and analysis parameters (table 2), participant demographics (table 3), drug use variables (table 4). Further, we summarised our Strobe score in table 5.

2.3.1. Resting State-fMRI acquisition, processing and analysis parameters of eligible studies

Study	MRI Parameters: TR/ TE/ FoV/ Flip angle/ spatial smoothing/ voxel resolution	Scanner	Eyes open or shut	Processing Parameters: Template/ frequency filter/ Nuisance regressors	Analysis covariates	Analysis
Cocaine						
Adinoff et al. (2015) [115]	1700 ms/ 25 ms/ Unknown/ 70º/ 6 mm FWHM/ 3.0 x 3.0 x 3.0 mm³	3T Philips	Open	Talairach/ 0.01-0.1 Hz/ 6 motion parameters, WM, CSF	Sex, education	Seed-based
Balducci et al. (2018) [156]	2000 ms/ 30 ms/ 240 mm/ 75º/ 6mm FWHM/ 3.0 x 3.0 x 3.0 mm³	3T Philips Ingenia	Open	MNI/ 0.01-0.08 Hz/ motion (opposite acquisition direction), segmentation, global signal, CSF, WM, physiological noise reduction (5 component analysis factors)	Sex, age, education, current depressive disorder, current dysthymia, current alcohol use	Seed-based
Berlingeri et al. (2017) [92]	3000 ms/ 60 ms/ 280 x 210 mm/ 90º/ 5 x 5 x 5 mm FWHM/ 3.0 x 3.0 x 3.0 mm³	1.5T General Electrics	Closed	MNI/ 0,01-0,08 Hz/ 6 motion parameters, WM, CSF, global signal	None reported	Seed-based
Camchong et al. (2011) [146]	2000 ms/ 30 ms/ 6 mm/ 90º/ 6 mm FWHM/ 3,4 x 3,4 x 4,0 mm³	3T Siemens Trio	Closed	MNI/100 Hz/ noise components as per MELODIC (FSL) manual (http://www.fmrib.ox.ac.uk/ fslcourse/lectures/melodic.pdf)	Age	Probabilistic ICA Seed-based
Camchong et al. (2014) [157]	2000 ms/ 30 ms/ Unknown/ 90º/ 6 mm FWHM/ 3,4 x 3,4 x 4,0 mm³	3T Siemens Tim Trio	Closed	MNI/ 100 Hz/ noise components as per MELODIC (FSL) manual (http://www.fmrib.ox.ac.uk/	None reported	Probabilistic ICA Seed-based

				fslcourse/lectures/melodic.pdf)		
Cisler et al. (2013) [128]	2000 ms/ 30 ms/ 240 x 240 mm (study 1)/ 192 x 192 mm (study 2)/ 90º/ 5 mm FWHM/ 3 x 3 x 3 mm³	3T Philips Achieva X series	Unknown	MNI/ 0.01-0.1 Hz/ Motion, WM, CSF	Age, race, education, sex	ICA and seed-based
Contreras-Rodriguez et al. (2015) [96]	2000 ms/ 35 ms/ 230 x 230 mm/ 90º/ 8 mm FWHM/ 2 mm³	3T Intera Achieva Philips	Closed	MNI/ High-pass (128 seconds)/ 6 motion parameters, WM, CSF	Motion, tobacco smoking, age	Seed-based
Ding et al. (2013) [116]	2000 ms/ 15 ms/ Unknown/ 90º/ 8 mm FWHM/ 3 x 3 x 4 mm³	3T Siemens Allegra	Open	MNI/ Unknown/ Motion	None reported	ICA
Geng et al. (2017) [94]	**NTS** 2000 ms/ 27 ms/ unknown / 77º/ 6 mm FWHM/ 3.44 x 3.44 mm³ **TCG** 1700 ms/25 ms/208 x 208 mm/70º/6 mm FWHM/ 3.25 x 3.25 mm	**NTS** 3T Siemens Allegra **TCG** 3T Phillips MR	Closed	Talairach/ <0,1 Hz - treatment/ 6 motion parameters, WM, CSF	Tobacco smoking, total years and current amount of use, age, head motion, education, IQ, days of use in last 90 days prior to admission.	Seed-based
Gu et al. (2010) [117]	2000 ms/ 27 ms/ 220 x 220 mm/ 77º/ 6 mm FWHM/ 3,44 x 3,44 mm	3T Siemens Allegra	Closed	Talairach/ 0,1 Hz/ 6 motion parameters, WM, CSF	Nicotine dependency, years of use, positive on day of scan	Seed-based
Kelly et al. (2011) [158]	2000 ms/ Unknown/ Unknown/ 90º/ 6 mm	3T Siemens	Open	MNI/ 0.009-0.1 Hz/ 6 motion parameters, WM, CSF, global signal	Scan order, age, sex, smoking history, history of a psychiatric	VMHC and seed-based

	FWHM/3 x 3 x 4 mm³	Allegra			disorder	
Konova et al. (2015) [100]	1600 ms/ 20 ms/ 200 mm/ 90º/ 8 mm/ 3 x 3 x 3 mm³	4T Varian/ Siemens	Open	MNI/ 0,01-0,10 Hz/ 6 motion parameters, global signal	Age, drug use severity	rsFCDM
Liang et al. (2015) [159]	2000 ms/ 27 ms/ 220 x 220 mm/ 77º/ 6 mm FWHM/ 3 x 3 x 3 mm³	3T Siemens Allegra MR	Unknown	Talairach/ low-pass cut-off of 0.1 Hz/ motion, CSF, WM, global signal	Age, sex, IQ, education years, tobacco smoking, years of use, current use, alexithymia	Modularity analysis
McHugh et al. (2013) [160]	1700 ms/ 25 ms/ 208 x 208 mm/70º / 6 mm FWHM/ 3,25 x 3,25 x 3 mm	3T Phillips MR	Open	Talairach/ 0,01-0,1 Hz/ 6 motion parameters, CSF, WM	Sex, impulsivity, cocaine use, duration, age of onset, abstinence, education, IQ, tobacco smoking, alcohol, treatment duration and clinic	Seed-based
McHugh et al. (2014) [161]	1700 ms/ 25 ms/ 208 x 208 mm/ 70º/ 6 mm FWHM/ 3,25 x 3,25 x 3 mm³	3T Phillips MR	Open	Talairach/ 0,01-0,1 Hz/ 6 motion parameters, CSF, WM	Education, cocaine use, trait stress reactivity/ anxiety and neurocognitive measures	Seed-based
McHugh et al. (2016) [162]	1700 ms/ 25 ms/ 208 x 208 mm/ 70º/ 6 mm FWHM/ 3.0 x 3.0 x 3.0 mm³	3T Phillips MR	Open	Talairach/ 0,01-0,1 Hz/ 6 motion parameters, CSF, WM	Education, outcomes of Wisconsin Card Sorting Task, Continuous Performance Task commissions	ICA
Moeller et al. (2016) [101]	1600 ms/ 20 ms/ 20 cm/ 90º/ 8 mm FWHM/ 3 x 3 x 3 mm³	4T Varian/ Siemens	Open	MNI/ 0,01-0,10 Hz/ 6 motion parameters, global signal, DVARS	Depression, age, tobacco smoking, additional substance use comorbidities	GrsFCD
Ray et al. (2015) [163]	2000 ms/ 25 ms/ 192 mm/ 90º/ 9 mm FWHM/ 3 x 3 x 3	3T Siemens Trio	Open	MNI/ 0,01-0,10 Hz/ 6 motion parameters and 6 before a time point	Years of use, frequency of use per week, money spent	ICA

	mm³			and 12 corresponding square of motion parameters, scrubbing with framewise displacement,, CSF, WM		
Ray et al. (2016) [164]	2000 ms/ 25 ms/ 192 mm/ 90º/ Unknown/ 3 x 3 x 3 mm³	3T Siemens Trio	Open	MNI/ Unknown/ 24 motion parameters, CSF, WM	None reported	EC and SDCM
Ray et al. (2017) [91]	2000 ms/ 25 ms/ 192 mm/ 90º/ Unknown/ 3 x 3 x 3 mm³	3T Siemens Trio	Open	MNI/ Unknown/ 6 motion parameters, CSF, WM	None reported	IMaGES
Rish et al. (2016) [95]	1600 ms/ 20 ms/ 200 mm/ 90º/ Unknown/ 3.125 x 3.125 mm²	4T Varian/ Siemens	Open	MNI/ 0.01-0.10 Hz/ 6 motion parameters, CSF, WM	None reported	MMLA
Verdejo-Garcia et al. (2014) [165]	2000 ms/ 50 ms/ 240 mm/ 90º/ 8 mm FWHM/ 256.299 voxels	1.5T Signa Excite (General Electric)	Closed	MNI/ high-pass (128 s)to remove low-frequency drifts <0.008 Hz/ CSF, WM, global signal	Moral judgments errors committed and total errors	Seed-based
Wang et al. (2015) [166]	2000 ms/ 30 ms/ 220 x 220 mm/ Unknown/ None/ Unknown	3T Siemens	Open	MNI/ 0.01-0.08 Hz/ motion, CSF, WM	Age, Cocaine, alcohol, cannabis, nicotine dependence	rsFCM
Wilcox et al. (2011) [114]	2000 ms/ 29 ms/ 240 mm/ 750º/ 8 mm FWHM/ 3,75 x 3,75 x 4,55 mm³	3T Siemens Trio	Open	Talairach/ high pass/ 6 motion parameters, CSF, WM, a constant and a linear term	Pre-morbid intelligence	Seed-based
Wisner et al (2013) [167]	2000 ms/ 30 ms/ Unknown/	3T	Closed	Unknown/ high pass/ 6 motion	Impulsivity, weekly use, cravings,	ICA

	90º/ Unknown/ 3,4 x 3,4 x 4,0 mm³	Siemens Trio		parameters, non-neural fluctuations	depression	
Zhang et al (2018) [168]	2000 ms/ 25 ms/ 220 x 220 mm/ 85º/ 4 mm FWHM/ unknown	3T Siemens Trio	Closed	MNI/ 0.009 Hz < f < 0.08 Hz/ pixel/ 6 motion parameters, CSF, WM, global signal, DVARS	Age, sex, framewise displacement	Seed-based
Methamphetamine						
Ipser et al (2016) [69]	2500 ms/ 30 ms/ 200 x 200mm/ 77º/ NA/ 3,125 x 3,125 mm³	3T Siemens Allegra	Open	MNI/ 0.01-0.1 Hz/ 6 motion parameters, quadratic function	Age, sex, GCOR (estimate of average connectivity between voxel time series across the brain), framewise displacement	ICA & seed-based
Kohno et al (2014)	2000 ms/ 30 ms/ 200 mm/ 90º/ 5 mm FWHM/ 3 x 3 x 4 mm³	3T Siemens Trio	Open	MNI/ High-pass/ 2 motion parameters, Task related regressors (BART), CSF, WM, DVARS	Age, sex, tobacco smoking status, cannabis use, framewise displacement	Seed-based
Kohno et al (2016) [102]	2000 ms/ 30 ms/ 200 mm/ 90º/ 5 mm FWHM/ 3 x 3 x 4 mm³	3T Siemens Trio	Open	MNI/ High-pass (100 s)/ 2 motion parameters, CSF, WM, DVARS	Mean time series across all voxels within midbrain from pre-processed images, age, sex, impulsivity	Seed-based
Kohno et al (2018) [103]	2000 ms/ 40 ms/ 240 mm/ 80º/ 5 mm FWHM/ 3.8 x 3.8 x 4.0 mm³	3T Siemens Trio	Open	MNI/ High-pass (100 s)/ 2 motion parameters, scrubbing with framewise displacement, CSF, WM, DVARS	Interleukin concentrations, age, sex	Seed-based
Mansoory et al (2017) [169]	3000 ms/ 30 ms/ 192 mm/ 90º/ None/ 36 x 63mm³	3T Siemens Tim Trio	Closed	MNI/ 0.01–0.08 Hz/ Motion	None reported	BCFD and GTP
Other Stimulants						

Meunier et al (2012) [98]	2000 ms/ 30 ms/ Unknown/ 78^0/ Unknown/ 3.0 x 3.0 mm^3	3T Siemens Tim Trio	Closed	MNI/ 0.031–0.062 Hz/ Motion	Severity of compulsive symptom rating, depression, smoking status, cannabis use	NCS
Regner et al (2016) [99]	2000 ms/ 30 ms/ Unknown/ 30^0/ 6 mm FWHM/ 3.4 x 3.4 mm^3	3T Signa Excite (General Electrics)	Closed	MNI/ 0.008 Hz < f < 0.15 Hz/ 6 motion parameters, CSF, WM	Impulsivity, behavioural approach, behavioural inhibition, negative affect	EC and ICA

Table 2: rsfMRI Parameters for studies that met eligibility criteria

(BCFD Box-Counting Fractal Dimension, CSF cerebrospinal fluid, DVARS, EC Effective connectivity, RSFCDM Functional connectivity density mapping, GRSFCD Global functional connectivity density, GTP Graph topological properties, ICA Independent component analysis, IQ intelligence quotient, MMLA Multivariate machine learning approaches, NCS Nodal connectivity strength, NTS Non treatment seeking, SDCM Spectral dynamic causal modelling, TCG Treatment completed, VMHC Voxel-mirrored homotropic connectivity, WM white matter)

2.3.2. Demographics of eligible studies

Study	Sample Size		Age		Gender		Education		IQ		
Cocaine											
	SUD	**HC**	**SUD**	**HC**	**SUD**	**HC**	**SUD**	**HC**	**SUD**	**HC**	**Group Differences**
Adinoff et al. (2015) [115]	40	21-1	44.7±6.4 relapsed, 44.3±6.7 remission	42.2±8.9	19M	13M	11.5±1.6 Relapse 12.8±1.8 Remission	13.8±1.0	87,8±9,4 Relapse 87,7±7,6 Remission	97.9±10.7	<females, <education, <IQ, <tobacco use
Balducci et al (2018) [156]	19	20-2	31±6	32±8	18M	18M	Junior high school	Technical degree	-	-	<education
Berlingeri et al. (2017) [92]	18	19	39.28±9.1	33.05±9.11	18M	13M	10.11±3.2	15±4.01	-	-	Age, education
Camchong et al (2011) [146]	27	24	39.73±6.14	39.76±7.09	22M	19M	13.41±1.93	15.16±1.62	-	-	None reported
Camchong et al (2014) [157]	21-3	16-1	22.05±2.64	24.21±5.76	10M	10M	Not reported	Not reported	-	-	None reported
Cisler et al (2013) [128]	41	19	42.71±7.71	31.68±9.06	32M	8M	12.33±1.38	14.75±2.28	-	-	>age, >males, education, ethnicity
Contreras-Rodriguez et al (2015) [96]	20	21	34.6±6.8	31.0±4.6	19M	20M	9.7±1.6 10.0±2.0 Relapse 9,5±1,3 Remission	10.4±2.0	101.8±7.6 101.0±8.3 Relapse 102,4±7,3 Remission	105.8±8.8	>age, <tobacco use

Ding et al (2013) [116]	29-5	24	35.12±8.4	35.11±7.5	21M	20M	13.83±1.35	14.08±1.76	-	-	>tobacco use
Geng et al (2017) [94]	64-5 59 non treatment 45 treatment	67	40.59±6.01 NTS 43.4±7.1 treatment	39,99±5,70	49M non treatment 39M treatment	46M	12.84±1.28 non treatment 12.5±2.1 treatment	13.34±1.91	56.44±7.67 non treatment 89.6±8.9 treatment	57.49±8.28	Tobacco use
Gu et al (2010) [117]	39	39	38±6.2	40±5.1	23M	29M	13.2±1.7	12.9±1.3	58±8.2	58±7.2	None reported
Kelly et al (2011) [158]	39-14	24	36.6±9 (full group) 35.0±8.8 (n=29)	35.1±7.5	23M	20M	7 HS/GED, 10 some college, 7 graduate, 1 advanced degree	1 some HS, 3 HS, 10 some college, 8 graduate, 2 advanced degree	-	-	Age
Konova et al (2015) [100]	19	15	46.2±7.5 45.6±7.3 orig. study	39.0±7.4	17M 16M orig. study	15M	13.2 12.9±1.8 orig. study	13.8	91.8±9.2 orig. study Verbal 9.3±3.1 orig. study Non verbal	-	>age, >tobacco use
Liang et al (2015) [159]	47	47	40±5.87	38±7.68	36M	30M	12.8±1.24	13.3±1.84	54±8.85	56±8.60	None reported
McHugh et al (2013) [160]	45	22	43.10±6.84 non-relapsed, 43.75±7.53	42.05±8.40	39M	14M	11.83±1.88 Relapse 13.29±2.05 Remission	13.91±1.41	88.61±8.63 Relapse 90.71±9.35 Remission	96.86±10.26	>age, >tobacco use
McHugh et al (2014) [161]	45	22	43.10±6.84 non-relapsed,	42.05±8.40	39M	14M	11.83±1.88 Relapse 13.29±2.05	13.91±1.41	88.61±8.63 Relapse 90.71±9.35	96.86±10.26	>age, >tobacco use

			43.75±7.53 relapsed				Remission		Remission		
McHugh et al (2017) [97]	45	22	43.10±6.84 non-relapsed, 43.75±7.53	42.05±8.40	39M	14M	11.83±1.88 Relapse 13.29±2.05 Remission	13.91±1.41	88.61±8.63 Relapse 90.71±9.35 Remission	96.86±10.26	>age, >tobacco use
Moeller et al (2016) [101]	22	21	46.4±7.0	39.0±6.5	20M	20M	13.2±1.9	14.0±1.5	93.1±9.5 Verbal 9.7±2.9 Non verbal	98.43±13.84 8 verbal 10.14±3.468 non-verbal	>age, >tobacco
Ray et al (2015)	20	17	46±6.4	46±7	15M	13M	13.4±2.4	13.5±2.1	-	-	>tobacco use
Ray et al (2016) [164]	20	17	46±6.4	46±7	15M	13M	13.4±2.4	13.5±2.1	-	-	>tobacco use
Ray et al (2017) [91]	20	17	46±6.4	46±7	15M	13M	13.4±2.4	13.5±2.1	-	-	>tobacco use
Rish et al (2016) [95]	18	15	45.6±7.3	39.0±7.4	16M	15M	12.9±1.8	-	91.8±9.2 Verbal 9.3±3.1 Nverbal	-	>age, >tobacco use
Verdejo-Garcia et al (2014) [165]	15-5	15-1	35.1±8.9	30.1±8.8	8M	13M	2.5±1.3	-	-	-	None reported
Wang et al (2015) [166]	20	19	42.15±4.3	39.9±4.5	20M	19M	12.07±1.7	14.9±2.9	-	-	>education, >tobacco use
Wilcox et al (2011) [114]	16-2	16	37.14±8.97	36.38±8.77	7M	7M	12.5±1.98	13.44±1.90	45±11.38	54.94±7.89	<IQ
Wisner et al (2013) [167]	33	32	39.27±6.65	38.06±7.86	26M	24M	27±87%	29±97%	-	-	None reported
Zhang et al (2018) [168]	70	70	40.7± 7.7	38.5± 9.4	50 M	46 M	-	-	-	-	>tobacco use
Methamphetamine											
Ipser et al (2016) [69]	27 46 (incl.	26	25.15±4.09	25.42±4.80	20M	21M	10.59±1.91	12.04±1.34	-	-	<education, >tobacco use

	psychosis)										
Kohno et al (2014) [93]	26-1 15 rs	27 18 rs	35.68±1.64	33.88±2.30	13M	16M	13.00±0.38	13.62±0.38	-	-	>tobacco use
Kohno et al (2016) [102]	39	44	30.95 ±8.17 study 1, 37.0±9.64 study 2	29.00±8.45 study 1, 38.9±9.63 study 2	23M	27M	12.46±1.84	14.18±2.08	-	-	>tobacco use
Kohno et al (2018) [103]	30-3	20	37.62±9.65	33.40±11.11	26M	9M	12.20±1.72	13.40±2.23	-	-	>males, >tobacco use
Mansoory et al (2017) [169]	17	18	30.52±4.57	31.67±7.98	17M	-	12±2.91	-	-	-	None reported
Other Stimulants											
Meunier et al (2012) [98]	18	18	34.33±7.2	32.7±6.9	15M	15M	11.2±1.0	12.4±1.8	109.0±8.1	108.4±6.0	None reported
Regner et al (2016) [99]	50	50	34.18±7.63	31.6±8.57	28M	25M	12.48±1.42	14.66±1.47	-	-	<education, <IQ

Table 3: Demographics (all group differences were reported with stimulant group as the referent, thus <females is to be interpreted as more females in the control group)

(HC = healthy controls, IQ = intelligence quotient, M = male, NVerbal = Non-verbal, SUD = stimulant use disorder, mean ± standard deviation)

2.3.3. Drug use variables of eligible studies

Study	Years of Use	Age at onset (years)	Quantity of use	Abstinence
Cocaine				
Adinoff et al. (2015) [115]	-	-	-	21.5 ± 4.2 Relapse 21.0 ± 4.6 Remission
Balducci et al (2018) [156]	8.6 ± 6.18	22.0 ± 6.18	185.11 ± 203.90 Mexican pesos	Current/ < 60 days
Berlingeri et al. (2017) [92]	-	-	-	141 ± 172.6 days
Camchong et al (2011) [146]	14.6 ± 6.83	25.56 ± 6.21	-	1.6 ± 0.82 days
Camchong et al (2014) [157]	0.5-5 years, 2.17 mean	-	-	35 days
Cisler et al (2013) [128]	16.02 ± 8.02	-	-	8.34 ± 27.84 days
Contreras-Rodriguez et al (2015) [96]	-	22.4 ± 7.4 26.6 ± 9.2 Relapse 18.9 ± 2.4 Remission	18.4 ± 26.2 23.1 ± 33.9g/month Relapse 14.5 ± 18.5g/ month Remission	≥15 days
Ding et al (2013) [116]	5.33 ± 5.1	-	-	>2weeks
Geng et al (2017) [94]	13.0 ± 6.6 NTS 8.3 ± 5.4 treatment	-	$198 ± 153 NTS	22.7 ± 3.9 days
Gu et al (2010) [117]	4.3 ± 2.0	-	$200 ± 129 /week	-
Kelly et al (2011) [158]	11.43 ± 8.5	22	8 daily, 2 5 x week, 13 3-4 x week, 2 2xweek	>2 weeks
Konova et al (2015) [100]	15.8 ± 7.5 15.3 ± 7.5 orig. study	27.2 26.9 ± 6.3 orig. study	2.7 ± 2.1 days/week orig. study	-
Liang et al (2015) [159]	13.2 ± 6.4	-	$224 ± 161	-
McHugh et al (2013) [160]	8.88 ± 6.48 Relapse 7.72 ± 3.99 Remission	26.48 ± 9.59 Relapse 27.15 ± 7.46 Remission	$5910.67 ± 5484.34 in last 90 days relapse $8075.05 ± 6296.51 in last 90 days remission	22.58 ± 3.62 days Relapse 22.81 ± 4.31 days Remission
McHugh et al (2014) [161]	8.88 ± 6.48 Relapse	26.48 ± 9.59 Relapse	$5910.67 ± 5484.34 in last 90 days relapse	22.58 ± 3.62 days Relapse

	7.72 ± 3.99 Remission	27.15 ± 7.46 Remission	$8075.05 ± 6296.51 in last 90 days remission	22.81 ± 4.31 days Remission
McHugh et al (2017) [97]	8.88 ± 6.48 Relapse 7.72 ± 3.99 Remission	26.48 ± 9.59 Relapse 27.15 ± 7.46 Remission	$5910.67 ± 5484.34 in last 90 days relapse $8075.05 ± 6296.51 in last 90 days remission	22.58 ± 3.62 days Relapse 22.81 ± 4.31 days Remission
Moeller et al (2016) [101]	16.4 ± 7.3	26.5 ± 6.5	3.03 ± 2.321 day/week $92.50 ± 129.721 amount spent	0-25, 2 days
Ray et al (2015) [163]	16 ± 8	-	$220 ± 131, $80-350 3 ± 1.2 days/week	72 hours
Ray et al (2016) [164]	16 ± 8	-	$220 ± 131, $80-350 3 ± 1.2 days/week	72 hours
Ray et al (2017) [91]	16 ± 8	-	$220 ± 131, $80-350 3 ± 1.2 days/week	72 hours
Rish et al (2016) [95]	15.3 ± 7.5	26.9 ± 6.3	2.7 ± 2.1 days/week	-
Verdejo-Garcia et al (2014) [165]	-	-	-	≥10 days
Wang et al (2015) [166]	-	-	-	4-8 days
Wilcox et al (2011) [114]	8.25 ± 6.66	27.5 ± 6.27	-	≥3 days
Wisner et al (2013) [167]	15.59 ± 7.42	-	3.30 ± 1.57 days /week	48 hours
Zhang et al (2018) [168]	19.2 ± 8.0	-	1.4 ± 1.3 gm per use 26.1 ± 32.0 monthly use (gm) in prior year	7-10 days
Methamphetamine				
Ipser et al (2016) [69]	6.59 ± 3.47	18.07 ± 3.63	2.42 ± 2.15 g/week, R602.31 ± R585.47/ week	22,39 ± 24,2 days
Kohno et al (2014) [93]	8.59 ± 1.37	24.8 ± 9.38	3.57 ± 1.04 g/week, 23.60 ± 1.29 day/month	4-7 days, 14 abstained 5.78 ± 1.84 days
Kohno et al (2016) [102]	Study 1 – 12.3 ± 6.74, Study 2 –	23.62 ± 8.41	Study 1 – 26.0 ± 6.25 days used in last 30, Study	26.0 ± 6.25 days/ 22.4 ± 7.37

	6.82 ± 4.91		2 – 22.4 ± 7.37 d/u	days
Kohno et al (2018) [103]	12.04 ± 8.55	19.89 ± 6.87	1.06 ± 0.94 g/day	4.03 ± 3.26/ >1-<6 months
Mansoory et al (2017) [169]	3.5 ± 1.74	-	-	54.12 ± 79.88 days
Other Stimulants				
Meunier et al (2012) [98]	11.7 ± 7.42	20.5 ± 5.40	-	-
Regner et al (2016) [99]	15.7 ± 7.4	17.3 ± 4.7	-	12.8 ± 12.4 months >60 days

Table 4: Drug use variables

(Orig. = original, g = grams, mean ± standard deviation)

Strobe score

	Title & abstract (max: 4)	**Introduction (max: 4)**	**Methods (max: 28)**	**Results (max: 20)**	**Discussion (max: 10)**	**Other Information (max: 2)**	**Total possible score (max: 68)**
Mean score for all studies	3.77±0.62	4±0	21.16 ± 5.02	11.19±2.99	9.52±0.89	1.75±068	51.34 ± 7.49
Cocaine (n = 26)	3.72 ± 0.68	4 ± 0	20.68 ± 5.42	11.08 ± 3.32	9.36 ± 1.08	1.76 ± 0.66	50.88 ± 6.60
Methamphetamine (n = 5)	4 ± 0	4 ± 0	22.4 ± 3.58	11.6 ± 0.89	9.6 ±0.89	2 ± 0	51.6 ± 17.73
Other stimulants (n = 2)	4 ± 0	4 ± 0	23 ± 1.41	11 ± 1.41	10 ± 0	2 ± 0	54 ± 0

Table 5: mean Strobe scores (mean ± standard deviation)

2.3.4. Demographics, MRI parameters and paper structure

Of the 33 studies included, sample sizes ranged from 10-70 stimulant misusers and 14-70 healthy controls [123, 168], in all there were 1041 stimulant misusers and 861controls (table 4). The majority of studies were conducted in the United States of America (n = 26), with 2 in conducted in Spain, 1 in Italy, 1 in Iran, 1 in Mexico, 1 in the United Kingdom and 1 in South Africa. Cocaine was the primary drug of choice in most papers (n = 26), with methamphetamine as the next most frequent (n = 5), one study did not specify which stimulants were used, while another tested subjects who used more than one type of stimulant (table 5). The age of substance misusers varied between 22.05 ± 2.64 and 46, 4 ± 7.0; heathy controls varied between 24.42 ± 4.80 and 46 ± 7 (total mean age 38.68 ± 5.96 for stimulant use disorder and 35.68 ± 5.11 for controls) (table 4).

MRI parameters differed for the studies, but most of the studies utilised a 3T MRI scanner (84,85%). Twelve studies scanned participants with eyes closed, 19 with eyes open and 2 did not disclose information on instructions provided to participants (table 3). The most commonly used methods to compare rsFC between subject groups and conditions were seed-based analysis (n = 19), followed by independent component analysis (ICA) (n = 9), with some studies employing a combination of these approaches (n = 4).

Included papers supplied all the STROBE checklist requirements for title, introduction, discussion and 'other information'. However, scores from the STROBE checklist for methods (19.52 ± 4.81, total possible score 28) and results (11.19 ± 2.99 total possible score 20) were relatively low (table 5). Common deficiencies in methods and results sections included: no explanation as to how study size was determined (n = 29); how missing information was managed (n = 33) and lack of use of flow diagrams to depict participant enrolment and retention through the program (n = 33).

Certain aspects of the studies should be taken into consideration when interpreting their findings; 8 of the studies had low power (below 20 participants) [92, 95, 98, 100, 114, 123, 156, 169] and 7 studies did not consider the effect of nicotine on neural correlates in their analyses [94, 98, 113, 117, 123, 167, 169]. Moreover, three studies conducted in the USA included participants with IQ scores measured below 60 [94, 113, 114]; whereby an IQ below 70 is considered cut off for intellectual impairment in the USA [170].

2.3.5. Resting-state connectivity findings

Table 6. summarises the rsFC findings from the included studies. The data is listed chronologically, and are divided into the following sections; brain network regions, type of analysis used (global efficiency/ clustering coefficient), abstinence vs relapse, cognitive affective disorders, executive function, reward, craving and introspection, moral judgement, endocrine links and lastly clinical predictors. This sectioning allowed us to cover all relevant aspects of the studies is such a way that they could be more easily

interpreted and compared with each other. The default mode network had a dominance of lower rsFC with cortical control regions as well as the hippocampus in SUD (n = 10). The ECN showed weaker rsFC in relapsers and SUD and stronger rsFC in abstinence (n = 6), while the SN also presented with a dominance of weaker activation to ECN regions (n = 4) in SUD. The DAN had a dominance of weaker activation with the DMN in SUD (n = 1).

When looking at abstinence vs relapse there were multiple instances of stronger and weaker rsFC between ROI depending on the region. Compulsive and impulsive behaviour showed a dominance of stronger rsFC between regions in SUD. Executive function was associated with stronger rsFC from deep grey matter regions to cortial regions in abstinence, while weaker rsFC was found between the ACC to the amygdala, hippocampus, insula and temporal gyrus in SUD.

Reward revealed both weaker and stronger rsFC between regions. In general the studies showed stronger rsFC from the insula to the striatum and within the dlPFC, with weaker rsFC in cortical areas.

Moral judgment showed weaker rsFC within and between all regions in SUD, although there was only one study covering this section. Neuroendocrine connection had a mix of weaker and stronger rsFC between differing regions, while predictors of relapse had stronger rsFC between regions in SUD.

2.3.5. Resting-state connectivity findings (chronological order)

Study	**DSM diagnosis, sample size, type of rsfMRI, length of abstinence**	**rsFC findings** Greater/ stronger = ↑ Weaker/ reduced = ↓	**Caveats**
rsFC Networks			
Default Mode Network (DMN)			
Gu et al (2010) [117]	Cocaine dependence, 39 SUD, 39 control, Seed-based, unknown length of abstinence	↓ rsFC between amygdala and hippocampus with medial PFC in SUD vs controls. ↓ rsFC between rostral anterior cingulate cortex and amygdala and hippocampus as well as posterior insula and sections of temporal gyrus in SUD vs controls.	Group IQ below 60.
Wilcox et al (2011) [114]	Cocaine dependence and or abuse, 14 SUD, 16 control, Seed-based, ≥ 3 days	Negative correlation between drug cue processing and the posterior cingulate cortex/ precuneus in SUD vs controls. Elevated anti-correlations for precuneus and posterior cingulate cortex, middle temporal gyrus, inferior parietal lobule and occipital cortex in SUD vs controls.	Low power.
Ding et al (2013) [116]	Cocaine dependence, 24 SUD, 24 control, ICA, >2weeks	Using model orders of 10, 20, 30, 40 and 50 a group effect found showing posterior DMN patterns were maintained, while anterior DMN activation reduced with increased model orders in SUD vs controls. ↓ rsFC in hippocampus, with left hippocampus having weaker rsFC in posterior DMN and right hippocampus in anterior in SUD vs controls.	*Not controlled for:* cigarette smoking. *Not matched for:* alcohol and cannabis, and not controlled for as a covariate.
Adinoff et al (2015) [115]	Cocaine dependence, 40 SUD, 20 control, Seed-based, 21,5 ± 4,2 Relapse 21,0 ± 4,6 Remission	↑ rsFC between posterior hippocampus with posterior cingulate cortex/ precuneus with elevated right CBF within posterior hippocampus SUD vs controls.	*No report on:* years or quantity of use.
Konova et al (2015)	18 cocaine dependence,	Greater functional connectivity density within the posterior cingulate cortex/ precuneus in SUD	Low power.

[100]	1 cocaine abuse, 19 SUD, 15 control, RSFCDM, unknown length of abstinence	vs controls. An abnormal number of short-range and long-range connections to DMN (specifically ventromedial PFC and posterior cingulate cortex) and basal ganglia hubs (thalamus, putamen, amygdala) positively correlated with years of use.	*Drug positive on scan day:* 9 *Drug positive on placebo day:* 8 *Polysubstance in drug group:* n = 1 heroin dependent n = 2 cannabis misuse. n = 2 alcohol misuse. *Not matched for:* age and cigarette smoking, age was controlled for as a covariate.
Liang et al (2015) [159]	Cocaine dependence, 47 SUD, 47 control, Modularity analysis, unknown length of abstinence	↓ rsFC between SN and DMN in SUD vs controls. ↓ rsFC between posterior cingulate cortex and ECN in SUD vs controls. ↓ rsFC between DMN and ECN in SUD vs controls. ↓ participation coefficient in right anterior cingulate cortex, posterior cingulate cortex and insula in SUD vs controls.	Group IQ below 60. *Cocaine positive on scan day:* n = 21 *Amphetamine + THC positive on scan day:* n = 1 *THC positive on scan day:* n = 1
Ipser et al (2016) [69]	Methamphetamine dependence, 27 SUD, 26 control, ICA and seed-based, 22,39 ± 24,2 days	↑ coupling between the posterior and anterior DMN in SUD vs controls. Intrinsic connectivity between CCN and DMN may normalise with increasing abstinence. ↑ coupling between the right ECN and anterior DMN in SUD vs controls.	
Regner et al (2016) [99]	Stimulant dependence, 50 SUD, 50 control, EC and ICA, 12.8 ± 12.4 months	↑ Granger Causuality connections from DMN to basal ganglia network in long term abstinence, with greater bidirectional connectivity in abstinent SUD vs controls.	Controversy regarding granger causality. *Polysubstance in drug group:* number not reported *Not matched for:* IQ and education not controlled for as a covariate.

Executive Control Network (ECN)			
Berlingeri et al (2017) [92]	Cocaine abuse, 18 SUD, 19 control, Multivariate machine learning approaches, 141 ± 172,6 days	↓ rsFC within the dlPFC in SUD vs controls.	Low power. *Not reported on:* time of abstinence. *Not matched for:* age and education and not controlled for as a covariate.
Geng et al (2017) [94]	Mix of cocaine dependence, abuse and past abuse, 59 NTS, 45 TS, 67 control, Seed-based, 22.7±3.9 days	↓ rsFC between right temporal pole and left dominated medial PFC negatively correlated with substance use with circuit strength predicting relapse, while increased years of education reduced risk in SUD vs controls.	Group IQ below 60. *Not matched for:* cigarette smoking, but was controlled for as a covariate.
Kelly et al (2011) [158]	Cocaine dependence, 25 SUD, 24 control, VMHC and seed-based, >2 weeks	↓ rsFC from the deep inferior frontal sulcus into the middle frontal gyrus and ventral premotor cortex, anteriorly from the inferior frontal junction along the superior part of pars opicularis and triangularis into frontal operculum in SUD vs controls. ↓ rsFC between inferior frontal sulcus and left lateral PFC and premotor cortex in SUD vs controls. ↓ rsFC between left inferior frontal sulcus and right posterior and inferior parietal cortices in SUD vs controls. ↓ rsFC associated with inferior frontal sulcus was negatively correlated with cognitive failure score (decreasing in significance with withdrawal symptoms) in SUD vs controls. ↓ rsFC between inferior frontal sulcus and bilateral pre-supplementary motor areas correlated with greater Cognitive Failure Questionnaire scores in SUD vs controls.	*Not matched for:* age, was controlled for as a covariate. *Comorbidity in drug group:* depressive disorders.
Kohno et al (2014) [93]	Methamphetamine dependence, 15 SUD, 18 control, Seed-based, 4 -7 days	↓ rsFC within the dlPFC during risk taking in SUD vs controls.	*Not matched for:* cigarette smoking and not controlled for as a covariate.

Liang et al (2015) [159]	Cocaine dependence, 47 SUD, 47 control, Modularity analysis, unknown length of abstinence	↓ rsFC within the ECN in SUD vs controls.	Group IQ below 60. *Cocaine positive on scan day:* n = 21 *Amphetamine + THC positive on scan day:* n = 1 *THC positive on scan day:* n = 1
Ipser et al (2016) [69]	Methamphetamine dependence, 27 SUD, 26 control, ICA and seed-based, 22,39 ± 24,2 days	↑ coupling between CCN right fronto-parietal and frontal medial cortex in SUD vs controls. ↑ rsFC between CCN right fronto-parietal and posterior cingulate cortex, to frontal medial cortex, which dissipated after one week of abstinence. Tobacco smoking and depression strengthened the group effect on pairwise rsFC other than between the frontal medial cortex and posterior cingulate cortex.	
Regner et al (2016) [99]	Stimulant dependence, 50 SUD, 50 control, EC and ICA, 12.8 ± 12.4 months	↑ Granger Causuality connections from right ECN to dorsal DMN in abstinent SUD vs controls. ↑ network density from right ECN to dorsal DMN, to basal ganglia network in SUD vs controls. The ECN was negatively correlated with impulsivity, while dorsal DMN was positively correlated in SUD vs controls.	Controversy regarding granger causality. *Polysubstance in drug group:* number not reported *Not matched for:* IQ and education and not controlled for as a covariate.
McHugh et al (2016) [162]	Cocaine dependence, 45 SUD, 22 control, ICA, 22,58 ± 3.62 days Relapse 22,81 ± 4,31 days Remission	↓ rsFC between left ECN and dlPFC of right ECN in relapsers vs responders with weaker rsFC between left ECN and sections of SN (right dorsal anterior cingulate cortex) and left cerebellum. ↓ rsFC with left middle temporal gyrus in ECN in SUD vs controls. ↓ rsFC within the ECN in SUD vs controls. ↓ rsFC between DMN and ECN in SUD vs controls. ↓ rsFC between right middle frontal gyrus and dorsal anterior cingulate cortex and left ECN in relapsers vs responders ↓ rsFC between left ECN and right ECN and SN in relapsers vs responders ↓ rsFC between right and left ECN in relapsers vs responders	*Not matched for:* age and cigarette smoking and not controlled for as a covariate.

Wilcox et al (2011) [114]	Cocaine dependence and or abuse, 14 SUD, 16 control, Seed-based, ≥ 3 days	Cocaine cues activated the OFC, dlPFC, pre-supplementary motor area, insula, parahippocampal gyri, continuing into the amygdala and anterior thalamus in SUD vs controls.	Low power.
Salience Network (SN)			
Cisler et al (2013) [128]	Cocaine dependence, 41 SUD, 19 control, ICA and seed-based, 8,34 ± 27,84 days	The right mid-insula and right ventral anterior insula have significant differences in co-activation across PFC networks in SUD vs controls. ↑ rsFC between right ventral anterior insula with right inferior frontal gyrus and dorsal medial PFC in SUD vs controls. ↑ rsFC of right dorsal insula with bilateral dlPFC and weaker rsFC with dorsal posterior insula in SUD vs controls.	*Not matched for:* age, sex, ethnicity. All controlled for as covariates.
Wisner et al (2013) [167]	Cocaine dependence, 33 SUD, 32 control, ICA, 48 hours	↓ inter-network rsFC between anterior insula to anterior cingulate cortex and striatum in SUD vs controls.	*Not matched for:* cigarettes and education, and not controlled for as a covariate. Inter-network connectivity metrics controversial.
Verdejo-Garcia et al (2014) [165]	Cocaine dependence, 10 SUD, 14 control, Seed-based, ≥ 10 days	↓ rsFC between anterior cingulate cortex and thalamus (mostly mediodorsal nucleus) and between periaqueductal grey and left insula and putamen and brainstem tegementum in SUD vs controls. ↓ activation in anterior mid-line areas and those involving limbic-paralimbic structures of anterior cingulate cortex, superior dorsal brain stem, adjacent parahippocampal cortex and insula in SUD vs controls. Insula seed connected with anterior cingulate cortex and hypothalamus in SUD, whilst in controls it is connected with thalamus bilaterally.	Low power.
Liang et al (2015) [159]	Cocaine dependence, 47 SUD, 47 control,	↓ rsFC between anterior insula and DMN in SUD vs controls. ↓ average rsFC between rostral anterior cingulate cortex and SN and medial temporal lobe in	Group IQ below 60. *Cocaine positive on scan day:* n = 21

	Modularity analysis, unknown length of abstinence	SUD vs controls.	*Amphetamine + THC positive on scan day:* n = 1 *THC positive on scan day:* n = 1
Geng et al (2017) [94]	Mix of cocaine dependence, abuse and past abuse, 59 NTS, 45 TS, 67 control, Seed-based, 22.7±3.9 days	↓ rsFC in bilateral insula and dorsal anterior cingulate cortex in SUD vs controls.	IQ below 60. *Not matched for:* cigarette smoking, was controlled for as a covariate.
Dorsal Attention Network (DAN)			
Ipser et al (2016) [69]	Methamphetamine dependence, 27 SUD, 26 control, ICA and seed-based, 22,39 ± 24,2 days	↓ of anti-correlated anterior DMN – DAN in SUD vs controls	
Regner et al (2016) [99]	Stimulant dependence, 50 SUD, 50 control, EC and ICA, 12.8 ± 12.4 months	↑ EC from sensorimotor network to visuospatial network coupled with greater bidirectional EC in SUD (controls more uni-directional).	Controversy regarding granger causality. *Polysubstance in drug group:* number not reported *Not matched for:* IQ and education and not controlled for as a covariate.
Wilcox et al (2011) [114]	Cocaine dependence and or abuse, 14 SUD, 16 control, Seed-based, ≥ 3 days	↑ activation in left dlPFC and left occipital cortex in SUD vs controls.	Low power.
Reward			

Gu et al (2010) [117]	Cocaine dependence, 39 SUD, 39 control, Seed-based, unknown length of abstinence	↓ correlated fluctuations between ventral tegemental area and basal ganglia, nucleus accumbens, thalamus, parahippocampal area, right anterior cingulate cortex/ medial PFC and medial frontal gyrus in SUD vs controls. ↓ rsFC between ventral tegemental area and mediodorsal thalamus with lentiform nucleus/ putamen and with bilateral thalamus and right nucleus accumbens, the later negatively correlated with years of use in SUD vs controls.	Group IQ below 60.
Wilcox et al (2011) [114]	Cocaine dependence and or abuse, 14 SUD, 16 control, Seed-based, ≥ 3 days	↑ rsFC between left ventral striatum seed and right OFC into rostroventral anterior cingulate cortex in SUD vs controls.	Low power.
McHugh et al (2013) [160]	Cocaine dependence, 45 SUD, 22 control, Seed-based, 22,58 ± 3.62 days Relapse 22,81 ± 4,31 days Remission	↑ rsFC between putamen and posterior insula and postcentral gyrus .	*Not matched for:* age and cigarette smoking, cigarette smoking was controlled for as a covariate.
Camchong et al (2014) [157]	Cocaine dependence, 18 SUD, 15 control, Seed-based, 35 days	↑ rsFC between nucleus accumbens and left frontopolar cortex and posterior cingulate cortex in those who relapsed vs responders. ↑ rsFC between subgenual anterior cingulate cortex and left PFC non-responders vs responders. Non-responders showed reduced rsFC between nucleus accumbens and posterior cingulate cortex vs responders at 13 weeks of abstinence.	Low power. *Not matched for:* education, and not controlled for as a covariate.
Kohno et al (2014) [93]	Methamphetamine dependence, 15 SUD, 18 control, Seed-based, 4 -7 days	↑ rsFC between midbrain and putamen, amygdala, hippocampus in SUD vs controls. ↑ activation within the ventral striatum in SUD vs controls.	*Not matched for:* cigarette smoking, but was controlled for as a covariate.
Contreras-Rodriguez	Cocaine dependence, 20	↑ rsFC between ventral caudate and subgenual anterior cingulate cortex in SUD vs controls.	*Not matched for:* cigarette smoking,

et al (2015) [96]	SUD, 21 control, Seed-based, ≥15 days	↑ rsFC between ventral putamen and dorsomedial PFC in SUD vs controls. ↑ rsFC between dorsal putamen and lenticular nucleus, to insula in SUD vs controls. ↑ rsFC between ventral caudate and insula, to OFC and between ventral putamen and OFC and insula operculum complex, and between dorsal putamen and postcentral gyrus and temporal cortex in SUD vs controls.	alcohol use and age, age and cigarette smoking was controlled for as a covariate.
Konova et al (2015) [100]	18 cocaine dependence, 1 cocaine abuse, 19 SUD, 15 control, RSFCDM, unknown length of abstinence	↑ functional connectivity density within putamen/ amygdala in SUD vs controls.	Low power. *Drug positive on scan day:* 9 *Drug positive on placebo day:* 8 *Polysubstance in drug group:* n = 1 heroin dependent n = 2 cannabis misuse. n = 2 alcohol misuse. *Not matched for:* age and cigarette smoking, and not controlled for as a covariate.
Kohno et al (2016) [102]	Methamphetamine dependence, 39 SUD, 44 control, Seed-based, study 1= 26,0 ± 6,25 days, study 2 = 22,4 ± 7,37 days	Positive relationship of midbrain rsFC with the left ventral striatum in MA misuse, while controls had a negative one.	*Not matched for:* cigarette smoking, and not controlled for as a covariate.
Ray et al (2016) [164]	Cocaine dependence, 20 SUD, 17 control, EC and SDCM, 72 hours	↑ EC from ventral tegemental area to nucleus accumbens, hippocampus and medial frontal cortex and within nucleus accumbens in SUD vs controls. ↑ reciprocal EC between hippocampus and medial frontal cortex in SUD vs controls.	*Not matched for:* cigarette smoking, and not controlled for as a covariate.
Berlingeri et al (2017) [92]	Cocaine abuse, 18 SUD, 19 control, Multivariate	↓ rsFC between nucleus accumbens and orbital and dorsal PFC and around rolandic sulcus and lateral parietal associative regions and bilateral retrosplenal cortices in SUD vs controls.	Low power. *Not reported on:* time of abstinence.

	machine learning approaches, 141 ± 172,6 days	Negative effect of strategic and controlled behaviour in rsFC between the nucleus accumbens and right orbito PFC, right insula, right superior temporal pole, right caudate and left cerebellum (with similar effects on the left in SUD vs controls). ↑ rsFC between the nucleus accumbens and dorsal striatum and OFC in non-responders vs responders.	*Not matched for:* age and education, and not controlled for as a covariate.
Ray et al (2017) [91]	Cocaine dependence, 20 SUD, 17 control, IMaGES, 72 hours	Two feedforward pathways (1) ventral tegemental area to hippocampus and ventral striatum to OFC, anterior cingulate cortex, medial frontal cortex and dlPFC, (2) from ventral tegemental area to insula in SUD. In controls three feedforward pathways, (1) hippocampus to ventral tegemental area to insula to dlPFC, (2) hippocampus to ventral striatum, (3) hippocampus to medial frontal cortex. Stronger causal influence of ventral striatum on dlPFC in SUD vs controls.	*Not matched for:* cigarette smoking, and not controlled for as a covariate.
Global Efficiency and Clustering Coefficient			
Konova et al (2015) [100]	18 cocaine dependence, 1 cocaine abuse, 19 SUD, 15 control, RSFCDM, unknown length of abstinence	Abnormal count of short- and long-range connections to the DMN (specifically ventromedial PFC and posterior cingulate cortex and thalamus, putamen/ amygdala to DMN) in SUD vs controls. These connections increase with every year of substance use (0.7 for short-range and 57 for long-range). MPH reduces the total count of short- and long-range connections to basal ganglia, bilateral thalamus/ putamen, supplementary motor area and postcentral gyrus in SUD vs controls.	*Drug positive on scan day:* 9 *Drug positive on placebo day:* 8 *Polysubstance in drug group:* n = 1 heroin dependent n = 2 cannabis misuse. N = 2 alcohol misuse. *Not matched for:* age and cigarette smoking, age was controlled for as a covariate.
Wang et al (2015) [166]	Cocaine dependence, 20 SUD, 19 control, rsFCM, 4 – 8 days	↑ inter-regional correlations, with larger nodes and more connections, but fewer node clusters in SUD vs controls. ↑ quantity of nodes in supplementary motor area, post central gyrus and inferior cortex from insula to rolandic operculum, temporal cortex to fusiform, lingual cortex extending to cuneus and visual cortex in SUD vs controls.	*Polysubstance in drug group:* n = 6 alcohol dependent n = 2 alcohol misuse n = 1 cannabis dependent n = 2 cannabis misuse.

			Not matched for: education or tobacco smoking, and not controlled for as a covariate.
Regner et al (2016) [99]	Stimulant dependence, 50 SUD, 50 control, EC and ICA, 12.8 ± 12.4 months	Higher global efficiency in abstinence in SUD vs controls.	Controversy regarding granger causality. *Polysubstance in drug group:* number not reported *Not matched for:* IQ and education, and not controlled for as a covariate.
Mansoory et al (2017) [169]	Methamphetamine dependence, 17 SUD, 18 control, BCFD and GTP, 54.12 ± 79.88 days	Lower clustering coefficient and global efficiency, indicating fewer network connections and weaker effective information transfer in SUD vs controls.	Low power.
Abstinence vs Relapse			
Gu et al (2010) [117]	Cocaine dependence, 39 SUD, 39 control, Seed-based, unknown length of abstinence	↓ rsFC between amygdala and hippocampus with medial PFC in SUD vs controls. Resent use resulted in ↓ rsFC between amygdala and left posterior insula, between the hippocampus and medial PFC, and ↑ rsFC between the primary-motor cortex and left anterior insula in SUD vs controls.	Group IQ below 60.
Camchong et al (2014) [157]	Cocaine dependence, 18 SUD, 15 control, Seed-based, 35 days	↑ rsFC between nucleus accumbens and left fronto-polar cortex and posterior cingulate cortex in those who relapsed vs responders. ↑ rsFC between subgenual anterior cingulate cortex and left PFC non-responders vs responders at 13 weeks of abstinence.	Low power. *Not matched for:* education and not controlled for as a covariate.
McHugh et al (2014) [161]	Cocaine dependence, 45 SUD, 22 control, Seed-	↓ rsFC in cortico-medial amygdala with ventromedial PFC to rostral anterior cingulate cortex in relapsers vs responders.	*Not matched for:* age and cigarette smoking, and not controlled for

	based, 22,58 ± 3.62 days Relapse 22,81 ± 4,31 days Remission	↓ rsFC in relapsers between basolateral amygdala and cuneus/ lingual gyrus into parahippocampal gyrus vs responders.	as a covariate.
Adinoff et al (2015) [115]	Cocaine dependence, 40 SUD, 20 control, Seed-based, 21,5 ± 4,2 Relapse 21,0 ± 4,6 Remission	↑ rsFC between posterior hippocampus with posterior cingulate cortex/ precuneus predicts relapse in SUD vs controls.	*Not report on:* years or quantity of use.
Contreras-Rodriguez et al (2015) [96]	Cocaine dependence, 20 SUD, 21 control, Seed-based, ≥15 days	↑ rsFC between ventral caudate and anterior cingulate cortex in SUD vs controls. ↑ rsFC between ventral putamen and anterior cingulate cortex in SUD vs controls. ↑ rsFC between ventral caudate/ nucleus accumbens with subgenual anterior cingulate cortex in SUD vs controls.	*Not matched for:* cigarette smoking, alcohol use and age, age and cigarette smoking was controlled for as a covariate.
Berlingeri et al (2017) [92]	Cocaine abuse, 18 SUD, 19 control, Multivariate machine learning approaches, 141 ± 172,6 days	↑ rsFC between NAc and ventral parietal regions in relapsers vs responders. ↓ rsFC between NAc and lateral dorsal PFC and parts of medial PFC around rolandic sulcus, parietal associative regions and retrosplenal cortices bilaterally in relapsers vs responders. ↑ rsFC between nucleus accumbens and dorsal striatum and OFC in SUD vs controls.	Low power. *Not reported on:* time of abstinence. *Not matched for:* age and education, and not controlled for as a covariate.
Geng et al (2017) [94]	Mix of cocaine dependence, abuse and past abuse, 59 NTS, 45 TS, 67 control, Seed-based, 22.7±3.9 days	Days to relapse correlated with circuit strength between the right temporal pole and left medial PFC in SUD vs controls.	IQ below 60. *Not matched for:* cigarette smoking but was controlled for as a covariate.
McHugh et al (2016) [162]	Cocaine dependence, 45 SUD, 22 control, ICA, 22,58 ± 3.62 days	↓ rsFC between left ECN and dlPFC of right ECN in relapsers vs responders. ↑ rsFC between left ECN and sections of SN in SUD vs controls. In right ECN, ↑ rsFC with left middle temporal gyrus in non-responders.	*Not matched for:* age and cigarette smoking, and not controlled for as a covariate.

	Relapse 22,81 ± 4,31 days Remission	↑ rsFC in right middle frontal gyrus and right dorsal anterior cingulate cortex in responders at 30 days of abstinence.	
Cognitive-Affective Abnormalities			
Compulsivity/ Impulsivity			
Camchong et al (2011) [146]	Cocaine dependence, 27 SUD, 24 control, Seed-based, 1,6 ± 0,82 days	↑ rsFC was found in frontal and temporal regions of the perigenual anterior cingulate cortex seed map, specifically in dlPFC, middle temporal gyrus and superior frontal gyrus with positive correlations between reversal learning scores and rsFC strength in dlPFC as well as delay discounting scores and rsFC strength in dlPFC in SUD vs controls. ↑ rsFC between perigenual anterior cingulate cortex and dlPFC was coupled with increased compromise in reversal learning and greater impulsivity in SUD vs controls.	*Comorbidity in drug group:* depressive disorders
Meunier et al (2012) [98]	Stimulant dependence, 18 SUD, 18 control, NCS, unknown length of abstinence	↓ rsFC between OFC and medial premotor cortex, dorsal and posterior cingulate cortex, right somatosensorimotor cortex and left temporal cortex with right superior OFC, negatively correlated with intensity of compulsive symptoms in SUD vs controls.	Low power. *Polysubstance in drug group:* number not reported.
Contreras-Rodriguez et al (2015) [96]	Cocaine dependence, 20 SUD, 21 control, Seed-based, ≥15 days	↑ rsFC between ventral caudate and subgenual anterior cingulate cortex in SUD vs controls. ↑ rsFC between ventral putamen and dorsomedial PFC correlated with impulsivity in SUD vs controls. ↑ rsFC between dorsal putamen and lenticular nucleus, to insula correlated with greater impulsivity in SUD vs controls. ↑ rsFC between ventral caudate and insula, to OFC and between ventral putamen and OFC and insula operculum complex, and between dorsal putamen and postcentral gyrus and temporal cortex associated with increased compulsivity in SUD vs controls.	*Not matched for:* cigarette smoking, alcohol use and age, age and cigarette smoking was controlled for as a covariate.
Kohno et al (2016) [102]	Methamphetamine dependence, 39 SUD, 44 control, Seed-based,	↑ rsFC between the midbrain and striatum, amygdala, hippocampus with medial OFC together with greater self-report impulsivity, with a positive correlation between cognitive impulsivity in BIS and negative correlation of rsFC between midbrain and ventral striatum in SUD vs controls.	*Not matched for:* cigarette smoking, and not controlled for as a covariate.

	study 1= 26,0 ± 6,25 days, study 2 = 22,4 ± 7,37 days		
Regner et al (2016) [99]	Stimulant dependence, 50 SUD, 50 control, EC and ICA, 12.8 ± 12.4 months	↑ score in BAS in abstinent SUD compared with controls. ↑ impulsivity reflected by BIS scores in SUD compared with controls.	*Polysubstance in drug group:* not reported. *Not matched for:* IQ and education, and not controlled for as a covariate. Controversy regarding granger causality.
Berlingeri et al (2017) [92]	Cocaine abuse, 18 SUD, 19 control, Multivariate machine learning approaches, 141 ± 172,6 days	↓ rsFC between NAc and orbital and dorsal PFC in SUD vs controls.	Low power. *Not reported on:* time of abstinence. *Not matched for:* age and education, and not controlled for as a covariate.
Geng et al (2017) [94]	Mix of cocaine dependence, abuse and past abuse, 59 NTS, 45 TS, 67 control, Seed-based, 22.7±3.9 days	↑ rsFC between amygdala and ventral medial PFC in abstinent SUD vs controls. ↓ rsFC between amygdala and insula, negatively correlated with lower non-planning impulsivity in abstinent SUD vs controls. ↓ rsFC between left temporal pole and cerebellum in SUD vs controls.	IQ below 60. *Not matched for:* cigarette smoking, but was controlled for as a covariate.
Balducci et al (2018) [156]	Cocaine dependence, 19 SUD, 18 control, Seed-based, Current/ < 60 days	↑ rsFC between right amygdala and left insula, correlated with impulsivity and emotional dysregulation in SUD vs controls.	Low power. *Not matched for:* education, but was controlled for as a covariate.
Executive Function			
Gu et al (2010) [117]	Cocaine dependence, 39	↓ rsFC between rostral anterior cingulate cortex and amygdala, hippocampus, posterior insula and	Group IQ below 60.

	SUD, 39 control, Seed-based, unknown length of abstinence	portions of the temporal gyrus in SUD vs controls.	
Camchong et al (2011) [146]	Cocaine dependence, 27 SUD, 24 control, Seed-based, 1,6 ± 0,82 days	↑ rsFC was found in frontal and temporal regions of the perigenual anterior cingulate cortex seed map, specifically in dlPFC, middle temporal gyrus and superior frontal gyrus with positive correlations between reversal learning scores and rsFC strength in dlPFC as well as delay discounting scores and rsFC strength in dlPFC in SUD vs controls. ↑ rsFC between perigenual anterior cingulate cortex and dlPFC was coupled with increased compromise in reversal learning and greater impulsivity in SUD vs controls.	*Comorbidity in drug group:* depressive disorders.
Kohno et al (2014) [93]	Methamphetamine dependence, 15 SUD, 18 control, Seed-based, 4 -7 days	↑ rsFC between the midbrain and putamen, amygdala and hippocampus in SUD	*Not matched for:* cigarette smoking, but was controlled for as a covariate.
Moeller et al (2016) [101]	21 cocaine dependence, 1 cocaine abuse, 22 SUD, 21 control, GRSFCD, 0 - 25,2 days	Improved rsFC in dlPFC in response to methylphenidate in SUD vs controls. Fewer dlPFC responses when measured by drug and colour word tasks in SUD vs controls. Modulation of dlPFC negatively correlated with recent drug use in SUD vs controls. Thalamic and dlPFC rsFC weaker in both groups with methylphenidate in SUD vs controls.	Incomplete datasets for some participants. *Not matched for:* age and cigarette smoking, but was controlled for as a covariate.
Rish et al (2016) [95]	Cocaine dependence, 18 SUD, 15 control, MMLA, unknown length of abstinence	Methylphenidate had a normalising effect on functional network properties and induced greater differences in voxel degrees in SUD vs controls.	Low power. *Drug positive on scan day:* 9 *Drug positive on placebo day:* 8 *Polysubstance in drug group:* n = 1 heroin dependent n = 2 cannabis misuse. n = 2 alcohol misuse. *Not matched for:* age and cigarette

			smoking, and not controlled for as a covariate. Controversy on limitations of filter-based approaches.
Craving and Introspection			
Wilcox et al (2011) [114]	Cocaine dependence and or abuse, 14 SUD, 16 control, Seed-based, ≥ 3 days	↑ activation in the left dlPFC and left occipital cortex during drug cues in SUD vs controls. ↓ rsFC between bilateral putamen and left posterior insula in SUD vs controls. ↓ rsFC from lateralised cluster on putamen into postcentral gyrus in SUD vs controls.	Low power.
McHugh et al (2013) [160]	Cocaine dependence, 45 SUD, 22 control, Seed-based, 22,58 ± 3.62 days Relapse 22,81 ± 4,31 days Remission	↑ rsFC between putamen and posterior insula and postcentral gyrus .	*Not matched for:* age and cigarette smoking, cigarette smoking was controlled for as a covariate.
Wisner et al (2013) [167]	Cocaine dependence, 33 SUD, 32 control, ICA, 48 hours	↓ insula volume in SUD vs controls. ↓ internetwork rsFC between anterior insula and striatum in SUD vs controls. ↑ rsFC within network for anterior insula and anterior cingulate cortex in SUD vs controls.	*Not matched for:* cigarette education, and not controlled for as a covariate. Inter-network connectivity metrics controversial.
Geng et al (2017) [94]	Mix of cocaine dependence, abuse and past abuse, 59 NTS, 45 TS, 67 control, Seed-based, 22.7±3.9 days	Thinner insula thickness and thicker temporal pole in SUD vs controls. ↓ rsFC in left and right insula and dorsal anterior cingulate cortex and between right middle/ superior temporal gyri, supramarginal gyri and medial PFC in SUD vs controls. .	*Not matched for:* cigarette smoking, but was controlled for as a covariate. IQ below 60.
Moral Judgement			

Verdejo-Garcia et al (2014) [165]	Cocaine dependence, 10 SUD, 14 control, Seed-based, ≥ 10 days	↓ activation of medial PFC, anterior and posterior cingulate cortex/ precuneus, bilateral angular gyri and parahippocampal cortex and insula in SUD vs controls. ↓ rsFC between anterior cingulate cortex and bilateral thalami and between periaqueductal grey and left insula, putamen and brainstem tegementum in SUD vs controls. Connection between insula and midbrain and parahippocampus extended to the anterior cingulate cortex and hypothalamus in SUD and only to the bilateral thalamus in controls.	Low power.
Link between the Endocrine and Nervous Systems			
Zhang et al (2018) [168]	Cocaine dependence, 70 SUD, 70 control, Seed-based, 7 - 10 days	↑ rsFC from the lateral hypothalamus to the dlPFC in SUD vs controls. ↑ rsFC from the lateral hypothalamus to ventral precuneus in SUD vs controls. ↑ rsFC from medial hypothalamus to inferior parietal lobule in SUD vs controls. ↓ rsFC from medial hypothalamus to ventromedial PFC, temporal gyrus, fusiform gyrus and ventral striatum in SUD vs controls.	*Not matched for:* cigarette smoking, and not controlled for as a covariate.
Clinical Predictors of Abnormal rsFC			
Kohno et al (2018) [103]	Methamphetamine dependence, 27 SUD, 20 control, Seed-based, 4.03 ± 3.26 days	Elevated IL-6 plasma concentration positively correlated with rsFC between ventral striatum and amygdala and insula in SUD vs controls.	*Not matched for:* cigarette smoking, and not controlled for as a covariate. Time difference between blood draws and MRI scan.
Ray et al (2015) [163]	Cocaine dependence, 20 SUD, 17 control, ICA, 72 hours	Years of use negatively correlated with rsFC strength in the sensorimotor cortex and left anterior cingulate cortex and left superior temporal gyrus, right medial temporal lobe and left superior angular gyrus in SUD vs controls. ↑ rsFC between left middle frontal gyrus and left inferior parietal lobule with negative correlation between rsFC strength and years of use in the sensorimotor cortex in SUD vs controls. ↑ rsFC in left anterior cingulate cortex and left superior temporal gyrus, right medial temporal lobe and left superior angular gyrus in SUD vs controls. ↑ rsFC between right middle frontal gyrus and right supramarginal gyrus in SUD vs controls.	Lack of correction for multiple corrections. *Not matched for:* cigarette smoking, and not controlled for as a covariate.

		Duration of use positively correlated with rsFC between right middle occipital gyrus and right cingulate gyrus, with frequency of use negatively correlated with rsFC between left middle occipital gyrus and left calcarine gyrus in SUD vs controls.	

Table 6: Resting state results for Stimulant Use Disorder

(BCFD = Box-Counting Fractal Dimension, BAS = Behavioural Activation Scale, BIS = Baratts Impulsivity Scale, CCN = cortical control network, DMN = default mode network, DORSAL ATTENTION NETWORK = dorsal attention network, dlPFC = dorsolateral prefrontal cortex, EC = Effective connectivity; ECN = executive control network, IL-6 = Interleukin 6, NTS = non treatment seeking, GRSFCD = Global functional connectivity density, GTP = Graph topological properties, MMLA = Multivariate machine learning approaches, NCS = Nodal connectivity strength, PFC = prefrontal cortex, rCBF = regional cerebral blood flow, rsFC = resting state functional connectivity, RSFCDM = Functional connectivity density mapping, SDCM = Spectral dynamic causal modelling, SN = salience network, SUD = stimulant use disorder, THC = tetrahydrocannabinoid, TS = treatment seeking)

2.4. Discussion

One of the most consistent findings of this systematic review is that rsFC within the ECN [92, 93, 97, 113] and within the SN [94, 117, 129] was weaker in people who chronically misuse stimulants than in healthy controls. Moreover weaker rsFC was also found between the DMN and SN [94, 113] and between the ECN and DMN in stimulant misusers compared with controls [97, 113], which contrasts with the finding from the only included study conducted in South Africa of greater rsFC between the right fronto-parietal and anterior DMN in MA misusers (Ipser et al. 2016) [69]. In addition, when exploring individuals who relapse compared with those who maintained abstinence using rsFC in stimulant use disorder a stronger connectivity was found between nodes in the DMN [115]. Further, stronger rsFC was found between the nucleus accumbens and both the posterior cingulate cortex and subgenual anterior cingulate cortex [157] and between the right temporal pole and left medial PFC in those who relapsed in contrast to those who remained abstinent, with strength of the rsFC predicting days to relapse [94]. A weaker rsFC was revealed in people who relapsed compared with those that remained abstinent between the amygdala and ventromedial PFC, projecting on to the rostral anterior cingulate cortex [161], as well as between the amygdala and hippocampus [117], and from the left ECN to the right dlPFC [97].

People who misuse stimulants displayed greater impulsivity which was associated with changes in connectivity in the OFC, striatum, amygdala and hippocampus than healthy controls [98, 102, 156] moreover they also had greater challenge with moral judgments [123]. Furthermore, they displayed abnormal executive function which was associated with the dlPFC, hypothalamus and anterior cingulate cortex [93, 95, 101, 114, 117, 146 171], and had a more dominant reward system, implicating the striatum, hippocampus, midbrain and ventral tegemental area when compared with healthy controls [91-93, 96, 98, 100, 114, 117, 157, 160, 164]. This will be discussed in greater detail below, whereby we will begin by exploring rsFC findings within four networks (DMN, ECN, SN and DAN), then discuss the pertinent question of abstinence vs relapse, followed by cognitive affective abnormalities in stimulant misuse disorders (compulsivity/ impulsivity, executive function, reward, craving and introspection as well as moral judgement), the link between the neural and endocrine systems and finally clinical predictors of abnormal rsFC.

2.4.1. Brain alterations within networks in individuals with stimulant use disorder

The scope of this section is to identify brain regions that fall into determined networks to ascertain agreement or contradictions within the literature.

2.4.1.1. Default Mode Network (DMN)

Within the DMN Ipser et al. (2016) found greater coupling between the anterior and posterior DMN in 27 MA dependent participants compared with 26 controls, which decreased in intensity as length of abstinence increased [69]. Moreover, Ipser and colleagues were able to provide preliminary evidence that intrinsic connectivity between cognitive control networks and the DMN may normalize with increasing

abstinence (it is noteworthy that this finding may have been confounded by duration of treatment with antipsychotics, as most patients with a history of psychosis were on medication) [69]. Wilcox et al (2011) found deactivation of the DMN in cocaine dependent adults in 14 subjects diagnosed with cocaine abuse and dependence compared with 16 controls [114]. Ding et al (2013) looked into group differences between the posterior and anterior DMN and revealed that posterior DMN patterns (weaker rsFC within the hippocampus in 24 cocaine dependent subjects abstinent for more than two weeks) remained significant across all of the five ICA's they ran (extracting 10, 20, 30, 40 and 50 components), which was the only pattern that displayed this robust quality [116]. They did also find that the anterior DMN's connectivity strength weakened with increasing number of components in people who misused stimulants when compared with 24 controls [116]. These findings suggests that the posterior DMN patterns may either be more resilient than the anterior DMN or the posterior DMN may be more sensitive to the model orders used in this study [116].

In addition to relatively weak intra-network connectivity in SUD patients, the DMN appears to have weak internetwork connections (as listed below) in patient groups, which could indicate a locus for potential neuroplasticity in rehabilitation. Liang et al (2015) reported weaker rsFC between the DMN and SN, coupled with greater reported alexithymia (as measured by the Toronto Alexithymia Scale) suggesting a more impaired connection between these networks in 47 non-treatment seeking cocaine dependent subjects, compared with 47 controls [113]. The implication of this may be that even though when the DMN is active in individuals with stimulant use disorder, subjects are not necessarily engaging in self-reflection, but possibly ruminating on drug use. Interestingly Ipser et al (2016) found greater positive coupling between the right ECN and the anterior DMN sub-network [69] in MA users, which are frequently reported as anti-correlated networks [172]. Little connectivity (R0.08) was observed in the healthy control group between these networks [172], it is possible that the DAN rather than the ECN is anti-correlated with activity in the DMN (it is worth noting that the DAN is often included in the ECN in studies on executive function due to its role in attention). Regner et al. (2016) used Granger Causality a statistical procedure in which one time series is used to forecast another, to interrogate connections from the DMN to the basal ganglia network in 50 long term abstinent (>60 days) stimulant misusers and observed greater bidirectional connectivity as opposed to 50 controls, who had greater unidirectional rsFC [99]. This greater connectivity in abstinent stimulant misusers suggests increased BOLD response to regions which may be required to remain abstinent, though it may also reflect the effect that MA had on the brain.

Greater functional connectivity density was discovered within the posterior cingulate cortex/ precuneus by Konova et al (2015) in 19 non-treatment seeking cocaine dependent subjects compared with 15 controls [100]. This greater functional connectivity density is resource expensive in both short and long range connections, and suggests greater energy expenditure in the dopamine rich reward network in addiction. Further, weak control over craving may be associated with strong memory of perceived drug-

use rewards through the activation of the posterior cingulate by the hippocampus, implicating the DMN in episodic memory processing [173]. Liang et al (2015) found weaker rsFC between the posterior cingulate cortex and ECN (hemisphere not specified) in cocaine misusers compared with controls [113]. This finding suggests that even with greater energy cost revealed by Konova et al. (2015) [100], effective functioning of the posterior cingulate may still not be guaranteed in stimulant misuse.

The hippocampus is associated with the formation of new memories, remembering the past and imagining the future [72]. Both Ding et al. (2013) and Gu et al. (2010) found that cocaine dependent participants (24 recently abstinent (>2 weeks) and 39 non-treatment seeking, respectively) versus controls (24 and 39, respectively) had weaker rsFC from the hippocampus to other brain regions and circuits [116, 117]. Gu's group found that the weaker rsFC extended to the medial PFC [117], while Ding's group found weak rsFC from the left hippocampus that extended into the posterior DMN while from the right hippocampus it extended into the anterior DMN [116]. Conversely Adinoff et al. (2015) found stronger regional cerebral blood flow and rsFC between the hippocampus and posterior cingulate cortex/ precuneus in 22 non-responders compared with 18 responders both diagnosed with cocaine dependence [115]. These conflicting findings of rsFC between the hippocampus and divergent brain regions may be a result of differences in cohorts, where reported IQ was below 60 in one study [117] and tobacco smoking was not controlled for in another [116]. Moreover, the reported weak rsFC to the medial PFC and DMN could signify reduced functionality within these brain regions which may be associated with increased rumination in the case of relapse. One speculative interpretation of the finding of greater rsFC from the hippocampus to the precuneus, is that it represents a shift from focused memory formation to involuntary attention in SUD.

The medial PFC is a brain area associated with emotionally relevant working memory [174] and the temporal pole is implicated in assigning meaning to sound as well as object identification and meaning [175]. Research suggests that rsFC between these areas may be useful in predicting relapse. Geng et al. (2017) found weaker rsFC between the temporal pole and the medial PFC in 64 cocaine misusers diagnosed with dependence (n = 59), abuse (n = 3) and abstinent cocaine misusers (n = 2, unknown time period) compared with 67 controls. This finding together with years of education was able to accurately predict relapse within 150 days within a subset of 45 subjects who had completed 30 day residential treatment [94]. Konova et al. (2015) found greater functional connectivity density within the ventromedial PFC in 19 non-treatment seeking cocaine misusers compared with 15 controls [100]. Previous research has shown that lesions in this region can result in increased risk taking as well as reduction of emotional responses and self-control [176, 177], inviting the conclusion that abnormal functionality of the ventromedial PFC may manifest as a similar behavioural profile in cocaine misusers as well.

The consistent find of abnormalities in rsFC in the DMN in stimulant misusers may reflect increased rumination, in the service of planning, reinforcing and avoiding aversive aspects of drug misuse, rather than self-reflection. Achieving and maintaining abstinence has been shown thus far to be associated with an increased BOLD response to brain regions which are likely to assist in the suppression of cravings. Overcoming cravings in abstinence could possibly be achieved though the engagement of the ECN, it has been suggested that this would lessen activity in the DMN [172] and subsequently increase goal driven behaviour.

2.4.1.2. Executive Control network (ECN)

The ECN refers to the fronto-parietal networks (bilateral symmetric networks that are distinct from the dorsal attention network (another fronto-parietal network)) which mediate cortical (top-down) control [93, 101, 114]. Although there is some disparity as to which brain regions constitute the ECN, in this review we looked at the dlPFC (executive function, working memory and planning [118]), OFC and posterior parietal regions (which supports control initiation and flexibility [178, 179]).

Liang et al. (2015) found weak rsFC within the ECN in 47 cocaine users compared with an equal number of controls [113]. Connectivity within the ECN and between networks has shown stronger rsFC between the left ECN and the right ECN (reciprocally) in the final week of a three week treatment program in 9 responders compared with 36 non-responders diagnosed with cocaine use disorder [97]. Moreover stronger pre-discharge rsFC was found between the ECN and the SN highlighting the direction of control exerted by the SN on the ECN by responders to treatment in abstinence compared with non-responders to treatment [97]. Regner et al. (2016) using Granger Causality Analysis uncovered greater connectivity from the right ECN (the ECN finding was negatively correlated with impulsivity, behavioural approach and negative affect) to the dorsal DMN (the DMN finding was positively correlated with impulsivity) in 50 abstinent (>60 days) stimulant dependent subjects compared with 50 controls, making them anti-correlated [99].

Effective activation of the ECN may be essential to recovery in stimulant use disorder, yet strong stimulation of the DMN and striatum, triggered by stimulant cues and impulsivity, may result in a struggle for stimulant misusers to become abstinent and to maintain that state. The ECN and DAN have been shown to be anti-correlated with the DMN, as such engaging of the ECN and DAN may show benefit in rehabilitation.

2.4.1.3. Salience Network (SN)

The SN has been hypothesised to function as a switch between activation of the DMN and the ECN [172]. Its primary nodes are the dorsal anterior cingulate cortex [114, 123] and the anterior insula (specifically the right anterior insula) [94, 113, 128, 129].

The insula plays a role in physiological craving associated with drug taking[180, 181 182] and cigarette smoking [183-186]. Geng et al. (2017) found weaker rsFC between the bilateral insula and the dorsal anterior cingulate cortex in 59 cocaine dependent and abusing subjects compared with 67 controls [94]. According to Garavan et al. (2010) this finding is consistent with the presence of cravings [180]. Liang et al. (2015) also found weaker rsFC at the nodal level between the anterior insula and DMN in 47 non-treatment seeking cocaine dependent subjects compared with 47 controls [113], which also implies that cravings may be present during a resting state [180]. Wisner et al. (2013) found weaker inter-network connectivity in the anterior insula and anterior cingulate cortex and reward network (specifically the striatum) with degree of connectivity strength being related to increased non-planning impulsivity in 33 non-treatment seeking cocaine dependent subjects compared with 32 controls [129]. Although the striatum is not part of the SN it is associated with reward and subsequently is likely to have an influence on cravings; moreover cocaine cues have been associated with dopamine release and craving in the striatum [187]. Cisler et al. (2013) also found that rsFC of the anterior insula differed in 41 cocaine dependent subjects compared with 19 controls, an effect that was predominantly in the right hemisphere, with stronger rsFC in the clinical group extending to the dorsomedial PFC, inferior frontal gyrus and dlPFC [128]. This finding can be taken to suggest the involvement of the cortex in either consciously controlling cravings as found in nicotine addiction and drug addiction [182, 188] or planning to obtain the drug [189].

In stimulant misuse disorder, anterior cingulate cortex connectivity extends beyond the dorsal anterior cingulate cortex and into the rostral anterior cingulate cortex which forms part of the DMN. Liang et al. (2015) found weaker rsFC between the rostral anterior cingulate cortex to the SN (dorsal anterior cingulate cortex and anterior insula) and medial temporal lobe in stimulant use disorder compared with controls [113]. This confirms the finding of Verdejo-Garcia et al. (2014) who identified weaker rsFC between the anterior cingulate cortex, and insula (this was also found in the thalamus and brainstem which is not part of the SN) as well as weaker connectivity in the anterior cingulate cortex, insula and brainstem in 10 recently abstinent (>10 days) cocaine dependent subjects in a moral dilemma task compared with 14 controls [123]. The anterior cingulate cortex is a key player in decision making [190] and this weaker rsFC may confer difficulties in this function in stimulant misusers.

To summarise the main finding of studies investigating SN connectivity in SUD is weaker rsFC extending from the SN nodes and increased craving which suggests ineffective toggling between the ECN and DMN by the SN in stimulant misusers, with a dysfunctional ECN and the associated cognitive deficits.

2.4.1.4. Dorsal Attention Network (DAN)

There has been very little research into stimulant used disorder and the dorsal attention network, with this review finding two papers that explored rsFC in this network [158, 191] (although other papers did explore the role of the dlPFC [92, 93, 114]). Kelly et al. (2011) found weaker interhemispheric rsFC in the dorsal attention network in 25 recently abstinent (>2 weeks) cocaine dependent subjects compared with 24 controls [158]. When the relationship between rsFC and the results of the Cognitive Failures Questionnaire (a measure of attention) was compared in this study, they found weaker rsFC was associated with more self-reported lapses of attention [158]. Ipser et al. (2018) found evidence for anti-correlations between the dorsal attention network and DMN, which was attenuated in patients with a history of methamphetamine induced psychosis, but not in methamphetamine users without such a history [191].

The dlPFC is correlated with a diverse range of executive functions, including response inhibition and problem solving [118] which is relevant for treatment effectiveness in stimulant misusers. Weaker rsFC within the dlPFC has been demonstrated in 8 non-responders compared with 10 responders both diagnosed with cocaine abuse and dependence [92]. Conversely stronger connectivity was identified in the left dlPFC and bilateral occipital cortex in 14 cocaine misusers diagnosed with abuse and dependence compared with 16 controls [114]. Further, stronger connectivity was reported within the OFC and dlPFC in the stimulant misusing group compared with controls in response to cocaine cues [114], which highlights the engagement of the dlPFC associated with craving in addiction and its likely role in either craving inhibition or action planning to obtain the drug. Kohno et al. (2014) saw weaker connectivity in the dlPFC when conducting the Balloon Analogue Risk Task (BART) which was also observed in when analysing rsFC in a cohort of 15 MA dependent subjects compared with 18 controls [93]. The activation of the dlPFC in stimulant dependent participants in response to cocaine cues, coupled with weaker connectivity in the dlPFC during the BART, may suggest that they are more likely to respond to drug associated cues rather than exert control over their response to them.

A possible area for future research could be the involvement of the dorsal attention network in stimulant use disorder, and its potential role in the top-down control required to sustain abstinence.

2.4.2. Associations of methamphetamine misuse and global efficiency

When comparing 17 non treatment seeking MA dependent subjects and 18 controls, controls were found to have relatively larger clustering coefficients and global efficiency scores across the brain than MA misusers, with lower global efficiency being linked to lower IQ and slower information processing than controls [169]. Brain networks in MA misusers displayed weaker small-world properties compared with controls [169]. This finding is relevant in that small world properties increase with brain development, associated with a shift toward regularity observed by improved decision making [169]. ‚Subsequently less evidence of small-world network properties in MA misuse may indicate cognitive impairments [169].

Conversely Regner et al. (2016) found that global efficiency was higher in 50 abstinent (>60 days) participants who misuse other substances as well as stimulants than in 50 controls, which suggests greater global integration in substance misusers [99]. Differences in findings may be due to relatively low power both cohorts in Mansoory et al (2017) [169], poor matching between groups for IQ and education as well as one cohort being poly-substance misusers [99].

Wang et al. (2015) conducted a study exploring the broad range of functional interactions within the brain in 20 treatment seeking cocaine dependent subjects and 19 controls [166]. They found, stronger inter-regional correlations in cocaine misusers than for controls, with the treatment group showing larger node degrees (bigger node size) and a greater number of connections, but fewer node clusters than controls [166]. Further, cocaine misusers had hyper-connected rsfMRI brain networks with a high wiring cost but weaker communication efficiency and diminished small-worldness compared with controls [166]. This hyper connectivity could have a negative impact on communication between nodes in stimulant use disorder coupled with greater energy expense.

Although the effects of methylphenidate as a therapeutic agent in stimulant misuse disorder is not a focus of this review, a few studies (n = 3) explored the effects of this agent in stimulant use disorder using rsFC, and we included those. Konova et al (2015) found that methylphenidate was able to reduce the total count of short- and long-range connections to hubs in the basal ganglia, bilateral thalamus/ putamen, supplementary motor area and postcentral gyrus in cocaine use disorder compared with controls (regions that have been linked with making automatic action plans and resulting in habit formation)[100]. Methylphenidate (20mg orally administered with a scan conducted 120 minutes after ingestion) can increase intra-synaptic dopamine levels within the striatum, and Konova et al. (2015) found that there was a greater count of short- and long-range connections to the DMN in 19 participants diagnosed with cocaine abuse and dependence compared with 15 controls post administration [100]. Specifically the ventromedial PFC and posterior cingulate cortex as well as subcortical/ basal ganglia hubs, such as the thalamus, putamen/ amygdala showed abnormal counts of short- and long-range connections to the DMN [100]. Greater count of short- and long-range connections indicates that there is greater representation of energy-expensive topological components in cocaine misuse [100]. Moreover, the study showed that this number of connections to DMN hubs increased with every one year of cocaine use at a rate of 0.7 for short-range and 57 for long-range functional connectivity density [100]. The authors suggest that this may be a result of a cost-value trade-off between efficiency and metabolic cost [100].

Small worldness is associated with communication efficiency between brain regions. Accordingly if there is less small worldness and communication efficiency in addiction, then this will imply a reduction of normal inter-regional communications. This may lead to poorer cognitive control, which together with less inhibition, is common in stimulant dependence [166]. Overall, analysis using global efficiency suggest

that stimulant use disorder has a stronger energy cost coupled with reduced efficiency of connections between brain regions, which may have implications for rehabilitation as focused cognitive control is required to quell cravings.

2.4.3. Abstinence vs Relapse

The cingulate cortex has been identified as a key area in relapse prediction, probably due to its role in the formation and processing of emotions as well as in learning and memory [192]. Greater rsFC between the posterior hippocampus and the posterior cingulate cortex/ precuneus (greater connectivity in the DMN) predicted relapse in 22 cocaine using non-responders compared with abstainers and controls [115], which may be due to increased cue-induced cravings facilitated by the posterior cingulate cortex [115].

This finding contrasts to that of Camchong et al. (2014), who discovered, stronger rsFC between the nucleus accumbens and both the posterior cingulate cortex and left frontopolar cortex as well as between the subgenual anterior cingulate cortex (emotion regulation) and left frontopolar cortex in 18 participants diagnosed with cocaine dependence at five weeks of abstinence at an intermediate outpatient care program compared with those that relapsed [157]. These differences were not observed after 13 weeks of abstinence [157]. This group of 18 participants was split into 12 responders and 6 non-responders, and the non-responders at 13 weeks displayed decreased rsFC between the two time points between the nucleus accumbens and posterior cingulate cortex compared with responders [157]. The authors hypothesised that this could reflect connectivity changes of recovery, which may be part of a compensatory mechanism responders utilise in maintenance of sobriety [157].

Contreras Rodriquez et al. (2015) observed stronger rsFC in 9 non-responders vs 11 responders with cocaine dependence (in the opposite direction to that of Camchong) at 3 months follow up, between the ventral caudate/ nucleus accumbens and the subgenual anterior cingulate cortex [96]. The literature comes close to contradicting one another, with stronger connectivity predicting relapse in two study's [115] [96], and stronger rsFC predicting abstinence in another [157].

Gu et al. (2010) found weaker rsFC strength between the amygdala and hippocampus with the medial PFC [117]. This weaker rsFC in 39 non-treatment seeking cocaine dependent misusers compared with 39 controls, may impact reversal learning [117]. Reversal learning is necessary to establish abstinence, in which previously rewarded behaviours and drug-seeking habits are "unlearned", and the low-reinforcing value of habits linked to drug non-use are valued and selected. Recent cocaine use was associated with weaker rsFC between the amygdala and left posterior insula, and stronger rsFC between the primary-motor cortex and left anterior insula [117], suggesting the presence of more dominant cravings with more recent use, given evidence for the involvement of the insula in cravings [180]. Weaker rsFC was also found with

recent cocaine use between the hippocampus and medial PFC which the authors attribute to the lack of ability to recall negative consequences of past cocaine use [117].

Geng et al. (2017) found that connectivity strength between the right temporal lobe and left medial PFC predicted days to relapse in 45 individuals diagnosed with cocaine abuse and dependence [94]. They reported that greater years of education decreased the risk of relapse post treatment [94]. This was confirmed by McHugh at al. (2017), who found that fewer years of education and more years of nicotine use in 24 non-responders predicted a greater likelihood of relapse when compared with 21 responders, although in this case these factors were unrelated to rsFC in the ECN [97]. McHugh et al. (2016) further highlighted the need for greater executive control in achieving abstinence in 21 cocaine dependent participants who were participating in the Minnesota model for treatment [97]. Network connectivity revealed stronger rsFC between the left ECN and the dlPFC (found in the DAN) in 21 responders compared with 24 cocaine dependent non-responders [97]. Furthermore, weaker rsFC was identified between the left ECN and sections of the SN, while in the right ECN weaker rsFC was reported with the left middle temporal gyrus in responders compared with non-responders [97]. At 30 days of abstinence there was stronger rsFC in the right middle frontal gyrus and right dorsal anterior cingulate cortex in responders compared with non-responders [97]. The greater interhemispheric rsFC within the prefrontal components of the ECN present in these responders at 3-6 months suggests better control over drug craving and seeking behaviour than non-responders [97]. Moreover, greater rsFC among responders (30 days abstinent) vs non-responders suggests that this rsFC may have a protective quality and introduces the possibility of guiding behavioural interventions targeting craving and drug-seeking [97].

The nucleus accumbens is a pivotal region involved in reward and dopamine release, and has strong connections with cortical areas. Berlinger et al. (2017) found weaker rsFC between the nucleus accumbens and lateral dorsal PFC and a section of the medial PFC and between the nucleus accumbens and ventral parietal regions in 8 non-responders (who relapsed three months after being abstinent, 141 ±172.6 days at first MRI scan) compared with 10 responders diagnosed with cocaine dependence [92]. Conversely responders to the psychosocial treatment displayed a more robust rsFC between the ECN and SN compared with non-responders, possibly reflecting increased top-down control [97] required by the individual to maintain abstinence.

Amygdala activation is connected with emotional responses (fear, anxiety and aggression) as well as emotional learning [193]. Negative emotion has been shown to be associated with relapse [194, 195], and subsequently it may play a role in recovery from drug dependence. When McHugh et al. (2014) evaluated rsFC of the amygdala in relapse in cocaine dependence, they found weaker rsFC between the left cortico-medial amygdala and a cluster in the ventromedial PFC which extended to the rostral anterior cingulate cortex in 24 non-responders compared with 21 responders measured at 30 days post discharge [161]. Weak

rsFC between these regions from a scan conducted in the final week of treatment was linked to escalated risk of relapse in 30 days and, in turn, was associated with less education [161]. The authors hypothesised that the weaker rsFC between ventromedial PFC and rostral anterior cingulate cortex to the cortico-medial amygdala may facilitate drug seeking behaviour, with the ventromedial PFC input having a disinhibitory effect, resulting in relapse [161]. Additionally, they discovered that those able to abstain from drug use had weaker rsFC between the right basolateral amygdala and an area including the cuneus, lingual gyrus extending into the parahippocampal gyrus [161]. The circuit involving the visual cortex may represent modulation of the visual processing of emotional stimuli [161]. It is also possible that the weaker rsFC between the amygdala and hippocampus may also be linked to erosion of emotional memories associated with drug use [196]. The strengthened rsFC between the left amygdala (specific prolonged stimulus appraisal [197]) and medial PFC in cocaine use coupled with weakened rsFC between the right amygdala (activated by emotional stimuli [197]) and left insula may be a factor in the attenuated defensiveness observed in stimulant misusers [198, 199].

The weaker rsFC between the amygdala and cortical regions in non-responders [117, 161] may indicate poor emotional learning and increased aggression with weaker top-down control. Moreover, the amygdala has direct reciprocal connections to the insula and direct connections to the dorsal anterior cingulate cortex [117, 161] which comprise the SN, hence it is frequently described as part of the extended salience network. The dorsal anterior cingulate cortex has been associated with reward-based learning and the insula with cravings, this could imply that the amygdala's inactivity may be due to desensitised cravings and reward based learning.

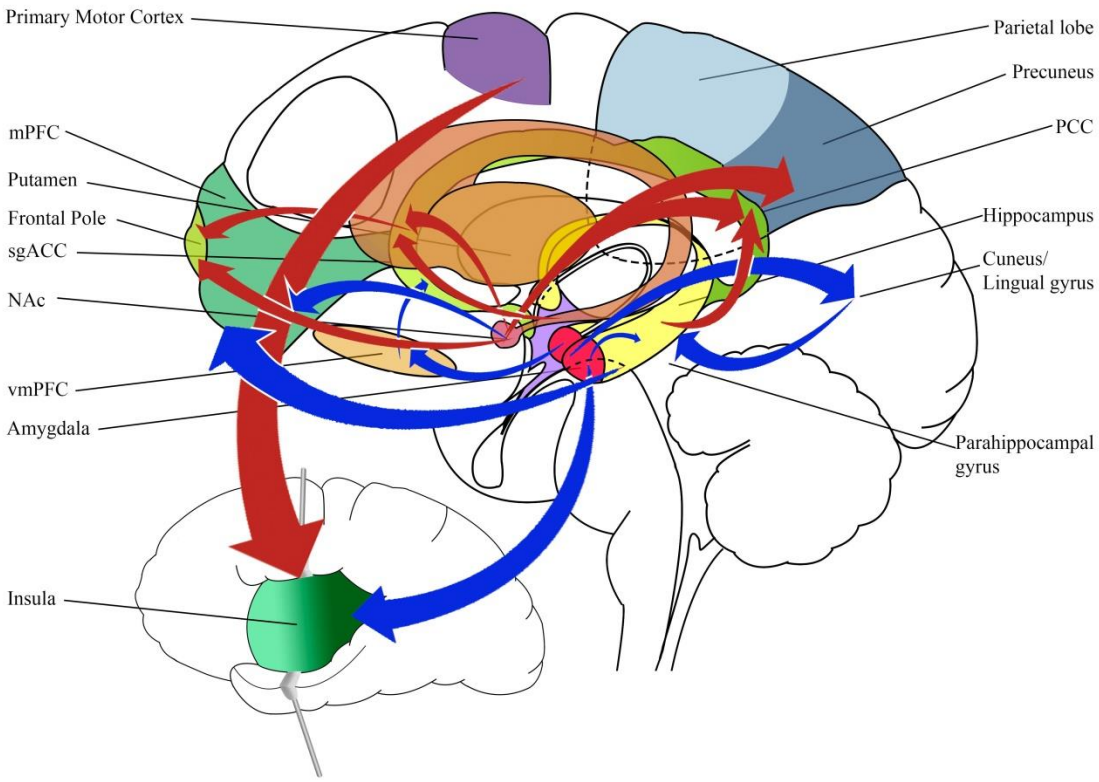

Figure 1: rsFC in relapse (red arrows represent greater rsFC and blue arrows represent weaker rsFC)

2.4.4. Cognitive-Affective Abnormalities in Stimulant Misusers

2.4.4.1 Compulsivity/ Impulsivity

People with stimulant use disorder have been shown to score high on the Obsessive Compulsive Drug Use Scale [98], making research into these domains pertinent for understanding this disorder.

When compared with 18 controls, 18 participants with stimulant dependence (undefined) had weaker rsFC strength of the inferior and superior right OFC with rsFC of the right superior OFC inversely correlated with severity of compulsivity related symptoms [98]. Contreras-Rodrigues et al. (2015) found stronger rsFC between the ventral caudate and insula to the OFC, as well as between the ventral putamen and OFC and insula operculum complex in 20 cocaine dependent adults compared with 21 controls [96]. When testing each pairwise inter-regional connection (wavelet correlation), correlation between the peak OFC co-ordinates and other brain areas, both stimulant dependent subjects and those with obsessive compulsive disorder had fewer connections between the OFC and medial premotor cortex, dorsal cingulate cortex, right somato-sensorimotor cortex, posterior cingulate cortex and left temporal cortex when compared with controls [98]. Due to the similarities between obsessive compulsive disorder and stimulant use disorder, specifically in the OFC, the presence of shared heritable genes predisposing for impulsive, compulsive behaviour should be explored in these two disorders [98].

Balducci et al. (2018) determined that stronger rsFC between the right amygdala and left insula, correlated with impulsivity and emotional dysregulation to a greater extent in 19 cocaine dependent participants when compared with 18 controls [156] , which may be implicated in the neurobiology of craving in stimulant use disorder. Conversely Geng et al. (2017), found weaker rsFC between the amygdala and insula, but greater rsFC between the amygdala and medial PFC in 45 abstinent adults with cocaine use disorder compared with 67 controls [94]. Kohno et al. (2016) reported that with thirty nine MA dependent misusers there was stronger rsFC strength between the midbrain and striatum, amygdala, hippocampus and medial OFC with a greater self-reported impulsivity (as measured by the Barratt Impulsivity Scale) than was found in 44 controls [102]. Further, MA dependent subjects had less motor responsiveness and greater impulsivity when compared with controls, with cognitive impulsivity being correlated to a rsFC of the midbrain to the ventral striatum [102]. This finding is due to greater strength of rsFC of the mesocorticolimbic structures in participants who misuse MA, and is argued by the authors as being likely due to decreased striatal D_2 receptor density in MA users [102].

Impaired ability to inhibit impulsivity among people with stimulant misuse can be defined as a bias towards substance-specific rewarding stimuli, which in turn increases the risk of impulsive drug use [102]. This increased bias towards reward has also been demonstrated through greater scores on the Behavioural Activation Scale (which measures sensitivity to pleasant reinforcers in the environment) in 50 abstinent (>60 days) stimulant dependent subject compared with 50 controls, specifically on drive and fun seeking [99]. Reward responsiveness scores were not particularly high in the stimulant misusing group, which could be due to the period of abstinence, or the fact that they misused more than one substance [99]. Moreover, the participants who misused stimulants displayed greater impulsivity in motor, non-planning and attentional subscales of the Barratt's Impulsivity Scale than controls [99].

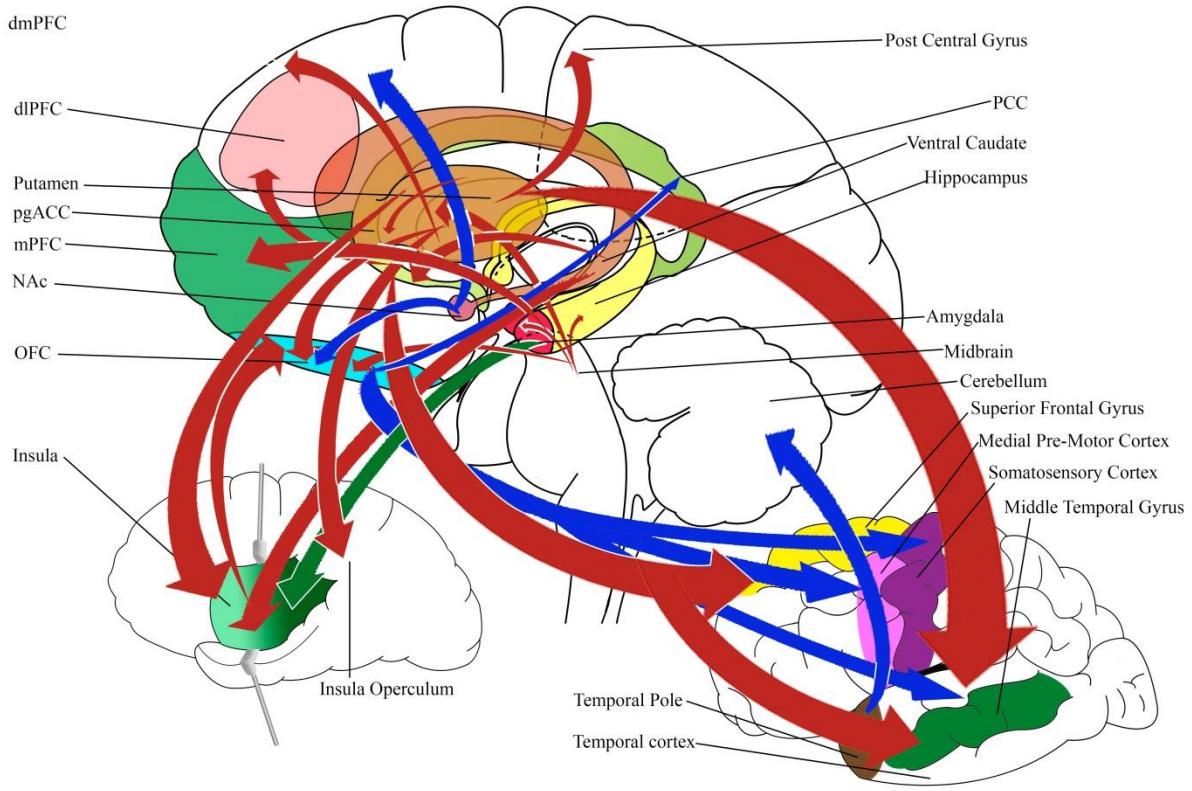

Figure 2: rsFC relating to impulsivity and compulsivity (red arrows represent greater rsFC and blue arrows represent weaker rsFC)

Weak self-generated and goal directed behaviour may be associated with loss of top down control in stimulant use disorder. Berlingeri et al. (2017) found weaker rsFC between the nucleus accumbens and orbital PFC and the dorsal PFC, as evidenced in a small sample of 8 cocaine dependent non-responders vs 10 responders [92] which may assist in the argument for a loss of top down control in stimulant misuse. Camchong et al. (2011) identified poor ability to execute reversal learning in 27 cocaine dependent misusers compared with 24 controls, with this being positively correlated to rsFC strength within the dlPFC [146]. Moreover, a positive correlation between delay discounting scores and rsFC strength within the dlPFC and perigenual anterior cingulate cortex associated with social processing and metalizing was also found in the same cohort of cocaine misusers [146].

Meunier et al (2012) uncovered weaker rsFC of the right inferior and superior OFC in 18 stimulant (undefined) dependent adults compared with 18 controls, with greater compulsivity predicting weaker rsFC of the right OFC as well as weaker rsFC between the OFC and dorsal medial pre-motor and cingulate cortex [98]. The OFC plays a role in impulse control and monitoring of socially appropriate behaviour [200] which is necessary in impulsive/ compulsive behaviour. These findings highlight the loss of executive control and greater input from the reward network in cocaine misuse [92], further it allows non-

substance users an insight into the challenge (lack of top-down control) that substance misusers face if they wish to abstain.

2.4.4.2. Executive Function

The possibility that stimulants negatively impact executive control has been a focal point of research, with specific attention given to the dlPFC which plays an important role with respect to working memory function. When exploring the extent to which activation shifted as a linear function of risk together with pending reward, as assessed by the number of pumps in the BART, a negative correlation was found between the timeseries for the right dlPFC and the midbrain rsFC with the OFC, putamen, ventral striatum, amygdala, insula, hippocampus, anterior cingulate cortex, orbital medial and superior frontal cortices and temporal and occipital cortices during the risk taking task in 15 MA dependent adults [93]. This is contrary to the findings in 18 matched controls, who showed positive correlation between these regions [93]. Accordingly the authors theorise that this supports the hypothesis that dysfunction in the right dlPFC rsFC contributes to impairments in MA misusers and may be facilitated by greater impulsivity as well as abnormally strong rsFC in the reward network [93].

There was stronger rsFC within the perigenual anterior cingulate cortex as well as between the anterior cingulate cortex and middle temporal gyrus in 27 cocaine dependent subjects compared with 24 controls, with the stronger rsFC being associated with abnormal task performance in a delay discounting task and poor reversal learning [146]. Further there was stronger rsFC in the frontal and temporal regions of the perigenual anterior cingulate cortex to the dlPFC, middle temporal gyrus and superior frontal gyrus in cocaine misusers [146]. Gu et al (2010) discovered weaker rsFC between the rostral anterior cingulate cortex and amygdala, hippocampus, posterior insula and portions of the temporal gyrus which impacts on emotional functioning [117]. The anterior cingulate cortex is associated with affect (subgenual involved in negative events and sadness, while the pregenual is involved in happy events and self-relevant tasks [201]) as well as attention, response inhibition, motivated behaviours and decision making [190].

The dlPFC is a target region for methylphenidate, a psychostimulant which has been associated with enhancing executive function (specifically working memory). Moeller et al (2016) explored the therapeutic effects of methylphenidate in 22 cocaine misusers (diagnosed with both dependence and abuse), and reported that the cocaine misusers had weaker dlPFC responses, as measured by the drug word task and colour word task when compared with 21 controls [101]. Conversely they reported a similar but not significant pattern of stronger rsFC in the dlPFC in control participants in response to methylphenidate compared with cocaine misusers [101]. The dlPFC modulation by methylphenidate in people who misused cocaine was negatively associated with recent drug use, suggesting that even though it has potential use as a therapeutic agent, it is dependent on the time from last drug use in acute stages of intoxication [101].

Thalamic and dlPFC rsFC was weaker with increasing methylphenidate dosage in both controls and stimulant misusers and created a pattern of more efficient signalling in stimulant misusers compared to controls [101]. Rish et al. (2016) found that it was easier to identify the effects of cocaine in 18 dependent adults compared with 15 controls when administered placebo than when administered methylphenidate, as the methylphenidate appeared to normalise functional network properties in acute cocaine misusers [95].

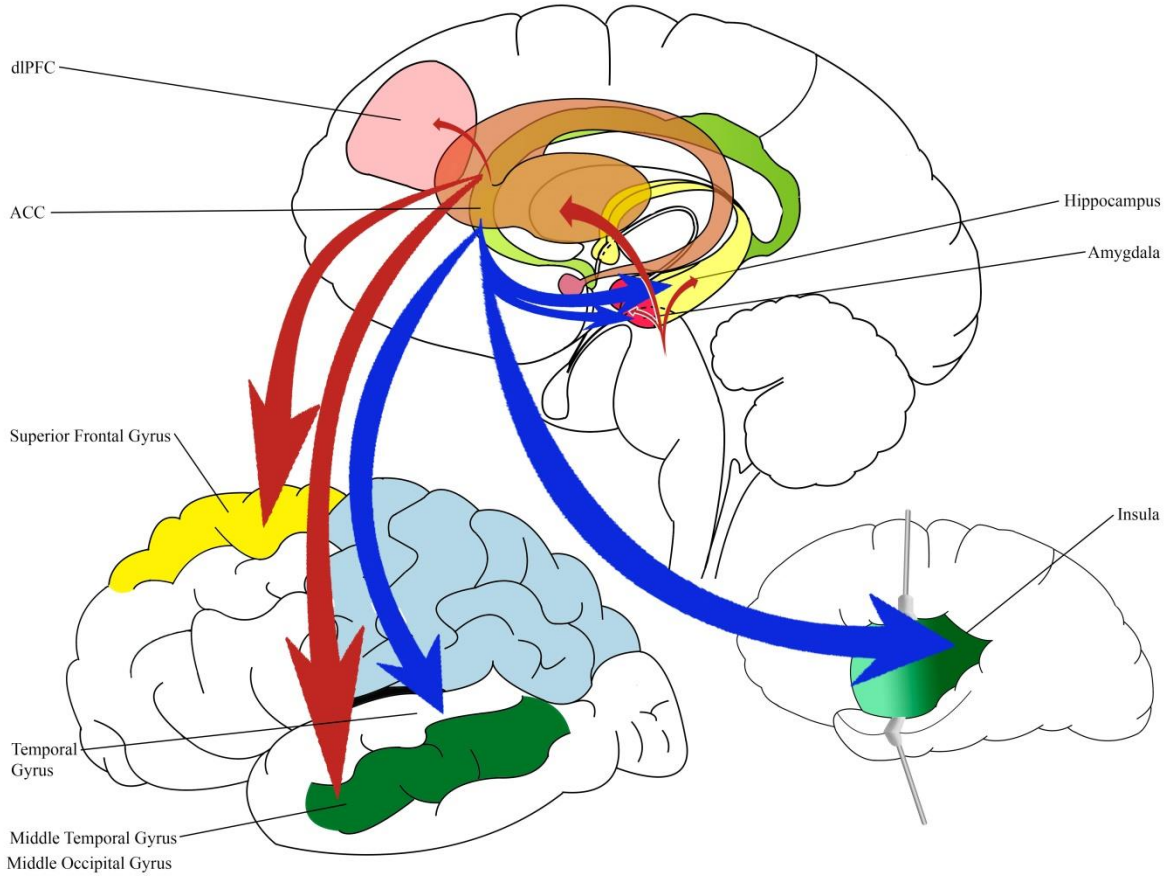

Figure 4: rsFC in executive function (red arrows represent greater rsFC and blue arrows represent weaker rsFC)

Stronger rsFC in the dlPFC is associated with cocaine cues and risk taking, together with the strong activation of deeper grey regions also involved in reward in people who misuse cocaine, suggest conflict between nodes associated with executive function and those involved in reward in stimulant use disorder.

2.4.4.3. Reward

The ventral tegemental area, nucleus accumbens, and dorsal striatum (caudate nucleus and putament) are associated with reward. The ventral tegemental area has been linked to specific emotions, including but not limited to those relating to motivation, avoidance and fear conditioning [52]. Gu et al. (2010) found weaker rsFC between the ventral tegemental area and both the mediodorsal thalamus and lentiform

nucleus/ putamen in 39 non-treatment seeking cocaine dependent adults compared with 39 matched controls [117]. Moreover, they identified weaker rsFC between the ventral tegemental area, bilateral thalamus and right nucleus accumbens which was negatively correlated with years of use [117]. These findings may reflect a Temporal Difference Learning Error [3] (* see footnote) within the DA system necessary for learning new reward associations [117]. Ray et al. (2016) on the other hand, found stronger effective connectivity from the ventral tegemental area to the nucleus accumbens, hippocampus and medial frontal cortex in 20 non treatment seeking cocaine dependent adults compared with 17 controls [164]. Further, they found reciprocal effective connectivity (the influence that one region exerts over another) between the hippocampus and medial frontal cortex as well as within the nucleus accumbens in cocaine misusers, which differed from controls who had stronger effective connectivity from the medial frontal cortex to the ventral tegemental area, from the nucleus accumbens to medial frontal cortex and within the hippocampus [164]. It is possible that the difference in connectivity findings could be attributed to variability between the studies with regards to years of use (Gu et al. 4,3±2,0 years, Ray et al. 16±8, 3-34 years) or length of abstinence (Gu et al. no abstinence reported, Ray et al. 72 hours) [117, 164].

In a follow up study of the same cohort, Ray et al. (2017), using a Bayesian search algorithm (IMaGES), found 2 feed-forward pathways from the ventral tegemental area (ventral tegemental area – hippocampus – ventral striatum – anterior cingulate cortex, dlPFC, OFC, medial frontal cortex; ventral tegemental area – insula) in abstinent cocaine misusers which was not found in controls, and 3 pathways originating in the hippocampus were found in controls which were not present in the cocaine abstinent group (hippocampus – ventral tegemental area – insula – dlPFC; hippocampus – ventral striatum; hippocampus – medial frontal cortex) [91]. These findings suggest abnormal dopamine neurotransmission in early abstinence.

Kohno et al (2014) reported that midbrain rsFC to limbic regions was stronger in 15 MA dependent subjects than 18 controls [93], which could explain a hyper-responsivity of MA misusers to environmental cues signalling potential reward. Kohno et al (2016) saw abnormal interaction of the midbrain in a group of 39 MA dependent adults, in which a negative relationship was observed between the ventral striatal binding potential and rsFC between the midbrain and striatum, OFC and insula, while a matched group of 44 controls demonstrated the opposite pattern [102]. Conversely they found a positive relationship of midbrain rsFC with the left ventral striatum (associated with cognitive impulsivity) in MA users, while controls had a negative relationship [102]. Further, MA misuse was positively correlated with cognitive impulsivity (impulsive choices or decisions) and rsFC between the midbrain and left nucleus of the ventral striatum while controls had decreased cognitive impulsivity as rsFC in these brain regions increased [102]. The midbrain has multiple functions including that of regulating alertness [42]. The authors reasoned that stronger rsFC of the midbrain in MA users with terminal fields may be due to low ventral

* Temporal difference learning is a form of reinforcement learning whereby there is no prior knowledge of the outcome, so estimated reward and actual reward is bootstrapped (values are updated based on estimates and not exact values), [3]. Error on tasks measuring temporal difference learning can be calculated using an algorithm which in turn can subsequently be applied to predict continued learning until the learning is complete [3]. DA neurons have been shown to increase firing during the error condition, and plateau when the learning is complete [3].

D_2 receptor availability together with reduced DA release that would attenuate a GABAergic inhibitory feedback and thus regulating DA neuronal activity [102].

DA is released from multiple brain areas, including the nucleus accumbens, and as such this region is highly active in stimulant use disorder. Berlingeri et al (2017) reported that 8 long term abstinent (who had completed psychosocial treatment) (141 ± 17.6 days) cocaine abusers who relapsed displayed weaker rsFC between the nucleus accumbens and parts of the dlPFC as well as around the rolandic sulcus and lateral parietal associative regions and retrosplenial cortices bilaterally than 10 responders [92]. Further, a negative association was found between strategic and controlled behaviour and rsFC between the right nucleus accumbens and right orbito-PFC, right insula, right superior temporal pole, right caudate and left cerebellum, with similar effects of the left [92]. They also reported stronger rsFC between the nucleus accumbens and dorsal striatum and OFC in non-responders vs responders [92] again implying the interference of the reward circuit in behaviour. Camchong et al.(2014) found stronger rsFC between the nucleus accumbens and left frontopolar cortex and posterior cingulate cortex (involved in visuospatial orientation and self-relevant assessment [157]) as well as stronger rsFC between the subgenual anterior cingulate cortex (associated with sadness [157]) and left frontopolar cortex in 6 non-responders compared with 12 responders who had been abstinent from cocaine dependence for five weeks [157]. This may be a reflection of the focus and struggles required to maintain abstinence in people who have misused stimulants.

The striatum can be divided into ventral (nucleus accumbens and olfactory tubercle) and dorsal (caudate nucleus and putamen) regions which appear to have different roles in the addiction process [202]. The ventral striatum has been identified as being involved in the initial impulsive behaviour of drug taking, while as dependence on the drug becomes more pronounced there appears to be a shift from ventral to dorsal striatum with a corresponding increase in compulsive drug use [202]. Stronger activation was found within the ventral striatum of 15 MA dependent subjects compared with 18 controls, also stronger rsFC from the midbrain to the putamen, amygdala and hippocampus negatively related to modulation of the right dlPFC activation in a risky decision task while controls were positively related [93].

Contreras-Rodriguez et al (2015) found greater rsFC between the ventral caudate and subgenual anterior cingulate cortex (connected with steeper delay discounting) and between the ventral putamen and dorsomedial PFC as well as between the dorsal putamen and insula in 20 treatment seeking cocaine dependent adults abstinent for >15 days compared with 21 controls [96]. Wilcox et al (2011) reported stronger rsFC between the left ventral striatum seed and right OFC extending into the rostroventral anterior cingulate cortex in 14 adults diagnosed with cocaine abuse and dependence compared with 16 controls [114]. Konova et al. (2015) confirmed a greater functional connectivity density with its associated resource expense within the putamen/ amygdala in 19 non-treatment seeking adults with cocaine abuse

and dependence compared with 15 controls [100], while Ray et al. (2017) exploring effective connectivity discovered that if onset of use was recent, then there was a stronger causal influence of the ventral striatum on the dlPFC in 20 non treatment seeking cocaine dependent misusers than 17 controls [91]. Conversely, McHugh et al (2013) found weaker rsFC between the bilateral putamen and posterior insula (mediating elevated impulsivity) and the right posterior gyrus in 24 non-responders compared with 21 responders in cocaine misuse [160]. Although two of these studies had low power [114] [100], differences between studies are likely due to the differences in cohorts (treatment responders and non-responders, and MA users and healthy controls) between Ray et al. (2017) and McHugh et al. (2013).

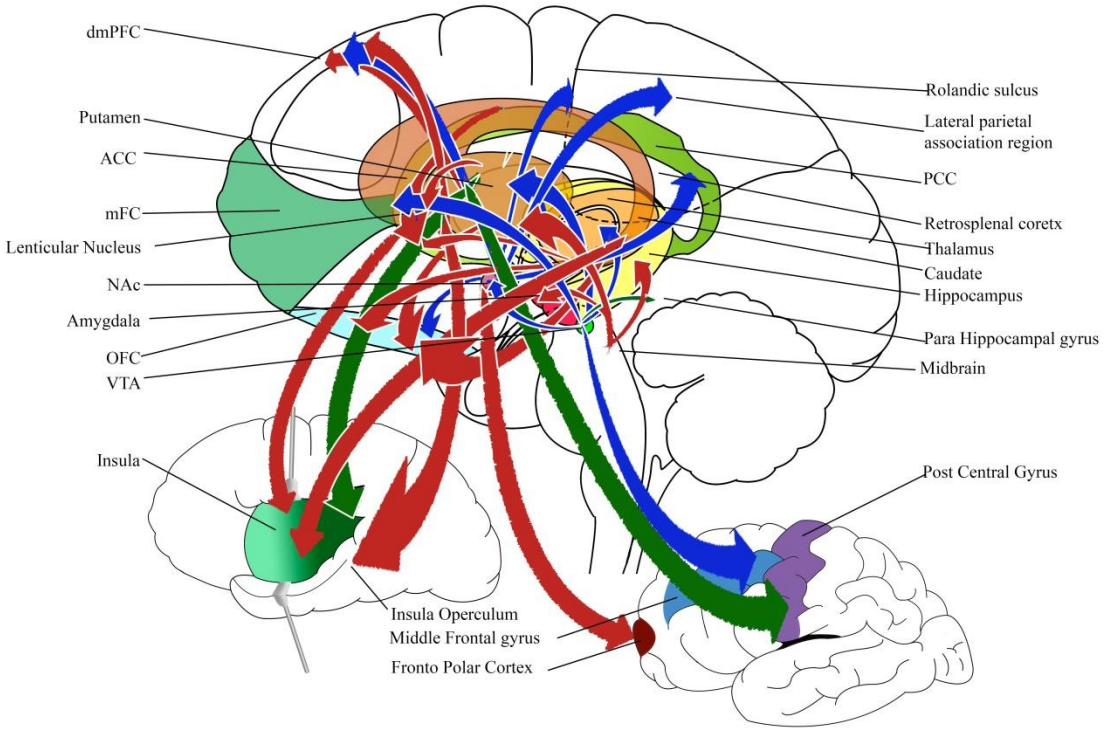

Figure 5: rsFC in reward (green arrows represent conflicting finding, red arrows represent greater rsFC and blue arrows represent weaker rsFC)

Stronger connectivity of the striatum in stimulant misusers is consistent with the drive and dominance of the reward pathway in this disorder. Kohno et al. (2018) found that plasma interleukin 6 (an inflammatory cytokine) was positively related to striatolimbic rsFC and negatively related to corticostriatal rsFC in 27 MA dependent subjects compared with 20 controls. This finding deepens our understanding by revealing that chronic stimulant misuse is correlated with increased inflammation in certain dopaminergic brain regions [103] and this inflammation can result in neurotoxicity and impaired cognitive functioning [52] with a greater focus on reward.

2.4.4.4. Craving and Introspection

The insula has been associated with multiple functions, including, but not limited to introspection and craving [131, 180]. Accordingly we describe findings from studies of this brain region in this section. Geng et al. (2017) found that 59 subjects with current and past cocaine abuse and dependence, have thinner insula thickness bilaterally and thicker temporal poles compared with 67 controls [94]. Further, they reported weaker rsFC in both left and right insula and dorsal anterior cingulate cortex and between the right temporal pole and left and right middle/ superior temporal gyri, supramarginal gyri and medial PFC (mostly left) in the cocaine misusers compared with controls [94]. Wisner et al. (2013) replicated the finding of reduced insula volume in a cohort of 33 non treatment seeking cocaine dependent adults compared with 32 controls, and this together with reduced volumes in the putamen was negative correlated with an absence of premediation in the cocaine misusers [129]. The anterior insula is part of the salience network, which may result in some overlap between this section and that of the SN. When exploring intrinsic connectivity networks Wisner ate al. (2013) found weaker internetwork rsFC between the anterior insula to anterior cingulate cortex network and striatum [129]. Further, this weaker rsFC had an inverse relationship with non-planning as measured by the Barratt's Impulsivity Scale [129]. Finally they reported a stronger rsFC within network for the anterior insula and anterior cingulate cortex, which predicting increased impulsivity (self-report) and reduced forethought in cocaine misusers [129].

Wilcox et al.(2011) reported weaker rsFC between the bilateral putamen and left posterior insula in people who misuse stimulants compared with controls, while McHugh et al. (2013) [114] found greater rsFC between these brain regions that continued on to the post central gyrus [160]. It is not clear the reason for these conflicting findings. More research should be conducted on this area, though it should be noted that Wilcox et al. (2011) was under-powered.

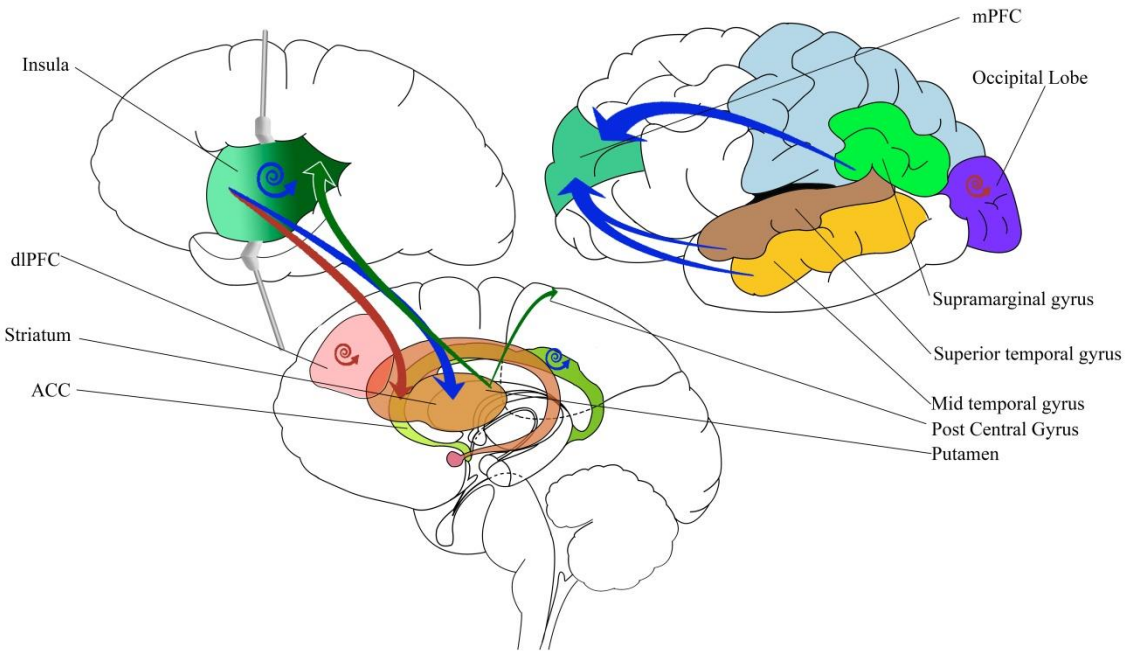

Figure 6: rsFC in craving and introspection (green arrows represent conflicting finding red arrows represent greater rsFC and blue arrows represent weaker rsFC)

Moral judgement

Moral judgement is another area in which stimulant misusers showed abnormalities when compared with controls [123]. In 10 treatment seeking, abstinent (>10 days) cocaine dependent misusers there was weaker activation of the medial PFC, anterior cingulate cortex, posterior cingulate cortex/ precuneus and bilateral angular gyri and diminished activation in the limbic-paralimbic structures (anterior cingulate cortex, superior dorsal brain stem, parahippocampal cortex and insula) when compared with14 controls in a moral dilemma task [123]. Furthermore, the stimulant using group had weaker rsFC between the anterior cingulate cortex and bilateral thalami and between the periaqueductal grey and left insula and putamen and brainstem tegementum compared with controls [123]. In both groups the insula and insula-operculum complexes bilaterally and the midbrain and parahippocampus were functionally connected, yet in the control group this extended to the bilateral thalamus, while in cocaine group it extended to the anterior cingulate cortex and hypothalamus [123]. Moreover weaker functioning of frontolimbic areas during the task-based fMRI were coupled with poor correlation between cognitive processes and emotional signals [123]. The insula and anterior cingulate cortex act to integrate emotional signals which guide decision making, while the periaqueductal grey and insula combine to bring emotion into awareness and both have weaker function in cocaine users, which the authors suggest reflects deficient interoception and the potential for poor decision making [123].

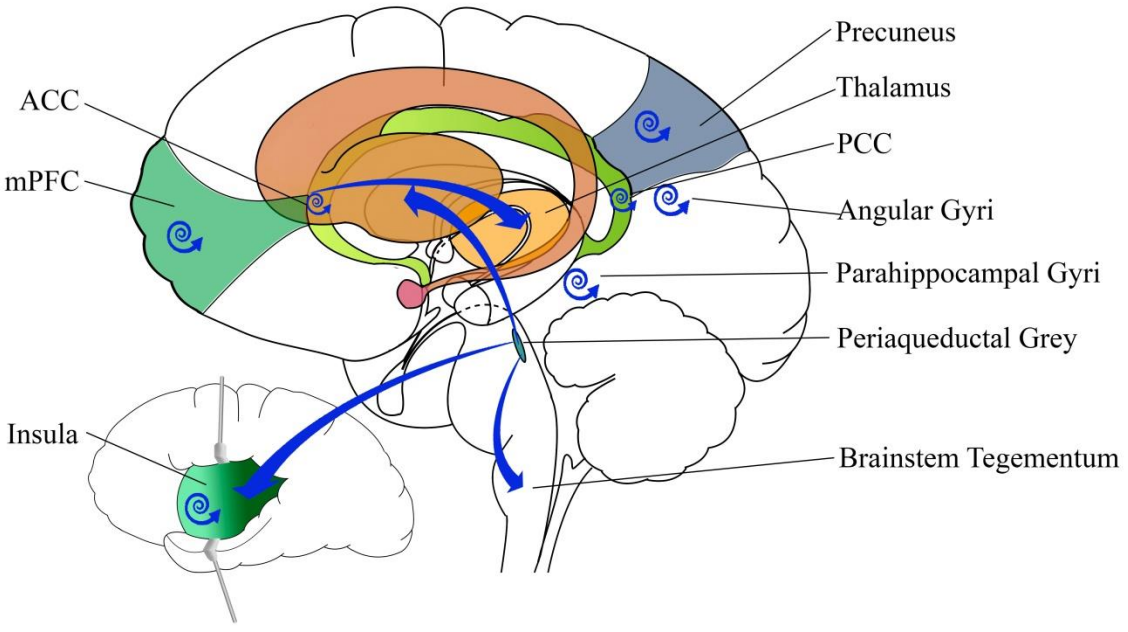

Figure 7: rsFC in moral judgement (red arrows represent greater rsFC and blue arrows represent weaker rsFC)

2.4.4.6. The link between the endocrine and nervous system

Zhang et al (2018) identified a stronger rsFC from the lateral hypothalamus to the dlPFC in persons recently abstinent (>7 days) from cocaine dependence (n = 70) compared with 70 controls [168]. This could suggest a dominance of more primal needs over cortical function or, when considering the bi-directionality of rsFC, it may suggest greater cortical regulation of the hypothalamus in cocaine misusers due to greater activation of this brain region. A weaker rsFC was found from the hypothalamus to the ventral precuneus [168] which may indicate a deficit in reflective self-awareness as suggested by Lou et al (2017) [203]. Further the weaker rsFC from the hypothalamus to the ventromedial PFC, temporal gyrus, fusiform gyrus and ventral striatum [168] may imply a exacerbated defensiveness [204] in early stage recovery. In summary, the stronger rsFC from the hypothalamus to the parietal cortex, coupled with weaker rsFC of this structure to the ventromedial PFC, and ventral striatum in people who misuse stimulants, suggests the dominance of the more primal brain regions over cortical areas in recent abstinence or greater cortical regulation of the hypothalamus in SUD..

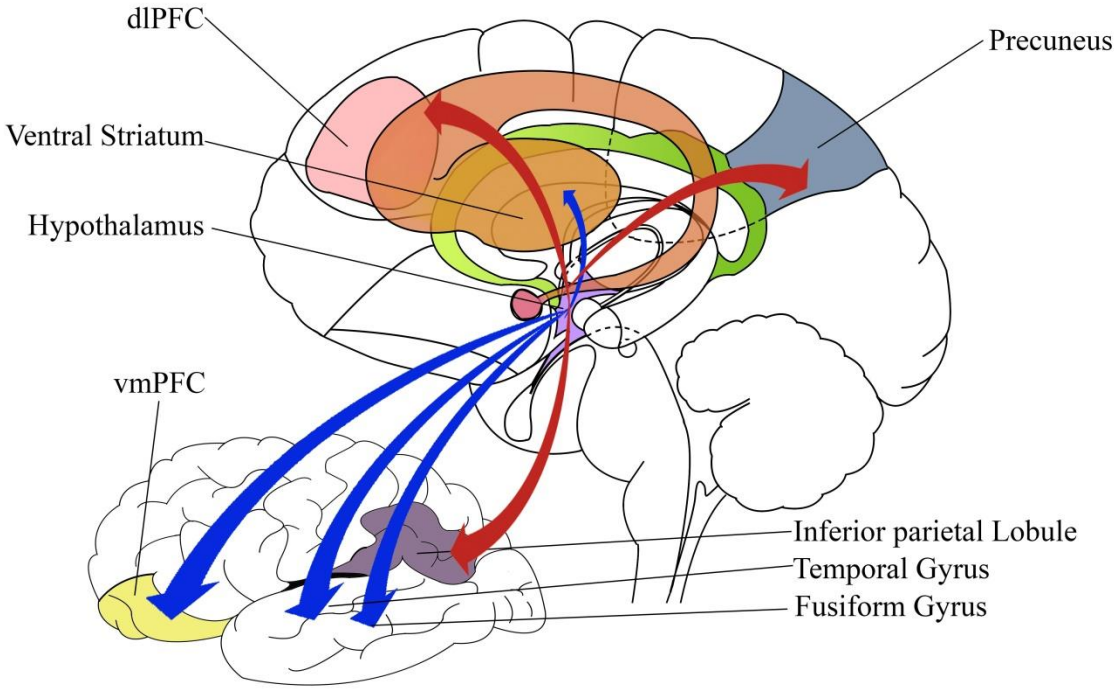

Figure 8: rsFC in Neuroendocrine link (red arrows represent greater rsFC and blue arrows represent weaker rsFC)

2.4.4.7. Clinical predictors of abnormal rsFC in stimulant misuse

There are various factors that intensify the impact of stimulant use disorder, including years of use, duration and frequency of use. Although not all papers found a moderating effect of these covariates in rsFC in people who chronically misuse stimulants, here we will discuss those that did. Ray et al (2015) found that years of use in 20 non-treatment seeking cocaine dependent subjects was negatively correlated with rsFC strength within the sensorimotor cortex and the left anterior cingulate cortex and left superior temporal gyrus, right medial temporal lobe and left superior angular gyrus [163]. Further, there was a positive correlation between years of use and rsFC between occipital-limbic regions, which suggests the possible development of neuroadaptation [163] or continuing effects of neurotoxicity. The rsFC between the right middle frontal gyrus and right supramarginal gyrus as well as between the right middle occipital gyrus and right cingulate gyrus was positively correlated with duration of use. While between the left middle occipital gyrus and left calcarine gyrus a negative correlation was found with frequency of use and, between the left calcarine gyrus and left and right middle occipital gyrus a negative correlation was found with amount spent [163]. Years of use was also negatively correlation with stronger rsFC within the sensory motor cortices and within the left frontal-parietal network in cocaine use and within the sensory motor cortex in cocaine used disorder [163]. These findings emphasise the long-term effect of chronic stimulant misuse including potential neuroadaptations within the occipital cortex, which may be consequential from drug seeking cues.

The previously cited finding by Kohno et al (2018) of an increased negative relationship between the pro-inflammatory cytokine interleukin-6 and the rsFC of the dlPFC and dorsal and ventral striatum in 27 MA dependent adults compared with 20 controls [103], together with evidence of a reduction of D2 receptors in the clinical group [102] highlight the importance of the role of these brain regions in treatment of SUD.

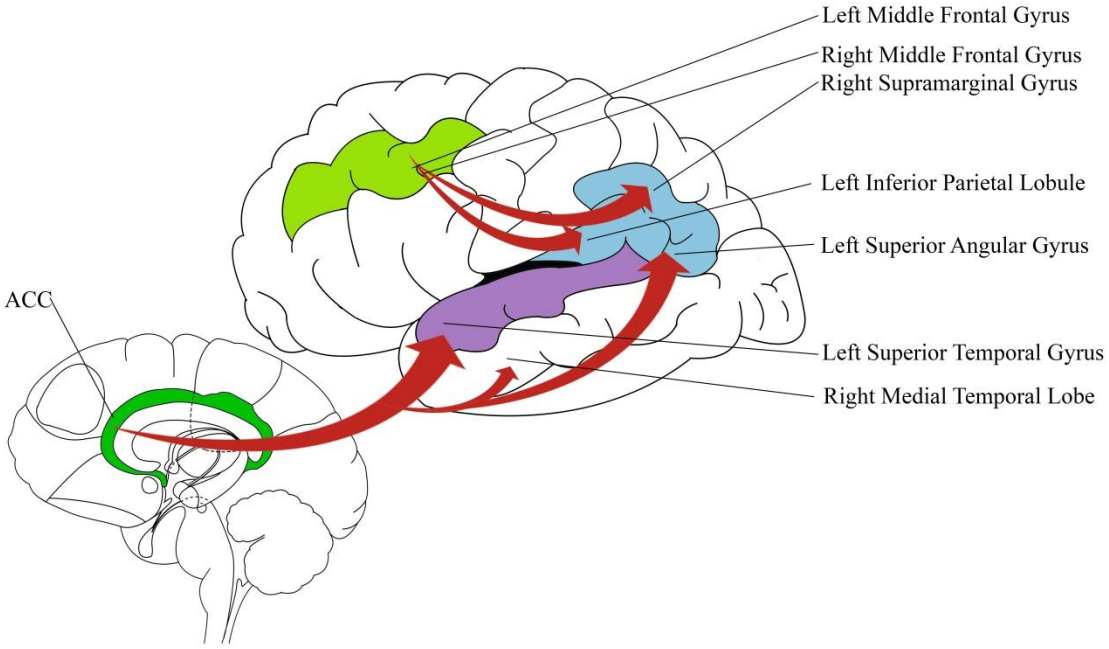

Figure 9: rsFC in predictors of relapse (red arrows represent greater rsFC and blue arrows represent weaker rsFC)

2.4.5. Critique of the papers

The cohorts: Obstacles in the interpretation of the findings of studies on substance misuse include under-representation of females in studies, comorbid use of various substances such as tobacco and alcohol, and small samples with corresponding low power, to detect group differences. Females with stimulant use disorder were underrepresented in these studies (4 studies had no females [92, 101, 166, 169], 14 studies with ≤ 5 females [91, 95-98, 100, 103, 116, 146, 156, 160, 161, 163, 164], 3 studies with ≤ 10 females [69, 94, 128]. In only 3 studies were at least half the cohort female [114, 115, 157]). This corresponds to the fact that women are underrepresented in treatment programs too, as evidenced by the World Drug Report 2015, in which it was revealed that whereas one in three substance misusers are female, only one in five misusers in treatment are female [88]. This may be due to inaccessibility to treatment as a result of poor consideration of women's needs, child care responsibilities as well as associated stigma and cultural norms [88]. Finally facilities for women in research trials should be considered by research institutions, such as childcare for children while the mother assists with the trial.

A small sample size increases the risk of false negatives (Type II error), as well as publication bias towards reporting smaller studies with inflated effects estimate (Type I error, limited ability for replication and misleading inferences [155]. Cremers et al. (2017) suggest that a minimum of n = 30 in fMRI studies is required to balance the negative effects of low power [155]. Of the studies included in this review (n = 32) 13 had a cohort that met this sample size threshold [94, 97, 99, 102, 103, 113, 115, 117, 128, 129, 158, 160, 161]. Four of the 32

studies reported how the effect size was determined [96, 123, 129, 166]), a commonly under-reported feature in fMRI studies [205]. To counter small sample sizes and increase potential power in MRI research, consortia offer opportunities for compiling larger samples with examples such as Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) [206] and Neurosynth [207].

It is important to bear in mind that imaging studies in stimulant use disorder have multiple challenges; not only is imaging expensive, but participant retention is challenging as well. Non-attendance and failure to remain abstinent for the required period represent two familiar problems for investigators in this field. Further, head movement in the scanner is common, especially if the cohort are non-treatment seeking and under the effects of the stimulant.

Cigarette smoking amongst stimulant users is prevalent and the effect of smoking on brain networks is extensive [208]. Notably, smoking is associated with sex differences with respect to effects on striatal DA receptor availability [209] and DA release [210]. Lerman at al. (2014) propose that in early abstinence from nicotine, the SN increases allocation of resources to attend to cravings which in turn enhances the activation of the DMN and decreases activation of the ECN [208]. Nicotinic acetylcholine receptors have the highest density in the midbrain, thalamus, insula and anterior cingulate cortex, and the anterior cingulate cortex and insula in particular have been linked to cognitive function [107, 211] which in turn is implicated in stimulant use disorder. This emphasizes the need to report the smoking status of cohorts in rsfMRI trials, as well as the necessity of matching groups for smoking and the possibly of using smoking status as a covariate in stimulant use disorder studies. Of the 32 studies, 23 did report smoking status [69, 91-95, 97-103, 114, 115, 117, 158, 160, 161, 163, 164, 166, 169].

Falling asleep in the scanner can affect the data, as a resting-state is likely to have different connectivity from an asleep-state [212, 213]. Two studies debriefed their participants post scan to determine whether they stayed awake during the scan [146, 157] and one used an eye tracker to determine if their participants stayed awake [156]. This is an area that could be improved upon in future resting state studies as falling asleep in the scanner is common and affects rsFC [214, 215].

Data analysis: The time series of signal intensity of all voxels in the brain created in an fMRI scan results in a global signal, however most imaging studies report outcomes using regions of interest or networks of interest [1]. One of the more controversial methodological decisions made in pre-processing rsFC datasets when conducting a seed-based analysis, is whether or not to regress out the global brain signal, as a way of minimizing motion-induced/ other; artifacts affecting BOLD signal across the brain [1]. Global signal effects are often regressed out from each time series using a variety of methods [1]. The influence of regressing out global signal and its effect on correlated networks in rsfMRI has created a fair amount of debate [1] largely as it is mathematically mandated to introduce negative correlations between time series [216].

Global regression analysis reporting anti-correlations between networks could therefore be due to regression of the global signal [1, 216]. Employing a sensitivity analysis can assists in a more reliable interpretation of the data when regressing out global signal [1], yet the majority of the studies included in this review) that used global regression analysis did not check the effect of this step by means of a sensitivity analysis (5/7 studies).

Comparison of the STROBE checklist to composition of the papers: The STROBE measures of quality included into this review, show high levels of variability, particularly in the methods and result sections. Few studies explained how study size was determined and how missing data were addressed, they also did not make use of flow diagrams [217] nor did they report category boundaries for continuous variables.

This review sought to consolidate the body of resting state fMRI findings, and was successfully able to combine the findings of rsFC abnormalities in networks and brain regions in stimulant use disorder as discussed below. Moreover we were able to assess the research exploring neural correlates of relapse and subsequently identify markers that could assist in relapse prevention. Although this body of work has been informative in exposing neural adaptations to stimulant use disorder there is still a vast amount of work that is still required before full understanding is achieved.

2.5. Limitations

There are a few important limitations of this review that should be borne in mind. We used three databases to search for studies using rsFC, yet it is difficult to be certain that all possible studies completed have been obtained, especially when considering the file-drawer effect [218] (* see footnote). Second, although we have suggested links between rsFC and executive function, these remain unproven, as the nature of resting state fMRI requires that participants are not engaging in a task assessing neurocognitive function. Future research comparing task based and resting state fMRI in the same sample would be informative in this regard. Third, the different studies used a wide variety of techniques, analyses, enrolment criteria and abstinence cutoffs, these variables may be important confounders, and our interpretation of findings did not formally adjust for them. Fourth, different terms for amphetamine type substances could have been used in the search, although this may not have resulted in the retrieval of additional relevant literature. Fifth, two studies did not define exactly which drugs were included under stimulant use and may have included stimulants that were not part of the inclusion criteria for this review.

Sixth, although the presence of psychiatric comorbidities is highly prevalent in Substance Used Disorders, it is difficult to ascertain if the SUD predates the comorbidity or vice versa. Further depression, as an example, has a major impact on brain function and structure [219], other comorbidities would also affect rsfMRI outcomes, and this is difficult to control for.

Seventh, polysubstance use, including tobacco smoking, alcohol and other narcotics is common amongst stimulant users. Although we endeavoured to list the substances co-used by participants in these studies in appendix T, this table is in no way exhaustive, as these substances were often not reported. Further, due to the amount of missing information on this aspect we did not consider the effects of poly substance use in the discussion. Effects are numerous, including sleep disturbances, depression and anxiety to name but a few. Moreover, withdrawal to any of the substances prior to scanning is a point that deserves consideration, as early withdrawal from stimulants includes sleepiness and dysphoria as well as increased appetite..

A strength of this review is that I was able to provide a systematic and comprehensive summary of the studies of rsFC in stimulant users, and identify methodological shortcomings that can be addressed in future research.

2.6. Conclusion

This systematic review found evidence of a weaker rsFC within the ECN [92, 93, 97, 113] and SN [94, 117, 129], and weaker rsFC between the DMN and SN in stimulant use disorder [94, 113], and between the ECN and DMN [97, 113]. Further there was stronger rsFC within the DMN in SUD when compared with controls [69]. This finding is consistent with the hypothesis of dysfunction in the ECN, and the inability of the SN to toggle between the DMN and ECN in this patient population. The finding of fewer node clusters, greater node degrees [166], as well as weaker clustering coefficient and global efficiency in stimulant users [169] suggests greater energy cost coupled with ineffective resource allocation in the brain. Subjects unable to achieve abstinence in general have stronger rsFC between the subcortical grey matter and cortical regions relative to responders [92, 95, 96] and controls, and this greater rsFC was positively correlated to laboratory measures of impulsivity [96, 102].

Dominance of the reward network over cortical control networks together with increased impulsivity is consistent with the high relapse rate of stimulant misusers. Most studies found greater activation of the reward networks in stimulant misusers [93, 102, 114, 164]. In contrast, there were mixed findings of rsFC within the cortical areas where stronger rsFC was reported for between cortical areas in some instances [146, 163] and weaker rsFC in others [158]. All studies reporting on effects of methylphenidate found that use of it lessened the effect of cocaine in users [95, 100, 101]. Findings from this review are consistent with the hypothesis that stimulant use disorder is characterised by difficulties in establishing stimulant abstinence among those diagnosed with it, with implications of the striatum being physiologically dominant over cortical regions. In this model strong cravings, when paired with ineffective top-down control activation, complicates reaching the goal of sustained abstinence.

The evidence discussed here has abnormal rsFC between and within cortical regions, including the OFC, medial PFC and dlPFC, in stimulant misusers vs controls, while mesocortical structures appear to be less affected. This demonstrated strength of rsFC of brain regions associated with reward compared with weaker rsFC of cortical regions involved in executive function and top down control highlight the challenges people who misuse stimulants face if they wish to become abstinent. Further it presents evidence that certain behavioural deviations displayed by individuals with stimulant use disorder have a strong physiological component. Subsequently the role of executive function in the rehabilitation of people with stimulant use disorder becomes more relevant and will be explored further in the next section.

*The file drawer effect refers to a publication bias that is affected by the results of a study, whereby the authors only choose to publish significant findings or those supporting the hypothesis of the study. Subsequently many studies are placed in the 'file drawer' and not published resulting in a bias in the literature.

Chapter Three: Study Design and Methods

Executive function and sustained attention have been shown to be affected by chronic methamphetamine (MA) misuse [220]. However there is little work on whether Contingency Management (CM) leads to changes in executive function, and resting-state MRI (rsMRI) in people who misuse Methamphetamine. More importantly for this study we aimed to compare responders to treatment with non-responders to treatment. We wanted to determine whether treatment response would be predicted by executive function and whether treatment with CM would result in changes to executive function post- treatment. The research design allowed for evaluation of correlations of behavioural outcomes from the CM intervention with a battery of neuropsychological (NP), demographic and drug use assessments, as well as neuroimaging data, at baseline and post treatment. In this chapter we outline the study design and methods we used to explore our aims.

3.1. Study Design

Contingency Management (CM) involves providing vouchers of escalating value in exchange for urine samples documenting continued methamphetamine abstinence. Eight weeks of urine sample collection three times a week is an intervention in itself, yet we believed that presenting vouchers for consecutive, scheduled negative urine samples was reflective of how CM will be applied in local communities post-trial. The research design allowed for evaluation of associations between behavioural outcomes from the CM intervention with a battery of neuropsychological (NP), demographic and drug use assessments, as well as neuroimaging data, at baseline and post treatment. The longitudinal study design containing repeated measurements allowed us to monitor changes in outcomes at each point in time as a function of treatment. This was a pilot study and as such had no imaging control group. Instead, participants acted as their own controls from baseline to post intervention.

This study gathered resting state functional Magnetic Resonance Imaging (rs-fMRI) and neuropsychological data on active MA users in the Western Cape (WC) undergoing an 8 week CM intervention. The study design includes both pre- and post-intervention data to evaluate correlates of behavioural outcomes (see figure 1 and 2). Initially we proposed to use a variety of screening tests including the scores obtained from the Wechsler Abbreviated Scale of Intelligence (WASI), the Structured Clinical Interview for the DSM-5 (SCID) to define methamphetamine addiction and to ascertain comorbidities as well as demographic details supplied by the participants. We used the Montreal Cognitive Appraisal (MoCA) to assess cognitive ability and the Childhood Trauma Questionnaire (CTQ) to determine traumas suffered as a child and their possible correlation with outcomes. Further we assessed addiction severity using the Addiction Severity Index (ASI) as well as severity of depression using the Revised Hamilton Rating Scale for Depression (RHRSD). We utilised the Stroop Word Task (Stroop) and the Trail Making Task (TMT-B minus A) as primary measures of executive function pre-

and post-intervention. We supplemented this with the Continuous Performance Task (CPT) as a measure of selective attention necessary in executive function.

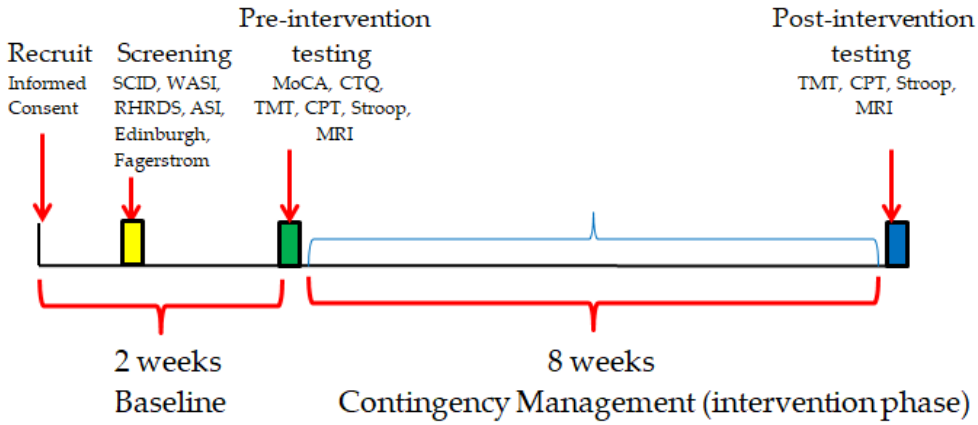

Figure 1: Study design for MA group

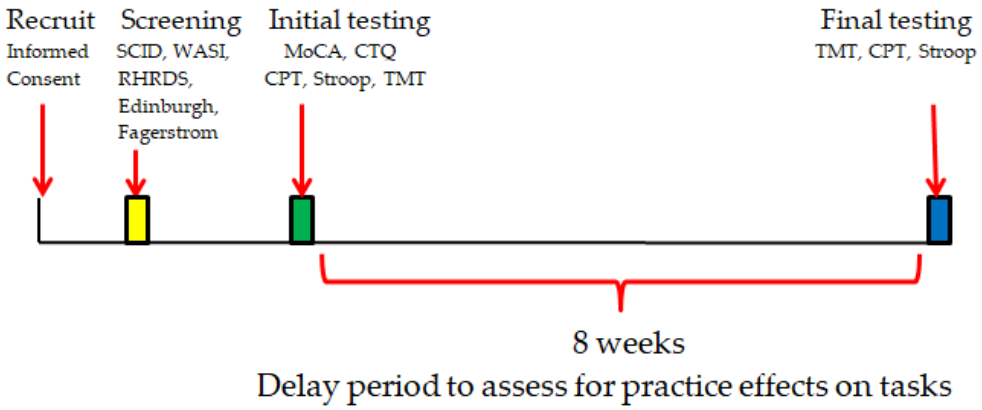

Figure 2: Study design for HC group

Participants were required to undergo a 2 week baseline period in which time they needed to provide one positive urine sample (this was not communicated to the candidates for ethical reasons) to document recent use of MA. The baseline period of 2 weeks provided time for the candidate to obtain a negative urine sample before MRI testing and allowed for them to display commitment to the study. Once the 2 week baseline period was complete, the participants started the 8- week trial.

3.2. Methods

Participants acted as their own controls from baseline to post intervention. CM has shown promise in the treatment of substance use disorders in high income countries [221], yet little is known about CM outcomes when implemented as treatment for MA in South Africa. Successful adherence in the trial was measured post-trial using a treatment effectiveness score (TES); the number of MA- negative samples provided out of 24 possible (range 0-24) [222].

3.2.1. Treatment Cohort

3.2.1.1. Inclusion Criteria:

Drug related criteria: Regular, current users of MA (as determined by one or more positive tests for drug urine in the screening stage). MA use disorder as determined by the DSM-5. Secondary drug use was allowed for nicotine, methaqualone and/ or cannabis only. MA related comorbidities were accepted as determined by the SCID interview, including depression, anxiety and mild psychosis.

Demographic criteria: If the candidate was not first language English then the Informed Consent procedure was explained to them in Afrikaans, with their signature only being added once they were fully briefed and admitted full understanding. There was no need to translate the informed consent into Xhosa or another South African language as all participants were either first language English or Afrikaans. Participants were between the ages of 18 and 45, with no comorbidities bar ASPD and substance use disorder. All candidates were right-handed to ensure consistency in MRI analysis.

We accepted participants with IQ points of 60 and above, compared with the conventional cut-off of 70 in US studies, to account for cultural bias in IQ assessment, the low SES of the sample and global inequity [223-225]. Moreover, this is consistent with the South African national IQ (using an IQ tests normed to a developing nation population) average of 77 [226] and the standard deviation for IQ tests being 15. IQ was estimated using the WASI subtest. The effectiveness of the WASI was compared by van Wyhe et al. using a sample of mixed race ancestry South African adolescents and comparing their results with an American normative sample [225]. The South African sample scores were significantly lower than their American counterparts [225], as the WASI is a culture-bound test. With regards to the vocabulary section, the South African sample was below the American average score by mean of 18.54, while in the matrix reasoning the mean was 16.95 lower [225]. In the USA 70 IQ points and below marks cognitive impairment and their national average is 98 IQ points [226].

3.2.1.2. Exclusion Criteria:

Drug related criteria: A history of substance dependence of another primary substance, (determined through self-report and urine testing) excluding nicotine, was conducted by a skilled researcher. If a candidate showed that they require a more intensive treatment than an outpatient treatment during screening, they were referred to a suitable establishment.

Physical criteria: Candidates who were HIV positive were excluded due to potential associated inflammatory changes in the brain. HIV status was established through blood testing for HIV after obtaining informed consent for this test. Other exclusion criteria include a physical, psychiatric or neurological illness. Any metal in the candidate's body was also exclusionary, due to the powerful effects of the MRI magnet on metal. These include a metal prosthesis, cardiac pacemaker, and metal clips, pins, plates or bullets in their

body. Other exclusionary factors included claustrophobia and pregnancy as these could affect or be affected by the MRI. If a candidate was unable to attend the regular clinic visits or failed to comply with measures or procedures during the study, they were excluded from the study. Finally candidates were asked if they had had a traumatic head injury (any loss of consciousness), which was grounds for exclusion, as it may impact on brain function and structure.

3.2.2. Recruitment

We screened a total of 269 potential CM participants and recruited 33 study participants of which 28 were used in the final analyses (see figure 3).

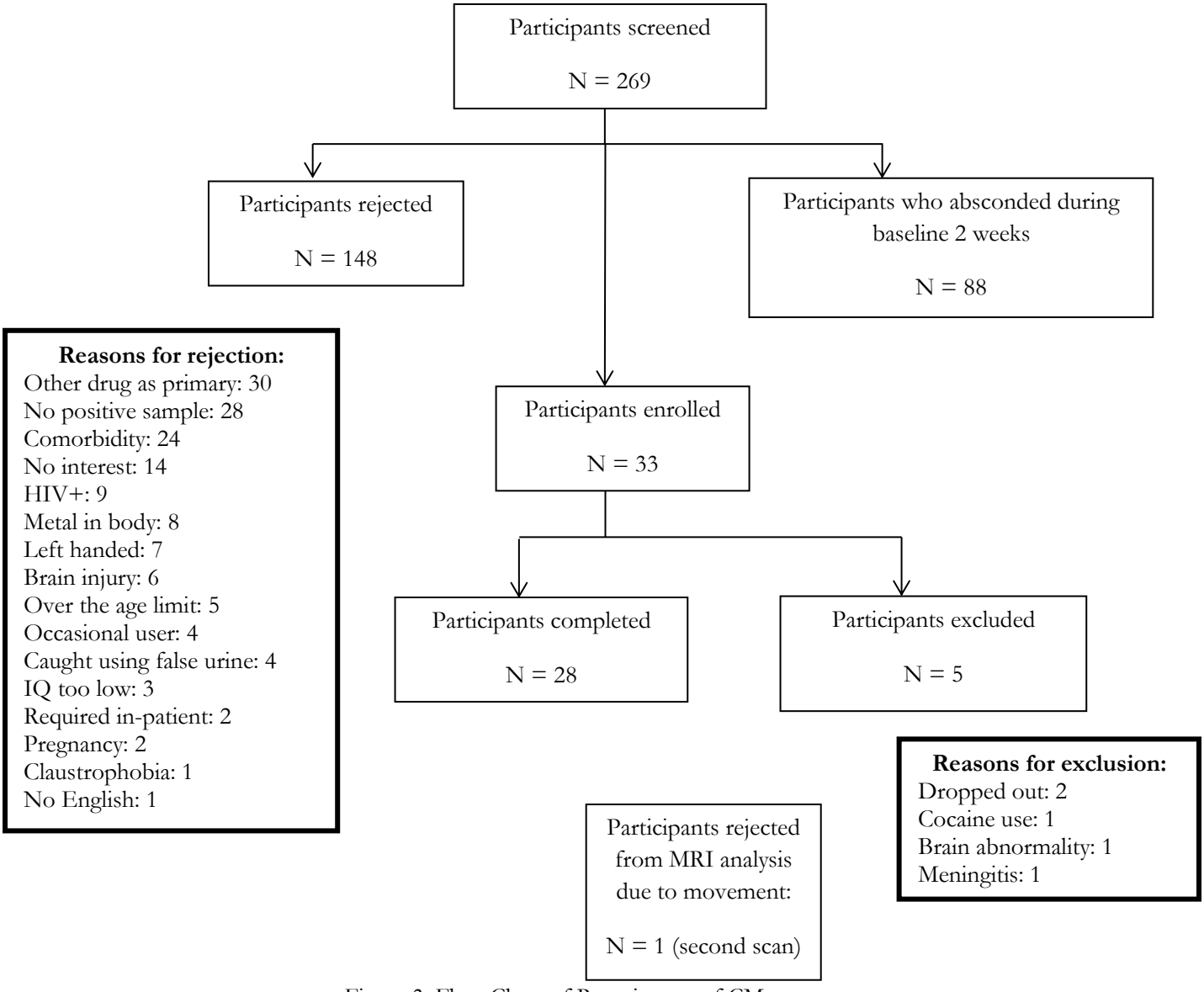

Figure 3: Flow Chart of Recruitment of CM group

3.2.2. Healthy Controls

Controls were matched via interview on gender, race, age (18-22, 23-27, 28-32, 33-37, 38-42 and 43-45 years), education (4-7, 8-10, 10-12, 13+ formal years education), IQ (60-69, 70-79, 80-89, 90-99, 100-109, 110-119, 120-129 IQ points), Fagerstrom score (0-2 (low), 3-4 (low-moderate), 5-7 (moderate) and 8+ (high)), number of cigarettes smoked daily (0-4, 5-10, 11-15, 16-20, 20+ cigarettes smoked daily) and household income (ZAR 0, ZAR 1-5.000, ZAR 5.001-25.000, ZAR 25.000-100.000, ZAR 100.001+). A match was required for all of these variables although we used frequency matching as opposed to individual matching. Controls were sourced from parent groups (support groups for parents with children who are abusing narcotics), clinics, night shelters, and communities where the MA participants reside, as well as by newspaper advertisement and flyers. Controls were excluded if they had a traumatic brain injury, were HIV positive, had ever abused any narcotics at all (excluding nicotine and caffeine) and if they were left handed (the keyboard used in the neuropsychological task testing was for right handers). We screened 149 healthy control subjects of which 24 were recruited and 21 completed (see figure 4). The healthy control group was added to create a normative measure for all neurocognitive tests and to control for practice effects on these tests.

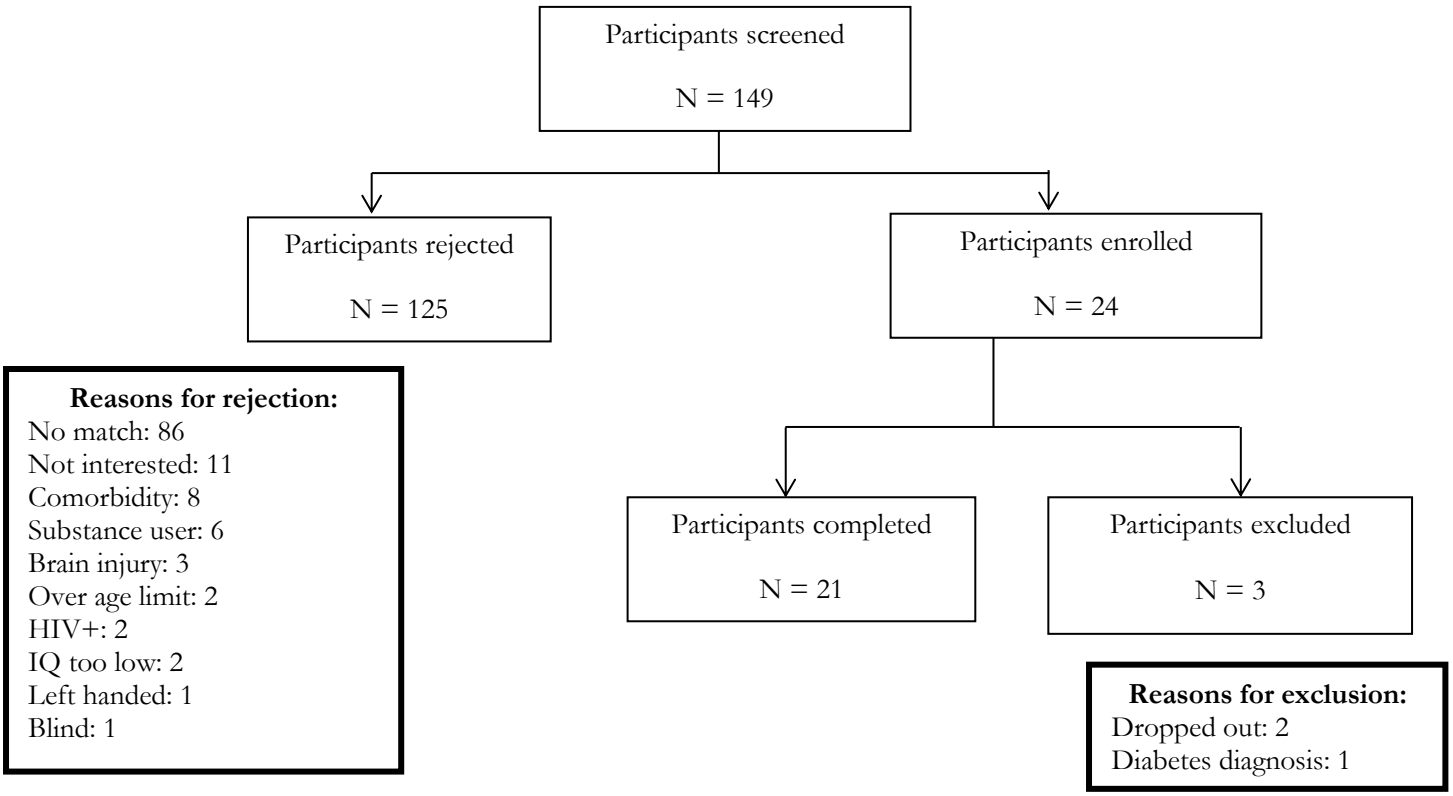

Figure 4: Flow Chart of Recruitment of HC group

3.2.3. Recruitment:

We recruited participants from various outpatient rehabilitation clinics (Cape town Drug Counselling Centre, SANCA and Saltan Bahu) and Night Shelters (the Haven) for homeless people in the Western Cape (WC) as well as via newspaper advertisement and handing out of flyers. This ensured that our

sample was reflective of the MA using population of the WC. Two of the rehabilitation clinics used Motivational Interviewing as their form of therapy, another used Group Therapy and the participants recruited from Night Shelters, newspaper advertisements and brochures were not receiving any formal therapy.

Participants referred from local drug rehabilitation centres underwent a pre-screening procedure with their therapist using the inclusion criteria as outlined in the brochure. Further, we placed posters and brochures in the clinics (Appendix J and K respectively). Interested candidates completed the Information sheet, and the therapist forwarded this, as well as the individual's contact details to the researchers, who then contacted the candidate and scheduled an in-person meeting.

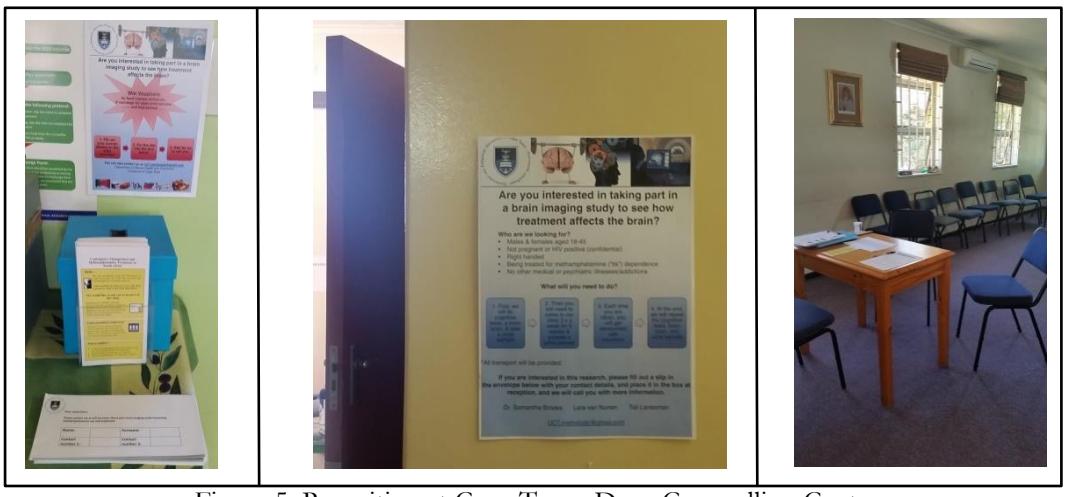

Figure 5: Recruiting at Cape Town Drug Counselling Centre
(left- recruitment box, centre- poster on display, right- recruitment area)

3.2.4. Informed consent

Participants were required to sign a letter of consent before commencing on the trial (Appendix B). MA users also complete an HIV testing informed consent form (Appendix B), which confirmed their willingness to undergo an HIV test before the beginning of the trial (MA group only). A trained researcher met with the candidates either at Groote Schuur Hospital (GSH) or at their treatment centre in a room separate from the one in which they received treatment, to outline their potential involvement in the trial. Requirements, procedures, confidentiality, risks and benefits were all explained in detail and all questions the candidate had were answered as thoroughly as possible. Throughout, the researcher took measures not to coerce the candidate. Once the informed consent forms were signed to show understanding and commitment a copy was given to the candidate. If the candidate chose not to participate in the study, the researcher explained that this would, in no way affect their treatment at their clinic. Participants were informed that participation in the study was entirely voluntary, and that they may withdraw from the study at any time without disclosing a reason. Each participant was given a study number to mask their identity. Informed consent forms were stored confidentially, and an electronic

record was kept to indicate that signed consent had been given.

3.2.5. Vouchers

This is a pilot study based on the 2005 study conducted by Shoptaw et al. (2005) in Los Angeles [29], USA. The amount of R4800 was decided upon as it is a direct conversion of the monetary incentive used in this former American study. Shoptaw et al. (2005) was able to show that Contingency Management actually resulted in savings over the long term, due to reductions of the financial burden of therapy in methamphetamine abuse [29].

We provided vouchers of increasing value for provision of consecutive urine samples documenting MA abstinence. All vouchers had a monetary value and could be exchanged for prosocial goods at local supermarkets. The value of the CM schedule is a direct computation of a prior CM schedule conducted in Los Angeles USA, exchanging ZAR10 to the dollar [30]. The initial urine sample that was negative for MA metabolites (post baseline) was worth ZAR25 and successive negative samples increased in value by ZAR12.50. For every three successive negative samples, a ZAR100 bonus reward was provided. Thus, the total possible to earn in this CM schedule assuming that the participant was present to provide every scheduled urine sample, and of which all were negative for MA metabolites, was ZAR4 850. The amount of R4800 is a direct conversion of the monetary incentive used by Shoptaw et al. (2006). Shoptaw et al (2006) was able to show that Contingency Management actually resulted in saving over the long term due to reductions of the financial burden of therapy in MUD [227].

Samples provided that were positive for MA or amphetamine metabolite or that were missing (e.g., participant failed to attend clinic) received no value. As soon as a drug negative urine sample was received, following a drug-positive or a missing sample, the participant earned ZAR25 in value as they returned to the initial starting point. To sustain motivation to remain in the program, a "rapid reset" rule was put in place so that participants returned to their prior place in the escalating schedule once they provided three consecutive MA-negative urine samples post a MA-positive or missing sample.

As part of the study design, we made every attempt to minimise the risk of false urine samples and voucher exchange. Vouchers were delivered via text message on participants' mobile phone and were only redeemable for prosocial goods at local supermarkets on presentation (cigarettes, alcohol and gift cards were prohibited for purchase). Further to this the participant needed to present the receipt of purchase to the researcher once the voucher has been redeemed. We believed these measures limited the improper cashing in of benefits. Although there is no guarantee that our cohort did not find a way around our measures, we believe that this study is representative of a real life scenario.

Weeks	Monday	Thursday	Friday	Bonus	Totals
1	R 25.00	R 37.50	R 50.00	R100	R 212.50
2	R 62.50	R 75.00	R 87.50	R100	R 325.00
3	R100.00	R112.50	R125.00	R100	R 437.50
4	R137.50	R150.00	R162.50	R100	R 550.00
5	R175.00	R187.50	R200.00	R100	R 662.50
6	R212.50	R225.00	R237.50	R100	R 775.00
7	R250.00	R262.50	R275.00	R100	R 887.50
8	R287.50	R300.00	R312.50	R100	R1,000.00
Grand Total					**R4,850.00**

Table 1: Voucher schedule

Healthy Controls were given a voucher for ZAR150 for the first and final meeting, but not for the screening interview. Further they were not required to provide receipts of purchases made with the voucher.

3.2.6. Drug testing

As MA and amphetamine take about three days to clear from the body, urine samples were scheduled 3 times a week to verify drug abstinence. Because of the short period of the CM program no excused absences were allowed for missed clinic visits, and missed appointments were interpreted as positive urine samples. Urine was collected 3 times a week and at each visit the temperature and validity of the urine was tested. Twice a week only d-amphetamine and methamphetamine were tested and once a week a full drug test was conducted including barbiturates, opioids, cocaine and THC. Tests were provided by CLIAwaived Inc.

The participants were escorted to the bathroom and asked to provide a urine sample in the cup as shown in diagram 5. This cup does not require observation of the provision of the urine sample as it has a temperature strip attached to it (CLIAwaived Inc., San Diego, California, United States). The temperature strip was very sensitive and the sample needed to fall within the correct range in order to be considered fresh, (32^{0} to 38^{0}C and 90^{0} to 100^{0}F).

To further determine if the urine was a valid sample we used UrineCheck 7 (figure 6), which tests for 6 components of urine as well as the potential addition of bleach to the sample (CLIAwaived Inc., San Diego, California, United States). It provides a normal and abnormal range for easy assay. Moreover, the pH section is able to ascertain if acidic components like vinegar had been added, and the oxidant section can detect the addition of oxidants such as hydrogen peroxide which may have been added to affect the drug test outcome (figure 7).

Figure 6: Urine cup

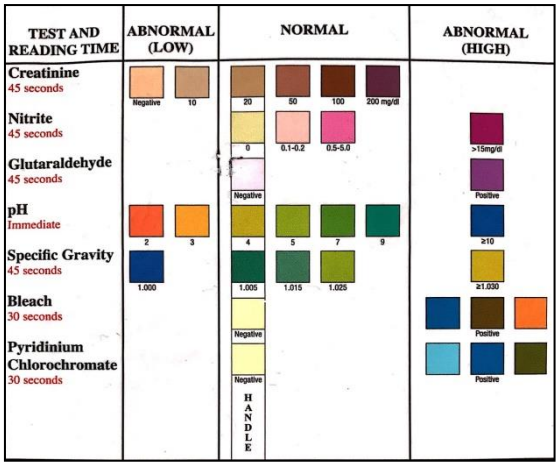

Figure 7: UrineCheck7 tests schedule

Once the validity of the urine sample was established we subjected it to drug testing. The Instant-View was used for each urine sample and detects the presence of D-amphetamine (a metabolite of methamphetamine), this allowed us to detect use of the drug 4 days after its use (CLIAwaived Inc., San Diego, California, United States), which was helpful if monitoring occurred early on a Friday morning and late on a Monday afternoon. There were potentially two marker lines on the tests, C and T. If a C line developed then the amount of amphetamine in the urine is above 300ng/ml, but if both C and T line develop (even if T was faint) it was considered below 300ng/ml which was interpreted as a negative reading. The test strip for Methamphetamine (CLIAwaived Inc., San Diego, California, United States) was also used three times weekly and had a 500ng/ml cut off level, and its sensitivity allows for detection of trace amounts of the drug. Finally once a week a full drug panel screening was conducted. This test was conducted on a random day during the week so that the participant was unaware of when the testing would occur, and indicated whether opioids, cocaine and tetrahydrocannabinol (THC) were present in the sample.

3.2.7. Treatment Effectiveness Score (TES)

Abstinence outcomes for the CM project was measured using the Treatment Effectiveness Score (TES): average number of MA-free urine specimens provided during the 8 week treatment period [222]. This score ranges from 0-24. By counting only negative samples, positive or missing samples receive no value. Total earnings were computed to create a monetary TES. The statistical computing platform R 3.3.1(9,9) was used to conduct all statistical tests [222].

3.2.8. Screening Tools

3.2.8.1. Structured Clinical Interview for DSM-5 (SCID-5)

The SCID-I is a comprehensive structured interview used to identify Axis 1 disorders (major mental disorders), while the SCID-II is used to determine axis-II disorders (personality disorders) as determined by the DSM-5. The SCID was administered by a trained mental health professional [228], and is an

accepted means for identifying eligible participants for research studies and can be customised to suit the needs of the research study [228]. This study utilised the full SCID-5 for research to identify comorbidities and eligibility. Candidates that presented with any primary disorder, asides from antisocial personality disorder (which is a common comorbidity associated with SUD in low SES demographics [229]), were deemed ineligible for the study and were referred to the appropriate health professional for assistance.

3.2.8.2. Wechsler Abbreviated Scale of Intelligence (WASI)

The WASI, was conducted during screening and is a nationally standardised, fast and reliable measure for intelligence that is easy to use in a research setting [230, 231]. We used the vocabulary and matrix reasoning subtests, which allows one to estimate general intellectual ability and can be utilised on participants between 6-89 years of age, inclusive [230, 231]. The WASI provides the Full Scale IQ score (FSIQ score) and is comparable to the WAIS-II [230].

There was some concern regarding the Vocabulary section of the WASI as our research population largely speaks English as a second language [232], and as a result the South African version of the WASI (SA-WASI) was used (an approved version that had been translated into Afrikaans) as well as the original English version. The SA-WASI is the result of the collaboration of multiple people (including psychologists, anthropologists, experts and scientists), universities and Pearson (the international publisher) [233]. The test has been shown to provide excellent reliability that matches that of the UK and US WAIS vocabulary, as well as presenting with the same factor and theoretical structure [233]. It is, however, important to note that the population studied is unlikely to excel in the vocabulary section, not as a reflection of low IQ, but rather as a result of poor exposure to the words presented in the WASI. Participants were asked if they were aware if they are colour-blind, and this was taken into consideration with regards to the matrix section of the WASI.

3.2.8.3. Edinburgh Handedness

This quick, simple assessment determines the handedness of a participant, and is ideal for screening procedures [234] (Appendix C). It has been found to be a reliable and valid means of determining handedness [235] and has been used as the gold standard for some 40 years in research. Determining handedness is important in MRI studies, as it has been shown to be linked to hemispheric language dominance [236]. It plays a role when analysing brains within a cohort to ensure they are structurally comparable, and this includes the location of the language centre.

3.2.8.4. Fagerstrom Test for Nicotine Dependence (FTND)

This test contains 6 questions to evaluate dependence, compulsion and average quantity of cigarettes smoked in a day [237] (Appendix D). Each question is awarded a score, and the higher the totalled score, the

greater the severity of dependence on nicotine [237]. The FTND has been validated and found to be an acceptable means of assessing dependence in a research setting [238].

Determining dependence on nicotine is important as there are multiple knock-on effects associated with smoking. Although cigarette smoking affects the body in multiple ways, nicotine directly affect the brain, which results in elevated release of dopamine (DA) and epinephrine in the blood which acts as a central nervous system stimulant [239] as well as increased activation of acetylcholine receptors.

3.2.8.5. Addiction Severity Index (ASI)

A qualified researcher conducted the Addiction Severity Index (ASI) interview with the MA participants. The ASI (see Appendix E) is a validated interview that explores various factors (work and family stability, current use, and problems with the law to name but a few) that may exacerbate or impact a current drug misuser negatively over a 30 day period [240]. These factors include medical history, employment assets and status, drug and alcohol misuse, legal status, family and social support and psychiatric status [240]. The ASI was calculated using the composite score, which was developed from a selection of questions within each subsection over a 30 day period [241]. These scores have been shown to be the most consistent approximation of current problem status, with higher scores reflecting greater severity in that subsection [241].

3.2.8.6. Childhood Trauma Questionnaire (CTQ)

The participants also completed a Childhood Trauma Questionnaire (CTQ) (see Appendix F) a reliable self-report questionnaire comprising of 28 questions to assess trauma's that the participant may have experienced as a child (25 questions for actual assessment and 3 as validation of questionnaire responses) [242]. The CTQ has 5 subsections each with a high score of 25 (cumulative total of 125) and a further score for denial so as to accommodate participants who have not reflected on childhood traumas [243]. Each subsection also has a none to severe range (table 1) for determining the gravity of abuse or neglect [243].

Subsection	None	Low	Moderate	Severe
Emotional abuse	5-8	9-12	13-15	16+
Emotional neglect	5-9	10-14	15-17	18+
Physical abuse	5-7	8-9	10-12	13+
Physical neglect	5-7	8-9	10-12	13+
Sexual abuse	5	6-7	8-12	13+

Table 2: comparative range for the CTQ

3.2.8.7. Montreal Cognitive Assessment (MoCA)

To assess cognitive ability of the groups, a qualified researcher conducted the MoCA neurocognitive battery with each participant. The MoCA [244] is a validated and reliable mini battery generally used as a

brief screening instrument that samples behaviour across eight performance areas (visiospatial, naming, memory, attention, language, abstraction, orientation, delayed recall) (Appendix G). The MoCA has sufficient sensitivity to diagnose organically based disorders, has been shown to have psychometric validity and can be used as a classifier of disorders [245, 246] as well as a quantitative task to assess cognitive ability [246]. Moreover, the MoCA total score has been determined to be an accurate reflection of likely treatment adherence [247]. Copersino et al. (2012) determined that if an individual was classified as cognitively impaired on the MoCA (score of 22 or less), they were significantly less likely than higher scoring subjects to attend all the sessions [247]. Although the highest score obtainable is 30, if a participant has less than 12 years of education they are awarded a bonus point, shifting to total possible score to 31. A normal score (no cognitive impairment) is 26 or above for an American audience, but South Africa has a uniquely diversified population, with noteworthy differences in culture, language, economic stability and education [248]. When investigating a healthy cohort of mixed race ancestry participants, scores were correlated with gender, age and education as well as presenting with a strong correlation with scores on the *Repeatable Battery* for the Assessment of Neuropsychological Status (RBANS) [249]. The international standard of a total score of >26 indicating no cognitive impairment did not prove effective for this cohort, rather Beath et al. (2018) found high sensitivity with low specificity at a score of 26, yet when the cut off was lowered to 23 sensitivity and specificity were more balanced [249]. Subsequently we took >23 to indicate cognitive health for this cohort.

3.2.8.8. Revised Hamilton Rating Scale for Depression (RHRSD)

This questionnaire is a reliable and widely used tool to determine depression severity [250] and is quickly completed in five to ten minutes (Appendix H). It provides six outcomes including RHRSD total score, which indicates whether an individual is not depressed, has minor depression, major depression or severe depression [250]. Other outcomes include whether the individual is having a major depressive episode, has melancholic features, as well as a tricyclic antidepressant responsiveness cluster score (TCAR) value which presents the likelihood that the individual will respond to antidepressant medication [250]. Finally the questionnaire provides a validity score and an inconsistency index which exposes whether the individual has consistently provided responses that correlate with each other and whether the test results are likely to be an accurate reflection of the individuals current state [250]. Although we used the total RHRSD score to determine depression (≤ 10 = not depressed, 11-16 = minor depression, 17-25 = major depression, ≥ 26 = severe depression), we did explore the other results to determine if the participant needed to be referred for treatment.

3.2.9. Neurocognitive Battery

Pre and post testing took place at GSH. The tasks selected for analysis were chosen as they reflect measurable executive function changes from pre to post treatment.

3.2.9.1. Controls for reliability

Repeated measures can be subject to practice effects, these can include improved processing speed as well as accuracy [251]. Previous research has revealed that practice effects are negatively correlated with age and positively correlated with IQ [251]. We included a control group to assist in determining the extent of practice effects.

3.2.10. Magnetic Resonance Imaging (MRI)

The MRI was conducted at the Cape University Body Imaging Centre (CUBIC) at GSH at baseline and post treatment for the MA group only. A T1 structural scan was conducted as well as a resting-state functional MRI (rsfMRI) scan. More in-depth details regarding the scan set up, pre-processing and analysis are provided in Chapter 5.

3.2.11. Potential Risks

Researchers always attended the scans. After each separate scan sequence the researcher spoke to the participant through a two-way system to ensure that the person was comfortable. During the scan, the participants was given a panic button (and taught how to use it before the scan commenced) in case they felt uncomfortable in the scanner. Researchers were present at all times during neuropsychological tasks, which were conducted before and after the scan. If, in the rare event abnormal neuroanatomical signs were detected in the participant by the radiologist, the researcher informed the participant and gave detailed information on next steps to follow.

There is minimal risk in completion of neurocognitive tests and questionnaires. Participants may have felt fatigued during testing; however breaks were given as needed. If participants became overly emotional or uncomfortable during the clinical interview, they were informed that they did not need to answer questions they do not wish to, and participants were referred for counselling at the Department of Psychiatry at UCT if necessary.

For participants whose methamphetamine addiction was too severe to be adequately treated on an outpatient basis, a rescue protocol was implemented that involved providing referrals to available inpatient or residential resources and actively facilitating the participant in seeking care at these facilities.

3.2.12. Potential benefits

Contingency management has been shown to effectively reduce relapse rates in those with substance abuse disorder. Knowledge gained from this project has enabled better understanding of the neurobiological mechanisms of MA dependence, and the mechanisms of a treatment procedure that is

currently offering effective results. Using a state of the art brain imaging paradigms with discrete hypotheses about how fronto-striatal regions are affected by MA abuse and the conditioning of impulse control using CM, we have significantly strengthened our understanding of the neural mechanisms of treatment for substance abuse disorders.

The knowledge gained is similarly important in that it builds a productive and successful link between established investigative teams at UCLA with an excellent and growing team at UCT.

3.2.13. Ethical Considerations

This NIH funded study (Grant number: 1 R21 DA040492-01) has completed all relevant ethic procedures and has been approved by the University of Cape Town (UCT) Health Research Ethics Council (HREC) (463/2015) as well as the University of California Los Angeles (UCLA) Ethics Board (IRB#15-000965-CR-00001). It has also been listed with the Clinical trials database.

3.2.14. Conflict of Interest

No staff member received any incentives for recruiting candidates or for any other purpose directly related to this study. Furthermore, no staff involved in this study had any proprietary interests that may have conflicted with the study.

3.2.15. Confidentiality

In the informed consent the participants were assured of confidentiality. They were assigned a study number and their identity was withheld from any person not directly involved in the study. Further, they were advised that any information they were to impart to us would not be shared with another party bar if they informed us they were going to cause harm to either their selves or to others. If this situation were to arise, they were informed that the correct authorities who were in a position to assist with the complexities that the participant was experiencing would be notified, and the participant referred for counselling.

3.2.16. Data Safety and Monitoring

All participant data was stored in a locked cabinet in a locked room, and no one aside from research staff had access to this data. Further all records (bar the initial intake records) had only the participant number as an identifier. Once the study recruitment phase was completed then all records were de-identified, whereby any item of paper that had an identifying feature (name, address, phone number, signature or initial) of the participant was given a new number known only to the project manager. This new number was linked by a computer generated excel spreadsheet to their study participant numbers and was again only known by the project manager. Once this was completed then all names and identifying information

bar signatures and initials was blacked out. All study data was then sent through for scanning to DVD and then shredded with the exception of the informed consent forms, which were kept if needed for ethical consideration at a later date.

Our next chapter explores the neurocognitive tasks in determining the effectiveness of executive function in the CM program. Initially this chapter seeks to establish any intrinsic differences between those that respond to treatment and those that did not at baseline, and then to determine any functional or structural alterations post treatment to determine any changes that may have occurred in executive function as a result of abstinence obtained due to CM treatment.

Chapter Four:
Executive Function and Contingency Management in Methamphetamine Use Disorder

4.1. Introduction

The aims of this chapter are 1) to establish whether treatment response can be predicted by executive function impairment at base-line and then 2) to establish whether treatment resulted in executive function improvements as established when comparing baseline with post-trial task results.

Executive function has been defined as a process whereby an individual identifies the appropriate actions required to achieve a goal, and subsequently utilises a collection of processes and cognitive control that directs behaviour and maintains focus to actualise the goal [252]. Executive function spans a combination of cognitive functions, including working memory, inhibitory control, cognitive flexibility, planning, reasoning and problem solving [253]. For sake of thoroughness we included the function of focus or sustained attention [253], which is often impaired in individuals who misuse methamphetamine (MA) [254].

In the treatment of MA Use Disorder the goal is the establishment of abstinence, whereas reduction of MA use is also highly prized. In a South African context achieving these objectives require overcoming the abundant availability of the drug and helping the patient achieve control over cue driven cravings for it. Such action requires the engagement of inhibitory control to overcome the propensity to make disadvantageous choices in favour of immediately reinforcing drug use. Individuals who meet the diagnostic criteria for MA Dependence exhibit executive dysfunction [255] with impairments in cognitive flexibility, working memory and decision-making [256]. It stands to reason, that if an individual presents with superior executive function at the start of rehabilitation (in this instance CM), that they may have an advantage in terms of attention on goals and inhibition of more instant reward desires over those that have inferior executive function.

Life in Cape Town, for those with a lower socioeconomic status and a greater propensity to misuse MA is not particularly supportive given the recent history of the country. Cape Town has been labelled as the 13th most dangerous city globally [257], with an exceptionally high rate of threat in lower socioeconomic communities as a consequence of gangsterism. Moreover, these previously disadvantaged communities still feel the knock on effect of South Africa's apartheid system. Notably, Substance Use Disorder (SUD) is higher in areas with residential instability[229]. Indeed, residential instability has also been associated with a greater frequency of diagnoses of antisocial personality disorder [229]. Adults who had previously experienced suppression in their socioeconomic environment in childhood, also are more susceptible to neurological disorders in adulthood [22]. Further, low SES demographics are associated with high school dropout rates, and places individuals at a disadvantage for academic achievement [258]. It stands to reason

that treatment which helps to build executive control may help individuals with MA Use Disorder to exercise inhibitory control in overcoming addiction.

In this study we hypothesised that assessment of executive function at baseline would allow us to differentiate between those that respond to an 8-week CM program for MA Use Disorder and those that do not respond. Initially we administered the Montreal Cognitive Assessment (MoCA), a brief cognitive battery assessment of cognitive impairments. We then administered three tasks of executive function: the Stroop Word Task (Stroop) and the Trail Making Task (TMT), followed by the task testing attention, the Conner's Continuous Performance Task (CPT). The Stroop measures the ability to ignore distractors while focusing attention on relevant information, the TMT measures visual attention and capacity for task-switching, and the CPT measures capacity for sustained attention.

4.2. Research Questions

Predictors of treatment

Does executive function at baseline predict outcomes for contingency management treatment in MA dependent participants?

Hypothesis 1

Predictors of treatment response will be superior inhibitory control quantified by the Stroop word task, better visual attention and task switching skills determined by the Trail Making Task at baseline in responders to treatment when compared with non-responders. Further responders to treatment will display better sustained and selective attention than non-responders, as measured by the Conner's' Continuous Performance Task, with performance more similar to that observed in the healthy controls. Moreover, participants with MA Use Disorder will perform more poorly at baseline when compared with healthy controls.

Differences between sessions (pre- to post-treatment)

Do responders to treatment show greater improvement in executive function tasks over time when compared with those who do not respond to treatment?

Hypothesis 2

Performance post-intervention in the Trail Making Task, Stroop Word Task and Conner's' Continuous Performance Task will differ, relative to baseline performance in those that do not respond to treatment compared with those that do respond to treatment and healthy controls.

4.3. Methods

The participants were given a two week period prior to commencing the CM trial to maximise their options of earning vouchers. Moreover, we required that our participants were not under the influence of MA during their scan or for their neuropsych tests, so we required 2 drug negative urine tests prior to scanning and testing. Our MA participants were subdivided into two groups, responders and non-responders. A non-responder was an individual who presented a drug positive urine test at any stage in the CM trial, or who failed to attend their scheduled testing meeting. If the participant failed to attend, then an hour's grace was given whilst trying to contact the person. If contact could be made then the meeting was rescheduled to such a time as the MA or its metabolites would still be in their urine should they have used. If this meeting was not attended then the participant fell into the non-responder group. We did not test for blood alcohol, but did test for THC, opioids, cocaine, barbiturates and d-amphetamine. Intoxication was measured purely through urine tests.

4.3.1. Clinical measures

Both the treatment group and healthy controls (HC) partook in a neurocognitive battery conducted at Groote Schuur Hospital (GSH) at baseline and after the CM intervention 8-weeks later. For the MA group this signified the end of the trial while the HC group received no treatment. Clear instructions were given to the participant as well as a practice session to document understanding. The order in which the tasks were conducted, had a rotating sequence, both within and between subjects, at baseline and post intervention, and a schedule of rotation (which was counter-balanced) was created to control this. Computer tasks were punctuated with paper tasks and breaks were given to prevent fatigue. Further, if the participant smoked cigarettes they were offered breaks to have a cigarette to prevent effects of nicotine withdrawal. The computer tasks were conducted in a quiet room and were presented on a Dell Intel core i3 laptop, Vostro 2520 with a 15 inch screen using E-Prime software version 2.0.

4.3.2. Neurocognitive Battery

Executive Function Tasks

4.3.2.1. Trail Making Tasks (TMT) (versions AB and BC)

The TMT (figure 1 and Appendix I) is a measure of executive function, with time taken to completion assessing speed of cognitive processing [259]. It can be used to test for brain damage and cognitive dysfunction [260], and has been successfully validated in a South African context [261]. It consists of two parts, part A in which the participant is required to draw lines which connect numbers in sequence and part B where numbers and letters alternate (figure 1). The ability of the participant to successfully complete part B requires the ability to switch between the recognition of numbers and letters and the ability to assess the page as a whole [259]. The TMT-A test visuoperceptual abilities and speed of information processing,

while the TMT-B tests working memory and task-switching ability and has been shown to be reflective of executive control [259]. The time a participant takes to complete the task is compared with the documented norms, with ability to complete the task within a specific time frame indicating current state of executive functioning. Time of completion was compared initially against the documented norms for the tasks (documented norms are as follows: TMT-A average 29 sec, deficient >78 sec, TMT-B average 75 sec, deficient >273 sec) [262] and then against healthy controls.

We used the difference score to analyse the TMT (B minus A) [259]. This score has been shown to be highly correlated with intelligence and sensitive to cognitive impairment [263]. Importantly the TMT difference scores controls for the effects of attention, which was assessed in this study with the CPT. The difference score has also been shown to be correlated with age, education and memory, but to a lesser extent than cognitive impairment [263]. Due to the small sample size of this cohort, and risk of multiple comparisons inflating the occurrence of false positives, we selected demographic covariates based on what was found to be significantly different between groups across the entire sample as potential predictors of treatment outcomes for CM. These included years of education and income. In addition, we also included sex as a covariate [75] as it has previously been shown to have significant effect on outcomes in Contingency Management. We also ran correlation tests comparing speed of completion with accuracy on the TMT to see if one aspect affects the other. Finally, we assessed performance at baseline and at termination of the trial to determine if there were any improvements in executive functioning.

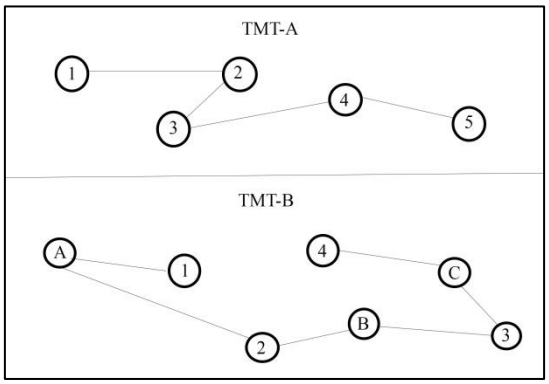

Figure 1: Parts A and B

4.3.2.2. Stroop-RT Task

This is a classic test of inhibitory control that requires suppression of a pre-potent response [264]. Although the validity of this task has not been formally tested in a South African context it has been successfully utilised in multiple South African studies [265-268]. The Stroop has been shown to be affected by demographics and cultural differences [269] as well as home language; those with English as first language are more challenged than others, because of a greater tendency to read the word [270]. Overseeing the ink colour has been shown to affect reaction time; with longer reaction times for English speaking groups [270].

Subsequently we checked the association of home language with accuracy and reaction time in addition to years of education, income and sex in our analysis.

In this task a word appears on the screen that is either congruent or incongruent with its ink colour (red, green or blue) (figure 2). The probes were 10 mm in height and appeared in the middle of the screen for 150 ms with 3 varying inter-trial intervals of 1850 ms, 1900 ms and 1950 ms. There were 69% congruent and 31% incongruent trials. The participant was instructed to respond to the ink colour of the word and not the meaning of the word by pressing on one of three arrows on the keyboard with their right hand (index, middle and ring fingers); the left arrow corresponded to red, the downward arrow to green and the right arrow to blue. They were encouraged to respond as quickly as possible while still being as accurate as possible. Congruent or incongruent trials were fully randomized as outlined in by Holmes/ Pizzagalli in their paper of 2007 [271]. The reading of an incongruent word becomes difficult in literate individuals as the reading response is automated, and this needs to be inhibited in order to provide a correct response in the task [264].

The default behaviour to read a word results in a faster reaction time with congruent words than incongruent ones [272]. The main brain areas involved in processing of the Stroop task are the ACC (selection of appropriate responses) and the dlPFC (memory and executive functions and creation of rules for functioning, countering biases and irrelevant information) [273-275]. The Stroop Colour Task used in this study was programmed by Holmes/ Pizzagalli [271]. The task is used to assess conflict monitoring; whereby performance post conflicting target and post error as well as the results of the conflict trial itself may be indicative of activation of cognitive resources and associated behavioural adjustments [271]. Historically MA dependent subjects appear to have deficits in this task [276]. Accordingly we investigated whether individuals with chronic MA Use Disorder who are treatment seeking would have altered performance when compared with HC's pre- and post- treatment.

In a study conducted over a 4-week period where participants practiced the Stroop task 3 times weekly and were tested 5 times within this period, the results showed that practice effects were measurable [277]. Practice effects have also been measured 1 year and then again at 3 years after initially completing the task [278]. The follow up sessions reflected improved performance and the durability of practice effects in this task [278]. Accordingly, in order to control for practice effects, all outcomes in the treatment group were compared with a well-matched group of healthy control participants (see Chapter 3 for matching criterion). Nevertheless, the control group did not participate in the intervention itself, a fact that needs to be borne in mind that when interpreting the results. Further we compared groups on RT and accuracy, with accuracy being measured as a percentage with a higher score indicating greater percentage accuracy, and also calculated the correlation between these outcomes within each group, to determine whether group differences could be understood in terms of speed-accuracy trade-offs.

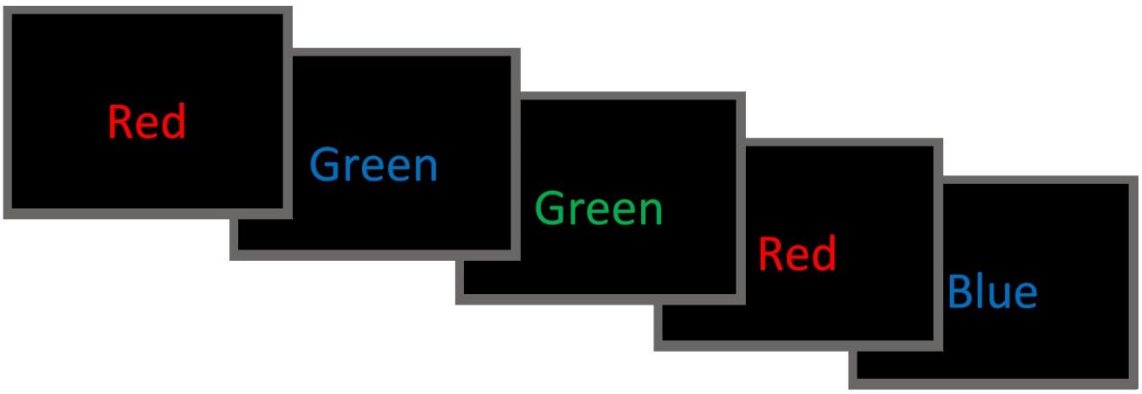

Figure 2: Stroop congruent and incongruent targets

4.3.2.3. Conner's'-Continuous Performance Task (CPT)

The CPT measures an individual's sustained and selective attention, neurocognitive functions that are sensitive to brain damage and dysfunction are reproducible in multiple populations [279]. The CPT involves frontal, temporal and parietal cortices, the limbic system, basal ganglia, thalamus and frontal lobes [279]. The task can be used to assess 4 aspects of attention, that being inattention, impulsivity, sustained attention and vigilance[280].

Participants completed the task on a screen that was a uniform black with a randomised series of letters 15 mm in height, being presented in white on the screen in 3 different speed staircases, of 750 ms, 1750 ms and 3750 ms, with a randomised duration of presentation (figure3). Using the index finger of their right hand, a participant was required to respond to every letter that presented on the screen excluding the "X", by pressing a downward arrow on the keyboard. Reaction times (RT) as well as number of omissions and commissions were recorded.

Performance in this task is influenced by environmental factors (noise, distracting stimuli, time of day etc.) as well as individual characteristics (gender, personality, age etc.) [280-282]. In this study the task was completed in a quiet room with little or no distractions. We gave the participant a break before the task was conducted to ensure they were feeling rested prior to commencing. Improved performance in this task has been observed with the presence of stimulants [279], but all participant's in this study had undergone a baseline period of abstinence at session one to rule out acute effects of drug. The potential influence of sex, income and years of education on the test outcomes was assessed. The CPT appears to provide a reliable pre to post intervention measure of attention with minimal practice effects [283]. Measures of attention including omission errors and relative accuracy are frequently used in scoring of the CPT together with RT, while commission errors are used more commonly as a measure of impulse control [282, 284-286]. We assessed results from the CPT pre- and post- intervention, assessing accuracy and RT (and

correlations between the two) to assess if there was any changed in attention between groups and between sessions.

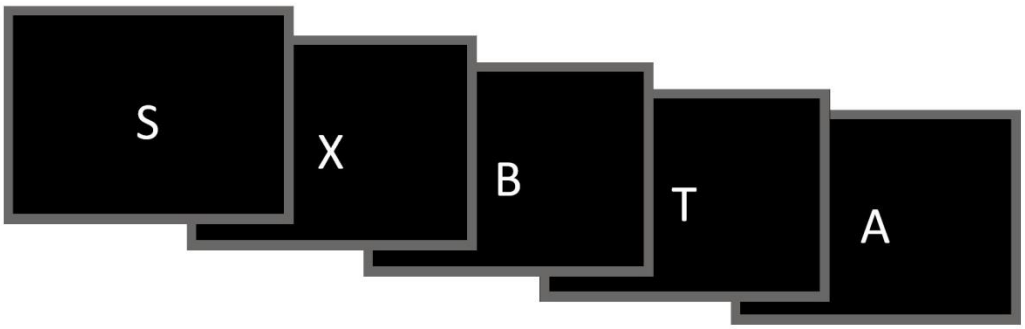

Figure 3: CPT targets and non-target

4.3.3. Data Analysis

The MA group was categorised into responders and non-responders and were compared with matched controls. Performance on tasks in session one was interpreted as a measure of potential responsiveness to treatment, while changes in performance between session 1 and session 2, was interpreted as an indicator of learning and improvement in brain function as a result of continued abstinence. Performance of participants who relapsed was compared with those who remained abstinent using a linear regression model. The pre-post research design allowed for a measure of changes in outcomes as a function of treatment. Regarding executive functioning we assessed the accuracy and reaction time (RT) of response to the computer tasks. In addition the number of errors and time taken for completion of the TMT was recorded.

For each hypothesis, the outcome of the neurocognitive tasks was tested to determine if the data were normally distributed. Following this we tested for homoscedasticity (equality of variances). If the data did not meet assumptions of normality and homoscedascity we proceeded with non-parametric testing, otherwise parametric tests were employed. To test for homoscedacity we used the lmtest package in R, and more specifically we used the studentised version or Koenker-Bassett test which is more effective with small sample sizes (appendix M table 4.30 to 4.44) [287]. The results of these tests are only described below in instances in which assumptions were violated.

Parametric analysis (used whenever the task outcomes were normally distributed) involved a multivariate linear regression analysis (provided by the nlme package in R). Reaction time (RT) in milliseconds and accuracy (addition of omissions and commissions) were tested as outcomes in models comparing MA groups to healthy controls and to determine if the covariates are confounding the outcomes. Alpha was set at $p<0.05$ as all research questions were prospectively framed. The βcoefficient was determined using the lm.beta package. To prevent Type I errors we used post hoc contrast tests (lsmeans package, tukey

function), and no family-wise alpha correction was conducted in order to minimise making Type II errors, i.e., accepting the null hypothesis when in fact; there is evidence for group differences. Moreover, a conservative approach was taken in the selection of covariates to include in the linear models, in order to conserve the power of the statistical tests at an alpha of 0.05. The effects of potential confounding variables were assessed by including variables that were statistically significantly associated with both task performance and treatment response (at alpha < 0.1). The suitable independent variables were identified using the Pearson correlation output from the pairs panel function (provided by the psych package in R) for clinical (RHRSD) and nuisance variables (years of education, sex, and income). Where the distribution of the covariate data was clearly not normally distributed non-parametric tests such as the Wilcoxon rank sum test implemented in the coin package in R were also conducted.

To test for differences between responders and non-responders on covariates, we used a two tailed t-test, (except were data was not-normally distributed), and to test for differences between the two MA groups and healthy controls we used a linear regression model. After the initial linear regression (on tests of the hypotheses without covariates added) with healthy controls as the intercept, each variable was visualised in a residuals plot to determine variability and any potential bias that the model was not accounting for. To determine if variability between groups in outcomes and residuals were equivalent, a Levene's test for homogeneity (provided by the car package in R) was conducted. All of the results were checked for outliers using Cook's Distance (using the base package in R) (Appendix L tables and figures 4.1 to 4.28). Scores identified as outliers (>4/n) were removed from subsequent analysis in order to minimise the risk of committing a type I error, on the condition that the variable in question correlated significantly with task performance [288]. Where data on task performance was not normally distributed we conducted a Kruskal Wallis Test to compare groups, and where data was normally distributed we ran an ANOVA to compare groups. We used a standard t-test to test for differences between the MA group as a whole and healthy controls.

To control for multiple corrections, we used a Benjamini Hochberg adjustment with a false discovery rate of 0.05. This correction was applied to account for tests of six outcomes for hypothesis one (accuracy and time to completion in the TMT and accuracy and RT in the Stroop and CPT). For hypothesis two we applied the Benjamini Hochberg adjustment for tests of three outcomes: accuracy on the Stroop, CPT accuracy as well as time to completion on the TMT. Further, we performed a contrast test on all linear regression results (provided by the lsmeans package in R) to minimise the chance of committing Type I errors. If any of the variables identified as potential confounders (years of education, household income and sex) significantly predicted outcome in the linear model in addition to group, then it was used as a covariate in the statistical analysis. Lastly, we calculated a Cohen's d, with bootstrapping applied to estimate variability of these statistics (the bootstrapping employed 1000 iterations as recommended for precise estimation of 90-95 percent confidence intervals [289]). The statistical computing platform R 3.3.1

was used to conduct all quantitative analyses reported in this chapter [290]. Reaction time and accuracy for each task was correlated as a measure of task efficiency.

4.3.4. Exploratory Analyses

Exploratory tests were completed to provide direction in planning hypotheses for subsequent studies. Accordingly adjustments for multiple comparisons are less critical and were not applied to these analyses [291].

4.3.4.1. The Stroop Word Task

The most common outcomes analysed on the Stroop task are the Stroop effect and RT (both post error and post conflict trials) [276, 292, 293]. We utilised the Stroop effect and the Laming/ Rabbitt effect as model outcomes. Omission RT's (RT = 0) were removed so as not to skew the data.

The Stroop effect, which is a measure of conflict evoked by the task [294], is calculated as follows:

> [RT: Incongruent – RT: Congruent] as well as [Accuracy: Congruent – Accuracy: Incongruent], whereby an elevated score reflects greater cognitive challenge[294].

The Laming/ Rabbitt effect, which is a measure of behavioural change post error [295, 296], is calculated as follows:

> [RT: Post incorrect trial – RT: Post correct trial] and [Accuracy: Post incorrect trial – Accuracy: Post correct trial], with elevated scores indicating greater cognitive challenge [295, 296].

4.3.4.2. Conner's'-Continuous Performance Task (CPT)

Specific analyses were conducted using the guidelines laid out in the Multi-Health Systems (MHS) brochure for the Conner's-CPT [297, 298]. Initially we assessed the task for inattentiveness using the following outcomes as summarized in table 2:

1. d Prime or detectability (d'): discrimination between non-targets – X and other letters (correct vs incorrect hits), whereby a higher d' value indicates increased sensitivity to the signal [299]. A target is any letter excluding X (324/360), while a non-target is only X (36/360). The false alarm rate is the ratio of incorrect-responses to the total number of non-target stimuli, and was calculated as (number of cancelled non-target stimuli + commission errors)/320. Cancellation of non-target stimuli refers to the number of times that a participant responded within 150ms of presentation of the non-target [299]. Further, d'Prime uses the hit rate in its formula, which compares the number of accurate responses to the total number of times a target was presented (formula 1) [299]; and false alarm rate or ratio of mis-responses to the total number of non-target stimuli (formula 2) [299]. d Prime is the z-transform of hit rate minus false alarm (formula 3).

Formula 1 (Hit Rate) (324 – number of cancelled targets – omission errors) -360, total correct hits/324; (correct hits-0.5)/324
Formula 2 (False Alarm) (number of cancelled non-target stimuli + commission errors) – 360; 0.5/ 360
Formula 3 (d') d' = z(Hit Rate) – z(False Alarm)

Table 2: d Prime formulas

2. Omissions or missed targets (number of omissions)
3. Commissions which is the incorrect response to a letter that is not an X
4. Hit reaction time (HRT): response speed (average speed of correct responses for the task)
5. Variability of HRT Standard Deviation (variability between segments of the task in relation to their own standard error) (standard deviation of the 18 standard deviations). A high variability reflects increased inconsistency in response speed

Next we explored sustained attention by dividing the task into four blocks to assess when (if at all) fatigue or boredom set in. Here we assessed:

1. HRT block change: changes in response speed across blocks of trials
2. Omissions by block: divided into 4 blocks
3. Commissions by block: divided into 4 blocks

4.3.5. Change Scores

Improvement in executive function as measured by the TMT, and Stroop across sessions was assessed to determine the effect of treatment on outcomes. In addition, changes in attention were assessed by score across sessions in the CPT.

Accuracy scores from all tasks were compared and the mean accuracy was calculated. If a lower score represented improved performance then the score was multiplied by -1, ensuring that higher scores can be interpreted as better performance for each of the tasks [82]. Cohen's d was calculated for each task, using total task/ total accuracy score for each individual, then subtracting the mean of the control group for session one and dividing by the standard deviation of the control group for session one. This was conducted for session one and session two separately and provided us with the difference between the

mean of the control group and each individual participant in standard deviation points [82] with an positive score showing superior performance compared to the control group. We then determined a change score, whereby outcomes from session one were subtracted from outcomes for session two, with an elevated score representing improvement. Next a Kruskal-Wallis test (provided by the coin package in R) was conducted on the change score [82], and finally the standardised means of the change score from all four tasks cumulatively was subject to a Cohen's d test (using the bootES package in R) to determine a composite change score [82].

4.3.7. Controls for reliability

Repeated administration of the same task can produce practice effects, including improved processing speed as well as accuracy [251]. Type I errors (false positive finding) are more likely when the sample size is small. To minimise the risk of committing Type I errors we conducted a contrast test on all linear regressions and a Benjamini Hochberg test for multiple corrections. Although we did not control for practice effects directly we did compare all group differences by collapsing performance across sessions then comparing the three different groups.

4.4. Results

4.4.1. Demographics

Of the 33 participants recruited for the MA group, two absconded during the trial and did not complete post-trial assessments, another revealed prior cocaine misuse after trial completion, one presented with an arachnoid cyst on the brain and one disclosed severe meningitis as a young child after trial completion. Data for the tasks of the participants with medical components (meningitis as a child/ subarachnoid cyst) and for the one with cocaine abuse were removed from analysis of the tasks, but were included for demographic purposes. Data for the two participants who absconded were included in baseline analyses and were classed as non-responders, as missed appointments were taken to mean a drug-positive urine sample by study design. Two of the 24 healthy controls absconded during the 8 week time period and one was diagnosed with diabetes post trial. Consequently data for the two that absconded was used in baseline data, but the participant with a medical component was used for demographic analysis only. At session two, four individuals tested positive for MA, which is something that should be considered when interpreting the results.

A rigorous matching approach was applied for this study using frequency matching, whereby controls and MA groups were matched at recruitment for sex, age (groups were 12-22, 23-27, 28-32, 33-37, 38-42 and 43-45 years of age), race, IQ (groups were 60-69, 70-79, 80-89, 90-99, 100-109 and 110-19 IQ points), household income (groups were R0, R1 – R5000, R5001 – R25 000), R25 000 – R100 000 or R100 000 +), education (groups were 4-7, 8-10, 10-12 and 13+ formal years of education), Fagerström scores (groups were 0-2 (low), 3-4 (low-moderate), 5-7 (moderate), 8+ (high)), and number of cigarettes smoked (groups were 0-4, 5-10, 11-15, 16-20 and 20+ daily) (table 3). Even though there was no statistical difference between groups with regards to cigarette smoking, it should be noted that 91% of the MA group smoked cigarettes, while only 67% of controls smoked ($p = 0.05+$). Groups differed in number of years of education with controls having significantly greater number of years than the MA group ($p = 0.01$). They also differed in depression status at start of trial with the MA group being significantly more depressed ($p = 0.01$) as measured by the Revised Hamilton Rating Scale for Depression (RHRSD) (table 3). Lastly 7 of the 28 participants in the MA group met the diagnostic criteria for anti-social personality disorder (ASPD) as measured by the Structured Clinical Interview for DSM 5 (SCID-5), while none of the controls met these criteria. These data are summarized in table 3.

	MA group (n = 30)	**Healthy Controls (n = 23)**	**Wilcoxon Rank Sum**
Age (M ± SD)	34.33 ± 6.18	35.17 ± 7.03	p = 0.58
Race (n)	28 MRA, 2 African descendent	21 MRA, 2 African descendent	
Education (M ± SD)	10.87 ± 2.86	12.48 ± 1.44	p = 0.01**

WASI IQ (M ± SD)	84.73 ± 15.71	83.48 ± 15.80	p = 0.78
RHRSD (M ± SD)	26.57 ± 23.17	5.39 ± 6.05	p = 0.01****
Income (monthly) (M ± SD)	R16250.0 ± R15725.97	R 20108.7 ± R17113.89	p = 0.21
Employment at time of trial (%)	9%	58%	
Cigarettes smoked daily (M ± SD)	8.30 ± 7.55	6.91 ± 6.72	p = 0.57
ASPD (n)	7	0	p = 0.01**
Previous attempts to stop (M ± SD)	4.1 ± 6.24	-	-
Grams per day (M ± SD)	0.99 ± 0.59	-	-
Years of misuse (M ± SD)	11.27 ±4.22	-	-
Amount spent monthly (M ± SD)	R1830.83 ± R1377.00	-	-
Age initiated (M ± SD)	22.47 ± 6.26	-	-
Number of urine tests drug free before scan (M ± SD)	3.8 ± 2.88	-	-
Number of psychotic symptoms (M ± SD)	4.3 ± 3.54	-	-

Table 3: Demographics between MA and control groups (M = means, MRA = Mixed race ancestry, RHRSH = Revised Hamilton Rating Scale for Depression, SD – standard deviation, stars (*) flag levels of significance with one star denoting a p value below 0.05, two if the p value is less than 0.01 and three for less that p = 0.001)

A participant was classified as a non-responder if he or she used MA during the trial or if he or she did not arrive for their scheduled urine testing even after researchers attempted to contact them for at least one hour after their appointment was missed with no success. Responders tended at trend level to having significantly more years of education than non-responders (p = 0.06) (table 4), but non-responders had significantly greater household income than responders (p = 0.01). Non-responders also tended at trend level to spend more on MA at baseline (p = 0.06), and had fewer MA-negative urine tests during the screening period (p = 0.01) than responders.

	Responders (n = 17)	**Non-Responders (n = 13)**	**Wilcoxon Rank Sum**
Age (M ± SD)	33.77 ±6.69	35.2 ± 5.62	p = 0.71
Race (n)	15 MRA, 2 African	13 MRA	

	descent		
Education (M ± SD)	11.82 ± 2.92	9.62 ± 2.33	p = 0.06+
WASI IQ (M ± SD)	86.18 ± 18.36	82.85 ± 11.82	p = 0.71
RHRSD (M ± SD)	28.71 ± 24.17	23.77 ± 21.45	p = 0.72
Household income (M ± SD)	R9117.65 ± R11522.44	R25576.92 ± R15947.63	p = 0.01**
Median IQR	R10000 R7500	R37500 R27500	
Employment at time of trial (%)	16%	0%	
Cigarettes smoked daily (M ± SD)	6.82 ± 6.02	10.23 ± 9.08	p = 0.49
ASPD (n)	3	4	
Previous attempts to stop (M ± SD)	3.71 ± 5.93	4.62 ± 6.83	p = 0.20
Grams per day (M ± SD)	0.87 ± 0.49	1.14 ± 0.69	p = 0.37
Years of misuse (M ± SD)	10.00 ± 4.10	12.92 ± 3.45	p = 0.12
Amount spent monthly (M ± SD)	R1399.71 ± R1112.38	R2394.62 ± R1524.73	p = 0.06+
Age initiated (M ± SD)	22.71 ± 6.26	22.15 ± 6.50	p = 0.95
Number of urine tests drug free before scan (M ± SD)	4.944 ± 3.33	2.31 ±1.03	p = 0.01**
Number of psychotic symptoms (M ± SD)	3.88 ± 3.55	4.85 ± 3.58	p = 0.38

Table 4: Demographics within the MA group (M = means, MRA = Mixed race ancestry, RHRSD = Revised Hamilton Rating Scale for Depression, SD = standard deviation, stars (*) flag levels of significance with one star denoting a p value below 0.05 and two if the p value is less than 0.01)

The three groups did not differ significantly in the MoCA total score (table 4.45 in Appendix N). The group mean of each of the groups (responders, non-responders and controls) was above the South African norm of 23 as determined by Beath and colleagues (2018) [300] and there was no significant difference in the proportion of each group that was impaired (responders = 6%, non-responders = 23% and controls = 14%, p = 0.40). Failure to detect a difference here possibly reflects inadequate power.

On analysing the ASI responders and non-responders did not differ in overall addiction severity or any subsection (table 4.46 Appendix N).

There were no significant differences on the CTQ within and between groups exception for significantly greater emotional abuse in the MA group (p = 0.02) (table 4.47 appendix N).

When looking at the normative ranges (none, low, moderate and severe abuse or neglect), non-responders reported more emotional and sexual abuse than responders (as reflected by a moderate normative range only), although this rating did not reach statistical significance (table 4.48 appendix N). Both MA groups reported moderate physical abuse when using the moderate normative range, but this effect also did not reach statistical significance.

4.4.2. Neurocognitive Battery

We hypothesise that responders to treatment will demonstrate better cognitive processing and executive function quantified by the Trail Making Task, superior inhibitory control determined by the Stroop word task and superior sustained and selective attention as measured by the Conner's' Continuous Performance Task at baseline when compared with non-responders to treatment. Moreover, we predict that participants with methamphetamine dependence will perform more poorly at baseline when compared with healthy controls.

Table 5 and 6 shown the results for the main outcomes on all of the tasks, with table 5 comparing the two MA groups to healthy controls and table 6 comparing the combined MA group to healthy controls.

Results – All Group Effects

Trail Making Task B minus A – Accuracy - Parametric **Responders to treatment n = 17, Non-responders to treatment n = 13, healthy controls = n = 23**									
	Mean & Std. dev.	**Linear regression group effects**	**F statistic and DF**	**β coefficient, Model fit**	**Contrast (post hoc) test t**	**Contrast (post hoc) test p**	**Cohens d**	**CI range**	**Benjamini Hochberg**
MA Group	6.73 ± 6.53	p = 0.69	0.12	0.62					0.69
Responders to treatment	6.24 ± 6.82	Sex p = 0.66	2 and 50	0.84	R-NR -0.48	0.88	0.18	[-0.54, 1.05]	
Non-responders to treatment	7.39 ±5.78	Education p = 0.96			R-C 0.18	0.98	0.06	[-0.55, 0.72]	
Healthy controls	6.61 ± 6.31	Income p = 0.26			NR-C -0.35	0.94	-0.12	[-0.77, 0.58]	
Non-parametric **Trail Making Task B minus A – Time to Completion**									
	Median	**IQR**			**Kruskal Wallis**			**Benjamini Hochberg**	
MA Group	85.94	67.40 - 137.86			p = 0.09+			0.35	
Responders to treatment	79.85	60.90 - 90.00							
Non-responders to treatment	136.94	89.32 - 184.69							
Healthy controls	65.00	53.35 - 181.05							
Stroop Word Task – Accuracy – Non-parametric **Responders to treatment n = 17, Non-responders to treatment n = 12, healthy controls = n = 22**									
	Median	**IQR**			**Kruskal Wallis**			**Benjamini Hochberg**	
MA Group	89.36	74.16 - 92.4			p = 0.01**			0.02*	
Responders to treatment	84.80	74.16 - 90.88							
Non-responders to treatment	91.64	75.51 - 97.14							
Healthy controls	95.44	90.88 - 95.44							
Stroop Word Task – Reaction Time - Parametric									
	Mean & Std. dev.	**Linear regression group effects**	**F statistic and DF**	**β coefficient, Model fit**	**Contrast (post hoc) test t**	**Contrast (post hoc) test p**	**Cohens d**	**CI range**	**Benjamini Hochberg**
MA Group	734.48 ± 142.85	p = 0.69	0.38	7.91					0.69
Responders to treatment	745.41 ± 107.68	Language p = 0.03*	2 and 49	0.69	R-NR 0.68	0.78	-0.18	[-1.02, 0.72]	
Non-responders to treatment	718.99 ± 186.09	Sex p = 0.79			R-C -0.99	0.59	-0.32	[-0.98, 0.32]	
Healthy controls	707.81 ± 123.38	Education p = 0.53			NR-C -0.16	0.99	-0.08	[-1.02, 0.73]	
		Income p = 0.79							
Conner's Continuous Performance Task – Accuracy – Non-parametric **Responders to treatment n = 17, Non-responders to treatment n = 13, healthy controls = n = 23**									
	Median	**IQR**			**Kruskal Wallis**			**Benjamini Hochberg**	
MA Group	16.50	11.00 - 26.75			p = 0.04*			0.21	
Responders to treatment	15.00	10.00 - 24.00							

Non-responders to treatment	18.00	14.00 - 33.00							
Healthy controls	11.00	7.50 - 17.50							
Conner's Continuous Performance Task – Reaction Time - Parametric									
	Mean & Std. dev.	**Linear regression group effects**	**F statistic and DF**	**β coefficient, Model fit**	**Contrast (post hoc) test t**	**Contrast (post hoc) test p**	**Cohens d**	**CI range**	**Benjamini Hochberg**
MA Group	365.98 ± 61.81	p = 0.24	0.95	-19.46					0.69
Responders to treatment	367.51 ± 56.75	Sex p = 0.29	2 and 50	0.39	R-NR 0.87	0.66	-0.06	[-0.81, 0.70]	
Non-responders to treatment	363.98 ± 70.22	Education p = 0.51			R – C 1.44	0.33	0.36	[-0.54, 0.92]	
Healthy controls	391.50 ± 71.99	Income p = 0.03*			NR-C 2.26	0.07	0.39	[-0.35, 1.05]	

Table 5: significance for all tasks (Benjamini Hochberg n = 6 tests, TMT accuracy, speed of completion, Stroop accuracy and reaction time, CPT accuracy & reaction time), (R = Responders to treatment, NR = Non-responders to treatment, C = Healthy controls)

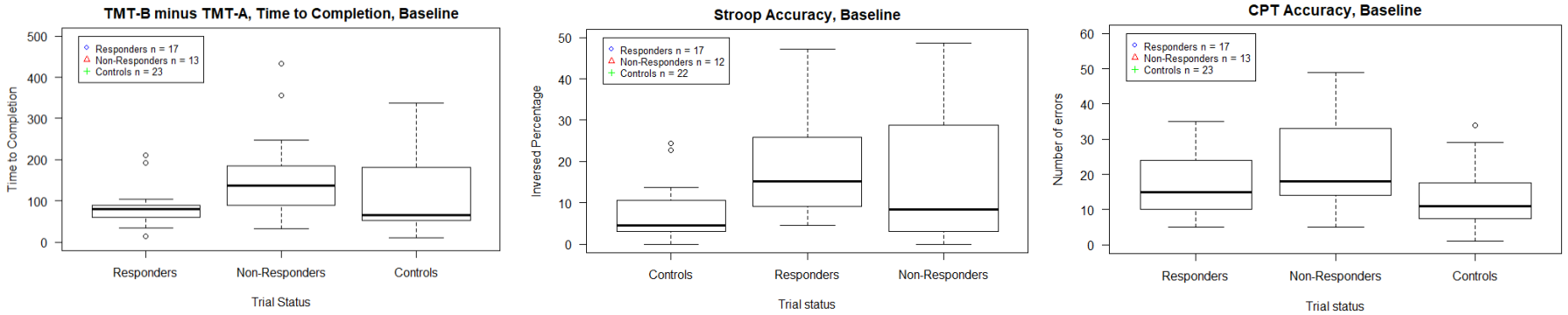

Figure 4: baseline results, with Stroop showing significance post correction for multiple comparisons.

Healthy controls were more accurate than the MA group in accuracy on both the Stroop and CPT (table 6).

Task	P value	T statistic	Degrees of freedom
Trail Making Task B minus A Accuracy	0.95	0.07	46.66
Trail Making Task B minus A Time to Completion	0.80	0.26	46.38

Stroop Accuracy	0.01**	3.26	44.04
Stroop Reaction Time	0.47	-0.72	49.60
Connors Continuous Performance Task Accuracy	0.01*	2.59	50.17
Connors Continuous Performance Task Reaction Time	0.18	-1.36	43.38

Table 6: two tailed t test comparing the MA group with the healthy controls

Trail Making Task B minus A

Methamphetamine group vs Controls

Accuracy in the Trail Making Task (Trail Making Task-B minus Task-A), which is a measure of executive function minus attention, revealed no significant difference between any of the three groups at baseline (see table 5). When looking at time taken to complete the task, we see that non-responders were slower than responders and controls (p = 0.01* table 7), although this only trended to significance after correction for multiple comparisons (0.07+).

Responders to treatment vs Non-responders to treatment

The Trail Making Task data did not meet the assumptions of normality and homoscedascity, and subsequently non-parametric tests were conducted. When comparing responders to treatment with non-responders to treatment there was no statistical significance (table 7). However, responders to treatment reacted significantly faster than non-responders to treatment with Trail Making Task-B minus Trail Making Task-A (p = 0.01). Although this effect did not survive correction for multiple comparisons, a trend towards significance was still apparent (0.07+).

Results – MA Group Effects

Trail Making Task B minus A – Accuracy **Responders to treatment n = 17, Non-responders to treatment n = 13**	
Wilcox Rank Sum	**Benjamini Hochberg**
p = 0.73	0.88
Trail Making Task B minus A – Time to completion **Responders to treatment n = 17, Non-responders to treatment n = 13**	
Wilcox Rank Sum	**Benjamini Hochberg**
p = 0.01*	0.07+

Table 7: – significance for the TMT B minus A, responders to treatment vs non-responders to treatment (Benjamini Hochberg n = 6 tests, TMT accuracy, speed of completion)

Exploring the time to completion in the Trail Making Task in more detail

Published international normative times to completion for Trail Making Task-A is 29 seconds with >78 seconds showing deficiency and Trail Making Task-B is 75 seconds with >273 seconds showing deficiency [259]. At baseline responders to treatment were faster than non-responders to treatment in the Trail Making Task-A and in the Trail Making Task-B (table 8), the speed of responders to treatment in the Trail Making Task-A was similar to that of controls, while the responders to treatment were faster than controls in Trail Making Task-B. Based on the large variance (which is observed for Task B), there

may be outlying cases who demonstrate more impaired executive function in the non-responders to treatment (see table 9 and figure5).

	Trail Making Task-A Session 1	**Trail Making Task-B Session 1**
Responders (M-SD)	44.99± 22.78	127.48 ± 56.39
Non-responders to treatment (M-SD)	53.91 ± 24.23	221.62 ± 115.17
Controls (M-SD)	44.96 ± 15.59	164.618 ± 98.41

Table 8: Speed to completion for Trail Making Task subtasks (M = mean, SD, standard deviation)

Cooks Distance – outliers	**Study Status**	**Value**	**Time taken**
CM215 (22 on bar graph)	Non-Responder	0.10	467.50 sec
HC099 (45 on bar graph)	Healthy Control/ absconder	0.07	366.30 sec
HC117 (50 on bar graph)	Healthy control	0.09	377.00 sec

Table 9: Outliers details for baseline TMT-B time taken to complete

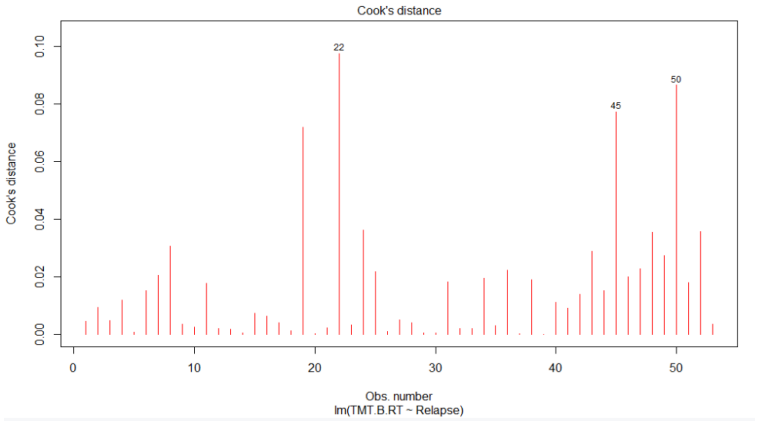

Figure 5: Graph of outliers for baseline TMT-B time taken to complete

Reaction time and accuracy was correlated which reflects efficiency.

The relationship of Accuracy and Time (time to completion and reaction time)

Accuracy and speed in the Trail Making Task (Trail Making Task-B minus Task-A) were significantly negatively correlated at baseline; time to completion was positively correlated with accuracy. This effect is driven by task performance in the control participants, who showed greater efficiency when compared with the MA group (table 9).

Stroop Word Task

Methamphetamine group vs Controls

One MA participant was removed from the Stroop analysis as he was colour-blind and one of the healthy controls' final test results was corrupted, rendering it unusable. Stroop accuracy was calculated as a percentage, with a high percentage reflecting greater accuracy. The data did not meet assumptions of normality and homoscedascity (Appendix M). The non-parametric testing comparing the means of the three groups presented with statistical significance ($p = 0.01$) (table 5 and figure 4) showing controls to outperform both MA groups, which held for correction of multiple comparisons ($p = 0.02$). With regards to reaction time there was no statistical significant differences between groups.

Responders to treatment vs Non-responders to treatment

With regards to the Stroop, non-responders to treatment and responders to treatment did not differ significantly at baseline (table 10)..

Results – MA Group Effects

Stroop Word Task – Accuracy **Responders to treatment n = 17, Non-responders to treatment n = 12**	
Wilcox Rank Sum	**Benjamini Hochberg**
p = 0.23	0.88
Stroop Word Task – Reaction Time **Responders to treatment n = 17, Non-responders to treatment n = 12**	
T Test	**Benjamini Hochberg**
p = 0.66	0.88

Table 10: – significance for the Stroop, responders to treatment vs non-responders to treatment (Benjamini Hochberg n = 6 tests, Stroop accuracy and reaction time)

The relationship of Accuracy and Time (time to completion and reaction time)

When looking at the Stroop at baseline, reaction time and accuracy were significantly negatively correlated ($p = 0.05$) (table 12). Yet, when each group was explored individually there was no significant association between these outcomes. Nevertheless it appears that the overall effect was driven by the faster reaction time and superior accuracy of the healthy controls compared with the MA groups.

Connors Continuous Performance Task

Methamphetamine group vs Controls

Accuracy on the CPT was measured by total number of errors. The data did not meet assumptions of normality and homoscedascity (Appendix M), accordingly non-parametric testing was used. Non-

responders to treatment made the most errors when compared with controls at baseline (p = 0.04) (table 5 and figure 4). This finding did not survived multiple comparisons correction (p = 0.21). Much like the Stroop, there was no statistically significant differences between groups when we explored reaction time.

Responders to treatment vs Non-responders to treatment

In the CPT there was also no statistically significant difference between responders to treatment and non-responders to in accuracy and reaction time (table 11).

Results – MA Group Effects

Conner's Continuous Performance Task – Accuracy **Responders to treatment n = 17, Non-responders to treatment n = 13**	
Wilcox Rank Sum	**Benjamini Hochberg**
p = 0.41	0.88
Conner's Continuous Performance Task – Reaction Tine **Responders to treatment n = 17, Non-responders to treatment n = 13**	
T Test	**Benjamini Hochberg**
p = 0.88	0.88

Table 11: – significance for the TMT B minus A, responders to treatment vs non-responders to treatment (Benjamini Hochberg n = 6 tests, CPT accuracy & reaction time)

The relationship of Accuracy and Time (time to completion and reaction time)

In the CPT, accuracy was significantly positively correlated with reaction time; number of errors decreased with increasing reaction time, which is driven by the control group who demonstrated superior sustained attention to both MA groups (table 12).

Relationship of Tasks Accuracy to Time (time to completion and reaction time)

Trail Making Task B minus A **Responders to treatment n = 17, Non-responders to treatment n = 13, healthy controls = n = 23**			
Session	**Rho**	**R^2**	**P**
Session 1 Controls to MA groups	0.51	0.26	0.01***
Session 1 Responders	0.38	0.14	0.13
Session 1 Non-Responders	0.26	0.07	0.40
Session 1 Controls	0.77	0.59	0.01*****
Stroop Word Task **Responders to treatment n = 17, Non-responders to treatment n = 12, healthy controls = n = 22**			
Session	**Rho**	**R^2**	**P**
Session 1 Controls to MA groups	0.29	0.08	0.05*
Session 1 Responders	0.18	0.03	0.48
Session 1 Non-Responders	0.10	0.01	0.79
Session 1 Controls	0.28	0.08	0.21
Conner's Continuous Performance Task **Responders to treatment n = 17, Non-responders to treatment n = 13, healthy controls = n = 23**			
Session	**Rho**	**R^2**	**P**
Session 1 Controls to MA groups	-0.32	0.10	0.02*
Session 1 Responders	-0.27	0.07	0.31
Session 1 Non-Responders	0.02	0.00	0.95
Session 1 Controls	-0.45	-0.09	0.03*

Table 12: correlation between accuracy and time (stars (*) flag levels of significance with one star denoting a p value below 0.05)

Exploratory Analysis

The exploratory analyses were run on the Stroop Word task, but revealed no statistically significant results at baseline. When exploring the CPT at baseline non-responders to treatment showed significantly worse attention than controls as shown by the exploratory analyses (see table 13, and figure 6).

Inattentiveness

Exploratory Analysis for CPT Inattentiveness

	Responders Means + SD **(n = 17)**	**Non-Responders** Means + SD **(n = 13)**	**Controls** Means + SD **(n = 23)**	**Linear regression Group Effect**	**Covariate**	**F statistic**	**Degrees of freedom**
d' prime	2.99 ± 0.34	2.93 ± 0.34	3.21 ± 0.34	p = 0.02*	Sex p = 0.04* Education p = 0.09+ Income p = 0.02*	3.64	2 and 50
Omissions	4.77 ± 7.47	8.08 ± 11.51	2.20 ± 4.19	p = 0.03*	Sex p = 0.04* Education p = 0.02* Income p = 0.03*	2.43	2 and 50

Table 13: Linear regression (Inattentiveness variable ~ group + sex/ education/ income) (covariates entered separately)with contrast test and Cohen's d for baseline CPT Inattentiveness (stars (*) flag levels of significance with one star denoting a p value below 0.05

Non-responders to treatment had significantly smaller d prime (p = 0.02) (a measure of a participants ability to discriminate between targets and non-targets) at baseline than controls, implying that they were less attentive than controls. This effect remained significant when sex and household income were added as covariates. Non-responders to treatment had significantly more omissions than healthy controls (p = 0.03), an effect that remained significant when the covariates sex, years of education and household income were added. There was no significance between groups when exploring commission errors, HRT (response speed) or variability (a measure of speed consistency). All covariates were homoscedastic with the exception of income in HRT which was heteroscedastic (p = 0.05) (Appendix M).

There were no statistically significant differences between responders to treatment and non-responders to treatment with regards to inattentiveness at baseline (d' Prime p = 0.61, omissions p = 0.38, commissions p = 0.66, HRT p = 0.91, variability p = 0.66).

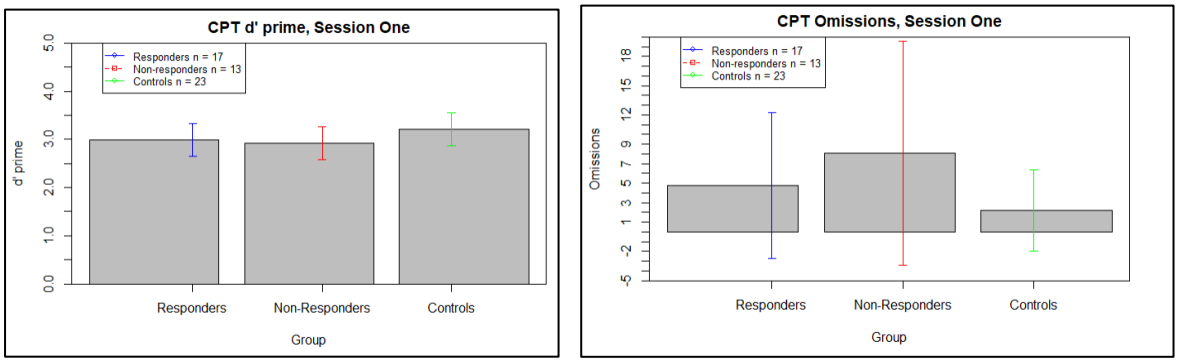

Figure 6: CPT, Inattentiveness at baseline

Sustained Attention – Omissions

Omissions	**Responders** Means + SD **(n = 17)**	**Non-Responders** Means + SD **(n = 12)**	**Controls** Means + SD **(n = 23)**	**Linear regression – Group effect**	**Covariate**	**F statistic**	**Degrees of freedom**
Block 1	0.53 ± 1.01	1 ± 1.29	0.47 ± 1.56	p = 0.36	Sex p = 0.33 Education p = 0.22 Income p = 0.44	0.56	2 and 50
Block 2	1.41 ± 2.27	2.39 ± 2.93	0.48 ± 0.90	p = 0.01**	Sex p = 0.01* Education p = 0.02* Income p = 0.01**	3.80	2 and 50
Block 3	1.47 ± 2.07	3.31 ± 4.80	0.65 ± 1.50	p = 0.01**	Sex p = 0.01* Education p = 0.01** Income p = 0.01*	3.73	2 and 50
Block 4	1.18 ± 2.53	3.23 ± 4.45	0.61 ± 0.84	p = 0.01**	Sex p = 0.01** Education p = 0.01** Income p = 0.01**	4.078	2 and 50

Table 14: Linear regression (CPT sustained attention omissions by block ~ group + sex/ education/income) (covariates entered separately) with contrast test and Cohen's d for baseline (, stars (*) flag levels of significance with one star denoting a p value below 0.05 and two if the p value is less than 0.01)

There were statistically significant group differences in number of omissions that emerged in block 2 of the CPT, and were largely attributable to greater relative increases on this outcome in non-responders to treatment compared with controls, possibly supporting the suggestion of fatigue effects amongst non-responders to treatment. Furthermore the effects remained significant with the addition of the covariates (table 14 and figure 7).

There were no significant differences in omissions between responders to treatment and non-responders to treatment across blocks at baseline (block 1 p = 0.29, block 2 p = 0.33, block 3 p = 0.22, block 4 p = 0.16).

Controls were significantly more accurate on the CPT than both MA groups as well as displaying a faster reaction time which is consistent with our hypothesis. Moreover controls had significantly superior d' prime and fewer omissions than non-responders to treatment. With regards to sustained attention non-responders to treatment had significantly more omissions in blocks 2, 3 and 4 and more commissions in block 2 than controls. Responders had significantly more commissions than non-responders to treatment in block 2 which is contrary to our hypothesis.

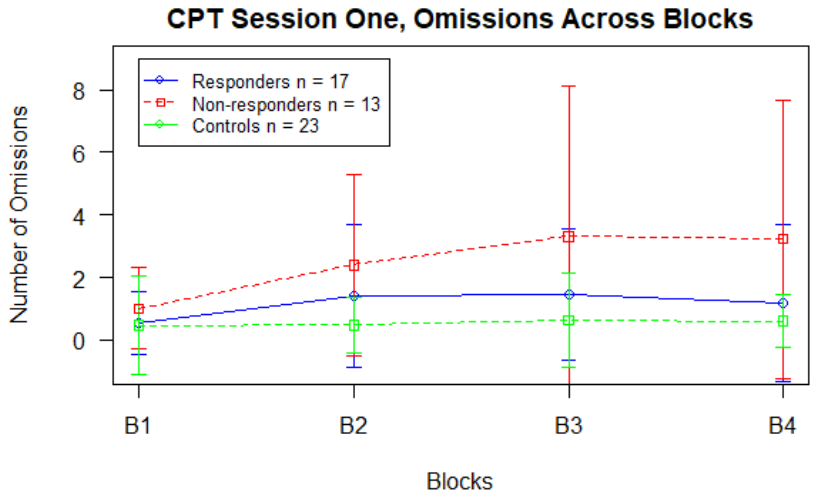

Figure 7: CPT, omissions in sustained attention at baseline

Outcomes of Hypothesis one

When comparing the two MA groups with controls, in the Stroop and CPT controls were more accurate than both MA groups. In the TMT the responders completed the task faster than non-responders, they were also more accurate in the Stroop and CPT, with the later showing greater inattention and poorer sustained attention in non-responders compared with responders. When comparing healthy controls with the combined MA group at baseline there was no statistical difference between the groups in the TMT,

but controls performed significantly better that the MA group on accuracy in the Stroop and CPT. This confirms our hypothesis that Controls will perform better than MA participants in executive function at baseline, and that responders to treatment will show superior executive function at baseline over non-responders.

4.4.2.2. Hypothesis 2 (Baseline to End of Trial)

We predict that performance post-intervention in the Trail Making Task, Stroop Word Task and Conner's' Continuous Performance Task will improve to a lesser extent in non-responders versus responders and healthy controls, as assessed using a difference score (change over time with pre- minus post intervention outcomes).

Table 15 and 16 are a compilation of all of the results for the various tasks, with table 15 covering the two separate MA groups and comparing them with controls, and table 16 comparing the combined MA group with controls.

Trail Making Task B minus A – Time to Completion Responders to treatment n = 17, Non-responders to treatment n = 11, Healthy controls = n = 21								
Between Sessions	**Linear regression group effects**	**F statistic and DF**	**β coefficient, Model fit**	**Contrast (post hoc) test t**	**Contrast (post hoc) test p**	**Cohens d**	**CI range**	**Benjamini Hochberg**
Responders to treatment Non-responders to treatment Healthy controls	p = 0.66 Sex p = 0.14 Education p = 0.43 Income p = 0.03*	1.31 3 and 94	28.76 0.28	R-NR -1.25 R-C -0.38 NR-C -1.69	0.43 0.92 0.24	0.32 -0.10 -0.42	-0.28 – 0.95 -0.55 – 0.35 -0.96 – 0.19	0.66
Stroop Word Task – Accuracy Responders to treatment n = 17, Non-responders to treatment n = 10, Healthy controls = n = 21								
Between Sessions	**Linear regression group effects**	**F statistic and DF**	**β coefficient, Model fit**	**Contrast (post hoc) test t**	**Contrast (post hoc) test p**	**Cohens d**	**CI range**	**Benjamini Hochberg**
Responders to treatment Non-responders to treatment Healthy controls	p = 0.02* Sex p = 0.01* Education p = 0.02* Income p = 0.03* Language p = 0.01**	3.93 3 and 91	5.34 0.01	R-NR -0.88 R-C 3.28 NR-C 1.89	0.66 0.01* 0.15	0.20 0.78 0.68	-0.43 – 0.67 0.41 – 1.12 0.06 – 1.23	0.05*
Continuous Performance Task – Accuracy Responders to treatment n = 17, Non-responders to treatment n = 11, Healthy controls = n = 21								
Between Sessions	**Linear regression group effects**	**F statistic and DF**	**β coefficient, Model fit**	**Contrast (post hoc) test t**	**Contrast (post hoc) test p**	**Cohens d**	**CI range**	**Benjamini Hochberg**
Responders to treatment Non-responders to treatment Healthy controls	p = 0.01* Sex p = 0.01* Education p = 0.01* Income p = 0.05*	3.97 3 and 94	5.50 0.01	R-RN -0.64 R-C 2.55 NR-C 2.90	0.80 0.03* 0.01*	0.15 -0.65 -0.78	-1.43 – 0.74 -1.09 - -0.21 -1.37 - -0.14	0.04*

Table 15: Linear regression for time to completion between sessions (Task ~ group + sex/ education/income) (covariates entered separately) with contrast test and Cohen's d (, stars (*) flag levels of significance with one star denoting a p value below 0.05, while the + signifies a trend towards significance with p values below 0.1), (Benjamini Hochberg conducted on Trail Making Task – Time to completion, Stroop – Accuracy and Connors CPT – Accuracy), (R = Responder to treatment, NR = Non-responder to treatment, C = Healthy control)

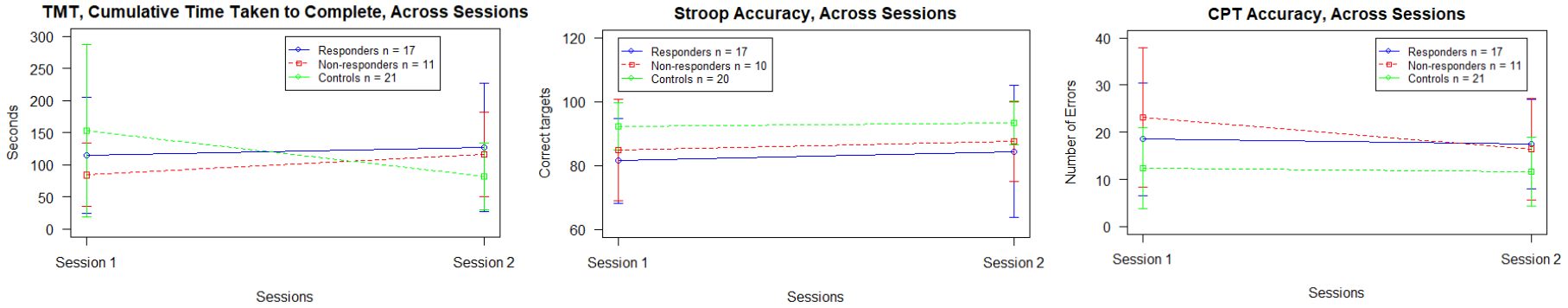

Figure 8: Outcomes between sessions

When comparing the combined MA group with controls, there was no difference between the two groups in TMT – time taken to completion, but controls performed superiorly to the MA group in both the Stroop and CPT accuracy.

Task	P value	T statistic	Degrees of freedom
Trail Making Task B minus A Time to Completion	0.66	0.59	1.01
Stroop Accuracy	0.01***	3.55	77.07
Connors Continuous Performance Task Accuracy	0.01***	-3.40	95.20

Table 16: two tailed t test comparing the MA group with the healthy controls

Trail Making Task, time to completion between sessions

When the Trail Making Task-A was subtracted from Trail Making Task-B, there was no statistically significant group effect with regards to time to completion between sessions. Furthermore, there was no significance post adjustments for multiple corrections ($p = 0.66$). All covariates were homoscedastic with the exception of education ($p = 0.04$). There were no significant differences between MA groups in the Trail Making Task-B minus Trail Making Task-A between sessions.

Stroop accuracy between sessions

Although all of the groups improved between sessions, controls continued to exhibit better accuracy in both session one and session two compared with responders to treatment ($p = 0.02$), but not non-responders to treatment, which held for the contrast test ($p = 0.01$) and Cohen's d (table 8 and figure 7). After controlling for multiple corrections accuracy remained statistically significant ($p = 0.05$). There were no statistically significant differences between responders to treatment and non-responders to treatment.

Exploratory Analysis between Sessions

Stroop Effect (accuracy – omissions)

Even though responders to treatment showed the greatest improvement between the sessions pre to post treatment (table 17), the strongest effect in this group was weaker inhibitory control in session one when compared with controls. When exploring between sessions, controls had significantly more accurate responses post congruent and incongruent targets (higher scores reflect the sum of errors) than responders to treatment ($p = 0.01$), which held for the addition of all covariates to the model and remained significant even after correcting for multiple comparisons. There was no statistically significant effect for reaction time (reaction time of congruent responses subtracted from incongruent responses). Further, with regards change in performance over time looking at reaction time only, we see that as a direct result of the there being far more congruent targets than incongruent ones the results reported have a negative value. Non-responders to treatment were significantly more accurate in the Stroop effect than responders to treatment across sessions ($p = 0.01$), which remained significant when sex ($p = 0.01$) and household income ($p = 0.01$) were added to the formula. There was no difference between groups in reaction time.

	Responders	Non-Responders	Healthy Controls	Linear Regression	Covariates	F Statistic	DF
The Stroop Effect							
Baseline							
Accuracy	9.93 ± 9.11	2.15 ± 4.18	4.60 ± 7.34	p = 0.01**			
RT	-182.45 ± 95.37	-188.27 ± 88.72	-161.21 ± 72.14	p = 0.77			
Post-Treatment							
Accuracy	5.10 ± 4.84	3.22 ±5.15	3.60 ± 4.31	p = 0.25			
RT	-129.60 ± 186.84	-137.95 ± 75.47	-125.13 ± 98.64	p = 0.96			
Between Sessions							
Accuracy				p = 0.01**	Sex p = 0.01** Education p = 0.01** Income p = 0.01*** Language p = 0.01**	3.67	3 and 91
RT				p = 0.90	Sex p = 0.91 Education p = 0.93 Income p = 0.90 Language p = 0.44		

The Lamming/ Rabbit Effect							
Baseline							
Accuracy	-10.66 ± 13.92	-6.85 ± 11.83	-0.71 ± 6.73	p = 0.05*			
RT	-44.47 ± 99.54	14.91 ± 273.19	-18.11 ± 337.46	p = 0.05*			
Post-Treatment							
Accuracy	-6.75 ± 6.73	-1.74 ± 13.92	0.16 ± 11.83	p = 0.05*			
RT	-31.45 ± 337.46	-45.45 ± 99.54	67.85 ± 273.19	p = 0.29			
Between Sessions							
Accuracy				p = 0.01**	Sex p = 0.01** Education p = 0.01* Income p = 0.01** Language p = 0.01**	4.545	3 and 91
RT				p = 0.47	Sex p = 0.46 Education p = 0.51 Income p = 0.89 Language = 0.34		

Table 17: exploratory analysis between sessions, linear regression (accuracy/ reaction time of congruent targets minus accuracy/ reaction time of incongruent targets ~ group + session + sex/ education/income) (covariates entered separately) (stars (*) flag levels of significance with one star denoting a p value below 0.05, two if the p value is less than 0.01 and three for less that p = 0.001)

The Lamming Rabbit Effect (accuracy)

The Lamming Rabbit effect is a measure of accuracy following an incorrect hit and subtracts from it the accuracy after a correct hit (it explores the same for reaction time). The lower the score, the more inaccurate the group was, and the greater the cognitive challenge. As seen previously all groups improved between session one and two. Responders, however, had significantly lower scores when compared with controls in accuracy in both session one and two ($p = 0.01$) this remained significant for all covariates (table 17 and figure 9). There was no statistically significant difference between groups in reaction time. Moreover, there were no significant differences across time between MA groups in the Lamming Rabbit effect (accuracy $p = 0.24$ and reaction time $p = 0.95$).

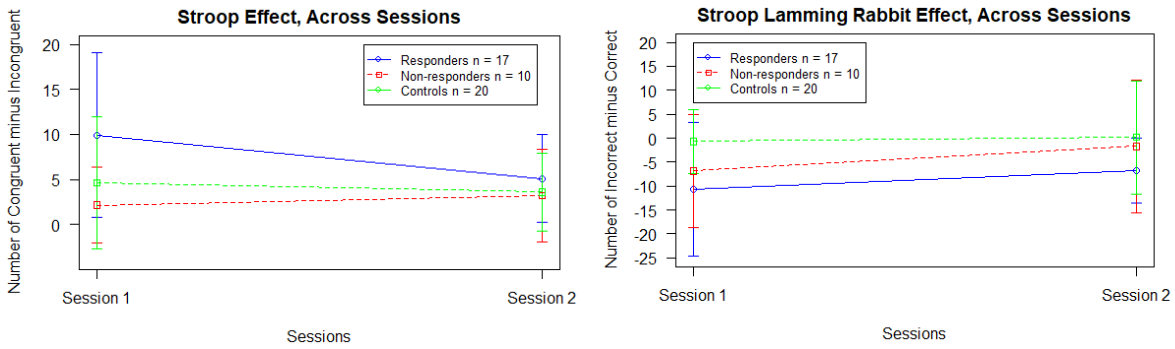

Figure 9: Stroop exploratory analyses, accuracy between sessions

CPT accuracy between sessions

Non-responders to treatment made significantly more errors in session one ($p = 0.02$, table 17) than controls, yet they also demonstrated the greatest improvement over time ($p = 0.01$, table 15, figure 8). This effect remained statistically significant with the addition of each covariate and this significance held for the contrast test ($p = 0.01$) and Cohen's d. Moreover controls made significantly fewer errors than responders to treatment over both sessions (contrast test $p = 0.03$) which held for Cohen's d (table 15). This effect remained after correction for multiple comparisons ($p = 0.04$). There was no significant difference between responders to treatment and non-responders to treatment between sessions until household income was added to the model which then showed non-responders to treatment to have significantly greater improvement in performance across sessions when compared to responders to treatment.

Exploratory Analysis between Sessions

	Responders to Treatment	Non-Responders to Treatment	Healthy Controls	Linear Regression	Covariates	F Statistic	DF
	Means ± Std.dev. (n = 17)	Means ± Std.dev. (n = 11)	Means ± Std.dev. (n = 21)				
The Continuous Performance Task - Inattentiveness							
Baseline							
d' Prime	2.99 ± 0.34	2.96 ± 0.34	3.23 ± 0.35	p = 0.05*			
Omissions	4.77 ± 7.47	9.00 ± 7.47	1.81 ± 3.28	p = 0.32			
Variability	46.64 ± 39.98	58.34 ± 39.98	35.51 ± 20.50	p = 0.07+			
Post-Treatment							
d' Prime	2.99 ± 0.38	3.08 ± 0.36	3.22 ± 0.33	p = 0.01*			
Omissions	0.81 ± 2.51	4.09 ± 5.70	0.91 ± 1.19	p = 0.01*			
Variability	45.14 ± 10.91	45.48 ± 33.34	26.30 ± 9.41	p = 0.01**			
Between Sessions							
d' Prime				p = 0.03*	Sex p = 0.05 Education p = 0.08 Income p = 0.01**	3.149	3 and 94
Omissions				p = 0.01***	Sex p = 0.01** Education p = 0.01***	4.975	3 and 94

					Income p = 0.01***		
Variability				p = 0.01**	Sex p = 0.01** Education p = 0.01** Income p = 0.01**	4.358	3 and 94

Table 18: CPT inattentiveness, linear regression (d' prime/ omissions/ commissions/ HRT/ variability ~ group + session + sex/ education/income) (covariates entered separately) (stars (*) flag levels of significance with one star denoting a p value below 0.05, two if the p value is less than 0.01 and three for less that p = 0.001*)*

	Responders to Treatment	**Non-Responders to Treatment**	**Healthy Controls**	**Linear Regression**	**Block**	**Covariates**	**F Statistic**	**DF**
	Means ± Std.dev. **(n = 17)**	**Means ± Std.dev.** **(n = 11)**	**Means ± Std.dev.** **(n = 21)**					
	The Continuous Performance Task – Sustained Attention (between blocks)							
Baseline								
Omissions - Baseline	1.15 ± 2.04	2.80 ± 3.90	0.45 ± 0.95	p = 0.01***				
Omissions – Post Treatment	0.91 ± 1.22	1.02 ± 1.84	0.23 ± 0.55	p = 0.01***				
Omissions Across Sessions				p = 0.01***	Block 2 - p = 0.19 Block 3 - p = 0.03*	Sex p = 0.01*** Education p = 0.01***	9.91	6 and 385

					Block 4 - p =0.02*	Income p = 0.01***		

Table 19: CPT sustained attention between sessions and blocks, linear regression (HRT/ omissions/ commissions ~ group + session + block + sex/ education/income) (covariates entered separately) (stars (*) flag levels of significance with one star denoting a p value below 0.05, two if the p value is less than 0.01 and three for less that p = 0.001)

Inattentiveness (Accuracy)

Non-responders to treatment showed the greatest improvement in d' prime (sensitivity to the targets) between sessions compared with controls (p = 0.03), an effect that remained significant when income was added to the model (table 18, figure 10). Non-responders to treatment also had significantly more omissions than controls between sessions (p = 0.01) which remained significant when each of the covariates were added, and when corrected for multiple comparisons. Both MA groups had fewer omissions in session two compared with session one. Non-responders to treatment showed greater improvement in session two compared with session one in variability (in that they were less variable than they had been at baseline), they also had lower variability (inconsistency of response speed) (p = 0.01) compared with controls between sessions. There were no differences between the MA groups and controls for commissions and HRT (average speed). There was no significant differences between MA groups regarding inattentiveness, with the exception of number of omissions, which became significant when income was added to the model (p = 0.03).

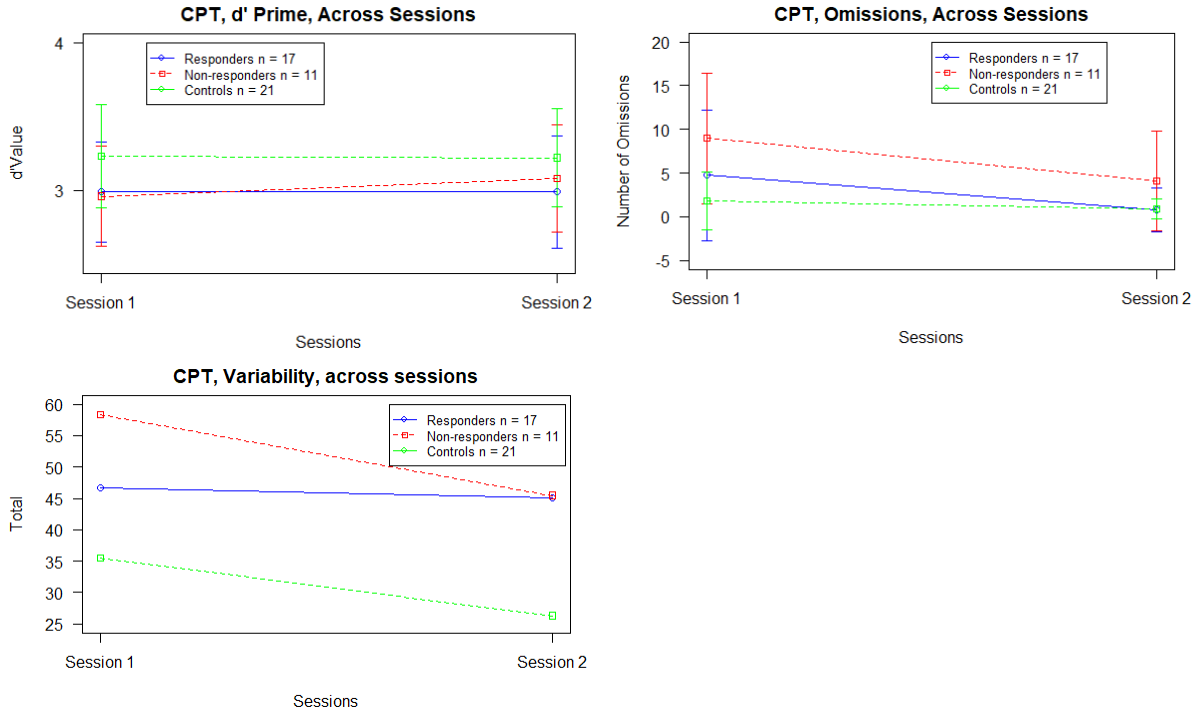

Figure 10: CPT Inattentiveness between sessions

Sustained Attention

In session two non-responders to treatment had significantly more omission errors that controls, but showed a decline in the fourth block when compared with both groups (table 19 and figure 11). In session two responders to treatment had significantly more commission errors that controls, this dropped

in blocks three and four, while controls increased in commission errors. Between sessions non-responders to treatment showed the greatest reduction in omission errors, while the number of commission errors was similar comparing groups.

Non-responders to treatment had significantly more omission errors in blocks 3 and 4 than controls in both sessions (p = 0.01). Responders had significantly more commission errors in block 4 compared with controls across sessions (p = 0.01). There was some cumulative effect of task performance on both outcomes in non-responders to treatment, reflecting greater inattention over time. There was no significance for HRT (response speed) across sessions. All covariates were homoscedastic with the exception of sex in HRT (p = 0.01) and in commissions (p = 0.01), both of which were heteroscedastic (Appendix M).

Non-responders to treatment had significantly more omissions (p = 0.01) in block 4 than responders to treatment (which remained significant with all covariates separately added sex = p = 0.01, number of years of education p = 0.01 and household income p = 0.01).

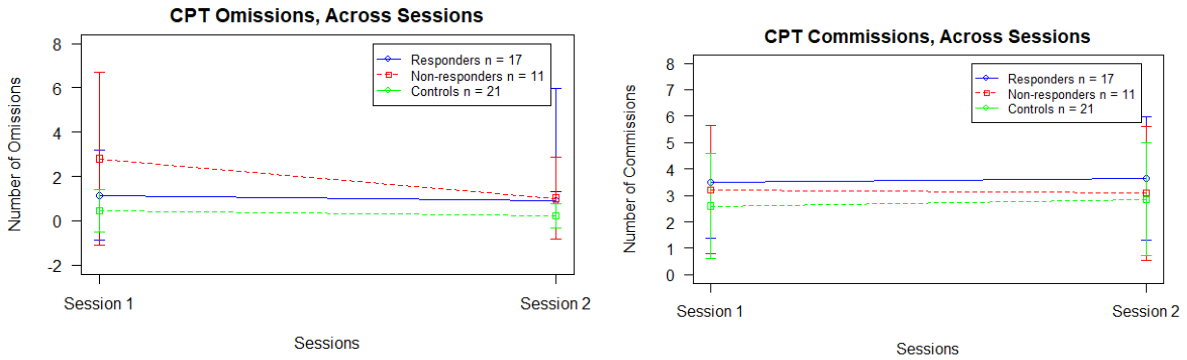

Figure 11: CPT sustained attention between sessions

4.4.3. Change Score

Cohen's d calculated on the total accuracy score (where a higher score (positive score) shows superior performance, Trail Making Task-B minus Trail Making Task-A), indicated that non-responders to treatment were more accurate in the Trail Making Task in session one (p = 0.03) than responders, with no significant group difference in session two (table 11 and figure 12). Non-responders to treatment were more accurate in the Stroop in session one (p = 0.04) when compared with responders to treatment, but there was no significance in session two. On the CPT, non-responders to treatment were more accurate in session one (0.02) compared with responders to treatment, but there was no difference in session two.

The standardised change score [(session two subtracted from session one) – mean) / standard deviation] across sessions revealed no significance between groups. The Cohen's d transformation was applied on

the change score, and therefore a greater score (positive score) demonstrates greater improvement in performance between the pre and after intervention test sessions, yet this too presented with no statistical significance between groups.

	Responders Means + SD **(n = 17)**	**Non-Responders** Means + SD **(n = 11)**	**Controls** Means + SD **(n = 21)**	**P score**
Trail Making Task Cohen's d on total score				
Session 1	0.02 ± 1.10	-0.37 ± 0.86	-0.01 ± 1.01	p = 0.03*
Session 2	-0.03 ± 0.85	0.05 ± 1.28	-0.01 ± 1.01	p = 0.87
Across session				
Change score	-0.29 ± 6.89	2.55 ± 11.03	0.29 ±7.98	p = 0.54
Cohens d on change score	-0.07 ± 0.86	0.19 ± 1.32	0.29 ±7.98	p = 0.85
Stroop Cohen's d on total score				
Session 1	-1.46 ± 1.79	-1.01 ± 2.14	0.01 ± 1.00	p = 0.04*
Session 2	-1.35 ± 30.18	-0.85 ± 1.81	0.01 ± 1.00	p = 0.19
Across session				
Change score	2.95 ± 14.71	2.74 ± 13.25	-2.20 ± 22.04	p = 0.15
Cohens d on change score	0.28 ± 0.66	0.27 ± 0.59	0.05 ± 0.98	p = 0.53
CPT Cohen's d on total score				
Session 1	1.24 ± 1.38	0.71 ± 1.72	0.01 ±1.00	p = 0.02*
Session 2	0.81 ± 1.31	0.67 ± 1.48	-0.01 ± 1.01	p = 0.21
Across session				
Change score	1.06 ± 13.48	6.64 ± 9.65	0.76 ± 6.20	p = 0.26
Cohens d on change score	0.05 ± 2.17	0.95 ± 1.56	0.01 ± 1.00	p = 0.39

Table 11: Change score of all neurocognitive tasks using Cohen's d (stars (*) flag levels of significance with one star denoting a p value below 0.05)

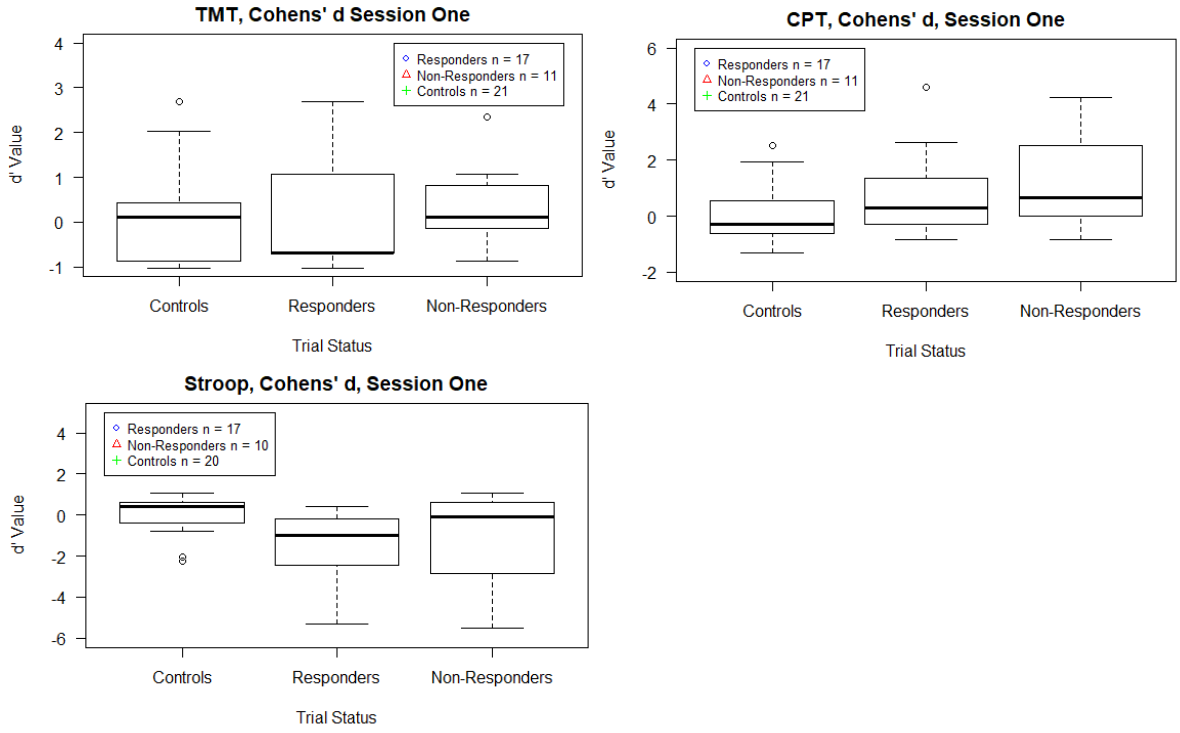

Figure 12: Cohens'd Change Scores for all tasks, Session One

When looking at the standardised change score for each of the tasks, it is apparent that on the Trail Making Task and CPT, responders to treatment more closely resemble controls with the greatest change between sessions being observed in the non-responders, while in the Stroop the two MA groups are more similar to one another than controls (table 12 and figure 13). The different effect sizes between groups for the tasks demonstrated at baseline is largely eradicated at session two (figure 14), although the responders to treatment do present with greater variability in the Stroop than the other groups.

	Trail Making Task Means + SD	**Stroop** Means + SD	**CPT** Means + SD
Responders	-0.29 ± 6.89	2.95 ± 14.71	1.06 ± 13.48
Non-responders to treatment	2.55 ± 11.03	2.74 ± 13.25	6.64 ± 9.66
Controls	0.29 ± 7.98	-2.20 ± 22.04	0.76 ± 6.20

Table 12: Change by task

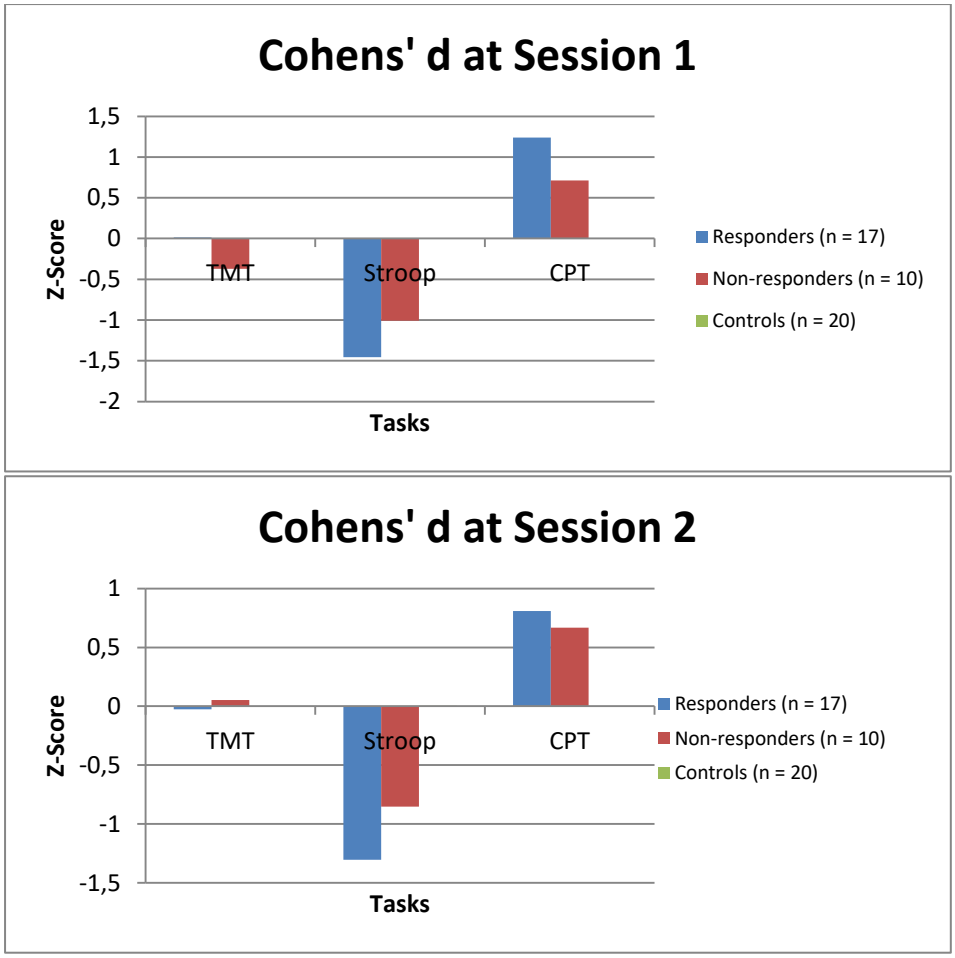

Figure 13: Cohens'd at each session

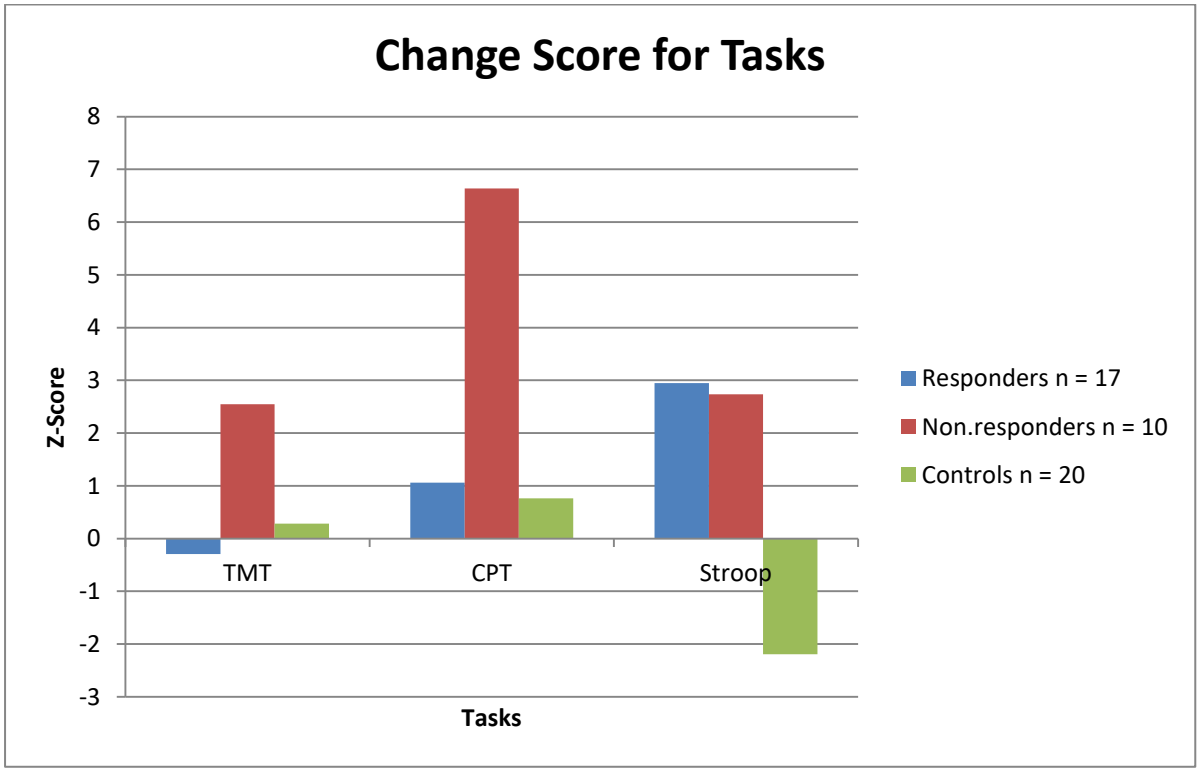

Figure 14: Change score for tasks

When looking at global standardised change score, computed as the mean change score of accuracy across all three tasks, we see that responders to treatment more closely resemble controls than non-responders to treatment with non-responders to treatment showing the greatest change overall (Cohen's d = 2.58) (table 13 and figure 15).

	Composite change score Means + SD	**Cohen's d**
Responders	0.97 ± 1.44	0.77
Non-responders to treatment	3.53 ± 2.09	2.58
Controls	-0.11 ± 1.41	0.00

Table 13: Global change

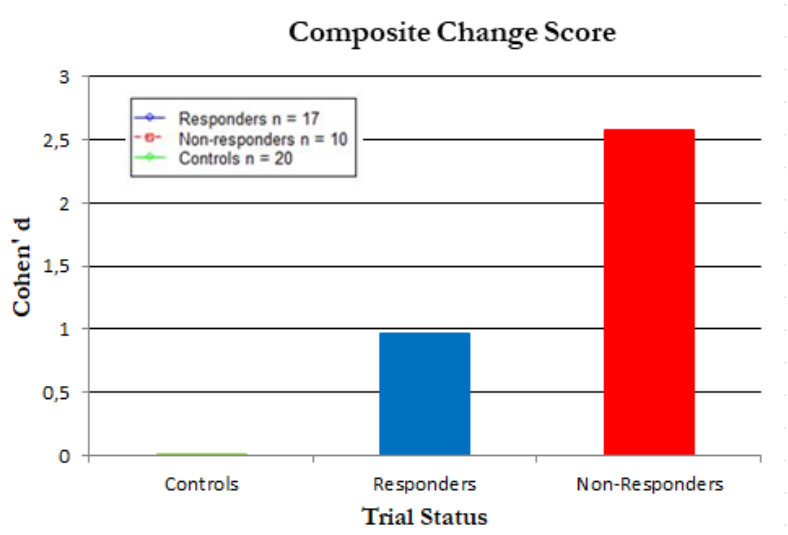

Figure 15: Global Change Score

Outcomes of Hypothesis Two

The TMT showed no differences between MA groups or between the combined MA groups and controls. In both the Stroop and CPT controls outperformed both MA groups, when compbined and when analysed individually. Non responders to treatment out-performed responders on the Stroop task over time, likely due to accuracy on congruent targets, with responders performing better in incongruent targets than non-responders. In the CPT non-responders had great number of omissions than responders and responders had better sustained attention than non-responders. Although the effect is not strong, the outcomes support our hypothesis that responders will demonstrate better performance than non-responders.

4.5. Discussion

In this study responders did not present with superior task switching skill in the TMT (Trail Making Task-B minus Task-A) (table 7) at baseline compared with non-responders, contrary to hypothesis one. Nevertheless, trend findings suggest that they may perform better than non-responders in this task. A larger sample size is needed to determine if this trend may become significant. Further responders did not perform better than non-responders in the Stroop task (table 10) or in the CPT (table 11) at baseline, which is contrary to our hypothesis.

Controls demonstrated superior performance at baseline in both Stroop accuracy and CPT accuracy (table 6) to the patients overall, although there was no significant difference between groups in the TMT. This suggests that controls in this small sample size have enhanced sustained attention and inhibitory control, but not in task switching. Again a larger sample would be needed to refute/ confirm that healthy controls have better overall executive function than patients diagnosed with MUD (hypothesis 2).

Hypothesis two was not supported as non-responders had the greatest improvement in the TMT (Trail Making Task-B minus Task-A) and CPT over time, while responders had the greatest change in the Stroop over time (figure 14). Yet overall the non-responders had the greatest change in tasks as a composite score (figure 15).

Controls outperformed the MA group again in the Stroop and CPT, but not in the TMT over time (table 15). Again this partially supports our hypothesis in that controls have superior aspects of executive functioning over the MA group.

Hypothesis one

Responders to treatment will demonstrate better cognitive processing and executive function quantified by the Trail Making Task, superior inhibitory control determined by the Stroop word task and superior sustained and selective attention as measured by the Conner's' Continuous Performance Task at baseline when compared with non-responders to treatment. Moreover, participants with methamphetamine dependence will perform more poorly at baseline when compared with healthy controls.

In previous research participants who misuse MA performed significantly more poorly in cognitive tasks than controls [77, 301-303], and performance has been shown to improve with prolonged abstinence [301] with notable, albeit statistically non-significant effects, observed after one month of abstinence [82]. Severity of cognitive decline and rate of recovery in MA users appear to be affected by moderator variables, including amount, frequency and length of use as well as age, education and genetics of the research participants [76].

Furthermore, the correlation between speed of completion and accuracy in the Trail Making Task (Trail Making Task-B minus Task-A) was strongest in the control group ($p = 0.01$) (table 12). Previous research on performance of MA users found that MA users displayed greater impairments in this task than healthy controls [304, 305]. Results of other studies are not directly comparable to this study, as this is the first published analysis to assess Trail Making Task performance as a predictor of treatment response [305 304 306]. Nevertheless in other studies MA using participants performed worse on this task as a group than controls, especially on the Trail Making Task-B task [82, 304], this may be reflective of those that did not respond to treatment.

The finding that the MA group and more specifically the responders, were less accurate at baseline in the Stroop task can be interpreted as significantly poorer inhibitory control in this group. This is consistent with a previous observation, that recently abstinent MA misusers perform more poorly in the Stroop task than controls (more errors and slower reaction time) (table 6) [77]. This has been found in yet another study which showed significantly worse word recognition in abstinent MA abusers (up to 6 months) than those who were currently using MA [306]. Moreover, these results may suggest that responders to treatment are more inflexible regarding accuracy when cognitively challenged. This cognitive inflexibility has been identified in the literature [52]. In MA users abstinent 5-7 day a deficit in response inhibition was detected in the Stop-Signal Task when compared with healthy controls [307]. Moreover in another study exploring salivary cortisol levels in 6 months abstinent amphetamine participants compared with controls, the participants were exposed to stress and assessed pre- and post- the stressor [308]. The stress resulted in lower sores in the Stroop task post-stress in the amphetamine group, but also lower cortisol pre- the stressor in the same group [308]. The authors concluded that not only was the stress regulatory system vulnerable in early abstinence , but so were the attentional / inhibitory control systems as a result of chronic use of amphetamines [308].

Recently abstinent MA dependent participants (>3 weeks) have been shown to have greater interference effects in reaction time (longer reaction time) than non-drug using controls and long-term abstinent MA abusers (>1 year) [309]. We did not find any group differences (table 5).

Although the cumulative Stroop effect indicated that responders to treatment had experienced greater difficulty at baseline, in that they presented with more errors than both non-responders to treatment and healthy controls, when looking more closely at the Stroop effect , non-responders to treatment were less accurate with congruent targets than controls, while responders to treatment were more accurate with incongruent targets. Previous research has shown that abstinent chronic MA misusers (one month to five years) showed performance similar to controls with congruent targets in an attention task (Attentional

Network Task), but had significantly greater conflict with incongruent targets [310], which is partially consistent with our findings.

The Stroop task has been used to research multiple aspects of executive function including cognitive flexibility. Reversal learning tasks are largely used to test cognitive flexibility [311] which is associated with conflict resolution and [312] and requires inhibitory control that is pivotal in supressing rewarding behaviour [313]. Notably reversal learning is related to low dopamine D2 receptor availability in the striatum [313]. Moreover greater intra-synaptic dopamine levels has been related to faster reversal in animal models [314].

Responders to treatment displayed poorer cognitive control than healthy control participants in the Lamming Rabbit effect, but exploration of this effect showed that responders to treatment had significantly reduced accuracy after an incorrect trial while non-responders to treatment had significantly reduced accuracy after a correct trial. Poor accuracy after error may reflect greater conflict and possible cognitive load. Less accurate responses following correct responses in non-responders to treatment may indicate that this group as a whole were less engaged with the task, given their deficits in attention as seen in the CPT task.

When comparing the MA group to controls, one study using the Trail Making Task (Trail Making Task-B minus Task-A) showed that MA users (4-days abstinent) performed significantly worse than healthy controls at baseline in the trail making task, and displayed no significant improvement over one month [82]. This observation was consistent with our findings of no significant improvements over eight weeks of CM treatment. When compared with internationally determined normative times to Trail Making Task subsections (which are used to determine cognitive impairment) the group average score for all of the groups were worse when compared with normative times in both sessions for both subtasks. Participants were slower in both subtasks when compared with international standards, which was driven by the large standard deviation and means. In turn this implies that this slower performance of our sample was likely due to individual extremes rather than group effect. Even though these findings suggest that our cohort may present with cognitive impairment, we refer to the MoCA scores (appendices N) which confirmed the participants physical presentation of no cognitive deficiency within the tested domains. This slower speed in completing the tasks may be unique to MA misusers in low and middle income countries, but further research with a larger sample size would be required.

Failure in attention is likely due to one or two reasons; reduced arousal subsequent to minimal stimulation, or fatigue caused by task overload with subsequent resource depletion. The Connors CPT accuracy showed that non-responders to treatment had significantly more errors than controls at baseline ($p = 0.01$) (table 13), and displayed greater inattentiveness than controls as evidenced by a significantly lower d' prime and significantly more omissions (table 13) and which could be described as a failure to

engage. Sustained attention in the CPT provides a measure of whether the participants attention waivered during the task. Apparent loss of attention in non-responders to treatment began in bock 2, and continued until the end of the task with significantly more omissions than controls (table 13).

These results are consistent with a report that withdrawal free, abstinent MA and morphine abusers (use within six months), exhibited significantly more omission errors and greater variability in performance than the control group [315], although responders to treatment and non-responders to treatment were not evaluated separately. Another study spanning six months found that among participants who abused stimulants (MA and cocaine), who were identified as responders to treatment and non-responders to treatment undergoing various in-clinic treatments (including the 12 step program, support groups, and local treatment centres with undefined treatment type) , those that relapsed had significantly more omission errors than those who remained abstinent in the Oddball task (a measure of attention); the authors attributed the errors to the participants becoming distracted [87]. When exploring correlation between accuracy and reaction time, the effect was most pronounced in non-responders suggesting greater randomness/ error in their responses. Failure to observe this trade-off in responders is likely due to low power.

In previous research abstinent chronic MA misusers (one month to five years) showed performance similar to controls with congruent targets in an attention task (Attentional Network Task), but had significantly greater conflict with incongruent targets (75), which is consistent with our findings in the Stroop task for the treatment of responders . The different pattern of deficits between responders to treatment and non-responders to treatment suggests that non-responders to treatment may be more impaired with respect to attention, while responders to treatment demonstrate greater response inhibition, which is consistent with findings of greater impulsivity in non-responders than responders [75]. Attentional deficits in non-responders to treatment were further supported by impairments on the CPT that were not observed in responders to treatment.

Hypothesis two

Performance post-intervention in the Trail Making Task, Stroop Word Task and Conner's' Continuous Performance Task will show a difference score (change over time with pre- minus post intervention outcomes) for those that do not respond to treatment compared with those that do respond to treatment and healthy controls.

Responders to treatment had significantly poorer accuracy than controls in the Stroop over time (table 15). Unexpectedly the Stroop effect was greater in responders to treatment and healthy controls than non-responders to treatment. This finding could be due to the performance enhancing effect of MA in the non-responders to treatment, or regression to the mean (table 4.53 in appendix N) [316]. The Lamming

Rabbit effect confirmed a weaker cognitive flexibility in responders to treatment with them having significantly lower scores in accuracy across sessions when compared with controls (table 17).

The Stroop task findings did not confirm our hypothesis of improved performance after-treatment, although we were able to use it to differentiate between responders to treatment and non-responders to treatment at baseline.

In our study, non-responders to treatment displayed greater improvement in accuracy in the CPT across time when compared with healthy controls, and although their d' prime and variability was significantly improved between sessions, they still had significantly more omission errors than controls at the end of the intervention. The number of missed targets by non-responders to treatment gained significance in the third and fourth blocks at baseline when compared with controls and in the fourth block the number of missed targets gained significance when compared with responders to treatment, likely due to fatigue and boredom. Moreover, in the fourth block non-responders to treatment also had significantly more commissions across time than controls.

Post hoc testing focused on change score and revealed that responders to treatment more closely mirrored controls with regards to the magnitude of change in performance in the Trail Making Task, Stroop and Connors CPT as well as in global accuracy change score. This raises the question; are responders to treatment intrinsically more similar to controls?

The presentation of more years of education and more drug-free urine samples at pre-trial in responders to treatment than non-responders to treatment together with the fewer omission errors in the Connors CPT by responders to treatment than non-responders to treatment is noteworthy. Faster completion time of responders to treatment at baseline compared with non-responders to treatment in the Trail Making Task may indicate that there are individual or genetic factors that assist responders to treatment to access more effective inhibitory control. An alternative explanation is that higher formal education provides one with greater inhibitory control. This greater inhibitory control exhibited in responders to treatment would be utilised by the individual in the treatment phase to assist them to become abstinent. Finally in figure x in the appendices we see that non-responders to treatment were more depressed than responders to treatment, which could also negatively impact performance in both the trial and on the tasks.

Previous research using the Trail Making Task, Stroop word task, digit span and memory task on a cohort of 27 MA dependent individuals comparing them to 28 controls showed that after a month of abstinence the MA group did not show marked improved executive functioning [82]. Yet after one year of abstinence an independent study demonstrated that performance for an MA cohort was comparable to controls in a memory task, the Stroop word colour task and the Trail Making Task [79]. Our study shows that this

change may begin at 2 months of abstinence likely to be as a result of abstinence which is promoted by the CM treatment.

In figure 14 it is apparent that the change score for responders to treatment more closely mimic the change score of controls than non-responders to treatment in the TMT and CPT, but not in the Stroop task. Although the pattern of non-responders to treatment also mimic the control group, their change score is far higher especially in the Connors CPT, Stroop and total change score. When reviewing figure 15 we see the global score shows responders to treatment performing more similarly to controls than non-responders to treatment. Subsequently we are able to distinguish the likelihood of achieving and retaining abstinence from the outcomes of the Trail Making Task and CPT at baseline. Moreover the change score reflects that responders to treatment present more similarly to controls.

Multiple factors should be considered when interpreting these data including the number of urine tests that were drug negative before start of trial (with responders having significantly more), amount of MA use (which was not controlled for in this study), household income, poly substance use (determined conclusively by blood tests). Not all aspects could be controlled for due to budget constraints and sample size, yet many factors were identified affecting treatment outcome (amount of use, household income, education and number of urine samples that were drug negative). These factors do, however, suggest to greater inhibitory control in the responders group, but a larger sample size would be needed to determine this.

It is important to note that not all participants completed the 8-week programme (n = 2), and should they have completed the trial it could have led to improved performance at the group level for non-responders at follow up. Moreover, the results for the participants who dropped out during the trial were included in the baseline analyses, making comparisons between the two time sets difficult, and introducing potential false positives findings. We need to bear in mind, however, that this is a small number, so the missing participants exclusion at follow-up may unlikely to introduce a large bias in the results.

4.6. Limitations

Several limitations deserve emphasis. First, the sample size of this pilot study was small, but it does provide insight for future research. Second, a number of hypotheses were not, or were only partially supported. This could be accounted for by the small sample size and associated low power to detect group differences, particularly following corrections for multiple comparisons. Third, the classification of treatment participants as responders or non-responders did not take into consideration any reduction of use, which in itself is still an improvement. It should be thus born in mind that the purpose of this trial was not to determine the effectiveness of CM, but rather to measure changes and differences in executive

function that have implications for understanding response to treatment. It should also be noted that controls were only seen twice, which could limit comparability with the intervention.

Fourth, the three groups (responders, non-responders and controls) differed significantly in years of education, but not in IQ. Although this finding may have been be due to greater high school dropout rates due to drug abuse in non-responders [317] this explanation proved unlikely as mean age initiated was 22.49 ± 6.45 for MA misusers with no significance differences within group. Another factor that may have accounted for this discrepancy could have been the presence of a good support structure for responders that was lacking in non-responders. We decided to explore outcomes of the CTQ to assess if differences in childhood traumas between groups (table 5). This revealed that although the MA group had significantly more emotional abuse than controls, there was no significant difference on the CTQ subscale scores between the responders and non-responders, causing us to reject the possibility of perceived childhood abuse lending to more years of education in responders. An additional potential explanation for differences in years of formal education in responders and non-responders is that responders (and controls) may have greater inhibitory control that enabled them to remain in the education system for longer. This inhibitory control is quantifiable in responders in the screening weeks of the trial, where they gave significantly more MA-negative urine samples than non-responders.

Fifth, although the demographic data revealed a significantly higher monthly household income for non-responders, this was not correlated with the amount that they spent on obtaining the drug, and 100% of non-responders were not employed at the time of the trial, which could suggests that the household earnings and boons were not necessarily shared with the MA using participant. Patient groups were comparable with respect to addiction severity as revealed by the ASI (table 4).

A sixth consideration that is significant in the demographic data and should be taken into account when interpreting the findings of the neurocognitive tasks, is the high RHRSD score and its potential effect on cognition [318] which could have negatively impacted executive function outcomes. Seventh, notably four of the eleven non-responders tested positive for MA at session two, due to the small sample size we were unable to control for this in the analysis.

Eighth, blood alcohol was not measured, nor was methaqualone tested for in the urine samples of the participants. It is important to bear in mind that differences between groups may be affected by unmeasured factors such as polysubstance use and withdrawal to name but two.

Ninth it is possible that improvements between sessions may be affected by ceiling effects whereby good performance in the baseline test in responders leaves little scope for change.

4.7. Conclusions

One of the primary objectives of this pilot study was to determine whether executive function could predict treatment outcomes . Responders to treatment demonstrated performance that was superior to that of non-responders at baseline in the CPT. Responders did not show superior performance over non-responders in the Stroop task at baseline, a finding that may reflect an effect of early abstinence as noted in the literature [77], with responders being abstinent significantly longer than non-responders at start of treatment.

We also sought to ascertain whether responders to treatment would show better outcomes in executive function than non-responders at trial termination. Non-responders appeared to show greater improvements than responders on a global change score, this was not statistically significant. This pilot study provided preliminary data that is consistent with evidence that baseline executive function may predict which clients with MA Use Disorder respond to CM treatment. Nevertheless, other factors, such as differences between responders and non-responders in years of education, household income and amount of MA used may also explain treatment response, and should be considered as possible confounds, further studies with larger samples are warranted.

We wished to determine if the executive function findings from the tasks would be reflected in the MRI data. The next chapter will cover functional and structural differences between those that responded to treatment at baseline and post-treatment with those who did not respond. This will allow us to compare the executive function outcomes found in this chapter with neural correlates found in the subsequent chapter.

Chapter Five

Neural Correlates of Contingency Management in Methamphetamine Use

5.1. Introduction

Having discussed the neuropsychology in the previous chapter, we now go on to explore rs-fMRI and structural MRI. We will start with a brief background that provides a rationale for our work. The goal of this pilot study was to determine whether outcomes for an 8- week contingency management (CM) treatment for individuals who misuse methamphetamine (MA) are consistent with findings from relevant neural imaging studies. Measures of brain function and structure were obtained at baseline and post-treatment using resting state-functional magnetic resonance imaging (fMRI) and structural MRI in order to identify whether these data modalities are informative with respect to response to the CM intervention. Of particular interest were potential neural correlates of executive function.

5.1.1. Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) utilises nuclear magnetic resonance to obtain images of the brain [319, 320]. It capitalizes on the properties of the nuclei of hydrogen atoms, which generate a magnetic signal that can be mapped to create tomographic images [319, 320]. The abundance of water makes this procedure very effective in differentiating between different types of brain tissues (e.g. grey matter, white matter, cerebrospinal fluid and bone), which have unique vasculatures [319, 320]. A radio pulse applied at a specific frequency imparts energy that is absorbed by hydrogen ions, and the release of this energy produces a signal than can be detected via the MRI coils [319, 320] to provide an effective non-invasive means of viewing the human brain [319].

5.1.2. Functional MRI

Functional MRI allows for the charting of activity in the brain either when a subject is performing a selected task, or whilst the individual is resting [319, 320]. The MRI signal is generated by the Blood Oxygen Level Dependent (BOLD) response, whereby oxy-haemoglobin in the blood becomes deoxy-haemoglobin as oxygen is extracted from the blood via diffusion to tissues in brain regions that use oxygen for metabolic activity required to perform a specific task [319-321]. Oxy-haemoglobin is weakly diamagnetic and has no unpaired electrons [321]. Once oxygen is released then deoxy-haemoglobin is formed with four unpaired electrons which are exposed at each ion centre, resulting in the molecule becoming strongly paramagnetic [321]. The BOLD effect is related to the concentration of deoxy-haemoglobin, which can vary from less than 0-2% in arterial blood to 0- 50% in venous blood [322]. If the oxygen levels in a brain region drop dramatically the signal increases [319, 320].

An initial deficit in oxygenated blood in both intra and extracellular regions is followed first by a slight delay (approximately 6 seconds [322]) and then an excess of oxygenated blood in the same regions. This

phenomenon of blood deficit then surplus is called the 'hemodynamic response' and limits the temporal resolution of (MRI timeseries) [322]. The oxygen provided by the initial blood flow to the area of interest is rapidly taken up by the working neurons, and subsequently the body continues to increased oxygenated blood flow response to those working regions until it is no longer required[322] [319]. The BOLD response is an indirect measure of brain function, as there are other reasons for variations in levels of blood oxygen in the brain. These include differences in the size of the vasculature and oxygen demand from glial cells to name but a few [319]. Although fMRI offers substantial spatial resolution it has a low temporal resolution [319] when compared with EEG (which amplitude peaks within 100 μs after the brain response [323]). Spatial distortion due to water movement is approximately 10μm in MRI. This is approximately the distance that water molecules move in a few tens of a millisecond [324] during an MR measurement, which is generally 2-3 seconds in duration [325]. One final limitation is the is the statistical issue of the many tests that are typically performed on MRI data, which increases the risk of false positives [326]. Multiple comparisons correction for these tests, on the other hand, increasing the likelihood of false negative outcomes [327], when not applied judiciously. It is important to balance the number of statistical comparisons with the likely loss of power resulting from corrections for excessive testing. Yet MRI techniques provide some of the best measures of real time non-invasive brain function.

5.1.3. Resting State fMRI

Resting state-fMRI (rs-fMRI) explores function while the individual is non engaged in any specific task and is at rest but not sleeping, with either eyes open, focusing on a simple visual stimulus, or with eyes shut. In fact rs-fMRI provides a proxy for functional connectivity underlying task performance [328]. The BOLD response reveals the co-activation between brain regions whilst the participant rests and tends to ruminate or plan and 'day-dream' [106]. Resting-state fMRI allows us to explore organisation of functional communication, within the brain, as well as how these functional connections relate to structural connections and how both underlie cognition [106]. Functional cconnectivity is typically inferred from correlation between the time series of activity between a specific brain region (ROI)/ networks and other regions/ networks in the brain [106].

5.1.4. Structural MRI

Structural MRI provides a non-invasive means of viewing the anatomy of the living brain. Such measures are useful because structure can influence function (and vice versa), and individual variations in structure can be informative regarding behavioural variability and disease states [319]. Parameters including echo time (TE) (a function that has a secondary perturbation, or echo, to the magnetic signal) and repetition time (TR) (the time taken to scan one whole brain image), can be adjusted to show different contrasts between anatomically differentiated regions and white and grey matter [319]. The high-resolution magnetization-prepared rapid acquisition with gradient echo (MPRAGE) protocol provides spatial displacement parameters that can be applied to the echo planar (EPI) scans, allowing images acquired within a

timeseries to be aligned with one another, and then transferred from native space to standard space, such as Montreal Neurological Institute (MNI) space or Talairach space, to facilitate group analysis.

5.1.5. Contingency Management

Contingency Management (CM) is a treatment for substance use disorder, which is particularly effective for cocaine [329] and opioid [330] misuse. It involves operant conditioning, whereby the allocation of rewards provides positive reinforcement for a behavioural change [331]. This study sought to not only determine the effectiveness of CM as a treatment for methamphetamine misuse in the Western Cape, but more specifically to identify the neural correlates associated with short-term abstinence in response to CM, and in particular those related to executive function, which is essential in cessation of drug-taking behaviour.

5.1.6. Executive Function

Executive function is a term used to define a number of processes that regulate behaviour. Largely mediated by the cortex, executive control involves participation of separate brain regions each performing different functions. Abilities associated with executive function comprise inhibitory control needed for working memory, cognitive flexibility and sustained attention, as well as planning, reasoning and problem solving [118, 332]. We don't know all of the functions performed by any given brain region with task-based fMRI, implicating a set of brain regions in executive function. The prefrontal cortex, caudate nucleus and subthalamic nucleus participate in inhibitory control [253], while the dorsolateral prefrontal cortex (dlPFC) (* see footnote) is largely associated with working memory [333], planning, error detection, attention, decision making and impulse control [334]. The anterior and posterior dlPFC contributes to executive function [335], while an area originating in the frontal lobe near the dlPFC and extending into the striatum has been linked to planning [336], the posterior dlPFC region has been associated more with attention [335]. Cognitive flexibility is thought to be facilitated by the prefrontal cortex, basal ganglia, anterior cingulate cortex (ACC) and posterior parietal cortex (PPC) [337]. A network aptly named the dorsal attention network and comprised of the dlPFC, superior parietal cortices, frontal eye fields and middle temporal motion complex is largely responsible for tasks that test top-down attention [135].

*Footnote: Although ROI discussed here have multiple functions, and their diversity cannot be succinctly summarised in the text, certain functions of the various ROI are listed so as to give the reader context for the findings.

Loss of inhibitory control and cravings for drugs can undermine attempts at abstinence from narcotics. A region that is affected by chronic MA use is the inferior frontal gyrus (IFG), associated with inhibitory control, focused attention and emotion and processing and regulation [338] as well as processing of speech and language. Moreover, the IFG region is negatively affected by chronic MA misuse [338-340], these include a reduction of grey matter in the region [341], and weaker activation during the Stroop task. Weaker activation of the IFG has been associated with poor decision-making [342].

5.1.7. Craving

When cravings arise, the individual recalls past drug usage, and if the recollection is associated with a positive feeling, then the risk of relapse is greater than if the recollection had unpleasant associations [181], such as arrest or violence. The insula has been associated with cravings and dependence in nicotine addiction, with structural changes which may manifest due to exposure to the drug [343]. It therefore seems likely that the insula could be similarly functionally affected by MA misuse. The insula has been shown to be effected by chronic MA misuse, with reduced grey-matter volumes in this structure (which also occur in the caudate, ACC, amygdala hippocampus and PFC) related to D2/D3 binding potential [344]. Moreover, the insula, ACC, PCC, amygdala, ventral striatum and parts of the PFC exhibit a deficit as measured by cerebral glucose metabolism, an index of local brain function in SUD. [345]. The metabolic deficiency in the ACC, OFC and left insula are negatively correlated with state and trait anxiety [345], which commonly accompanies drug craving [343]. The neurotransmitter dopamine is released in response to craving and in turn appears to induce cravings, especially in the presence of drug related cues [346-348]. Cravings often precede the action of obtaining and using the drug, and are associated with the perceived reward of using the drug [349, 350]. Cravings play a major role in organising behaviour and once in action, powerful inhibitory and/or cognitive control processes are required to prevent eventual use [254, 351].

5.1.8. The Reward System

The striatum, including the nucleus accumbens, caudate and putamen, has been well documented for its roles in dopamine related disorders, including Stimulant Use Disorder. The caudate has a role in both learning as well as inhibitory control [352] while the putamen is associated with reinforcement learning [353] and the nucleus accumbens which processes and evaluates reward and drug associated cues [354].

5.1.9. Rationale

Although brain regions that play a central role in various executive control functions have been well established, whether changes in these areas correspond with outcomes of an 8-week CM treatment for MA Use Disorder is not known. Data collected through the treatment episode can be utilised to assist in understanding the underlying processes in MA Use Disorder, as well as in optimizing treatment interventions.

5.2. Research Questions

Resting state fMRI

Does baseline resting state functional connectivity (rsFC) of brain regions involved in executive function (right anterior and posterior dlPFC, the bilateral IFG and the dorsal ACC) compared with regions involved in reward and craving (posterior insula, putamen and nucleus accumbens) predict outcomes in an 8-week CM-program? See footnote *. Does the CM trial produce change in rsFC within (and between) these regions post-trial compared with pre-trial?

Hypothesis One

- At baseline, participants who are responders to treatment will have greater rsFC compared with those who do not respond to treatment between brain regions that play a key role in executive control and weaker rsFC within the basal ganglia.
- At follow-up greater connectivity will be observed in responders to treatment when compared with baseline results within executive function and attention ROI (cognitive control circuit), as well as weakened connectivity in the striatal/ reward circuit compared with non-responders to treatment.

Structural MRI

Do baseline structural measures of cortical surface area and thickness predict outcomes to treatment? Do these measures change over the course of the 8-week CM trial?

Hypothesis Two

- Responders to treatment will have greater in cortical surface area and cortical thickness in executive function regions at baseline compared with non-responders.
- At follow-up responders to treatment will have greater cortical surface area and cortical thickness in executive function regions when compared with non-responders to treatment.

Footnote *: The caudate, especially its dorsal aspect is part of the frontostriatal circuitry involved in executive function, although it is also involved in reward [4]

5.3. Methods

5.3.1. Resting State fMRI (rs-fMRI)

Diagram 1: Scanner in Groote Schuur's Cubic, Cape Town

MRI data were acquired using a Siemens 3T Skyra Magnetom whole body scanner (software version VE11) with a 32 channel receive head coil at the Cape Universities Brain Imaging Centre (CUBIC). The resting-state fMRI sequence employed echo-planar imaging (EPI) (TE/TR=30/2000 ms, FA=80°, matrix 64x64, FOV=220 mm, 34 axial slices, slice thickness 4 mm, voxel size $3mm^3$). The participants remained awake with their eyes open, focusing on a cross on the screen, presented on a mirror in the scanner bore.

5.3.2. Structural MRI (S-MRI)

Structural imaging included a whole-brain multi-echo MPRAGE (MEMPR) sequence including real-time motion correction (TR = 2530 ms, TE = 1.53, 3.21, 4.89, 6.5 ms; TI (or longitudinal relaxation time/ time constant) 1200 ms; fractional anisotropy (FA) 7; field of view (FOV) 256 mm; matrix 256x256; voxel size 1 mm^3, scan time: 9 minutes).

5.3.3. Data Analysis

5.3.3.1. Rs-fMRI pre-processing

After converting the raw DICOM files acquired from the scanner into the NIFTI format using dcm2nii (in R neuroconductor [355]), we employed Freesurfers (version 5.3) recon-all tool to skull-strip the data. Using a bash script the skull-stripped data was converted from .mgz file to a NIFTI file, with de-identified participant names. The quality of the skull-stripped data was checked in the AFNI viewer against an MNI152 structural mask as an underlay. We then generated nuisance regressor masks using 3-dcalc.

Next the afni-proc.py script was run to create a study-specific preprocessing script [69]. Afni-proc creates single subject processing scripts for resting state in the tcsh language in order to align response magnitudes as input for group analysis [69]. The derived script applied the following steps, in order: 1)

removal of the first 4 volumes of the EPI sequence to ensure magnetic field equilibrium was attained using 3dTcat; 2) removal of spikes from the 3D+time input data, which then writes a new dataset with spike values replaced. Spikes were truncated if they were more than 4 times the standard deviation using 3dDespike; 3), alignment of the EPI to standard space using the MNI 152 atlas, via intermediate registration with subject-specific anatomical images; 4) and spatial smoothing of the EPI using a 6-mm Gaussian kernel [69]. The influence of motion and physiological artefacts derived from WM and CSF were mitigated by simultaneously regressing out high motion volumes (identified as those displaced by more that 0.3mm relative to the preceding volumes, or for which at least 10% of their voxels were determined by 3dToutcount as being outliers) and temporal motion estimates, as well as average signal from physiological (cerebrospinal fluid and white matter) masks.(see footnote*) Finally we restricted the BOLD time-series to the 0.01 to 0.1 Hz frequency band [69].

At least 4 minutes of BOLD data were required after the pre-processing and identification of high motion volumes, in order for a participant's data to be included in the analysis. As an additional safeguard against the effect of subject motion framewise displacement was included as a covariate in all resting state analyses. The resting state fMRI output was then subject to a stringent manual quality control using the AFNI viewer. Each participant's BOLD dataset was checked using their T1 data as an underlay as per the guidelines described by Kelly et al. (2010) [356]. One participant was removed for excessive motion in post-treatment (responder), and none were removed from baseline.

We conducted a Fisher-Z transformation to the mask and resting-state data for each subject so as to shift the distribution of correlation coefficients so that it provided a closer fit to the normal distribution.

5.3.3.2. Creation of ROI seeds:

Seeds were generated using peak co-ordinates from previous reports of functional activation in regions of interest in either a resting or task-based fMRI studies (if a resting state co-ordinate was not available). Seeds were created in stereotaxic space and not anatomical space because many regions, such as the dlPFC, are not anatomically defined. The coordinates were confirmed with Neurosynth [207] and AFNI [357], whereby the co-ordinate found in the papers were input into Neurosynth, and if the output papers showed that the meta-analyses of Neurosynth had the same co-ordinates or similar co-ordinates for those ROI (co-ordinates out by maximum 2 mm), then they were accepted (see table 1). We then checked these co-ordinates against the maps provided by AFNI, to ensure that they were within range of the co-ordinates provided there by checking the 'where am I' option in the GUI (see table 1). Moreover if neither rsfMRI or task-based fMRI provided satisfactory co-ordinates, then co-ordinates were obtained from solely from Neurosynth and AFNI [207, 357]. Seeds were created with a 9mm radius, and checked again for accuracy of position using the AFNI viewer and Neurosynth co-ordinates.

*Footnote: We did not regress out average signal/ global signal as this is still controversial [1, 2]

5.3.3.2.1. Within session analysis (baseline minus post-treatment)

We selected fourteen regions of interest (ROI) and compared connectivity estimates between each of them at both baseline and post-treatment. The statistical computing platform R 3.5.3 was used to determine correction for multiple comparisons for behavioural and clinical comparisons, while AFNI's 3DClustSim was used for multiple comparisons of the rsfMRI data, at both the voxel and cluster level. Correction for the number of voxel-wise analyses was not performed, as this is not standard procedure in the literature. For each of the seeds, the most up-to-date guidance on setting a sufficiently conservative statistical threshold at the voxel and cluster level was followed [358].

We used the Benjamini Hochberg false discovery rate correction for multiple comparisons due to the small sample as opposed to the familywise error rate (as in Bonferroni)[359] equation from the FSL library [360]. Initially we ran it on every comparison conducted, then on every comparison conducted on a specific seed and finally we removed all output (the entire between region analysis) that was above 0.1 and ran the comparison again. We then completed multiple corrections for 3 executive function outcomes (trail making task time to completion, Stroop accuracy and Continuous performance task accuracy).

Region of interest (9mm seed)	Coordinate	Brodmanns area codes	Where sourced and confirmed by
Right anterior dlPFC [335].	x = 30, y = 43, z = 23	BA 9-46	Cieslik et al. 2012 Neurosynth & AFNI
Right posterior dlPFC [335].	x = 37, y = 33, z = 32	BA 46	Cieslik et al. 2012 Neurosynth & AFNI
Right and left interior frontal gyrus (IFG) [361]	x = -36, y = 16, z = -4 x = 42, y = 18, z = -6	BA 45 BA 47	Hampshire et al 2010 Neurosynth & AFNI
Right and left dorsal anterior cingulate cortex (dACC) [362]	x = -12, y = 15, z = 51 x = 3, y = 12, z = 54	BA 6 and 8 BA 24 and 8	Moeller et al 2014 Neurosynth & AFNI
Right and left posterior insula [363, 364]	x = -38, y = -6, z = 5 x = 35, y = -11, z = 6)	BA 1, 2, 3 and 43 BA 52	Dean et al 2011, and Faulkner et al 2019 Neurosynth & AFNI
Right and left putamen [207].	x = 28,y = 2, z = 0 x = -28,y = 2, z = 6	BA 8 BA 3	Yarkoni et al. 2011 Neurosynth & AFNI
Right and left nucleus accumbens [207].	x = -10, y = 8, z = -10 x = 14, y = 10,z -10	BA 25, 33 and 34 BA 25, 33 and 34	Yarkoni et al. 2011 Neurosynth & AFNI
Right and left caudate [207].	x = -8, y = 10, z = 4 x = 14, y = 18, z = 2	BA 26 BA 26, 29 and 30	Yarkoni et al. 2011 Neurosynth & AFNI

Table 1: Selected potential regions of interest and their corresponding coordinates with the source of the coordinate referenced.

5.3.3.2.2. Between session correlations

Correlation maps that were too noisy (having strong activation outside of the brain) were checked for excessive motion, and if these were too extreme they were rejected from analysis following agreement between two researchers (LvN and JI). This led to only one participant (non-responder) being excluded post-treatment. Group differences in whole-brain connectivity were tested using AFNI's 3dttest++, adjusting for participant framewise displacement estimates. The ClustSim flag was passed to 3dttest++ to correct for multiple comparisons at the voxel-level.

Covariates that may confound estimates of the association between the primary independent variable (treatment response) and network connectivity estimates were identified using bivariate test statistics for each covariate and network connectivity. These were subsequently included in separate models to determine the extent to which they weaken group effects on model estimates. We did not enter more than one covariate, in addition to framewise displacement in the statistical models, given concern regarding the limited power of these analyses due to the small sample size.

In the AFNI viewer we used MNI152 as an underlay, set the coordinates to SPM order, nearest neighbour was set to 2 as was number of voxels. Voxel alpha was set to $p<0.001$. Any statistically significance was measured at a cluster-wise alpha of 0.05.

5.3.3.3. Structural MRI (T1)

5.3..3.1. Pre-processing:

The raw DICOM files for the MPRAGE T1w sequence were converted to NIFTI formatting using dcm2nii. Freesurfer's recon-all was applied to skull-strip the data. Estimates of cortical thickness and surface area were extracted from resulting segmentation output. The output was subjected to manual checking as quality control by checking that only subjects were listed in the rows, and no random folders were included into the .csv files. Moreover we followed the ENIGMA protocol for quality control [365]. This involves a three step procedure; '(1) extracting cortical measures from FreeSurfer, (2) using ENIGMA Cortical QC scripts and the breakdown of cortical QC code, and (3) assess population summary statistics of cortical traits and related histograms' [365].

5.3.3.3.2 Structural MRI (T1) analysis:

The T1 preprocessing outcomes were analysed in R version 3.5.3. T-tests were performed to establish regions where cortical thickness and surface area differed significantly between responders to treatment and non-responders to treatment. Regions that were statistically significant or that trended towards significance were selected for further analysis with an ANCOVA including relevant covariates to

determine their effect on the outcomes. Due to the small sample size, the effect of each covariate was analysed separately such that only one covariate appeared in the model at any given time. The covariates added were inter-cranial volume (ICV) [366] as well as years of education and household income, which showed statistically significant differences between group in the demographic analysis (table 2 below). Sex was also included as a covariate as it has been shown to be an influential factor in risky decision making in MA misuse [75]. We assessed these covariates effects on surface area, as well as cortical thickness.

5.4. Results

5.4.1. Demographics

Differences between groups were found in household income (non-responders to treatment having greater average income than responders to treatment) and number of urine tests drug negative before the trial (responders to treatment providing more negative urine samples than non-responders to treatment). Trend effects were seen for years of education and monthly amount spent on methamphetamine (see Table 2).

	Responders (n = 17)	**Non-Responders (n = 13)**	**Wilcoxon Rank Sum**
Age (M ± SD)	33.77 ±6.69	35.2 ± 5.62	p = 0.71
Race (n)	15 MRA, 2 African	13 MRA	
Education (M ± SD)	11.82 ± 2.92	9.62 ± 2.33	p = 0.06+
WASI IQ (M ± SD)	86.18 ± 18.36	82.85 ± 11.82	p = 0.71
RHRSD (M ± SD)	28.71 ± 24.17	23.77 ± 21.45	p = 0.72
Household income (M ± SD)	R9117.65 ± R11522.44	R25576.92 ± R15947.63	p = 0.02**
Median IQR	R10000 R7500	R37500 R27500	
Employment at time of trial (%)	16%	0%	
Cigarettes smoked daily (M ± SD)	6.82 ± 6.02	10.23 ± 9.08	p = 0.49
ASPD (n)	3	4	
Previous attempts to stop (M ± SD)	3.71 ± 5.93	4.62 ± 6.83	p = 0.20
Grams per day (M ± SD)	0.87 ± 0.49	1.14 ± 0.69	p = 0.37
Years of misuse (M ± SD)	10.00 ± 4.10	12.92 ± 3.45	p = 0.12
Amount spent monthly (M ± SD)	R1399.71 ± R1112.38	R2394.62 ± R1524.73	p = 0.06+
Age initiated (M ± SD)	22.71 ± 6.26	22.15 ± 6.50	p = 0.95
Number of urine tests drug free before scan (M ± SD)	4.944 ± 3.33	2.31 ±1.03	p = 0.01**
Number of psychotic symptoms (M ± SD)	3.88 ± 3.55	4.85 ± 3.58	p = 0.38

Table 2: Demographics within the MA group (MRA = Mixed race ancestry, RHRSD = Revised Hamilton Rating Scale for Depression, stars (*) flag levels of significance with one star denoting a p value below 0.05 and two if the p value is less than 0.01)

5.4.2. Resting-state fMRI

5.4.2.1. Between regions of interest (rsFC at baseline)

No clusters survived after multiple comparisons, indicating that there was no evidence for differences between groups at baseline. Results using censored motion as a covariate are presented in table 3. When adding the results from the neuropsychological tests from chapter 4 to our analysis, no clusters survived after correction for multiple comparisons.

	ROI (9mm)	Co-ordinates	Required vox to reach p = 0.05	Actual voxels	Region	Brodmann's Area
Executive Control Network	Left IFG	-12, -72, +63	51	16	Left precuneus	BA 7
	Right IFG	-12, -72, +63	48	9	Left Precuneus	BA 7
	Right anterior dlPFC	+48, +54, -3	47	22	Right middle frontal gyrus	BA 10
	Right posterior dlPFC	-60, -48, +54	55	7	Left inferior parietal lobule	BA 40
Salience Network	Left dACC	-75, -18, +9	53	4	Left superior temporal gyrus	BA 42
	Right dACC	-15, -36, +81	55	16	Left postcentral gyrus	BA 3
	Left posterior Insula	+66, +27, -15	53	32	↓ Right inferior frontal gyrus	BA 45
	Right posterior insula	+12, +15, +48	48	11	Right medial frontal gyrus	BA 32
Striatum	Left Caudate	+39, -57, -48	52	10	Right cerebellum	
	Right Caudate	-33, -54, +42	52	13	Left inferior parietal lobule	BA 40
	Left Putamen	+27, +21, -15	53	5	Right inferior frontal gyrus	BA 47
	Right Putamen	+36, -75, -24	49	18	Right cerebellum	
	Left nucleus accumbens	+9, -81, +51	53	10	Right precuneus	BA 7
	Right nucleus accumbens	+54, -42, +36	61	19	Right supramarginal gyrus	BA 40

Table 3: outcomes of comparisons of rsFC between regions of interest at baseline. (dACC = dorsal anterior cingulate cortex, dlPFC = dorsolateral prefrontal cortex, IFG = inferior frontal gyrus, L = left, NAC = nucleus accumbens, R = right)

5.4.2.2. Resting-state fMRI: between sessions (differences between ROI Pre- to Post-Treatment)

When exploring the difference between sessions (correlation maps for post-treatment subtracted from baseline correlation maps), we find no significant clusters between groups (after correcting for multiple comparisons) see table 4.

	ROI (9mm)	Co-ordinates	Required vox to reach p = 0.05	Actual voxels	Region	Brodmann's Area
Executive Control Network	Left IFG	-0, -57, +69	50	37	↑ Left precuneus	BA 7
	Right IFG	-12, +3, +27	52	8	Left cingulate gyrus	BA 33
	Right anterior dlPFC	+60, +9, -3	52	11	Right superior temporal gyrus	BA 22
	Right posterior dlPFC	+57, +21, +48	52	5	Right middle frontal gyrus	BA 8
Salience Network	Left dACC	-54, +12, -9	49	42	↑ Left superior frontal gyrus	BA 22 and 38
	Right dACC	+9, -15, +27	65	9	Right cingulate gyrus	BA 23
	Left posterior Insula	-24, -81, +45	51	6	Left precuneus	BA 7
	Right posterior insula	+27, -72, +60	40	19	Right superior parietal lobule	BA 7
Striatum	Left Caudate	+42, -48, +9	47	8	Right superior temporal gyrus	BA 13 and 39
	Right Caudate	-39, -24, +9	59	14	Left superior temporal gyrus Left insula	BA 13 BA 41
	Left Putamen	-57, +9, -18	49	13	Left temporal pole	BA 21
	Right Putamen	+45, -36, -6	49	4	Right middle temporal gyrus	BA 21
	Left nucleus accumbens	+33, -66, +15	63	3	Right middle temporal gyrus	BA 19
	Right nucleus accumbens	-39, +6, +63	56	8	Left middle frontal gyrus	BA 6

Table 4: Correlation between brain regions pre- to post-CM treatment. (dACC = dorsal anterior cingulate cortex, dlPFC = dorsolateral prefrontal cortex, IFG = inferior frontal gyrus, nucleus accumbens = nucleus accumbens)

5.4.2.3. Exploratory Analysis – post treatment outcomes

There was no significant differences found between sessions for any of the regions of interest in comparing responders and non-responders (see Table 5).

	Response to treatment	Means ± std. dev.	T.test	t stat	Degrees of freedom
Session 1					
IFG	Responders Non-responders	0.45 ± 0.17 0.48 ± 0.15	0.60	-0.54	23.37
dlPFC	Responders Non-responders	0.38 ± 0.29 0.38 ± 0.21	0.96	0.05	25.63
dACC	Responders Non-responders	0.45 ± 0.15 0.49 ± 0.18	0.54	-0.63	19.09
Insula	Responders Non-responders	0.28 ± 0.10 0.28 ± 0.22	0.95	-0.06	12.86
Caudate	Responders Non-responders	0.40 ± 0.16 0.42 ± 0.23	0.76	-0.31	16.21
NAc	Responders Non-responders	0.52 ± 0.16 0.58 ± 0.17	0.36	-0.93	20.67
Putamen	Responders Non-responders	0.32 ± 0.16 0.41 ± 0.12	0.09+	-1.74	25.31
Session 2					
IFG	Responders Non-responders	0.50 ± 0.17 0.48 ± 0.15	0.74	0.34	24.09
dlPFC	Responders Non-responders	0.35 ± 0.27 0.40 ± 0.23	0.61	-0.51	23.89
dACC	Responders Non-responders	0.45 ± 0.17 0.51 ± 0.15	0.28	-1.11	23.04
Insula	Responders Non-responders	0.23 ± 0.20 0.28 ± 0.14	0.41	-0.84	25.78
Caudate	Responders Non-responders	0.39 ± 0.14 0.40 ± 0.19	0.83	-0.21	17.44
NAc	Responders Non-responders	0.56 ± 0.19 0.57 ± 0.12	0.84	-0.21	26.00
Putamen	Responders Non-responders	0.35 ± 0.25 0.44 ± 0.12	0.26	-1.16	24.12
Between sessions					
ECN **IFG**			0.79	0.14 non-responders 0.68 Session 2	53
ECN **dlPFC**			0.94	0.32 non-responders -0.15 Session 2	53
SN **dACC**			0.46	1.24 non-responders 0.20 Session 2	53
SN **Insula**			0.61	0.64 non-responders -0.76 Session 2	53
Striatum **Caudate**			0.89	0.40 non-responders -0.25 Session 2	53
Striatum **NAc**			0.61	0.80 non-responders 0.60 Session 2	53
Striatum **Putamen**			0.19	1.76 non-responders 0.60 Session 2	53

Table 5: outcomes of comparisons of rsFC between regions of interest pre to post-treatment. (dACC = dorsal anterior cingulate cortex, dlPFC = dorsolateral prefrontal cortex, ECN = executive control

network, IFG = inferior frontal gyrus, L = left, NAC = nucleus accumbens, R = right, SN = salience network)

There was no significant differences in motion (framewise displacement) between participants at either session and between sessions, see table 6.

Response to treatment	**Means ± std. dev.**	**T.test**	**t stat**	**Degrees of freedom**
Session 1				
Responders Non-responders	0.06 ± 0.03 0.07 ± 0.02	0.26	-1.16	24.79
Session 2				
Responders Non-responders	0.07 ± 0.03 0.08 ± 0.04	0.45	-0.77	16.98
Between sessions				
		0.22	1.312 non-responders 1.19 Session 2	53

Tablle 6. Comparison of motion (framewise displacement) between participants and sessions.

5.4.4. Structural Outcomes

5.4.4.1 Baseline

Non-responders to treatment had greater cortical thickness than the responders to treatment in the left hemisphere while in the right hemisphere the inverse was observed. The left cuneus (p = 0.032) and left pars opercularis (p = 0.023) was thicker in non-responders to treatment at baseline over responders to treatment and the right medial orbitofrontal cortex (p = 0.043) and right frontal pole (p = 0.01) had significantly greater cortical thickness in responders to treatment at baseline over non-responders to treatment, with only the right frontal pole surviving correction for multiple comparisons (p = 0.05), see table 7 and diagram 2.

	responders to treatment (n = 17)	**non-responders to treatment (n = 13)**				
	Means & Std.dev.	**Means & Std.dev.**	**T.Test**	**T.stat**	**Degrees of Freedom**	**Benjamini Hochberg**
L_parsorbitalis_surfavg	650.71 ± 77.21	708.39 ± 95.87	0.09+	-1.77	22.67	0.09+
L_cuneus_thickavg	1.87 ± 0.13	1.97 ± 0.11	0.03*	-2.27	27.17	0.09+
L_parsopercularis_thickavg	2.58 ± 0.19	2.73 ± 0.15	0.02*	-2.40	27.99	0.09+
R_medialorbitofrontal_thickavg	2.51 ± 0.19	2.39 ± 0.11	0.04*	2.12	26.04	0.09+
R_frontalpole_thickavg	2.76 ± 0.21	2.54 ± 0.22	0.01*	2.80	24.78	0.05*

Table 7: Cortical Thickness and surface average for the brain at Baseline

When adding the covariates to the uncorrected values (table 8) we see that the pars orbitalis and medio-orbitofrontal cortex loose significance. The par orbitalis does, however, maintain a trend to significance.

responders to treatment (n = 17) **non-responders to treatment (n = 11)**	**Ancova - Relapse**	**Relapse & ICV**	**Relapse & Number of years of education**	**Relapse & household income**	**Relapse & Sex**
L_parsorbitularis_surfavg	0.08+	0.04*	0.08+	0.06+	0.07+
L_cuneus_thickavg	0.03*	0.04*	0.04*	0.03*	0.04*
L_parsopercularis_thickavg	0.03*	0.03*	0.03*	0.03*	0.03*
R_medialorbitofrontal_thickavg	0.06+	0.06+	0.06+	0.06+	0.06+
R_frontalpole_thickavg	0.01*	0.01*	0.01**	0.01*	0.01*

Table 8: ANCOVA for the overall model

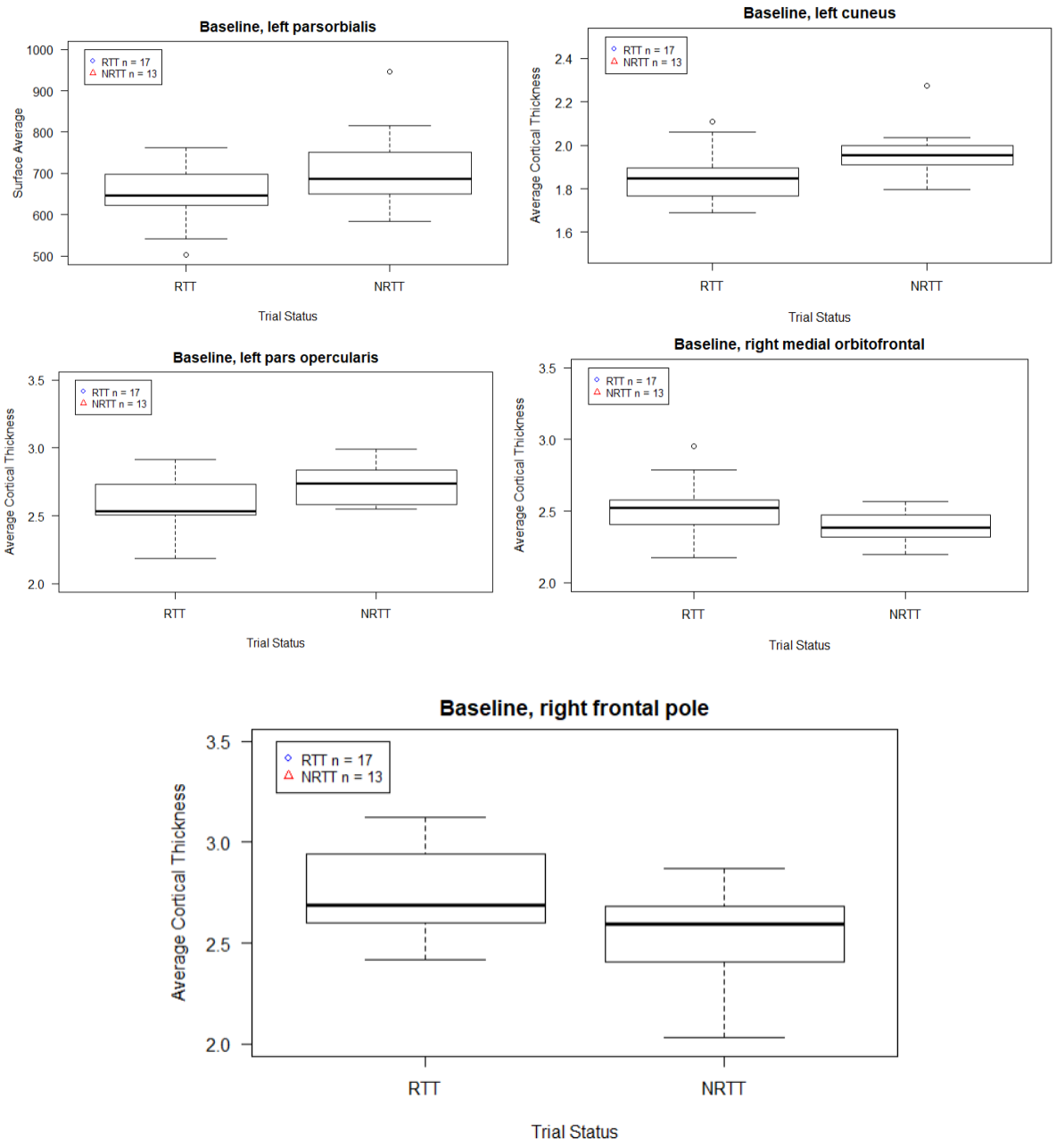

Figure 2: Baseline whisker and box plot of surface average and cortical thickness

5.4.4.2. Between sessions (Baseline minus post-treatment structural outcomes)

There were only two statistically significant differences between ROI when measured at baseline compared with completion of treatment (baseline minus post-treatment), with post-treatment showing increased surface average in the left par orbitalis (p = 0.04) in non-responders to treatment than responders to treatment, but cortical thickness was increased in the right medial orbitofrontal cortex (p = 0.03) in responders to treatment than non-responders to treatment see table 9. None of the outcomes survived correction for multiple comparisons.

	Responders to treatment (n = 17)	**Non-responders to treatment (n = 11)**				
	Means & Std.dev.	**Means & Std.dev.**	**T.Test**	**T.stat**	**Degrees of Freedom**	**Benjamini Hochberg**
L_parsorbitalis_surfavg	-3.65 ± 24.12	15.82 ± 21.49	p = 0.04*	-2.23	23.28	0.32
L_parsopercularis_surfavg	-17.65 ± 51.47	92.00 ± 214.33	p = 0.13	-1.67	10.75	0.33
L_cuneus_thickavg	-0.01 ± 0.10	0.01 ± 0.07	p = 0.48	-0.72	25.29	0.74
L_inferiortemporal_thickavg	-0.05 ± 0.11	0.02 ± 0.11	p = 0.12	-1.65	21.13	0.63
L_fusiform_thickavg	-0.05 ± 0.11	0.03 ± 0.09	p = 0.07+	-1.92	24.27	0.54
L_lateraloccipital_thickavg	-0.05 ± 0.11	0.02 ± 0.11	p = 0.11	-1.65	21.13	0.63
L_parsopercularis_thickavg	0.00 ± 0.11	0.04 ± 0.13	p = 0.50	-0.69	19.80	0.74
L_parstriangularis_thickavg	-0.00 ± 0.13	0.01 ± 0.13	p = 0.74	-0.34	22.66	0.74
R_medialorbitofrontal_thickavg	0.08 ± 0.18	-0.04 ± 0.07	p = 0.02*	2.42	23.17	0.24
R_frontalpole_thickavg	0.04 ± 0.22	-0.01 ± 0.15	p = 0.69	-0.40	25.94	0.74

Table 9: Baseline comparison minus post-treatment for change over time

The uncorrected ANCOVA shows the parorbitalis and medial orbitofrontal cortex presenting with statistically significant findings, (see Table 10).

Responders to treatment (n = 17) **Non-responders to treatment (n = 11)**	**Ancova - Relapse**	**Relapse & ICV**	**Relapse & Number of years of education**	**Relapse & household income**	**Relapse & Sex**
L_parsorbitalis_surfavg	p = 0.04*	p = 0.04*	p = 0.04*	p = 0.04*	p = 0.04*
L_parsopercularis_surfavg	p = 0.05+	p = 0.06+	p = 0.06+	p = 0.06+	p = 0.05+
L_cuneus_thickavg	p = 0.50	p = 0.50	p = 0.51	p = 0.51	p = 0.51
L_fusiform_thickavg	p = 0.08+	p = 0.08+	p = 0.08+	p = 0.09+	p = 0.08+
L_inferiortemporal_thickavg	p = 0.11	p = 0.11	p = 0.11	0.12	0.10
L_lateraloccipital_thickavg	0.11	0.11	0.11	0.12	0.10
L_parsopercularis_thickavg	0.49	0.50	0.47	0.50	0.50
L_parstriangularis_thickavg	0.74	0.75	0.14	0.30	0.85

R_frontalpole_thickavg	0.72	0.72	0.72	0.73	0.71
R_medialorbitofrontal_thickavg	0.05*	0.05+	0.05*	0.05+	0.05+

Table 10: ANCOVA for the overall model with covariates

Non-responders to treatment had greater surface area in the left pars opercularis compared with responders (Table 11), as well as greater cortical thickness in the left inferior temporal lobe in session two.

	RTT (n = 17)	**NRTT (n = 11)**				
	Means & Std.dev.	**Means & Std.dev.**	**T.Test**	**T.stat**	**Degrees of Freedom**	**Benjamini Hochberg**
L_parsopercularis_surfavg	1586.941 ± 285.5391	1395.455 ± 146.7006	0.028*	2.3303	25.047	0.094+
L_cuneus_thickavg	1.874588 ± 0.1318565	1.965273 ± 0.1344887	0.094+	-1.756	21.186	0.094+
L_fusiform_thickavg	2.679235 ± 0.08930253	2.620545 ± 0.08263094	0.089+	1.7778	22.717	0.094+
L_inferiortemporal_thickavg	2.733353 ± 0.1280590	2.628364 ± 0.1003277	0.023*	2.4216	24.901	0.094+
L_lateraloccipital_thickavg	2.114588 ± 0.09105909	2.037273 ± 0.12314064	0.091+	1.7897	16.998	0.094+
L_parstriangularis_thickavg	2.528 ± 0.1865814	2.413 ± 0.1372465	0.072+	1.8754	25.461	0.094+

Table 11: Cortical Thickness for the left hemisphere of the brain Post-treatment

5.5. Discussion

The purpose of this pilot study was 1) to determine whether treatment response was predicted by brain functional and structural alterations between responders to treatment and non-responders. 2) to assess whether treatment led to changes in brain functional and structural and alterations

At both baseline and follow up there was no significant diffeneces between groups, which is contrary to our hypothesis. Our structural analysis at baseline showed that responders to treatment had greater cortical average thickness in the right frontal pole than non-responders to treatment. This region is associated with executive function, and may be linked to the responders to treatment focusing more on monitoring of their actions than non-responders to treatment. Moreover structurally there were no outcomes that survived corrections for multiple comparisons between sessions.

Hypothesis One

- *At baseline, participants who are responders to treatment will have greater rsFC compared with those who do not respond to treatment between brain regions that play a key role in executive control and weaker rsFC within the basal ganglia.*
- *At follow-up greater connectivity will be observed in responders to treatment compared with baseline, within executive function ROI (cognitive control circuit), as well as weakened connectivity in the striatal/ reward circuit compared with non-responders to treatment.*

5.5.1. Resting-state fMRI Baseline

Hypothesis one was not supported by our findings, as no statistically significant differences in network connectivity were observed between groups at baseline. There was no statistical significance between groups at baseline, subsequently no networks were identified as having significant connectivity. One probable explanation for this null finding is that these analyses were under-powered, largely due to small sample size.

5.5.2. Between sessions (baseline minus post-treatment)

There was no statistically significant differences in network connectivity between groups across sessions either. This too is likely also an effect of the small sample size.

Hypothesis Two

- *Responders to treatment will have greater in cortical surface area in executive function regions of the brain and cortical thickness in these same regions at baseline compared with non-responders.*

- *At follow-up responders to treatment will have greater cortical surface area and cortical thickness when compared with non-responders to treatment.*

We did find greater cortical thickness in responders compared with non-responders in the right frontal pole, but surprisingly we also found greater cortical thickness in non-responders compared with responders in two cortical regions (the left cuneus and the left pars orbicularis) before correcting for multiple comparisons.

5.5.3. Structural MRI

When looking at our second hypothesis, at baseline non-responders to treatment presented with great surface average in the left pars-orbitalis and greater cortical thickness in the pars-opercularis, both part of the IFG which is associated with speech and language as well as inhibitory processing involved in reward. Individuals using MA have been shown to have elevated amount of talkativeness related to the alertness associated with a stimulant drug, which may explain these findings [367], or as mentioned previously, the greater surface average and cortical thickness may simply be the inability to inhibit cravings. It is important to consider that anatomical presentations may well be premorbid and unrelated to the use of MA. The inclusion of a control group and a larger sample size would help to clarify this concern in future studies.

Consistent with the finding associated with the IFG above, is the greater cortical thickness within the left cuneus. The cuneus is associated with receiving and processing visual information, and visual problems are commonly reported in MA use [368], although the extent of it has not been fully explored. The finding of greater cortical thickness in the non-responders over responders in the left cuneus in alcohol dependent studies has been shown to be larger in relapsers than abstainers [369].

Responders to treatment differed in that all areas in the right hemisphere presenting with statistical significance post correction for multiple comparisons. Responders to treatment had greater cortical thickness in both the right medial orbitofrontal region and the right frontal pole, which are both regions associated with executive function, including cognitive processing in decision making, as well as emotions and reward [70] and monitoring of the outcomes of actions consequential to the cortical thickness of the frontal pole [370].

The greater cortical thickness in the frontal pole ($p = 0.01$) in responders at baseline remained statistically significant at post-treatment ($p = 0.016$). The frontal pole is functionally connected to the posterior visual cortex. While the dorsal ventral gradient within the frontal pole is likely used to guide behaviour (in monkeys it has been seen to monitor action outcomes [371]), the dorsal regions connect to the IFG. This connection to the IFG imply that the rsFC is possibly used in the processing of goals and planning of

actions while ventral regions connect to brain areas processing stimuli information (amygdala and temporal pole)[370] (conceivably drug related cues).

The frontal pole is important in executive control including dealing with reward expectations and selection of sub-goals allowing an individual to select the priority between a stimulus orientated and stimulus independent cognitive process [372]. This has important bearing in our study, as the responders displayed these qualities typical of the frontal pole at baseline and at termination of the study. Thus we can deduce that the frontal pole played an important role in obtaining and maintaining abstinence. Due to the goal orientated nature of CM, it is likely that this treatment is uniquely suited to individuals with a greater cortical thickness in the frontal pole region. Moreover the frontal pole has been implicated in prospective memory, and likely involved with maintenance more than execution of a delayed intention [373], again supporting the theory that this anatomical structure in responders gave them an advantage in maintaining abstinence.

It is possible that these anatomical findings reflect the hypothesised greater executive control that responders possess which results in more favourable outcomes to the CM trial. On closer analysis, these connections imply that the reason for the frontal pole having greater thickness at baseline and end of trial in responders to treatment, is that responders to treatment display greater resolve in obtaining and maintaining abstinence. Moreover, a study using continuous theta burst stimulations to the left frontal pole in cocaine and alcohol users, found that in cocaine users the bursts reduce BOLD signal in the caudate, nucleus accumbens and ACC as well as the OFC and parietal cortex [374]. This may demonstrate the role of the frontal pole in the reduction of the dominance of the reward system and pain associated with cravings in Substance Use Disorder. The reduced BOLD signal may also be a viable reason why the frontal pole has greater thickness in responders to treatment over non-responders to treatment in MA misuse, whereby responders to treatment diminish the dominance of the reward system pre- and during-treatment using this brain region.

Post-treatment (see table 10) the non-responders to treatment had far more changes than responders to treatment, which was largely in the language and visual areas, which did not survive correction for multiple comparisons. The left pars opercularis is associated with, but not limited to, language and self-control [375]. The other significant finding was in the left inferior-temporal lobe which is involved in language [367, 368]. Although these are interesting findings, it is also beyond the scope of this discussion to go into the language and visual functions here.

The pars tiangularis, is part of the IFG as well as the pars opercularis and subsequently may also be involved in inhibitory control [361, 376-378], this inhibitory control was clearly displayed by the responding group. As mentioned previously the frontal pole also has greater cortical thickness compared with non-responders to treatment.

5.6. Strengths and Limitations

Firstly, it is important to bear in mind that some non-responders to treatment may have only had one or a small number of urine tests that were drug positive, (which may even have been at the very start of the trial) compared with other non-responders to treatment. The presence of partial responders to treatment in the data may result in a skewing of results, as their structural manifestations post treatment may mirror those of the responders to treatment. The only way to determine if this is the case would be to repeat the trial with a larger sample size.

Secondly, the presence of anatomical findings may have been premorbid and not as a consequence of MA use. Thirdly, although this sample size is acceptable for an fMRI study, it is still considered small when divided into responders and non-responders and subsequently a larger sample size may confirm our findings. Fourthly, there are multiple potential confounds that were not controlled for, including but not limited to; blood tests for the presence of other substances like methaqualone and alcohol, the effects of cravings and withdrawal on resting-state data and sleep state in the scanner.

Fifthly there was no untreated MA control group, so we are unable to determine if changes rsFC or structural changes are attributable to abstinence or to CM. All we can currently say is that it is attributable to abstinence through a CM program. Sixthly, there is a lack of effective connectivity studies with which to compare our results and that address functional connectivity alterations.

Seventh, we were unable to establish directionality, and this study would have been complimented with a DTI analysis to establish this. Eighthly, we did not correct for the number of seeds for which voxel-wise connectivity analyses were conducted. Although though it is not standard procedure to do so, it may have added value to the analysis.

5.7. Conclusion

There was no statistically significant clusters found at baseline or between sessions for either group of participants, subsequently disproving our first hypothesis. However, responders to treatment did show greater increase in cortical volume in executive function regions (the frontal pole) than non-responders to treatment, consistent with CM leading to increased inhibitory control.

This concludes the analysis of data from this study. In the next final chapter I will focus on amalgamating the findings from the various chapters in a critical way. This includes chapter 2 (the systematic review) and its predicting outcomes, as well as chapter 4 and 5 which contain the outcomes of the CM trial conducted on MA misusers.

Chapter 6:

Conclusion

In this chapter I will initially lay out the main findings then I will critically review the various results put forward in the different chapters of this thesis. The thesis has reviewed the burden of methamphetamine (MA) dependence on individuals and communities in South Africa and assessed the literature to date on resting state-fMRI (rs-fMRI) in stimulant use disorder (SUD). Further the thesis has covered the neuroimaging and neuropsychological findings in an 8-week contingency management (CM) study on responders and non-responders to treatment with respect to executive function. My key aims in the CM study were to determine 1) whether treatment response could be predicted by executive function impairment and brain functional and structural alterations, and 2) whether treatment would lead to changes in executive function and brain functional and structural alterations in responders to treatment when compared with non-responders to treatment. I'll begin the chapter by briefly reviewing the main findings of each chapter.

Systematic review – Chapter 2

Previous studies have observed weaker resting state functional connectivity (rsFC) in executive control networks (ECN) [92, 93, 97, 113] as well as in the salience network (SN) in SUD [94, 117, 129]. Further, these studies have reported weaker rsFC between the default mode network (DMN) and the SN [94, 113] and between the ECN and DMN [97, 113] in individuals who abuse stimulants when compared with controls. Moreover the reward network has been shown to dominate over executive function domains in active users and those that relapse with stimulant misuse [93, 102, 114, 164]. Notably, there is little literature on the predictors or impact of contingency management with regards to brain functional and structural alterations in treatment seeking chronic MA misusers. We therefore sought to evaluate whether responders to CM would show greater rsFC within and between executive function brain regions and weaker rsFC in reward based regions of the basal ganglia firstly at baseline as a predictor of treatment outcomes. Secondly, we hypothesised that there would be functional and structural changes post-treatment for responders to treatment compared with non-responders to treatment within executive function domains.

Demographics

There are certain findings from this study that may act as potential confounders to the outcomes, some of these were controlled for in the analysis, but due to the small sample size, not all could be added at covariates. Never-the-less these variables should be born in mind in the interpretation of the results. Firstly responders had more education and more drug negative urine tests pre-trial than non-responders to treatment, which may suggest commitment and stronger inhibitory control. The greater length of education in responders to treatment calls into question whether this was due to a superior executive control than non-responders, and whether this potential superior executive control was utilised to assist in abstinence during the CM trial. Secondly, non-responders to treatment had greater household income

and also greater expenditure on the narcotic than responders to treatment, possibly reflecting a more severe usage of MA than responders. Moreover the availability of money within the households of non-responders may reduce the motivational salience of the vouchers.

Neuropsychological tests – Hypothesis one – Chapter 4

With respect to performance in executive function at baseline, responders to treatment were faster in the trail making task than non-responders to treatment, but this did not survive for multiple comparisons. Moreover there was no difference in accuracy between groups. Controls also did not show superior performance in the trail making task when compared with the MA group. Possibly this is due to the small sample size and greater numbers would reveal differences our sample was unable to. Previous research comparing SUD with healthy controls, showed that the MA group performed worse on this task than healthy controls [82, 304]. Due to the significant finding of responders performing better with speed to completion than non-responders pre correcting for multiple comparisons (which reduced significance to a trend), this would indicate that non-responders to treatment act in accordance with the literature. The faster speed seen in responders to treatment is consistent with the greater inhibitory control that they display in obtaining abstinence.

Healthy controls were more accurate than the combined MA group in both the Stroop task and the Connors continuous performance task. Responders and non-responders did not differ at baseline in these tasks, which is contrary to our hypothesis.

Surprisingly non-responders to treatment were more accurate on the Stroop than healthy controls at baseline. This finding is inconsistent with our hypothesis that responders to treatment would perform better than non-responders to treatment. Accordingly, we decided to explore this finding further; the preliminary findings showed that even though non-responders to treatment were more accurate, it was only in congruent targets that this occurred, as responders to treatment were more accurate in incongruent targets. All of the groups improved post treatment, with responders to treatment showing greater accuracy than non-responders to treatment, with fewer errors.

In the Connor's continuous performance task non-responders to treatment had more errors than responders at baseline with regards to d' prime showing greater sensitivity to the signal in responders, while non-responders also had a greater number of omissions from block two to block four than responders to treatment, which confirms our hypothesis that responders to treatment will have superior sustained attention over non-responders to treatment.. This finding is consistent with the literature in SUD.

Neuropsychological tests – Hypothesis two – Chapter 4

With regards to the second aim of the study, the change score for the trail making task and the Connors continuous performance task showed that the performance of responders to treatment changed with the intervention in a way that was more similar to changes seen in the healthy controls than non-responders to treatment. In the Stroop, on the other hand, changes over time were more similar for the two MA groups compared with what was observed for the HC's. The finding that in the MA groups did not differentiate with respect to performance on the Stroop task was unexpected. As mentioned above, this apparent discrepancy may be due to the fact that there were far more congruent targets (in which non-responders to treatment excelled), than incongruent targets (in which responders to treatment excelled) in the Stroop task, which is likely the reason for the apparent superior performance by non-responders to treatment compared with responders to treatment. The latter condition can be considered a more challenging, goal-driven, executive function as it requires greater conflict resolution than congruent targets aspect of the task [379].

From these data we can deduce that although our sample size may have been too small to conclusively state that responders have superior executive function than non-responders,the general direction of group differences observed do provide some preliminarysupport for out hypothesis. This is suggested by the finding that responders were more accurate with the more difficult incongruent targets in the Stroop, and had greater d'prime or sensitivity to the signal in the CPT than non-responders. In turn non responders had more omissions in the CPT in later sections of the task showing poor sustained attention. Bearing in mind the fewer number of years of studying in non-responders, this could tie in with the poor sustained attention, which in turn may impair their response to CM. Moreover the change scores show that non-responders had the greatest change overall, which could be due to a ceiling effect from the other two groups, and therefore does not necessarily support the hypothesis that CM improves executive function per se. Possibly CM combined with cognitive training would possibly be more effective.

Resting-state fMRI – Chapter 5

No statistically significant differences were observed between groups either at baseline or across sessions in rsFC, providing little support for hypothesis one, However as predicted, differences were observed between the MA groups with respect to structural anatomy.

When looking at brain structure, we found that responders to treatment had greater cortical thickness at baseline compared with non-responders in a brain region implicated in executive function (right frontal pole $p = 0.01$. Moreover greater greater cortical thickness of the right frontal pole was observed in the responders at both baseline and post-trial. This is consistent with the premise that responders not only had greater years of education, but that this is likely due to superior executive function prior to commencement of the CM trial. Post-treatment this outcome remained similar, with fewer regions of significance (right frontal pole $p = 0.016$ in responders to treatment).

Having briefly summarized the main findings of my work, I will now discussion limitations and strengths of the current study, as well as future directions for research.

6.1. Limitations

Several limitations of this study are important to emphasise. First, with regards to the literature review, only 3 databases were used including PubMed, Scopus and Medline, and consequently I may not have identified all potentially eligible studies, such as those published in other languages besides from English. Moreover in the systematic review we were unable to do a meta-analysis due to insufficient studies meeting our requirements.

Second, our findings of functional and structural alterations in responders to treatment compared with non-responders to treatment were obtained using neurocognitive tasks performed outside of the scanner. In future research it may be useful to conduct a functional task inside the scanner as a task-base fMRI in order to confirm my findings. The limitations of the fMRI results extend into poor temporal and spatial resolution due to movement in the scanner, which is common with this cohort. Subsequently motion was used as a covariate in all analyses. Moreover, the participants were not debriefed after the scan to determine if they fell asleep during the rsfMRI scan. This is important as sleep during the scan would likely confound the results [213], with a decrease in fronto-parietal cortical loops[380]. Possibly for future studies an MRI compatible EEG could be employed during the resting state fMRI scan to monitor potential sleep in the participant [213]. With regards to MRI data there was no healthy control group to act as a control for MRI data, this could be considered for future studies, with larger sample sizes.

Third we had a small sample size which limits the statistical power. This small sample size did not allow us to take into consideration partial responders to treatment, and those that became drug free a week or more into the trial. In future research, a larger sample size would be able to assist in distinguishing this important group.

Fourth, there may have been practice effects between sessions. We were able to account for this to some extent by including a healthy control group to which we were able to compare the changes that occurred in the two MA groups over time with a normal population.

Fifth, there were some differences in socio-demographic variables between those that responded to treatment and those that did not respond to treatment. Non-responders to treatment had statistically significantly fewer years of education, greater household income and less drug negative urine samples prior to commencing with the trial than responders. Due to the small sample size, these variables could

only be included in models one at a time. The greater years at school and more drug negative urine tests likely indicate greater inhibitory control, while the household income may mean that with fewer expenses to concern themselves with, non-responders to treatment may have more cash available for drug purchase.

Sixth many of the measures used in the study were self-report, and are subject to subjective biases and difficulty in recall. The finding on household income did not correlate with amount spent on drug in the last 30 days on the addiction severity index (ASI), for instance, and may reflect many users may not have been aware of the amount they spend. This is especially true in a South African context, where the ASI revealed that the drug was often freely provided. Other self-report measures employed in the study include the revised Hamilton rating scale for depression and the childhood trauma questionnaire. Accordingly results from these measures should be interpreted cautiously. Another potential concern with data acquired on the psychometric tasks is fatigue. In order to try to combat this we offered multiple breaks, including for cigarettes if they were smokers. Moreover, the administration of computer tasks was punctuated with paper tasks to avoid monotony.

Seven, very few clinical trials in substance abuse have any form of post-intervention maintenance, which is also true also for most drug rehabilitation programs. This trial is no different in that it offers no-post intervention maintenance. In numerous substance abuse studies, a larger portion of patients relapse than those who remain abstinent at follow up. Bearing this in mind we need to remember that this is a pilot study and uncovering limitations like this are valuable and noteworthy, as they could be prioritised to be considered in future studies.

Eighth, reward based testing and risky decision making was not conducted in this particular thesis, yet it was covered in the study in another body of literature [75].

6.2. Strengths

Despite these limitations, this work had a number of strengths.

First, The systematic review provided a solid platform on which to build the analysis on this research project, by providing a systematic and comprehensive summary of the rsFC studies in stimulant users. Further we registered the review with Prospero to avoid duplication.

Second, there were few missing data. The conducting of tasks was stringently monitored and data capturing occurred immediately after the task was completed to avoid loss.

Third, a notable strength was the stringent selection criteria of both participants and the matching of healthy controls.

Fourth, we had both neuropsychological testing as well as rsfMRI data to compare and confirm our findings. A double dissociation was observed in tasks of attention and executive function (response inhibition). Although no differences were observed with respect to rsFC, responders to treatment show greater cortical volume increase in a region implicated in executive function than non-responders to treatment.

6.3. Clinical implications

For clinicians, these findings have a number of implications.
It is apparent from this study that CM is an effective treatment for MUD [29], yet it is important to bear in mind that multiple residuary factors influence its effectiveness; these include demographic features as well as executive function status pre-treatment. It is possible that the influence of executive function on treatment response may be enhanced with cognitive training during treatment.

First, This study has shown that part of the reason for the efficacy of CM in a subset of MA using subjects is due to the greater executive function that responders to treatment employ when entering a trial, and that these strengths are retained during abstinence when compared with non-responders to treatment. This was evidenced by the superior performance in both the trail making task and Connors continuous performance task of responders to treatment over non-responders to treatment both at baseline and post-treatment. Moreover insight in this superior executive function in non-responders to treatment was gained by the greater cortical thickness of a brain region thought to support executive function in responders to treatment when compared with non-responders to treatment.

Second, these data support the possibility that that executive function exercises may be useful as a supportive treatment for MA use disorder. This is consistent with a growing literature in this area [381, 382]. Further research is needed to determine the exact neural correlates underlying the benefits of neurocognitive training as well as associated neurotransmitter exchange. Finally current research has been largely based on cocaine as a stimulant. More clinical research with patients diagnosed with methamphetamine use disorder is warranted.

6.4. Future research directions

These findings suggest a number of avenues for future research.

First this study provides preliminary evidence for the engagement of executive function in overcoming MA dependence. The specific mechanism through which this takes place is an area for future research to explore.

Second, as noted above, future research should consider cognitive training as a potential complement to the CM program to aid in strengthening participants' cognitive abilities. Different executive function tasks could be used to uncover more aspects of executive function differences within the MA group. Examples of such tasks include the Six Element test for attention, Hayling Sequence Completion for suppressing an automated response and the Brixton Spatial Anticipation Test (similar to the Wisconsin Card Sorting Test, just faster and less stressful) for the discovery of rules [118].

Thirdly, it is important that future trials be conducted with larger groups for greater statistical power. Moreover, these groups should include healthy controls, as a reference group for responders and non-responders to treatment. The larger MA groups will help to differentiate more clearly between responders to treatment and non-responders to treatment, as well as allowing for the inclusion of a fourth group for partial responders to treatment. Studies with multiple intervention arm like CBT and CM would help to determine the extent to which these findings are specific to CM.

6.5. Conclusion

Taken together, the findings of this research provide partial support for the hypothesis that better executive function facilitates abstinence in a CM program. There is considerable support for the hypothesis that contingency management further strengthens executive function, in association with changes in directly relevant imaging parameters in one brain region (the Frontal Pole). These findings have important clinical implications in that they provide useful and cost effective tools that clinicians can use to assist in the rehabilitation process for treatment seeking stimulant misusers. Moreover these findings provide a foundation for a number of specific research directions in the future, with a focus on cognitive training as an important example.

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Appendix A

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Appendix B

CONSENT TO PARTICIPATE IN BRAIN SCAN RESEARCH

Neuroplasticity and methamphetamine (MA) use in South Africa

You are being asked to participate in a research study being conducted together with investigators from University of California Los Angeles (UCLA) and supported by the National Institute on Drug Abuse (NIDA), which is part of the National Institutes of Health in the United States.

This research study is being conducted by:

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Your participation in this study is entirely voluntary, and should you wish to withdraw at any time, your rights and treatment will not be affected. Please read the information below and ask questions about anything you do not understand, before deciding whether or not you would like to be part of the study. We will also ask you some questions before you place your initials on the form to ensure that you fully understand what we are asking you to participate in.

You have been asked to participate in this study because we would like to try to understand more about the brain processes that help a person to control their methamphetamine ("tik")

use. To do this we need to volunteers who are willing to receive treatment for methamphetamine dependence.

- **PURPOSE OF THE STUDY**

At the moment we do not know how drug addiction and specific ways of thinking are linked in with brain functions. In the United States, the university we are working with has created a technique to help reduce craving, to assist in avoiding taking the drug, and even in preventing relapse. This technique is called "Contingency Management" and helps to train a person's brain to want the drugs less and less. We want to use a safe brain scan method (an MRI scan) to see how this technique works in the brain, and why it works.

- **PROCEDURES**

If you volunteer to participate in this study, you will be asked to do the following things:

a. The study begins with a two week period where you will need to come to Groote Schuur Hospital J2 Psychiatric Department 3 times a week (Monday, Thursday and Friday after you have been to the clinic for your regular appointment). We will then take urine samples and we will also ask you to spit into a tube. This will allow us to see if there is a hereditary component to your desire to use drugs. Lastly we will need you to take an HIV test. We will give you full counselling before and after you get your results.

b. After the two weeks, if , we will ask you to have a brain scan (which lasts about one and a half hours) at Groote Schuur Hospital.

c. Before going into the brain scanner at the clinic you will first be asked some basic questions about your age, education and your general feelings and understanding of the tasks, which will be fully explained to you.

d. The task inside the scanner involves playing a memory game, where you will be asked to press a button that you will hold in your hand during the scan, when you see a 'repeated letter' or a letter 'X'. But this will be shown to you before you enter the scanner.

e. At the end of the brain scan you will be given some tasks to complete that will take approximately an hour.

f. After your first scan, you will begin your treatment using contingency management at the clinic. During your visits to the clinic, we will ask you to provide a urine sample on Mondays, Thursdays and Fridays after you have visited the clinic, for which we will provide a clean sample cup on site. This will allow us to work out the value of vouchers we can give you for the clean urine sample. This is called 'Contingency Management'.

g. Contingency Management is a means of giving rewards in the form of vouchers. The vouchers increase in value in exchange for urine samples that are clean and remain clean. The initial voucher we can give you will be worth R25 but this will increase with each clean urine sample by R12.5. For every three consecutive clean samples a R100 bonus will be given. This means that a total of R4840 can be earned after 8 weeks (3 days per week) . If a sample is dirty, then no voucher will be received. After a dirty sample, three consecutive clean samples returns you to where you left off with the increasing voucher value.

h. When we take the urine samples a researcher will be with you whilst you give the urine sample.

i. We will also conduct a short interview once a week when you come through to give your urine sample to see how you are doing.

j. During the treatment period of eight weeks we will also ask you to keep a timeline to monitor any use of the drug.

k. At the end of the study you will be given another brain scan to see the changes that have happened in your brain over the eight week period. You will also be asked to play the same computer tasks you did at the beginning, to see how your brain has changed.

l. If you feel uncomfortable at any time during any part of this study (both inside and outside the brain scanner), you are free to tell us that you no longer want to be part of the study and you will be free to continue normal treatment at the clinic if that is what you wish. All the information that we collected about you will be completely confidential at all times. You can receive information about the results of our study by contacting us on the emails given above.

- **POTENTIAL RISKS AND DISCOMFORTS**

There are low risks in receiving a brain scan. It is one of the safest ways that is available to measure what is going on inside the brain. However, some people find the brain scan to be a little noisy, and sometimes a little cold, so we will have ear plugs and a blanket to keep you warm. Some people can feel that the space inside the scanner is a bit small, so there will also be a panic button resting in one of your hands during the scan, so that if at any time you feel uncomfortable and want to be taken out, you can let us know by pressing the button. There will be radiologists and researchers close by to assist you at all times.

There are also low risks to being part of this study such as potential loss of confidentiality which we will make sure does not happen by giving you a research code number and using that on all paper documents in place of your actual name.

Initial_____

- **POTENTIAL BENEFITS TO SUBJECTS AND/OR TO SOCIETY**

Previous research has suggested that Contingency Management will probably change the way your brain functions, making it healthier, and this should result in you being able to lower your drug taking. This form of treatment has previously been successfully tested in the United States, however, it has never been tested in South Africa. If this study is a success, your help in this study will help to improve the lives of many people who have a Methamphetamine use disorder.

- **CONFIDENTIALITY**

Any information that can be identified with you in this study will stay confidential and will only be shared with your permission or as required by law. Confidentiality will be kept by:

a. All Paper information will be kept in a secure and locked location and only the researchers involved in this study will be able to access it.

b. Computer information will only be available to researchers involved in the study by using passwords.

c. People involved in the study will sign statements agreeing to protect your security and confidentiality of any information that can identify you.

d. We will use codes for all questionnaires that we collect.

e. If it does come out in the study that you are involved in abuse, self-harm or harm to others we will need to report this to the authorities. This means that we will report to authorities if what you tell us causes us to suspect child abuse. If you tell us that you might harm yourself or others, we will make a referral for your immediate evaluation by a qualified professional and if determined credible, we will notify local authorities to ensure the safety of you or someone else.

- **PARTICIPATION AND WITHDRAWAL**

You can choose whether or not to be in this study. If you volunteer to be in this study, you may withdraw at any time without consequences of any kind or loss of benefits. You may also refuse to answer any questions you do not want to answer.

Initial_____

There is no penalty if you withdraw from the study and you will not lose any benefits to which you are otherwise entitled. We will let you know the outcome of our study if you would like to know. If you are interested, please supply us with an email or postal address, so that we can send you this information.

IDENTIFICATION OF INVESTIGATORS

If you have any questions or queries after taking part in the study, please do not hesitate to contact the University of Cape Town investigators:

Professor Dan Stein: dan.stein@uct.ac.za

Lara van Nunen: laravannunen@gmail.com

Marilyn Lake: Maz.lake@gmail.com

UCLA investigators include:

Professor Steve Shoptaw: sshoptaw@mednet.ucla.edu

Professor Edythe London: elondon@mednet.ucla.edu

- **COMPLAINTS/CONCERNS/DISCUSSION OF YOUR RIGHTS**

If you have any complaints about the research, the investigators or any concerns at all about the project and the procedures, please contact the independent monitor for this study Sumaya Ariefdien on :Tel: 021 406 6492 or E-mail: sumaya.ariefdien@uct.ac.za

Initial_____

I understand the procedures described above. My questions have been answered to my satisfaction, and I agree to participate in this study. I have been given a copy of this form.

_____

Initials of Participant

_____ _____

Signature of Participant Date

_____ _____

Signature of Witness Date

The University of Cape Town (UCT) undertakes that in the event of you suffering any significant deterioration in health or well-being, or from any unexpected sensitivity or toxicity, that is caused by your participation in the study, it will provide immediate medical care. UCT has appropriate insurance cover to provide prompt payment of compensation for any trial-related injury according to the guidelines outlined by the Association of the British Pharmaceutical Industry, ABPI 1991. Broadly-speaking, the ABPI guidelines recommend that the insured company (UCT), without legal commitment, should compensate you without you having to prove that UCT is at fault. An injury is considered trial-related if, and to the extent that, it is caused by study activities. You must notify the study doctor immediately of any side effects and/or injuries during the trial, whether they are research-related or other related complications.

UCT reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected. Copies of these guidelines are available on request.

Complaints or concerns should be directed to the Human Research Ethics Committee on

Tel: 021 406 6492

E-mail: sumaya.ariefdien@uct.ac.za

DATE OF APPROVAL: 05/08/2015
ETHICS NUMBER: HREC Ref 463/2015
PROJECT EXPIRATION DATE: 05/08/2017

Informed Consent for HIV Testing

Neuroplasticity and methamphetamine (MA) use in South Africa

Researchers include

Prof. Dan J. Stein: dan.stein@uct.ac.za

Lara van Nunen: laravannunen@gmail.com

Marilyn Lake: maz.lake@gmail.com

At the **Department of Psychiatry and Mental Health, University of Cape Town**.

Dear Participant

As part of the above research study, you are being asked to undergo an HIV test. Before agreeing to participate in this research study, it is important that you read and understand the following explanation of the HIV testing. You may not participate in the study if you decide you do not want to have the HIV test performed. However, the result of this test will not only determine whether you are suitable to continue with the research study, but could also have a profound influence on your health and lifestyle.

All costs associated with the HIV test, as well as the pre-test and first post-test counselling will be paid for by UCT.

PURPOSE

This test is performed to exclude any participants who are HIV positive because these participants are more likely to have abnormal laboratory tests, as well as side effects due to their underlying condition which may interfere with assessment of the study medication. This would make accurate analysis of the information gathered during the study impossible. In addition, the taking of new and experimental medication may pose additional risks to your health if you were suffering from an underlying disease of which the study doctors are not aware.

HIV (Human Immunodeficiency Virus) infection is a serious medical condition that leads to AIDS (Acquired Immune Deficiency Syndrome). HIV is spread by sexual contact with an HIV infected partner, exposure to infected blood (such as sharing needles during injection drug use) and from an HIV-infected mother to a child during pregnancy, delivery or breastfeeding. Persons who may be at high risk for infection include people who are having unprotected sex with an HIV infected partner, men who have sex with other men, injection drug users and their sexual partners, persons who received blood transfusions between 1978 and 1985 and persons who have had unprotected sex with multiple partners.

PROCEDURE

You will receive counselling both before and after you have taken the test.

The HIV test will be done on a sample of your blood. The test can detect antibodies that your immune system makes when HIV is present. The HIV antibody test is used to determine of you has been infected with HIV. An HIV test is extremely accurate if performed three months after exposure.

A negative test means that it is extremely unlikely that you are infected with HIV. If you had a recent exposure (less than three months), an HIV test will need to be repeated to assure that you are not in the "window" period of HIV infection before the antibodies are present.

A confirmed positive test means that it is very likely that you have been infected with HIV. This test does not determine how advanced the illness is and is it not a test for AIDS. Medical care and additional testing will be needed to help plan treatment. If you test is positive, you may not continue as a participant in the study. You will be referred to a specialist clinic for further testing and counselling. This clinic can provide counselling and treatment that conforms to the national standard of care for HIV prevention and treatment.

If you test positive, you will not have any recourse to the Sponsor or study site for compensation or treatment.

ADVANTAGES AND DISADVANTAGES OF HIV TESTING

Advantages may include:

- Making yourself available to healthcare and counselling for HIV which has many benefits
- Preventing the transmission of HIV to your sexual partners
- Informing your partner so he/she can also prevent the spread of HIV
- Avoiding blood donations
- Preventing mother to child HIV transmission

Initial_____

Disadvantages may include:

- Emotional stress, depression and despair
- Stigmatisation
- Discrimination
- Rejection by family, friends, sexual partners and / or spouse

These advantages and disadvantages should be carefully considered before signing the consent form.

RISKS

Possible side effects from drawing blood include feeling faint, inflammation of the vein, pain, bruising or bleeding at the site of puncture.

CONFIDENTIALITY

Your HIV testing information and test results cannot be released to anyone without your written consent. A general consent for health care and information release does not cover HIV-related information. If you are found to be HIV-infected, you are not required to personally tell anyone about this diagnosis. However, it is very important to notify your sexual partners and those that might have been exposed to your blood.

Initial_____

CONSENT STATEMENT

1. I hereby agree to have blood drawn in order to undergo the HIV tests as described before in order to determine my suitability for participation in a clinical study. I understand that until all pre-dose checks have been carried out and reviewed by the study doctor before the first dosing day, may participation in the study is not guaranteed.
2. I confirm that I have read and understood the above information leaflet and that I have been informed by the study personnel about the nature, conduct, potential benefits and risks of HIV testing and have had the opportunity to ask questions.
3. I do not consider myself to be in a high risk group for contracting HIV and have no reason to believe that I have been previously exposed.
4. I understand I will be informed of the results of the test in confidence, and that I will be advised regarding further counselling and care, should the result be positive.
5. I understand that should I be tested and found to be HIV positive during the screening period, I cannot hold the SPONSOR of the study liable for my treatment or care
6. I will receive a signed copy of the Patient Information Leaflet and Consent Form.

_____ _____

Participant Signature Date

_____ _____

Researcher Date

I hereby verify that verbal consent was obtained from the above participant. The participant has been informed about the risks and the benefits of the research, understands such risks and benefits and is able to give consent to participation, without coercion, undue influence or inappropriate incentives.

_____ _____

Signature of Witness Date

DATE OF APPROVAL: 05/08/2015 Initial_____
ETHICS NUMBER: HREC Ref 463/2015
PROJECT EXPIRATION DATE: 05/08/2017

Appendix C

Edinburgh Handedness Inventory

Please indicate your preferences in the use of hands in the following activities *by putting a check in the appropriate column*. Where the preference is so strong that you would never try to use the other hand, unless absolutely forced to, *put 2 checks*. If in any case you are really indifferent, *put a check in both columns*.

Some of the activities listed below require the use of both hands. In these cases, the part of the task, or object, for which hand preference is wanted is indicated in parentheses.

Please try and answer all of the questions, and only leave a blank if you have no experience at all with the object or task.

	Left	Right
1. Writing	☐☐	☐☐
2. Drawing	☐☐	☐☐
3. Throwing	☐☐	☐☐
4. Scissors	☐☐	☐☐
5. Toothbrush	☐☐	☐☐
6. Knife (without fork)	☐☐	☐☐
7. Spoon	☐☐	☐☐
8. Broom (upper hand)	☐☐	☐☐
9. Striking Match (match)	☐☐	☐☐
10. Opening box (lid)	☐☐	☐☐
TOTAL(count checks in both columns)		

Difference	Cumulative TOTAL	Result

Scoring (Office use only):
Add up the number of checks in the "Left" and "Right" columns and enter in the "TOTAL" row for each column. Add the left total and the right total and enter in the "Cumulative TOTAL" cell. Subtract the left total from the right total and enter in the "Difference" cell. Divide the "Difference" cell by the "Cumulative TOTAL" cell (round to 2 digits if necessary) and multiply by 100; enter the result in the "Result" cell.

Interpretation (based on Result):

below -40 = left-handed
between -40 and +40 = ambidextrous
above +40 = right-handed

Appendix D

The Brief Tobacco Intervention Training Program

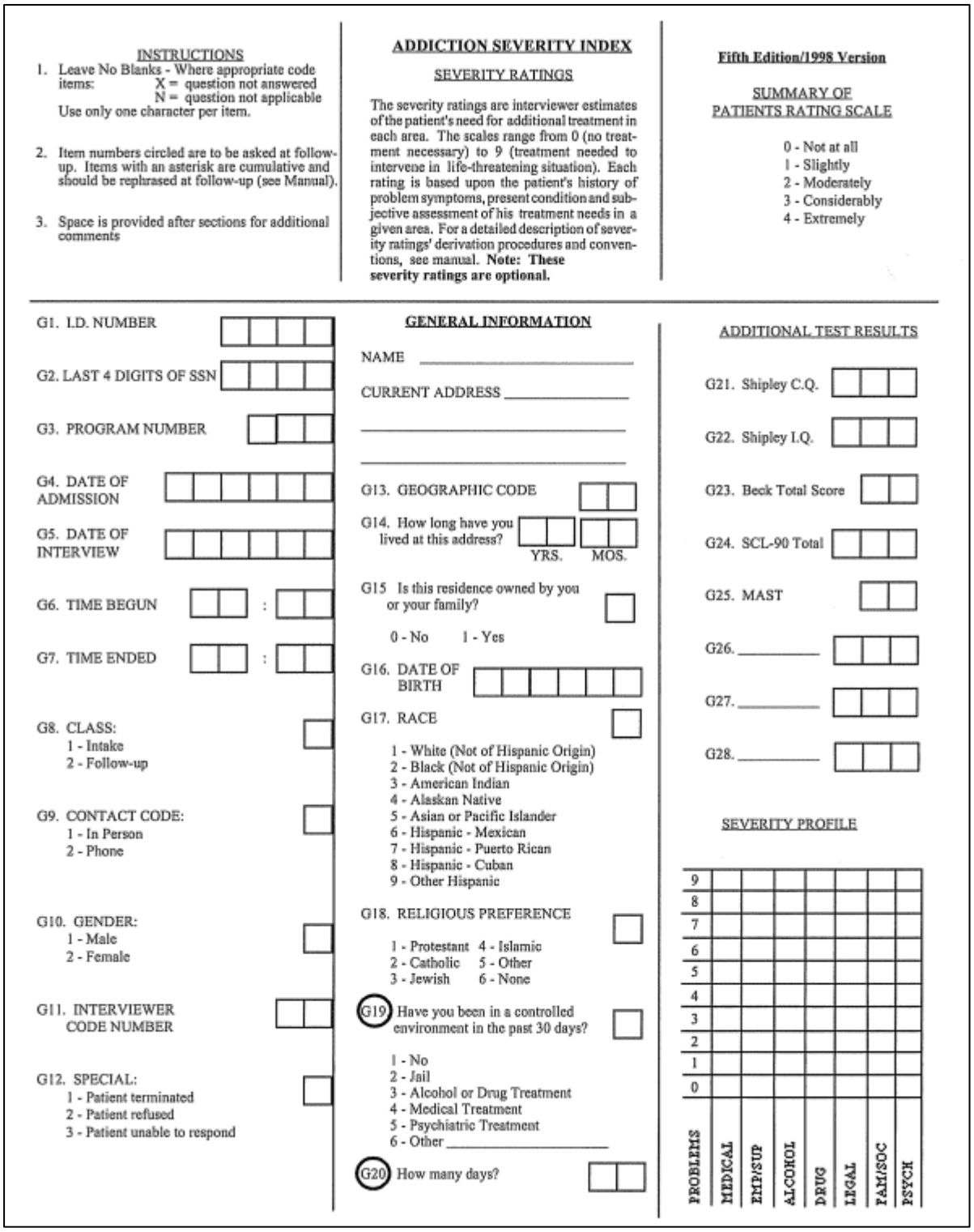
Fagerstrom Test for Nicotine Dependence

	PLEASE TICK (✓) ONE BOX FOR EACH QUESTION		
How soon after waking do you smoke your first cigarette?	Within 5 minutes 5-30 minutes 31-60 minutes	☐ ☐ ☐	3 2 1
Do you find it difficult to refrain from smoking in places where it is forbidden? e.g. Church, Library, etc.	Yes No	☐ ☐	1 0
Which cigarette would you hate to give up?	The first in the morning Any other	☐ ☐	1 0
How many cigarettes a day do you smoke?	10 or less 11 – 20 21 – 30 31 or more	☐ ☐ ☐ ☐	0 1 2 3
Do you smoke more frequently in the morning?	Yes No	☐ ☐	1 0
Do you smoke even if you are sick in bed most of the day?	Yes No	☐ ☐	1 0
	Total Score		

SCORE		
	1- 2 = low dependence 3-4 = low to mod dependence	5 - 7= moderate dependence 8 + = high dependence

Add up the scores from the questionnaire.

Appendix E



INSTRUCTIONS

1. Leave No Blanks - Where appropriate code items: X = question not answered
   N = question not applicable
   Use only one character per item.
2. Item numbers circled are to be asked at follow-up. Items with an asterisk are cumulative and should be rephrased at follow-up (see Manual).
3. Space is provided after sections for additional comments

ADDICTION SEVERITY INDEX

SEVERITY RATINGS

The severity ratings are interviewer estimates of the patient's need for additional treatment in each area. The scales range from 0 (no treatment necessary) to 9 (treatment needed to intervene in life-threatening situation). Each rating is based upon the patient's history of problem symptoms, present condition and subjective assessment of his treatment needs in a given area. For a detailed description of severity ratings' derivation procedures and conventions, see manual. **Note: These severity ratings are optional.**

Fifth Edition/1998 Version

SUMMARY OF PATIENTS RATING SCALE

0 - Not at all
1 - Slightly
2 - Moderately
3 - Considerably
4 - Extremely

G1. I.D. NUMBER

G2. LAST 4 DIGITS OF SSN

G3. PROGRAM NUMBER

G4. DATE OF ADMISSION

G5. DATE OF INTERVIEW

G6. TIME BEGUN :

G7. TIME ENDED :

G8. CLASS:
1 - Intake
2 - Follow-up

G9. CONTACT CODE:
1 - In Person
2 - Phone

G10. GENDER:
1 - Male
2 - Female

G11. INTERVIEWER CODE NUMBER

G12. SPECIAL:
1 - Patient terminated
2 - Patient refused
3 - Patient unable to respond

GENERAL INFORMATION

NAME _____

CURRENT ADDRESS _____

_____

_____

G13. GEOGRAPHIC CODE

G14. How long have you lived at this address? YRS. MOS.

G15 Is this residence owned by you or your family?

0 - No 1 - Yes

G16. DATE OF BIRTH

G17. RACE

1 - White (Not of Hispanic Origin)
2 - Black (Not of Hispanic Origin)
3 - American Indian
4 - Alaskan Native
5 - Asian or Pacific Islander
6 - Hispanic - Mexican
7 - Hispanic - Puerto Rican
8 - Hispanic - Cuban
9 - Other Hispanic

G18. RELIGIOUS PREFERENCE

1 - Protestant 4 - Islamic
2 - Catholic 5 - Other
3 - Jewish 6 - None

G19 Have you been in a controlled environment in the past 30 days?

1 - No
2 - Jail
3 - Alcohol or Drug Treatment
4 - Medical Treatment
5 - Psychiatric Treatment
6 - Other _____

G20 How many days?

ADDITIONAL TEST RESULTS

G21. Shipley C.Q.

G22. Shipley I.Q.

G23. Beck Total Score

G24. SCL-90 Total

G25. MAST

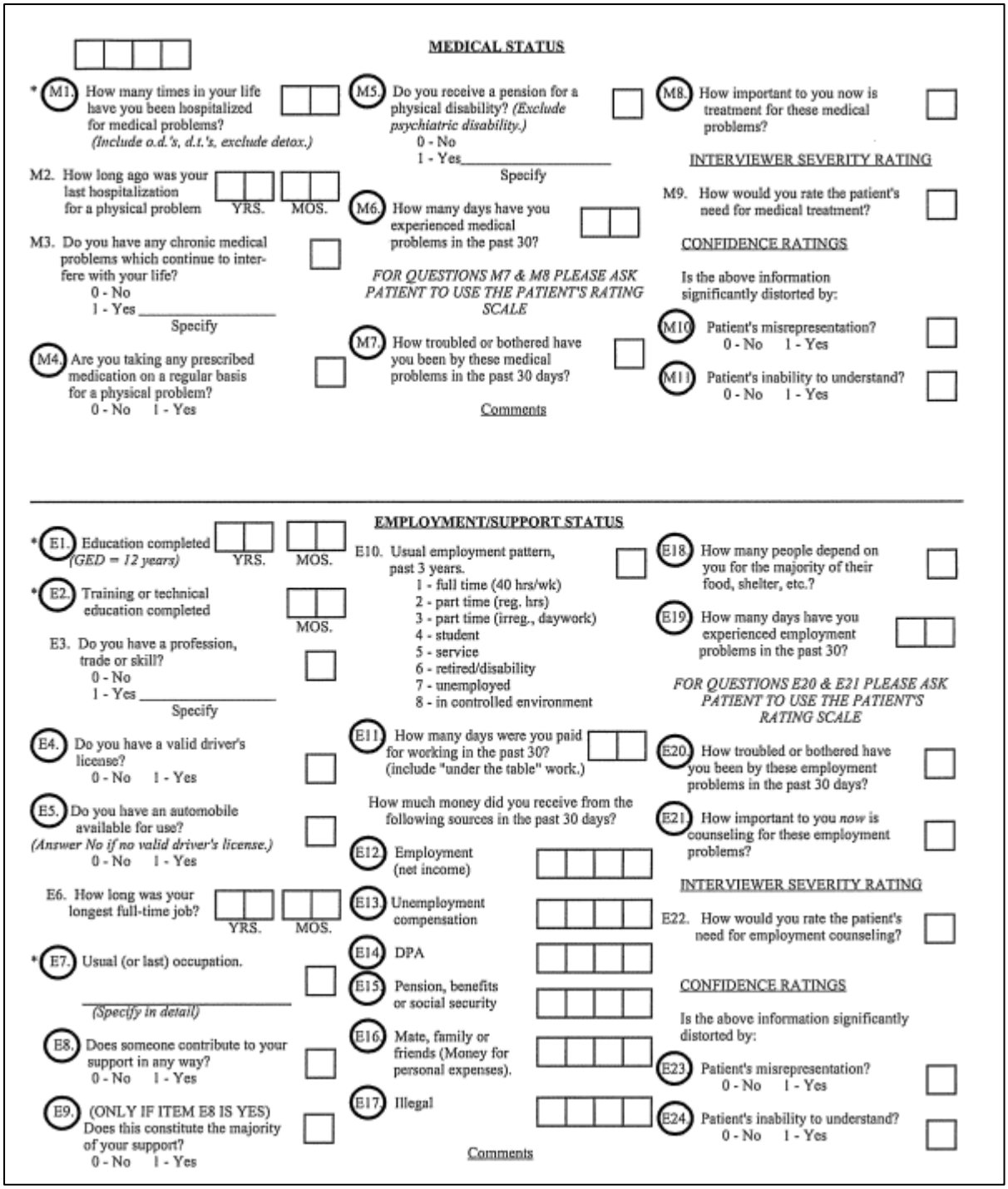
G26. _____

G27. _____

G28. _____

SEVERITY PROFILE

	PROBLEMS	MEDICAL	EMP/SUP	ALCOHOL	DRUG	LEGAL	FAM/SOC	PSYCH
9								
8								
7								
6								
5								
4								
3								
2								
1								
0								



MEDICAL STATUS

* M1. How many times in your life have you been hospitalized for medical problems? *(Include o.d.'s, d.t.'s, exclude detox.)*

M2. How long ago was your last hospitalization for a physical problem YRS. MOS.

M3. Do you have any chronic medical problems which continue to interfere with your life?
0 - No
1 - Yes _____
Specify

M4. Are you taking any prescribed medication on a regular basis for a physical problem?
0 - No 1 - Yes

M5. Do you receive a pension for a physical disability? *(Exclude psychiatric disability.)*
0 - No
1 - Yes_____
Specify

M6. How many days have you experienced medical problems in the past 30?

FOR QUESTIONS M7 & M8 PLEASE ASK PATIENT TO USE THE PATIENT'S RATING SCALE

M7. How troubled or bothered have you been by these medical problems in the past 30 days?

Comments

M8. How important to you now is treatment for these medical problems?

INTERVIEWER SEVERITY RATING

M9. How would you rate the patient's need for medical treatment?

CONFIDENCE RATINGS

Is the above information significantly distorted by:

M10. Patient's misrepresentation?
0 - No 1 - Yes

M11. Patient's inability to understand?
0 - No 1 - Yes

EMPLOYMENT/SUPPORT STATUS

* E1. Education completed *(GED = 12 years)* YRS. MOS.

* E2. Training or technical education completed MOS.

E3. Do you have a profession, trade or skill?
0 - No
1 - Yes _____
Specify

E4. Do you have a valid driver's license?
0 - No 1 - Yes

E5. Do you have an automobile available for use?
(Answer No if no valid driver's license.)
0 - No 1 - Yes

E6. How long was your longest full-time job? YRS. MOS.

* E7. Usual (or last) occupation.
_____
(Specify in detail)

E8. Does someone contribute to your support in any way?
0 - No 1 - Yes

E9. (ONLY IF ITEM E8 IS YES) Does this constitute the majority of your support?
0 - No 1 - Yes

E10. Usual employment pattern, past 3 years.
1 - full time (40 hrs/wk)
2 - part time (reg. hrs)
3 - part time (irreg., daywork)
4 - student
5 - service
6 - retired/disability
7 - unemployed
8 - in controlled environment

E11. How many days were you paid for working in the past 30? (include "under the table" work.)

How much money did you receive from the following sources in the past 30 days?

E12. Employment (net income)

E13. Unemployment compensation

E14. DPA

E15. Pension, benefits or social security

E16. Mate, family or friends (Money for personal expenses).

E17. Illegal

Comments

E18. How many people depend on you for the majority of their food, shelter, etc.?

E19. How many days have you experienced employment problems in the past 30?

FOR QUESTIONS E20 & E21 PLEASE ASK PATIENT TO USE THE PATIENT'S RATING SCALE

E20. How troubled or bothered have you been by these employment problems in the past 30 days?

E21. How important to you *now* is counseling for these employment problems?

INTERVIEWER SEVERITY RATING

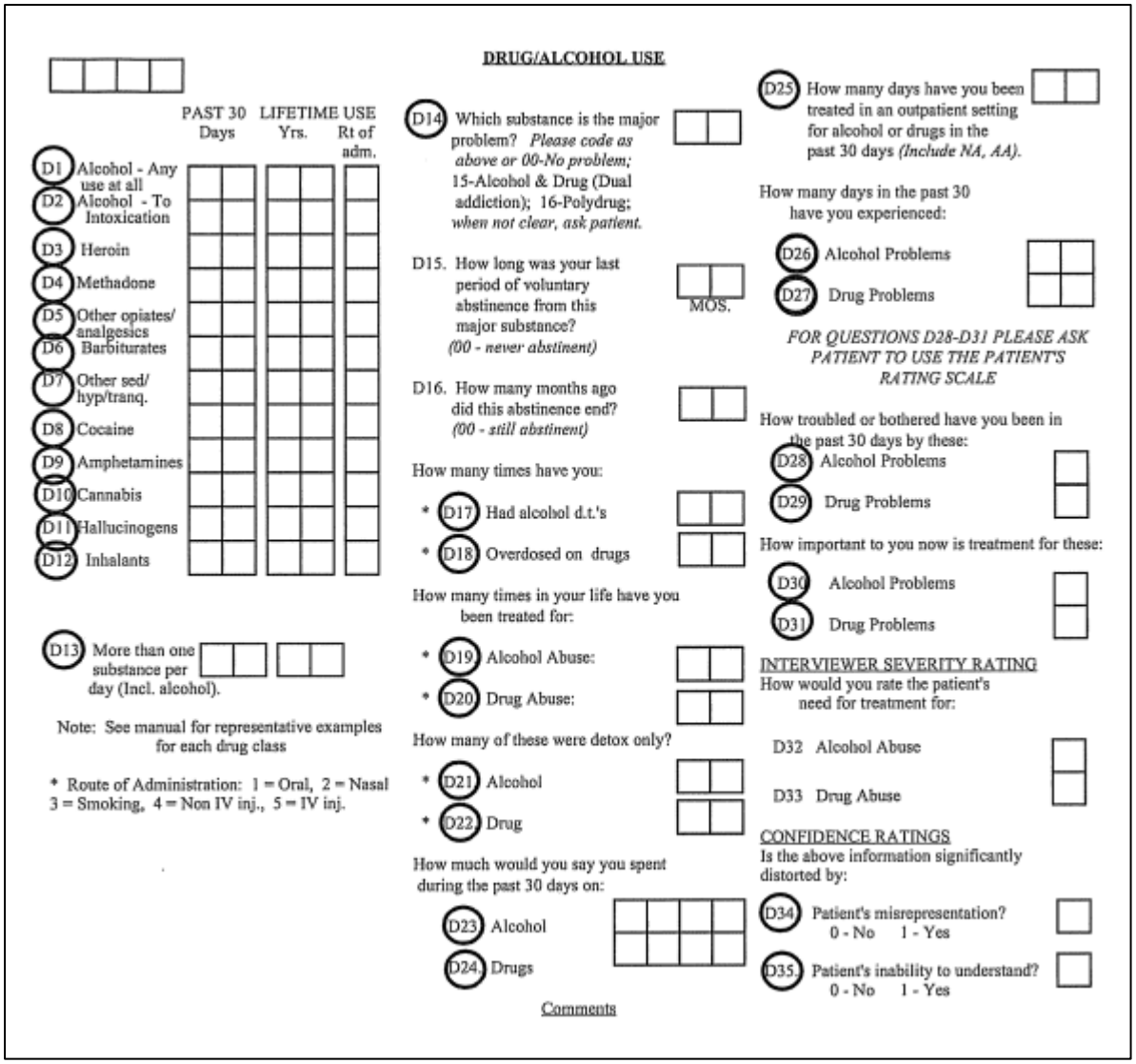
E22. How would you rate the patient's need for employment counseling?

CONFIDENCE RATINGS

Is the above information significantly distorted by:

E23. Patient's misrepresentation?
0 - No 1 - Yes

E24. Patient's inability to understand?
0 - No 1 - Yes



DRUG/ALCOHOL USE

	PAST 30 Days	LIFETIME USE Yrs.	Rt of adm.
D1 Alcohol - Any use at all			
D2 Alcohol - To Intoxication			
D3 Heroin			
D4 Methadone			
D5 Other opiates/ analgesics			
D6 Barbiturates			
D7 Other sed/ hyp/tranq.			
D8 Cocaine			
D9 Amphetamines			
D10 Cannabis			
D11 Hallucinogens			
D12 Inhalants			

D13 More than one substance per day (Incl. alcohol).

Note: See manual for representative examples for each drug class

* Route of Administration: 1 = Oral, 2 = Nasal 3 = Smoking, 4 = Non IV inj., 5 = IV inj.

D14 Which substance is the major problem? *Please code as above or 00-No problem; 15-Alcohol & Drug (Dual addiction); 16-Polydrug; when not clear, ask patient.*

D15. How long was your last period of voluntary abstinence from this major substance? *(00 - never abstinent)* MOS.

D16. How many months ago did this abstinence end? *(00 - still abstinent)*

How many times have you:

* D17 Had alcohol d.t.'s
* D18 Overdosed on drugs

How many times in your life have you been treated for:

* D19 Alcohol Abuse:
* D20 Drug Abuse:

How many of these were detox only?

* D21 Alcohol
* D22 Drug

How much would you say you spent during the past 30 days on:

D23 Alcohol

D24 Drugs

Comments

D25 How many days have you been treated in an outpatient setting for alcohol or drugs in the past 30 days *(Include NA, AA).*

How many days in the past 30 have you experienced:

D26 Alcohol Problems

D27 Drug Problems

FOR QUESTIONS D28-D31 PLEASE ASK PATIENT TO USE THE PATIENT'S RATING SCALE

How troubled or bothered have you been in the past 30 days by these:

D28 Alcohol Problems

D29 Drug Problems

How important to you now is treatment for these:

D30 Alcohol Problems

D31 Drug Problems

INTERVIEWER SEVERITY RATING

How would you rate the patient's need for treatment for:

D32 Alcohol Abuse

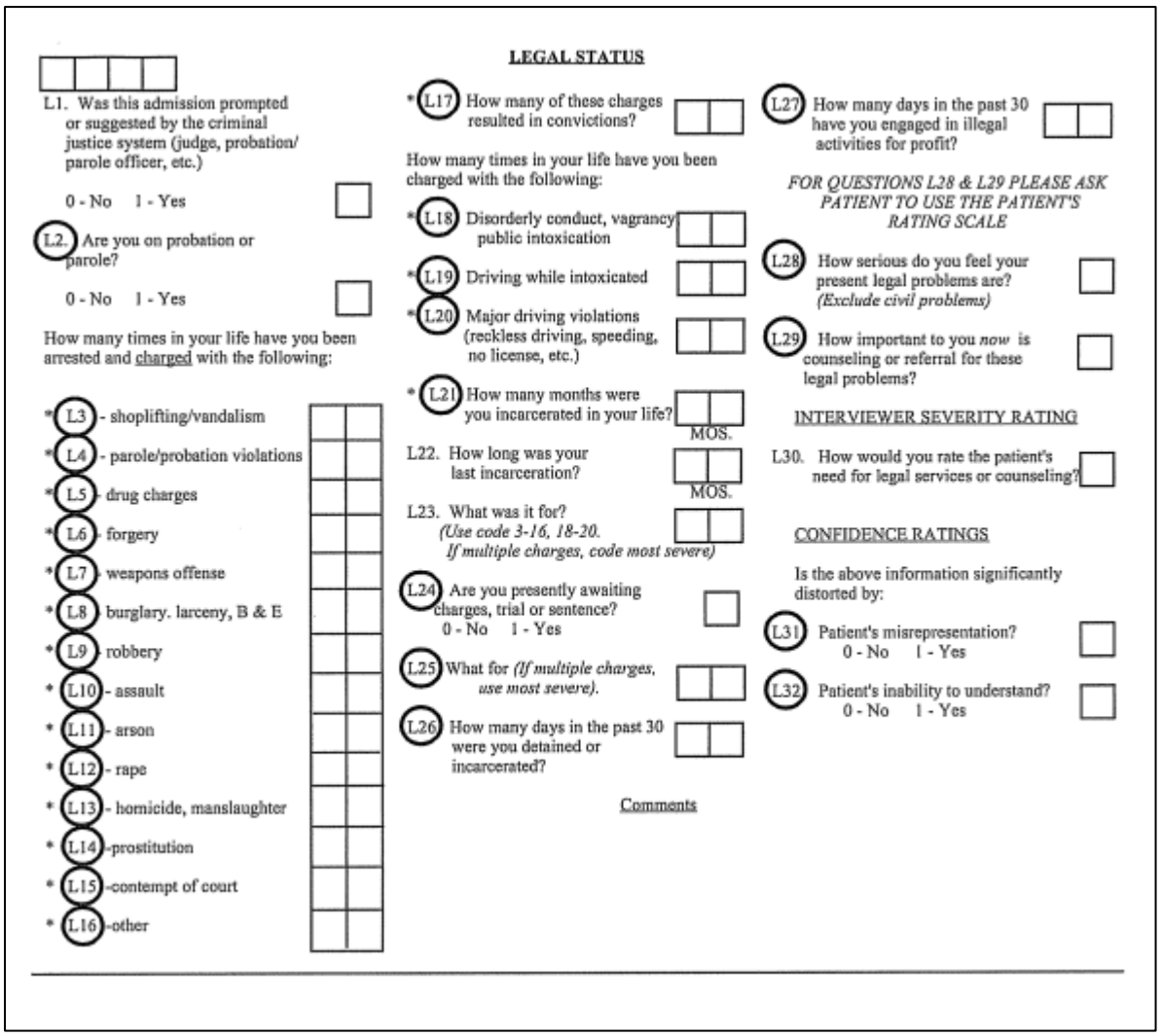
D33 Drug Abuse

CONFIDENCE RATINGS

Is the above information significantly distorted by:

D34 Patient's misrepresentation? 0 - No 1 - Yes

D35 Patient's inability to understand? 0 - No 1 - Yes



LEGAL STATUS

L1. Was this admission prompted or suggested by the criminal justice system (judge, probation/ parole officer, etc.)

0 - No 1 - Yes

L2. Are you on probation or parole?

0 - No 1 - Yes

How many times in your life have you been arrested and charged with the following:

* L3 - shoplifting/vandalism
* L4 - parole/probation violations
* L5 - drug charges
* L6 - forgery
* L7 - weapons offense
* L8 - burglary. larceny, B & E
* L9 - robbery
* L10 - assault
* L11 - arson
* L12 - rape
* L13 - homicide, manslaughter
* L14 -prostitution
* L15 -contempt of court
* L16 -other

* L17 How many of these charges resulted in convictions?

How many times in your life have you been charged with the following:

* L18 Disorderly conduct, vagrancy public intoxication
* L19 Driving while intoxicated
* L20 Major driving violations (reckless driving, speeding, no license, etc.)
* L21 How many months were you incarcerated in your life? MOS.

L22. How long was your last incarceration? MOS.

L23. What was it for? *(Use code 3-16, 18-20. If multiple charges, code most severe)*

L24 Are you presently awaiting charges, trial or sentence? 0 - No 1 - Yes

L25 What for *(If multiple charges, use most severe).*

L26 How many days in the past 30 were you detained or incarcerated?

Comments

L27 How many days in the past 30 have you engaged in illegal activities for profit?

FOR QUESTIONS L28 & L29 PLEASE ASK PATIENT TO USE THE PATIENT'S RATING SCALE

L28 How serious do you feel your present legal problems are? *(Exclude civil problems)*

L29 How important to you *now* is counseling or referral for these legal problems?

INTERVIEWER SEVERITY RATING

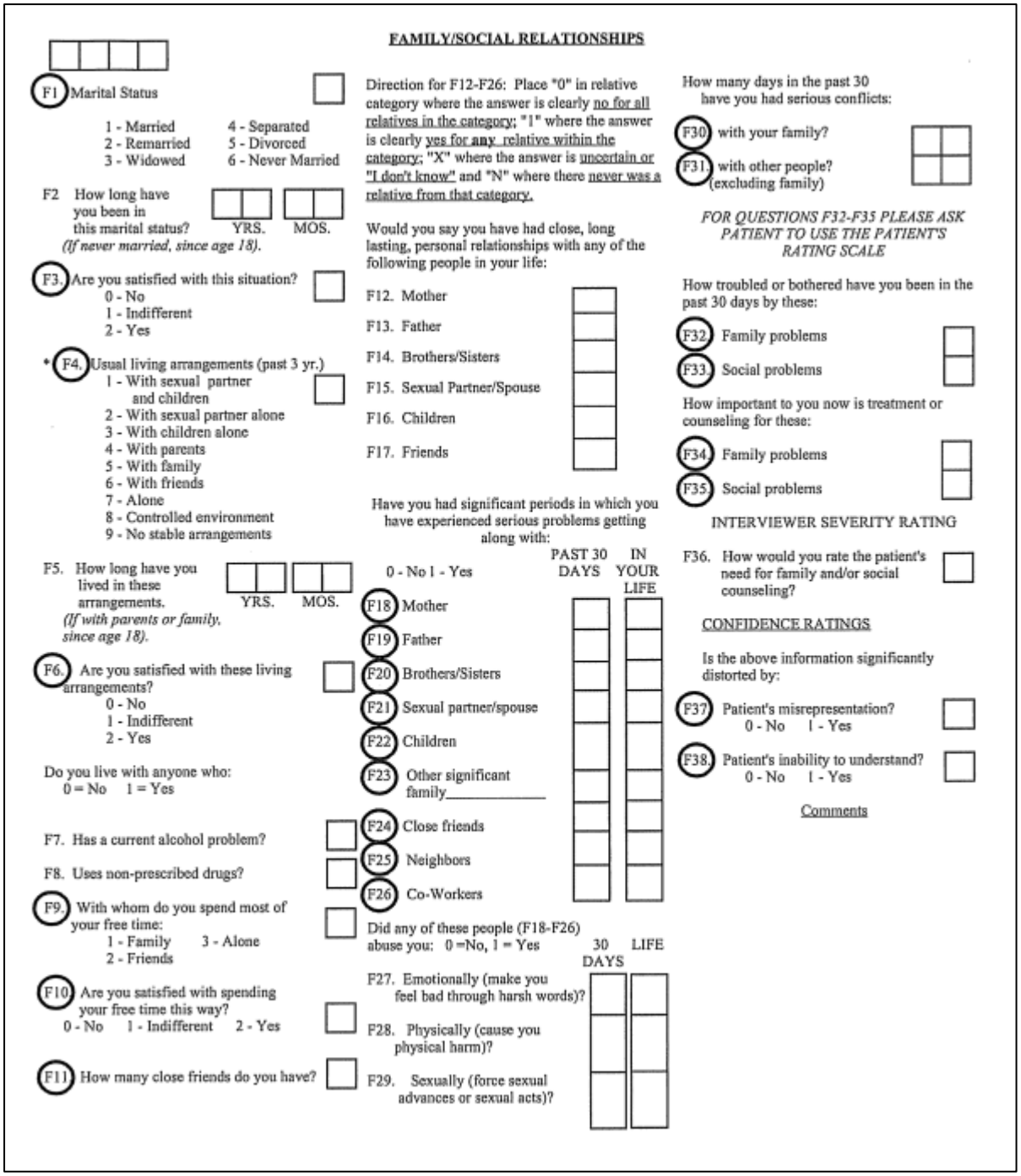
L30. How would you rate the patient's need for legal services or counseling?

CONFIDENCE RATINGS

Is the above information significantly distorted by:

L31 Patient's misrepresentation? 0 - No 1 - Yes

L32 Patient's inability to understand? 0 - No 1 - Yes



FAMILY/SOCIAL RELATIONSHIPS

F1 Marital Status

1 - Married
2 - Remarried
3 - Widowed
4 - Separated
5 - Divorced
6 - Never Married

F2 How long have you been in this marital status? YRS. MOS.
(If never married, since age 18).

F3. Are you satisfied with this situation?
0 - No
1 - Indifferent
2 - Yes

* F4. Usual living arrangements (past 3 yr.)
1 - With sexual partner and children
2 - With sexual partner alone
3 - With children alone
4 - With parents
5 - With family
6 - With friends
7 - Alone
8 - Controlled environment
9 - No stable arrangements

F5. How long have you lived in these arrangements. YRS. MOS.
(If with parents or family, since age 18).

F6. Are you satisfied with these living arrangements?
0 - No
1 - Indifferent
2 - Yes

Do you live with anyone who:
0 = No 1 = Yes

F7. Has a current alcohol problem?

F8. Uses non-prescribed drugs?

F9. With whom do you spend most of your free time:
1 - Family 3 - Alone
2 - Friends

F10. Are you satisfied with spending your free time this way?
0 - No 1 - Indifferent 2 - Yes

F11 How many close friends do you have?

Direction for F12-F26: Place "0" in relative category where the answer is clearly no for all relatives in the category; "1" where the answer is clearly yes for any relative within the category; "X" where the answer is uncertain or "I don't know" and "N" where there never was a relative from that category.

Would you say you have had close, long lasting, personal relationships with any of the following people in your life:

F12. Mother
F13. Father
F14. Brothers/Sisters
F15. Sexual Partner/Spouse
F16. Children
F17. Friends

Have you had significant periods in which you have experienced serious problems getting along with:

0 - No 1 - Yes	PAST 30 DAYS	IN YOUR LIFE
F18 Mother		
F19 Father		
F20 Brothers/Sisters		
F21 Sexual partner/spouse		
F22 Children		
F23 Other significant family_____		
F24 Close friends		
F25 Neighbors		
F26 Co-Workers		

Did any of these people (F18-F26) abuse you: 0 =No, 1 = Yes

	30 DAYS	LIFE
F27. Emotionally (make you feel bad through harsh words)?		
F28. Physically (cause you physical harm)?		
F29. Sexually (force sexual advances or sexual acts)?		

How many days in the past 30 have you had serious conflicts:

F30 with your family?
F31 with other people? (excluding family)

FOR QUESTIONS F32-F35 PLEASE ASK PATIENT TO USE THE PATIENT'S RATING SCALE

How troubled or bothered have you been in the past 30 days by these:

F32 Family problems
F33 Social problems

How important to you now is treatment or counseling for these:

F34 Family problems
F35 Social problems

INTERVIEWER SEVERITY RATING

F36. How would you rate the patient's need for family and/or social counseling?

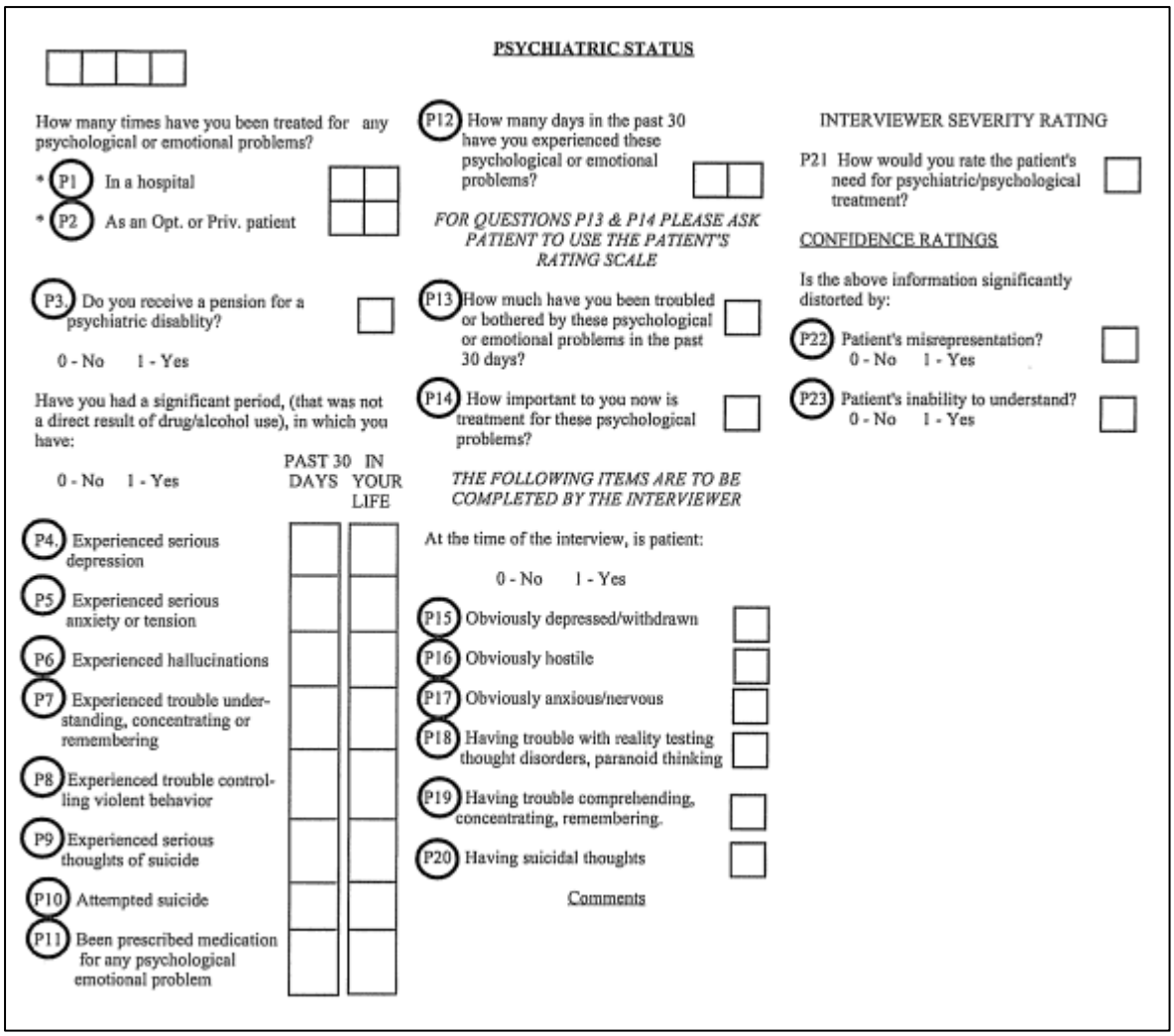
CONFIDENCE RATINGS

Is the above information significantly distorted by:

F37 Patient's misrepresentation? 0 - No 1 - Yes

F38 Patient's inability to understand? 0 - No 1 - Yes

Comments



PSYCHIATRIC STATUS

How many times have you been treated for any psychological or emotional problems?

* P1 In a hospital
* P2 As an Opt. or Priv. patient

P3. Do you receive a pension for a psychiatric disablity?

0 - No 1 - Yes

Have you had a significant period, (that was not a direct result of drug/alcohol use), in which you have:

0 - No 1 - Yes	PAST 30 DAYS	IN YOUR LIFE
P4. Experienced serious depression		
P5 Experienced serious anxiety or tension		
P6 Experienced hallucinations		
P7 Experienced trouble understanding, concentrating or remembering		
P8 Experienced trouble controlling violent behavior		
P9 Experienced serious thoughts of suicide		
P10 Attempted suicide		
P11 Been prescribed medication for any psychological emotional problem		

P12 How many days in the past 30 have you experienced these psychological or emotional problems?

FOR QUESTIONS P13 & P14 PLEASE ASK PATIENT TO USE THE PATIENT'S RATING SCALE

P13 How much have you been troubled or bothered by these psychological or emotional problems in the past 30 days?

P14 How important to you now is treatment for these psychological problems?

THE FOLLOWING ITEMS ARE TO BE COMPLETED BY THE INTERVIEWER

At the time of the interview, is patient:

0 - No 1 - Yes

P15 Obviously depressed/withdrawn

P16 Obviously hostile

P17 Obviously anxious/nervous

P18 Having trouble with reality testing thought disorders, paranoid thinking

P19 Having trouble comprehending, concentrating, remembering.

P20 Having suicidal thoughts

Comments

INTERVIEWER SEVERITY RATING

P21 How would you rate the patient's need for psychiatric/psychological treatment?

CONFIDENCE RATINGS

Is the above information significantly distorted by:

P22 Patient's misrepresentation? 0 - No 1 - Yes

P23 Patient's inability to understand? 0 - No 1 - Yes

Appendix F

Patient Name		Date	DD	MMM	YYYY

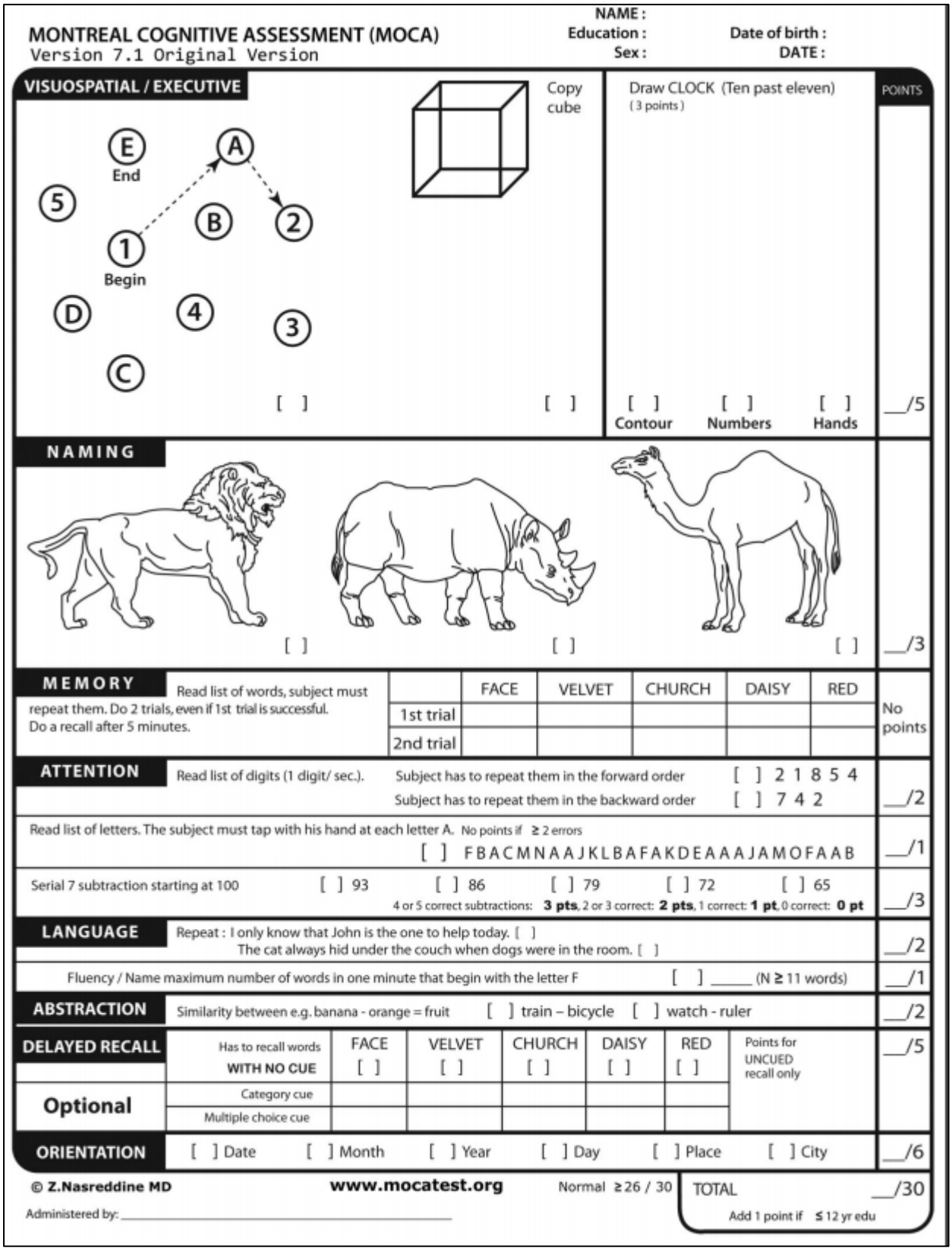
Childhood Trauma Questionnaire – Short Form (CTQ-SF)

Copyright 1996 David P. Bernstein, Ph.D., Laura Fink, Ph.D.

Instructions: These questions ask about some of your experiences growing up **as a child and a teenager**. For each question, circle the number that best describes how you feel. Although some of these questions are of a personal nature, please try to answer as honestly as you can. Your answers will be kept confidential.

When I was growing up, …	Never True	Rarely True	Sometimes True	Often True	Very Often True
1. I didn't have enough to eat.	1	2	3	4	5
2. I knew there was someone to take care of me and protect me	1	2	3	4	5
3. People in my family called me things like "stupid", "lazy", or "ugly".	1	2	3	4	5
4. My parents were too drunk or high to take care of me.	1	2	3	4	5
5. There was someone in my family who helped me feel important or special.	1	2	3	4	5
6. I had to wear dirty clothes.	1	2	3	4	5
7. I felt loved.	1	2	3	4	5
8. I thought that my parents wished I had never been born.	1	2	3	4	5
9. I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.	1	2	3	4	5
10. There was nothing I wanted to change about my family.	1	2	3	4	5
11. People in my family hit me so hard that it left bruises or marks.	1	2	3	4	5
12. I was punished with a belt, a board, a cord, or some hard object.	1	2	3	4	5
13. People in my family looked out for each other.	1	2	3	4	5
14. People in my family said hurtful or insulting things to me.	1	2	3	4	5
15. I believe that I was physically abused.	1	2	3	4	5
16. I had the perfect childhood.	1	2	3	4	5
17. I got hit or beaten so badly that it was noticed by someone like a teacher, neighbour, or doctor.	1	2	3	4	5
18. I felt that someone in my family hated me.	1	2	3	4	5
19. People in my family felt close to each other.	1	2	3	4	5
20. Someone tried to touch me in a sexual way, or tried to make me touch them.	1	2	3	4	5
21. Someone threatened to hurt me or tell lies about me unless I did something sexual with them.	1	2	3	4	5
22. I had the best family in the world.	1	2	3	4	5
23. Someone tried to make me do sexual things or make me watch sexual things.	1	2	3	4	5
24. Someone molested me.	1	2	3	4	5
25. I believe that I was emotionally abused.	1	2	3	4	5
26. There was someone to take me to the doctor if I needed it.	1	2	3	4	5
27. I believe that I was sexually abused	1	2	3	4	5
28. My family was a source of strength and support.	1	2	3	4	5

Appendix G



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Appendix H

RHRSD Problem Inventory

Name: _____ ID # _____ Age: _____ Gender: ☐ M ☐ F Date: _____ Examiner: _____

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12031 Wilshire Blvd., Los Angeles, CA 90025-1251
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Circle T for each statement that applies to you.
Circle F if the statement does not apply to you.

T F 1. My mood is no different than usual.
T F 2. I have felt unusual sadness, emptiness, or hopelessness that has lasted for several days or weeks.
T F 3. I have been unusually irritable or tired for no reason.
T F 4. I have received treatment or medication or been hospitalized because of my moods.
T F 5. I am aware of problems in my daily life that are caused by my moods.
T F 6. My moods have interfered with my everyday activities.
T F 7. My family has been disturbed by my moods or has expressed concern about my moods.
T F 8. I have felt unusually low, tired, or irritable for more than 2 weeks at a time.
T F 9. My social life or friendships have changed because of my moods.

T F 10. I feel unusually sad.
T F 11. I cry for no reason.
T F 12. There's so little to look forward to in the future that I don't feel like doing anything now.
T F 13. I find it hard to do anything but cry.

T F 14. I am no worse than most people.
T F 15. I have let people down.
T F 16. I have done or thought about things for which I should have been punished.
T F 17. If I were a better person, I would not be ill.
T F 18. I have heard voices or seen people who want me punished for my past mistakes.

T F 19. With all its problems, life is still worth living.
T F 20. I have thought about killing myself.
T F 21. I think my family would be better off without me.
T F 22. Life is pointless.
T F 23. I have tried to kill myself.

T F 24. I have no difficulty sleeping.
T F 25. It sometimes takes me more than half an hour to fall asleep.
T F 26. It almost always takes me more than half an hour to fall asleep.

T F 27. I frequently awaken or get up in the middle of the night because I can't sleep (not just to go to the bathroom).
T F 28. I sleep fitfully.

T F 29. I've been waking up earlier than usual, but I go back to sleep.
T F 30. I've been waking up earlier than usual, and I can't get back to sleep.

T F 31. There's been no change in my ability to get things done.
T F 32. I find it hard to decide what to do, and I have to push myself to do anything.
T F 33. I am spending less time in my usual activities and am getting less done.
T F 34. I feel too tired or weak to participate in my everyday activities.
T F 35. I have stopped working because of my moods.

Answer Items 36 and 37 only if you are a woman.

T F 36. I have noticed some changes in my menstrual cycle.
T F 37. My menstrual cycle has changed very noticeably.
T F 38. I am experiencing less sexual desire than usual.
T F 39. I am no longer interested in sex at all.

(TURN FORM OVER TO CONTINUE)

W-290B

Circle T for each statement that applies to you.
Circle F if the statement does not apply to you.

T F 40. My only problem right now is that I need a little rest.
T F 41. I do not have any unusual problems.

T F 42. I have difficulty concentrating.
T F 43. I find it very difficult to move around.
T F 44. People say that I am talking or moving too slowly.
T F 45. People say that I speak more slowly than usual.

T F 46. I am more nervous than usual.
T F 47. People say that I'm fidgety.
T F 48. I find it very hard to stop fidgeting.
T F 49. I find it impossible to sit still.

T F 50. I am no more worried than usual.
T F 51. I feel unusually tense or jumpy.
T F 52. I worry about things more than I used to.
T F 53. I often feel full of fear or panic.
T F 54. I am afraid almost all the time.

T F 55. I have no unusual physical complaints.
T F 56. Recently I've had some difficulty with my breathing, hearing, vision, or digestion.
T F 57. I am experiencing some unusual physical discomfort.
T F 58. I frequently have problems with my breathing, hearing, vision, or digestion.
T F 59. It is very difficult for me to do anything because of my physical problems.

T F 60. My eating habits have not changed.
T F 61. I have lost my appetite.
T F 62. I need help eating, and I need medication for my stomach or bowels.

T F 63. I am very worried that I might have cancer or AIDS.
T F 64. My body is unusually heavy and achy.

T F 65. I am more worried about my physical health than most people.
T F 66. I worry about my physical health most of the time.
T F 67. I frequently need other people to help take care of me.
T F 68. I suffer from physical problems not mentioned in this report.

T F 69. I have noticed no unusual changes in my weight.
T F 70. I have lost weight because of my current problems, but my clothes still fit.
T F 71. Even though I have not been dieting, I've recently lost so much weight that my clothes no longer fit.

T F 72. My mood is noticeably worse at certain times of the day.

T F 73. I feel that I am not real.

T F 74. The world around me seems unreal.

T F 75. I think someone is trying to hurt me.

T F 76. There are certain things I cannot stop thinking about or doing, no matter how hard I try.

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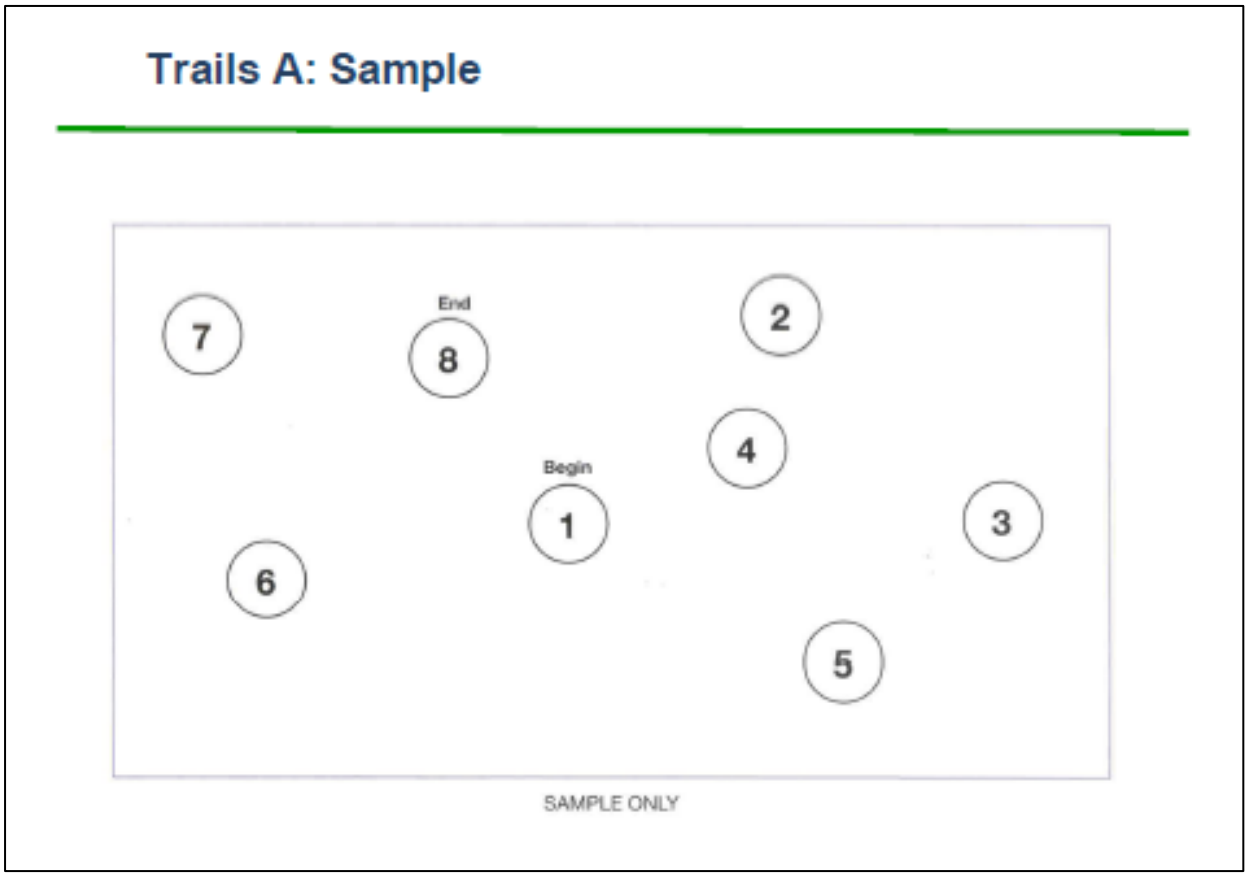
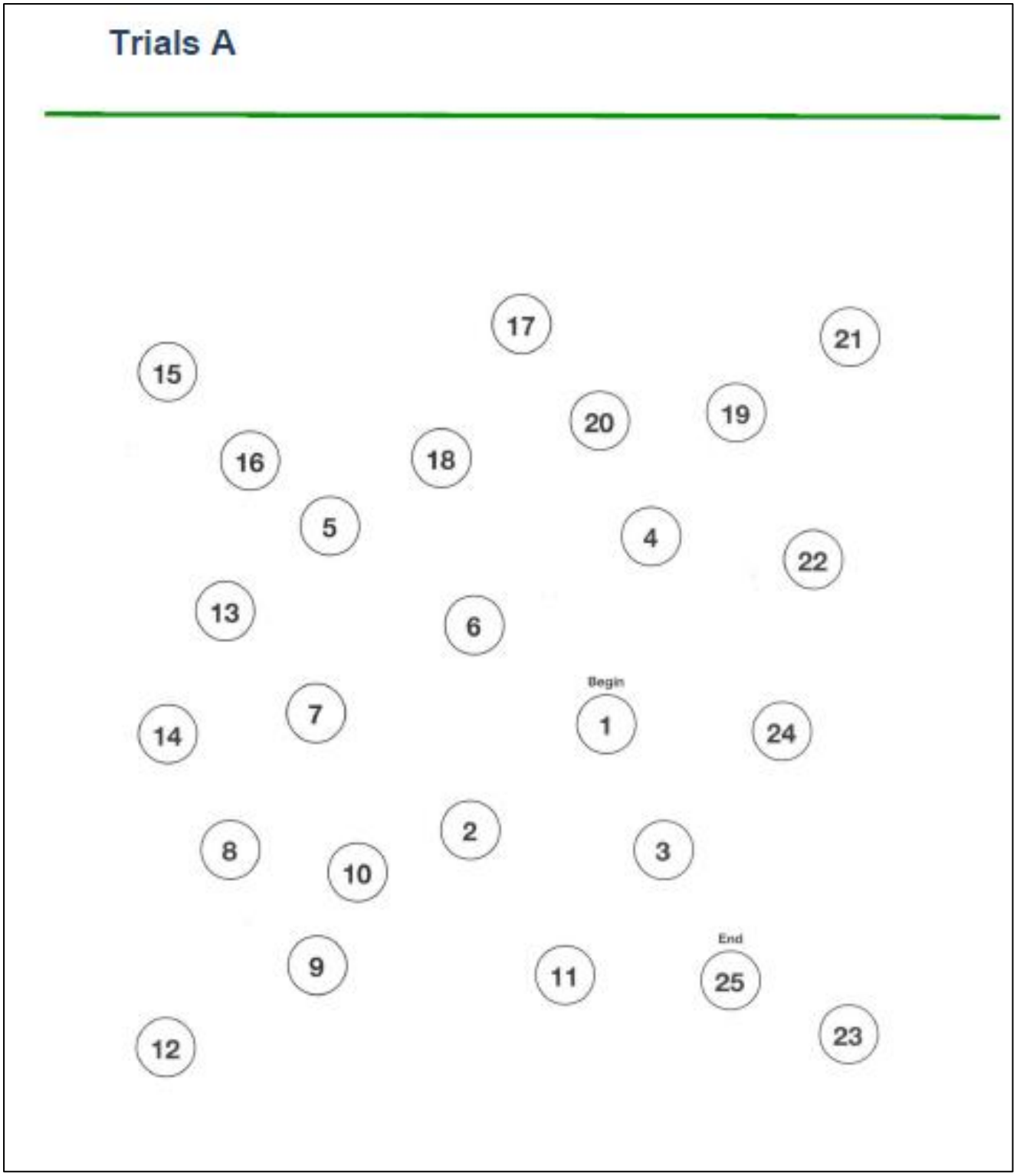
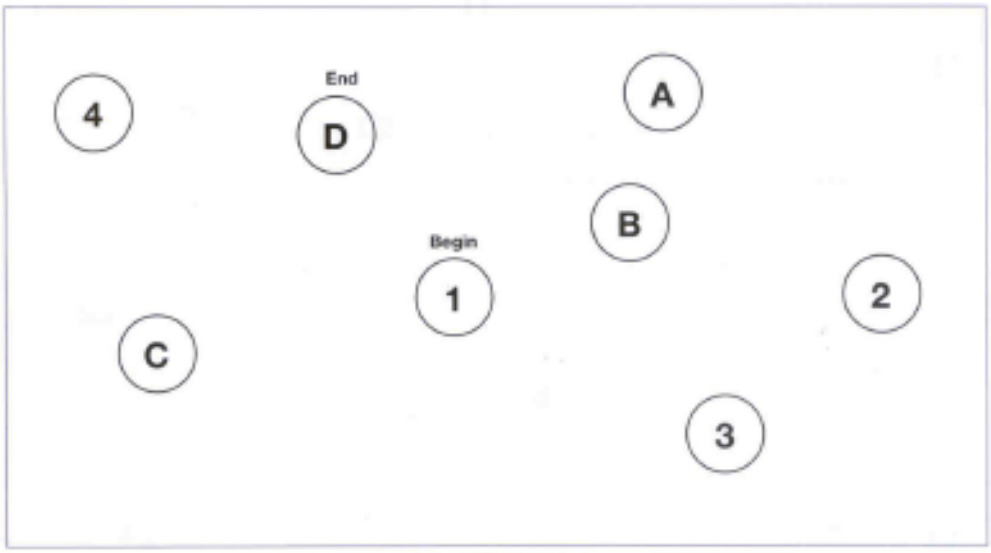
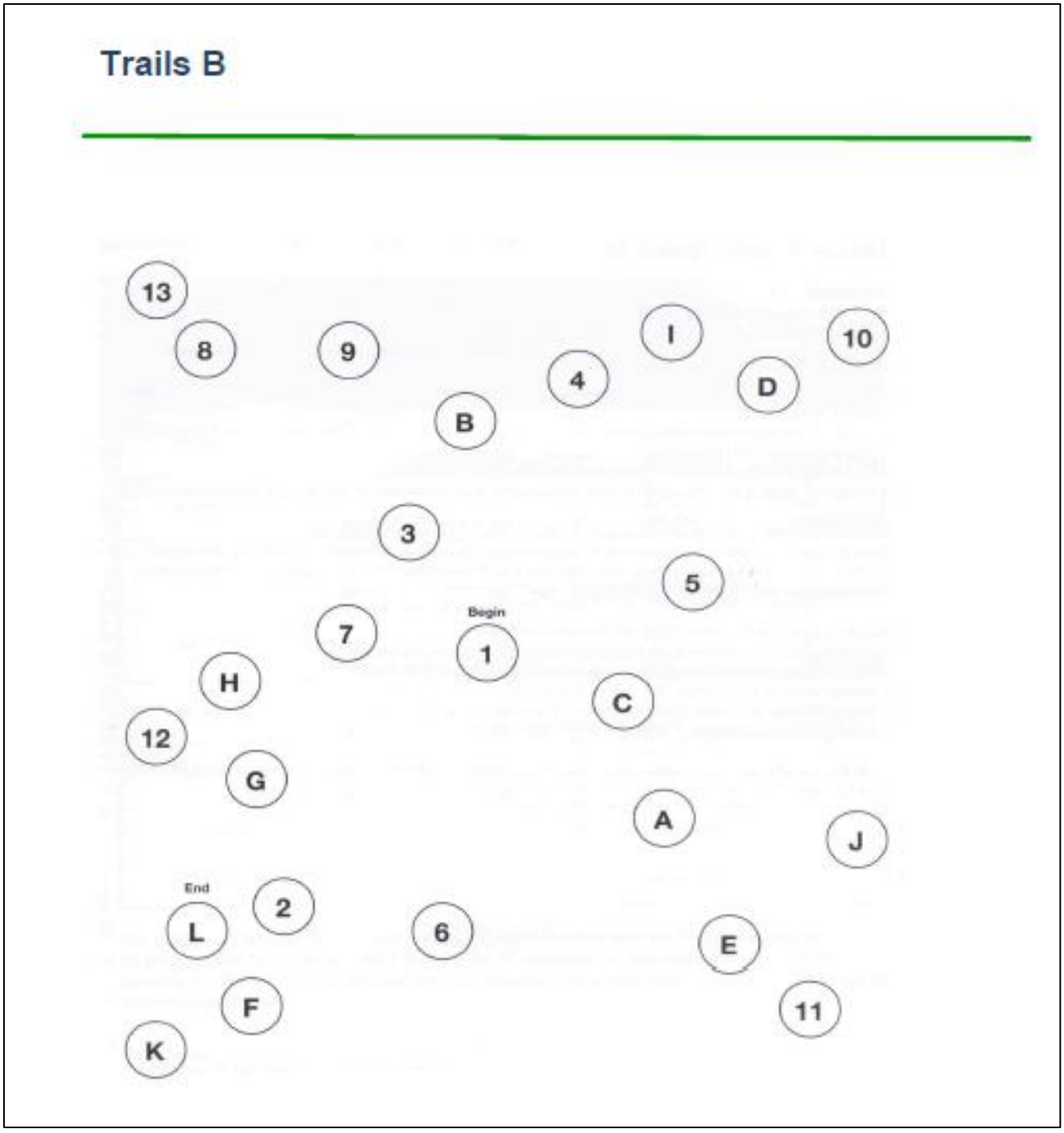
Appendix I




Trials A
17
21
15
20
19
16
18
5
4
22
13
6
Begin
7
1
14
24
2
8
3
10
End
9
11
25
12
23

Trails B: Sample




Trails B
13
8
9
I
10
4
D
B
3
5
Begin
7
1
H
C
12
G
A
J
End
2
L
6
E
F
11
K

Appendix J

Are you interested in taking part in a brain imaging study to see how treatment affects the brain?

Who are we looking for?

- Males & females aged 18-45
- Not pregnant or HIV positive (confidential)
- Right handed
- Being treated for methamphetamine ("tik") dependence
- No other medical or psychiatric illnesses/addictions

What will you need to do?

1. First, we will do cognitive tests, a brain scan, & take a urine sample
2. Then you will need to come to our clinic 3 x a week for 8 weeks & provide a urine sample
3. Each time you are clean, you will get reimbursed with vouchers
4. At the end, we will repeat the cognitive tests, brain scan, and urine sample

If you are interested in this research, please contact us on the number provided.

Renier Swart 072 855 3845

Marilyn Lake 076 360 5722

Lara van Nunen 072 048 0884

Appendix K

Contingency Management and Methamphetamine Treatment in South Africa

Hello…

We are researchers from the University of Cape Town and we would like to invite you to participate in a research study on:

Understanding the brain processes that help a person to control their drug dependence.

We would like to ask you to be part of this study

Participation is entirely optional.
Read through this brochure to help you to decide if you wish to participate.
Should you decide not to be part of the study you will not miss out on any services the clinic offers.

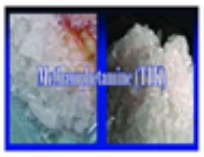
Understanding is important

If English is not your first language you are entitled to an interpreter, so please make sure that you understand what we are asking from you and what you will be compensated with.

Who is eligible?

- If you use methamphetamine (tik) regularly, and you are currently looking for treatment.
- If you are between the ages of 18 and 45.
- If you are right handed, not pregnant or HIV+

Methamphetamine addiction (*TIK*)



Excessive methamphetamine (tik) use is associated with impulsive behaviors despite damage to health and relationships, as well as risky sexual behavior and violence.

Excessive use of tik means that:

- You use methamphetamine (tik) more than you should or for longer than you mean to.
- You don't engage in social activities because you would rather be using methamphetamine (tik).
- You use methamphetamine (tik) often and in dangerous situations.
- Your body is very used to the drug and you will suffer withdrawal symptoms if you stop.

What is Contingency Management (CM)?

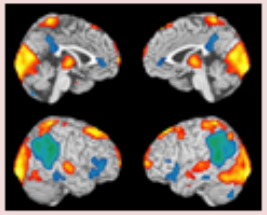
CM is a treatment for excessive methamphetamine (tik) use that has had a successful trial in the United States.
It helped individuals to stop taking the drug and to avoid going back onto it by providing vouchers that increase in value with each clean urine sample.

Food Clothes Airtime

Although CM has been shown to be effective in the United States it is not guaranteed that the CM program will result in long-lasting abstinence.

What will I get out of it?

You have the opportunity to earn vouchers for 'clean' urine samples



You will be provided with refreshments during the study if requested.

The information we get out of this study could help others who are battling with excessive methamphetamine (tik) use.

What will the vouchers be for?

Vouchers will be for specific items such as clothes, food, and airtime. You are encouraged to spend your vouchers after receiving them at the end of each week. A negative urine sample is worth a reward.

If I take part, what will be asked of me?

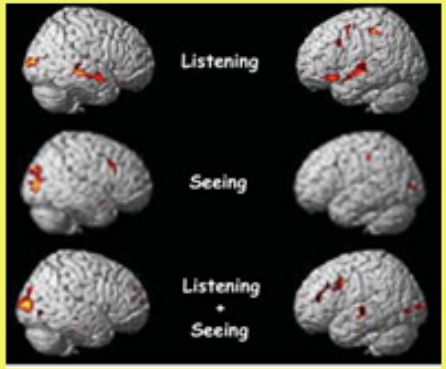
You will need to complete an informed consent form.

You will have a research interview which does not take the place of a full psychiatric evaluation.

You will need to provide observed urine samples 3 times a week for 8 weeks.

You will need to do 2 MRI brain scans, one at the beginning of the study and one at the end. Each takes about 1 ½ hours.

Whilst in the brain scan you will be asked to perform certain tasks.



On the same day as the scan you will be asked to complete a few tests which will also take about 1 ½ hours.

You will also be asked to do a few tasks during the study like keeping a record of your drug usage.

Are there any risks I need to be concerned about?

There is minimal risk.
This study has been given approval by the UCT **Human** Ethics Committee to ensure that risks to you will be kept to a minimum.

Remember:
If you get tired, uncomfortable, or upset during any part of the sessions, you may ask to stop for a rest-break, or can stop your part in the study.
If you find a question in the assessment makes you feel uncomfortable, you may discuss it with the interviewer, or you may choose not to answer.
No personal information we get from you will be discussed with anybody outside of the study, your privacy will be protected at all times.

Is the MRI brain scan dangerous?

No.
This is a safe procedure in most hospitals. Trained professionals will be with you to make sure of your comfort. It is noisy and the space is small inside it so some people might feel anxious or claustrophobic being in the scanner, but you will be given a panic button and shown how to use it if you wish to stop the scan.

Do I need to study for the tests and tasks?

No.
The tests are not to see how much you know, rather they are designed to make you use different parts of your brain. These parts will show up in the brain scan which will help us to see what task activate which brain areas.

You are not eligible if you:

- Have a significant physical, psychiatric or neurological illness.
- Are HIV/AIDS positive.
- Have a past history of significant alcohol and/or other substance abuse.
- Have a metal prosthesis.
- Have a cardiac pacemaker.
- Have metal clips, pins or plates in your body.
- Know that you get claustrophobia.
- Are pregnant.
- Are currently receiving treatment for stimulant addiction.
- Require a more intensive treatment than this outpatient procedure.
- Are not able to attend the visits required during the study.
- Fail to complete any measures or procedures during the study.
- Have had a 'serious' head injury

Contact information

Support:
Cape Town Drug Counselling Centre: 021 447 8026
Lifeline: 0861 322 322 www.lifeline.co.za
Researchers:
Dr Samantha Brooks/ Lara van Nunen
laravannunen@gmail.com / 072 148 0884
Complaints or concerns:
Tel: 021 406 6492
E-mail: sumaya.ariefdien@uct.ac.za

Please note that the University of Cape Town carries a No Fault Clinical Liability policy for participants who suffer a research-related injury in researcher-initiated clinical research: http://www.health.uct.ac.za/usr/health/research/hrec/forms/No_Fault_Insurance_2013.pdf

Appendix L

Chapter 4: Outliers Hypothesis One

Trail Making Task

Cooks Distance – outliers	Study Status	Value	Number of errors
CM003 (1 on bar graph)	Non-Responder	0.13	21 errors
CM056 (8 on bar graph)	Responder	0.15	23 errors
HC117 (50 on bar graph)	Healthy control	0.10	23 errors

Table 4.1: Outliers details for baseline TMT-B accuracy

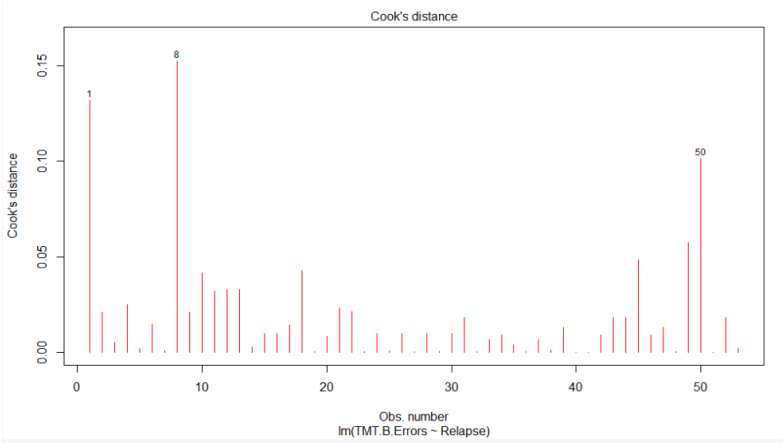


Figure 4.1 : Graph of outliers for baseline TMT-B accuracy

Cooks Distance – outliers	Study Status	Value	Time taken
CM215 (22 on bar graph)	Non-Responder	0.10	467.50 sec
HC099 (45 on bar graph)	Healthy Control/ absconder	0.07	366.30 sec
HC117 (50 on bar graph)	Healthy control	0.09	377.00 sec

Table 4.2: Outliers details for baseline TMT-B time taken to complete

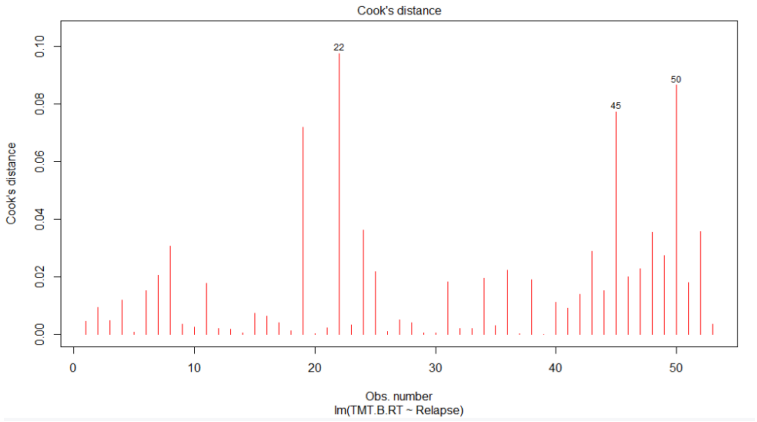


Figure 4.2 : Graph of outliers for baseline TMT-B time taken to complete

Cooks Distance – outliers	**Study Status**	**Value**	**Errors**
CM056 (8 on bar graph)	Responder	0.19	23 errors
HC114 (49 on bar graph)	Healthy control	0.08	19 errors
HC117 (50 on bar graph)	Healthy control	0.13	23 errors

Table 4.3: Outliers details for baseline TMT-B minus TMT-A accuracy

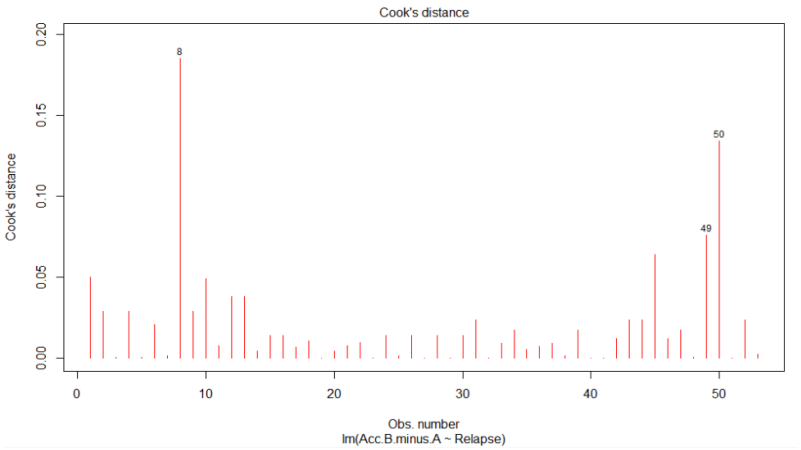


Figure 4.3 : Graph of outliers for baseline TMT-B minus TMT-A accuracy

Cooks Distance – outliers	**Study Status**	**Value**	**Time taken**
CM215 (22 on bar graph)	Non-Responder	0.11	433.60 sec
HC099 (45 on bar graph)	Healthy Control/ absconder	0.08	325.80 sec
HC117 (50 on graph)	Healthy control	0.10	338.40 sec

Table 4.4: Outliers details for baseline TMT-B minus TMT-A time to completion

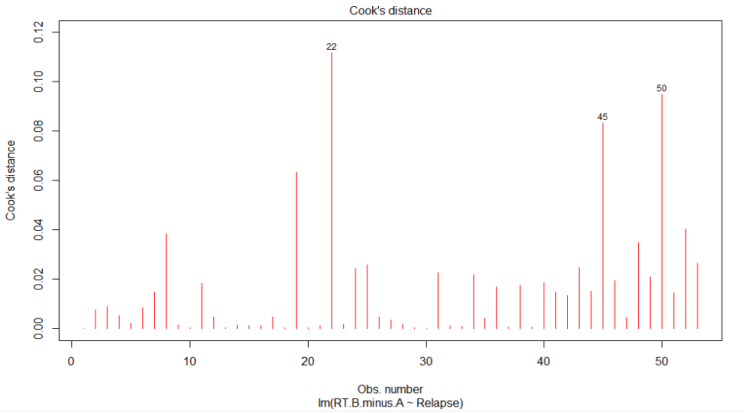


Figure 4.4 : Graph of outliers for baseline TMT-B minus TMT-A time to completion

The Stroop Word Task

Cooks Distance – outliers	Study Status	Value	Percentage accurate
CM003 (1 on bar graph)	Non-Responder	0.29	51.36%

Table 4.5: Outliers details for baseline Stroop accuracy

Outlier in wrong group

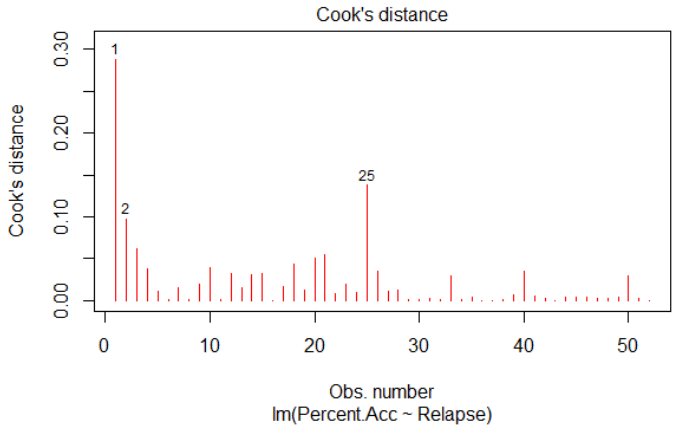


Figure 4.5 : Graph of outliers for baseline Stroop accuracy

Cooks Distance – outliers	Study Status	Value	RT
CM003 (1 on bar graph)	Non-Responder	0.13	449.17
CM161 (17 on bar graph)	Non-Responder (absconder)	0.16	422.55
CM199 (20 on bar graph)	Non-Responder	0.15	1009.04

Table 4.5: Outliers details for baseline Stroop reaction time

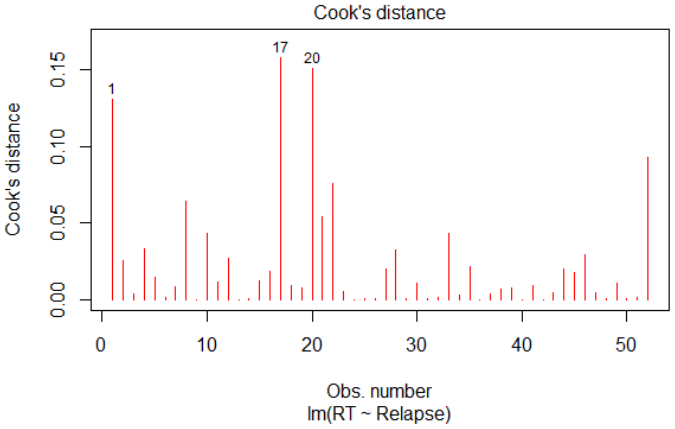


Figure 4.6 : Graph of outliers for baseline Stroop reaction time

Cooks Distance – outliers	**Study Status**	**Value**	**Accuracy**
CM026 (4 on bar graph)	Responder	0.17	33.00
CM161 (17 on bar graph)	Non-Responder (absconder)	0.32	29.82
HC085 (40 on bar graph)	Healthy Control	0.11	0.00
Cooks Distance – outliers	**Study Status**	**Value**	**RT**
CM161 (17 on bar graph)	Non-Responder (absconder)	0.01	1.14
CM186 (19 on bar graph)	Non-Responder	0.14	342.87
CM253 (27 on bar graph)	Responder	0.12	382.70

Table 4.7: Outliers details for baseline Stroop Effect

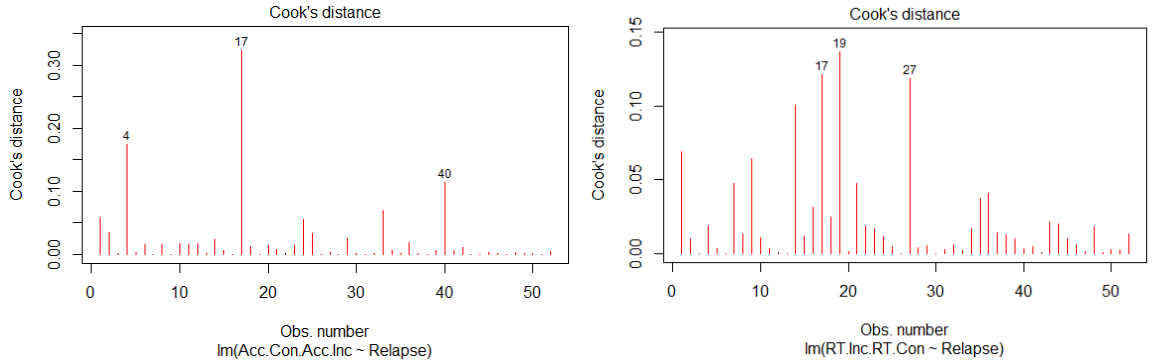


Figure 4.7: Graph of outliers for baseline Stroop Effect

Cooks Distance – outliers	**Study Status**	**Value**	**Accuracy**
CM021 (3 on bar graph)	Non-Responder	0.11	-26.04
CM199 (20 on bar graph)	Non-Responder	0.07	-22.68
CM242 (25 on bar graph)	Responder	0.18	-40.58
Cooks Distance – outliers	**Study Status**	**Value**	**RT**
CM215 (21 on bar graph)	Non-Responder	0.14	541.77
HC033 (33 on bar graph)	Healthy control	0.18 0.20	817.35

HC040 (35 on bar graph)	Healthy control		-913.70

Table 4.8: Outliers details for baseline Stroop Lamming Rabbit Effect

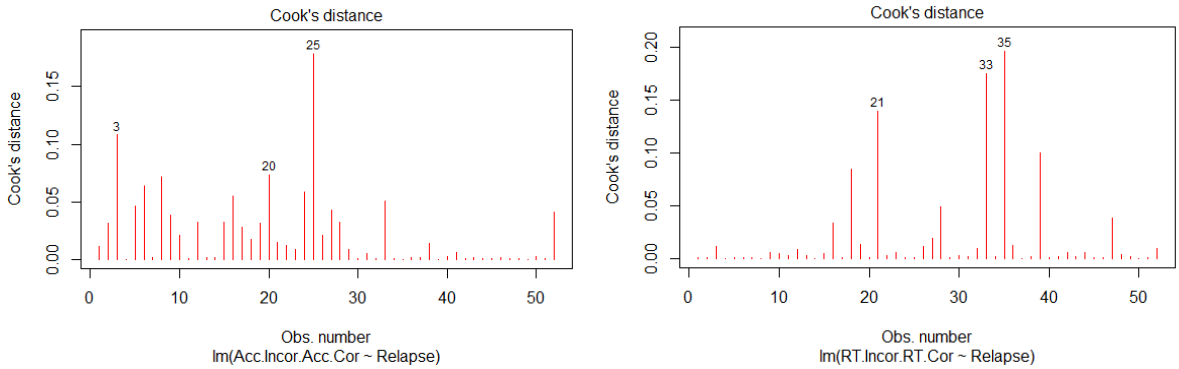


Figure 4.8: Graph of outliers for baseline Stroop Lamming Rabbit Effect

Cooks Distance – outliers	**Study Status**	**Value**	**RT IpC IpI**
CM057 (8 on bar graph)	Responder	0.13	-168.30
CM186 (19 on bar graph)	Non-Responder	0.08	-78.33 -273.93
HC033 (33 on bar graph)		0.21	
Cooks Distance – outliers	**Study Status**	**Value**	**RT CpI CpC**
CM105 (14 on bar graph)	Responder	0.09	-72.86
CM222 (22 on bar graph)	Non-Responder	0.20 0.08	-115.90
CM253 (27 on bar graph)	Responder		82.61

Table 4.9: Outliers details for baseline Stroop Kerns Effect

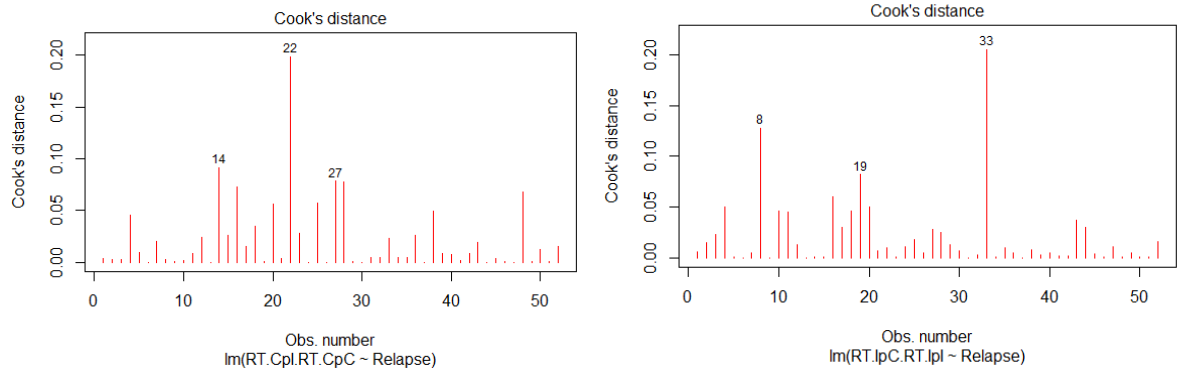


Figure 4.9: Graph of outliers for baseline Stroop Kerns Effect

The Continuous Performance Task

Cooks Distance – outliers	Study Status	Value	Accuracy
CM021 (3 on bar graph)	Non-Responder	0.1	429.26
CM075 (14 on bar graph)	Responder	0.20	424.63
CM145 (17 on bar graph)		0.09	512.84

Table 4.10: Outliers details for baseline CPT accuracy

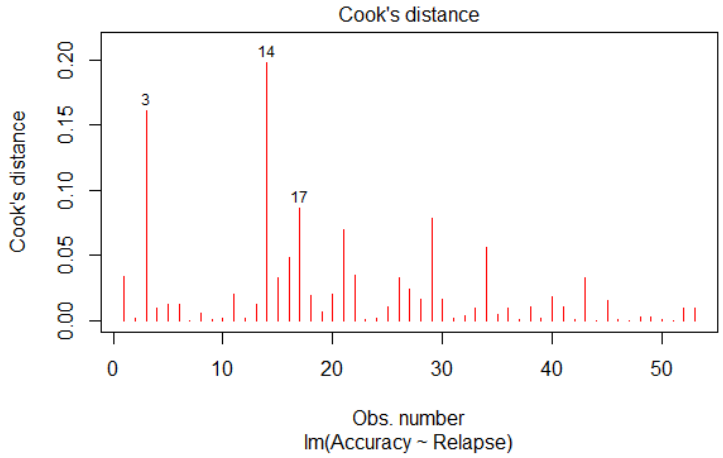


Figure 4.10: Graph of outliers for baseline CPT accuracy

Cooks Distance – outliers	Study Status	Value	RT
CM060 (12 on bar graph)	Responder	0.11	452.69
HC099 (45 on bar graph)	Healthy control – (absconder)	0.08	557.82
HC128 (52 on bar graph)	Healthy control	0.12	586.53

Table 4.11: Outliers details for baseline CPT reaction time

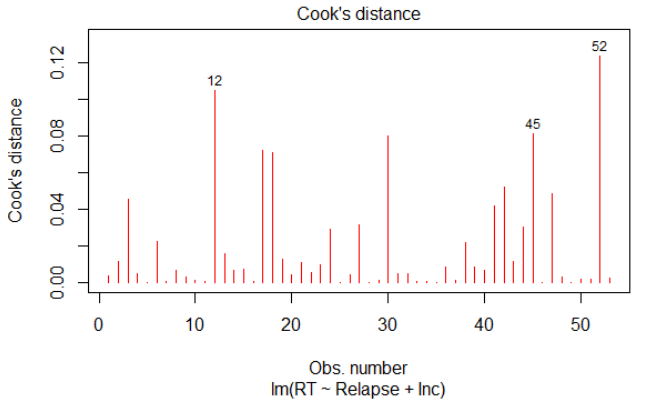


Figure 4.11: Graph of outliers for baseline CPT accuracy

Cooks Distance – outliers	**Study Status**	**Value**	**D' Prime**
CM075 (14 on bar graph)	Responder	0.10	2.27
CH199 (21 on bar graph)	Non-Responders	0.10	3.54
HC085 (40 on bar graph)	Healthy control	0.10	4.05
			Omissions
CM021 (3 on bar graph)	Non-Responders	0.19	27
CM075 (14 on bar graph)	Responder	0.27	31
CM145 (17 on bar graph)	Non-Responders	0.25	30
			Commissions
CM003 (1 on bar graph)	Non-Responders	0.03	29
CM254 (29 on bar graph)	Non-Responders	0.09	19
HC089 (43 on bar graph)	Healthy control	0.10	27
			HRT
CM145 (17 on bar graph)	Non-Responders	0.15	512.84
HC099 (45 on bar graph)	Healthy control (absconder)	0.11	362.22
HC093 (52 on bar graph)	Healthy control	0.13	586.53
			Variability
CM003 (1 on bar graph)	Non-Responder	0.29	157.54
CM075 (14 on bar graph)	Responder	0.42	193.53

Table 4.12: Outliers details for baseline CPT inattentiveness

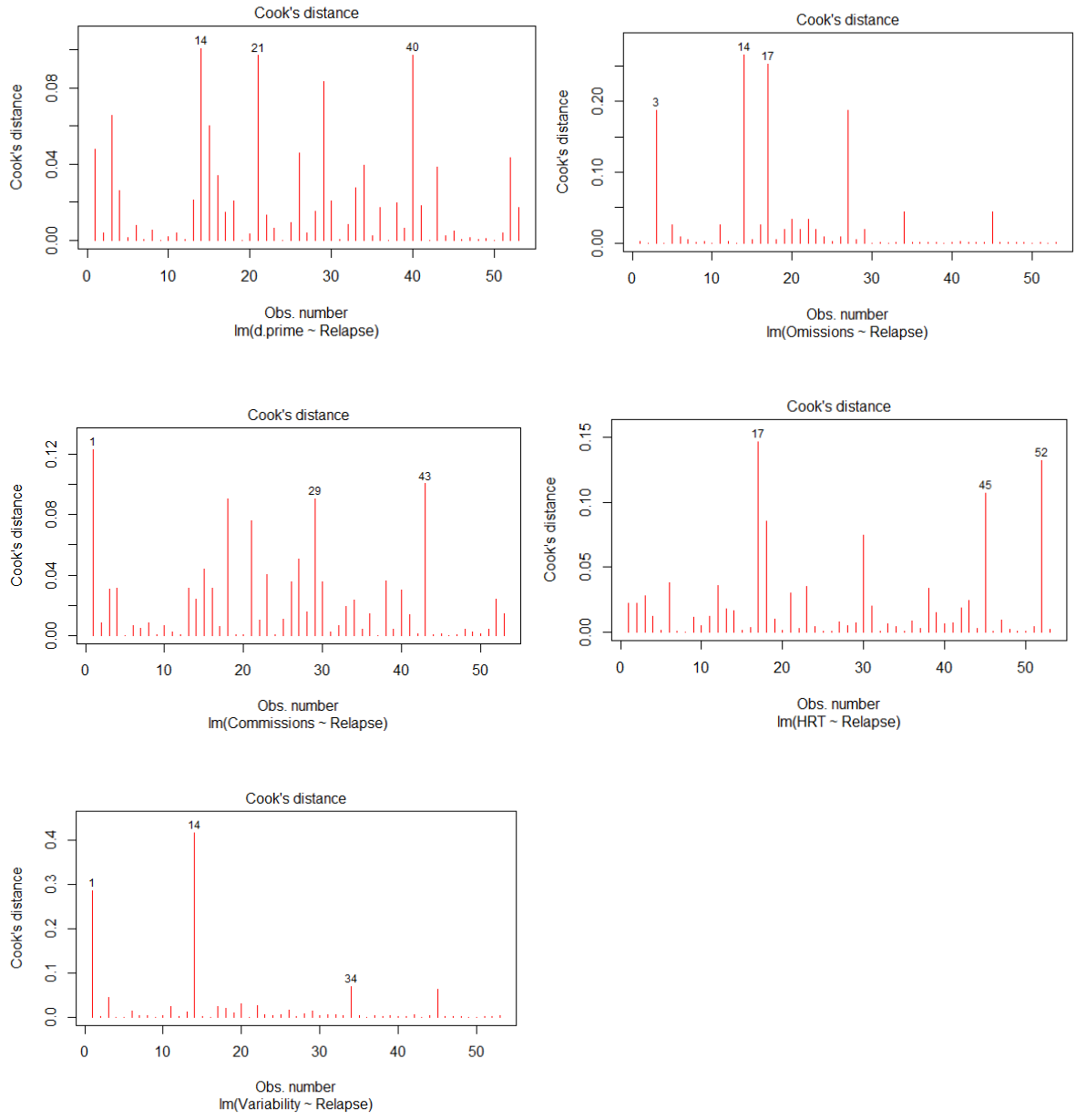


Figure 4.12: Graphs of outliers for baseline CPT accuracy in inattentiveness

Cooks Distance – outliers	**Study Status**	**Value**	**HRT**	**Block**
CM145 (17 on bar graph)	Non-Responder	0.14	524.37	Block 1
HC099 (45 on bar graph)	Healthy control (absconder)	0.09 0.12	587.19	
HC126 (52 on bar graph)	Healthy control		364.57	

CM145 (17 on bar graph) CM260 (30 on bar graph) HC099 (45 on bar graph)	Non-Responder Responder Healthy control (absconder)	0.17 0.10 0.13	551.20 524.28 603.99	Block 2
CM145 (17 on bar graph) CM161 (18 on bar graph) CM199 (21 on bar graph)	Non-Responder Non-Responder (absconder) Non-Responder	0.13 0.17 0.14	476.78 198.41 484.19	Block 3
HC099 (45 on bar graph) HC128 (52 on bar graph)	Healthy control (absconder) Healthy control	0.23 0.15	717.95 653.49	Block 4

Table 4.13: Outliers details for baseline HRT in CPT sustained attention

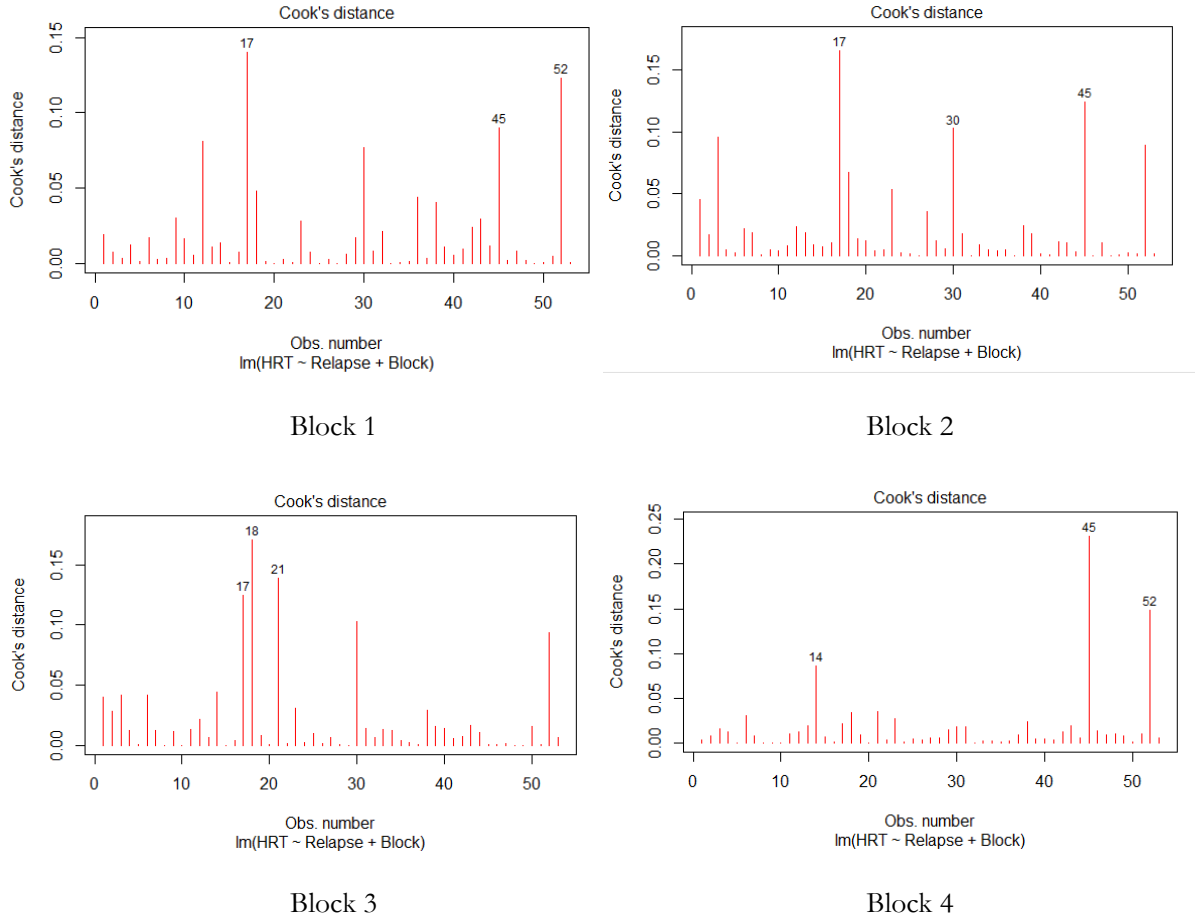
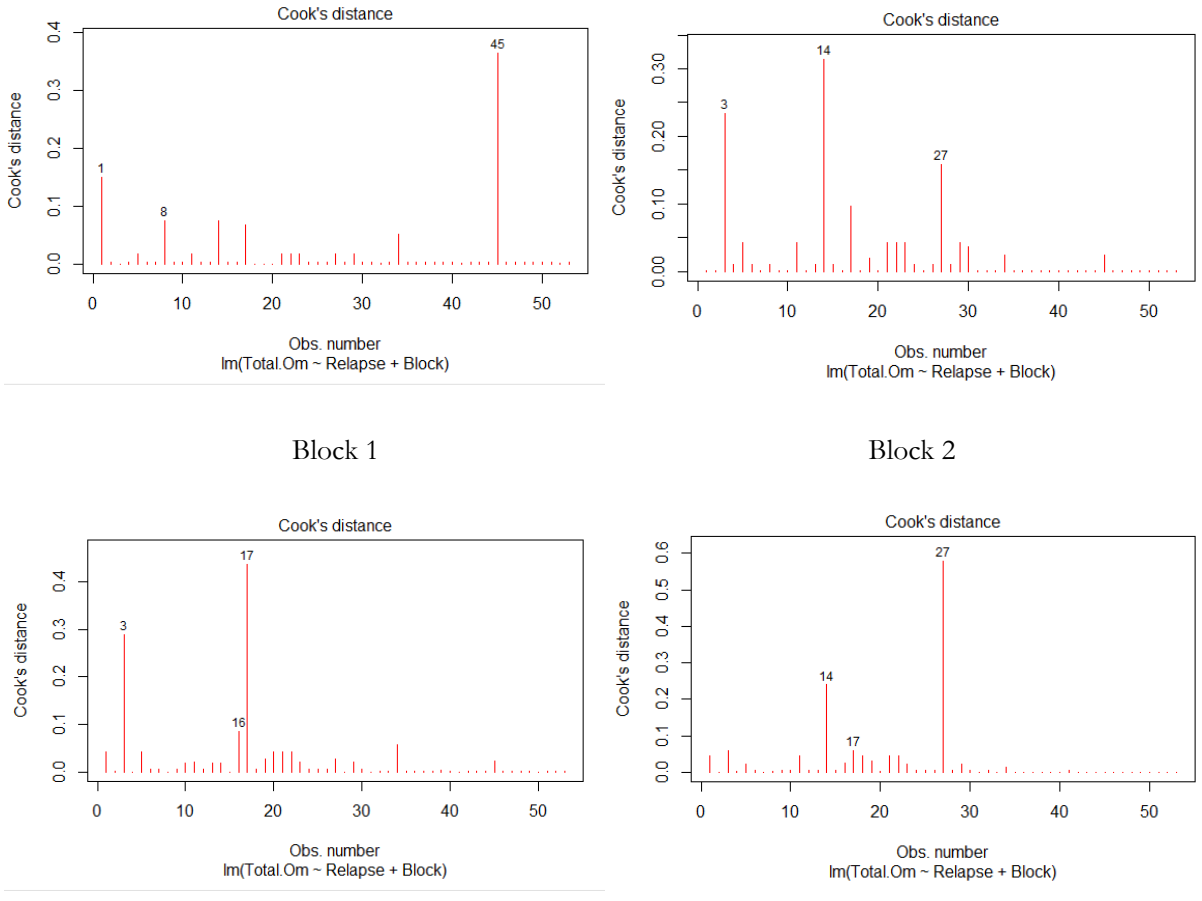


Figure 4.13: Graph of outliers for baseline HRT in CPT sustained attention

Cooks Distance – outliers	Study Status	Value	Omissions	Block
HC099 (45 on bar graph)	Healthy control (absconder)	0.37	7	Block 1
CM021 (3 on bar graph) CM075 (14 on bar graph) CM243 (27 on bar graph)	Non-Responder Responder Non-Responder	0.23 0.31 0.16	8 9 7	Block 2
CM021 (3 on bar graph) CM145 (17 on bar graph)	Non-Responder Non-Responder	0.29 0.44	12 14	Block 3
CM243 (27 on bar graph)	Non-Responder	0.58	15	Block 4

Table 4.14: Outliers details for baseline omissions in CPT sustained attention



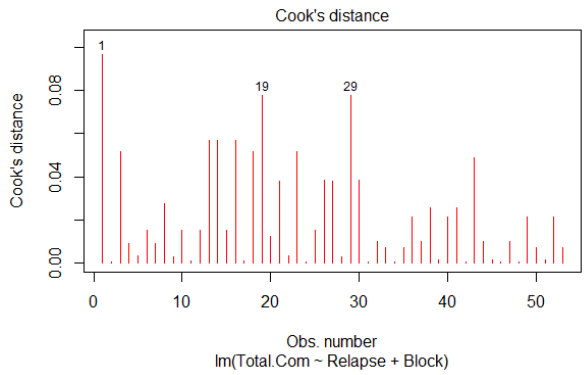
Block 1 Block 2

Block 3 Block 4

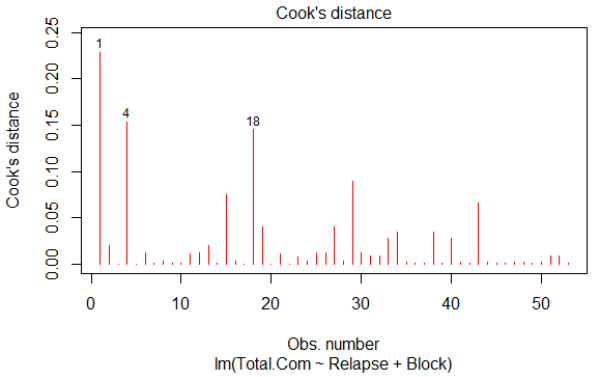
Figure 4.14 : Graph of outliers for baseline omissions in CPT sustained attention

Cooks Distance – outliers	Study Status	Value	Commissions	Block
CM003 (1 on bar graph)	Non-Responder	0.10	7	Block 1
CM173 (19 on bar graph)	Non-Responder	0.08	0	
CM254 (29 on bar graph)	Non-Responder	0.08	5	
CM003 (1 on bar graph)	Non-Responder	0.23	8	Block 2
CM026 (4 on bar graph)	Responder	0.15	9	
CM161 (18 on bar graph)	Non-Responder (absconder)	0.15	7	
CM075 (14 on bar graph)	Responder	0.13	9	Block 3
CM161 (18 on bar graph)	Non-Responder (absconder)	0.12	8	
HC093 (43 on bar graph)	Health control	0.10	8	
CM003 (1 on bar graph)	Non-Responder	0.08	8	Block 4
CM021 (3 on bar graph)	Non-Responder	0.13	9	
CM173 (19 on bar graph)	Non-Responder	0.08	0	

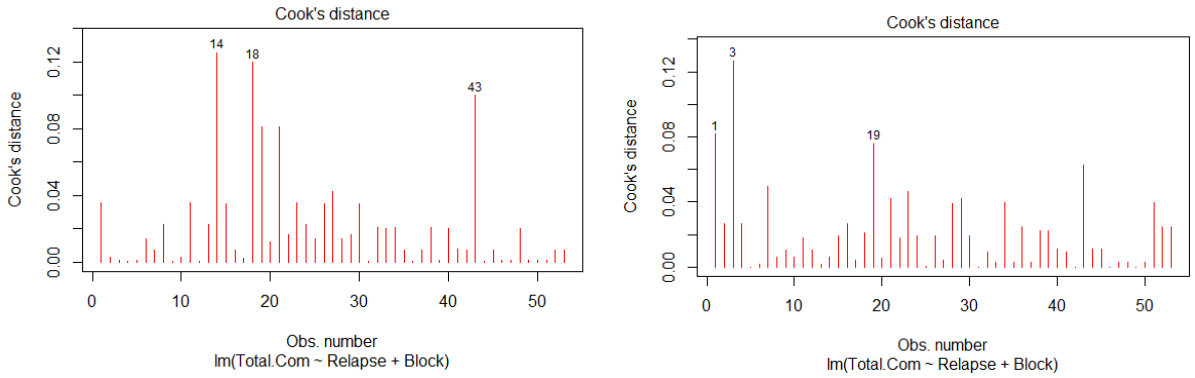
Table 4.15: Outliers details for baseline commissions in CPT sustained attention



Block 1



Bock 2



Block 3 Block 4

Figure 4.15: Graph of outliers for baseline commissions in CPT sustained attention

Chapter 4: Outliers Hypothesis two

Trail Making Task

Cooks Distance – outliers	Study Status	Value	Time session 2	Session 1
CM173 (17 on bar graph)		0.10	91.80	356.14
CM215 (20 on bar graph)		0.19	124.30	433.60
CM260 (56 on bar graph)		0.09	342.30	103.32

Table 4.16: Outliers details for the TMT, time to completion across sessions

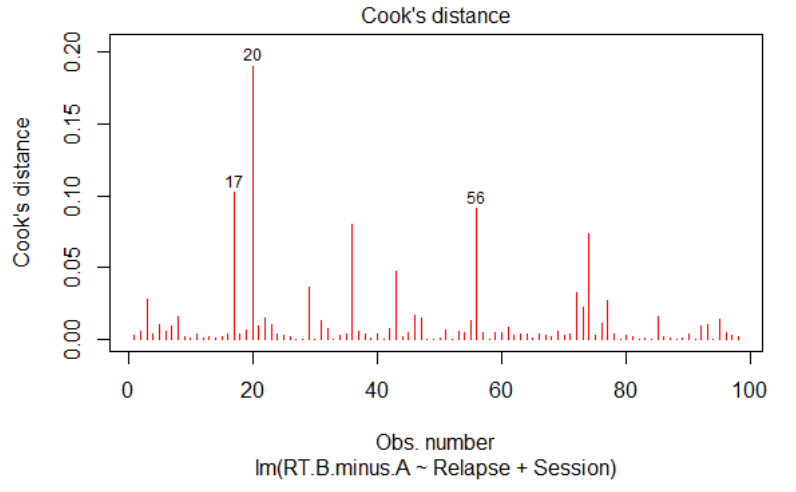


Figure 4.17: Graph of outliers for the TMT, time to completion across sessions

Cooks Distance – outliers	Study Status	Value	Time
CM003_1 (1 on bar graph)		0.30	120.10
CM115_1 (15 on bar graph)		0.21	16.75
CM115_2 (43 on bar graph)		0.07	79.80

Table 4.18: Outliers details for the TMT-A, time to completion across sessions

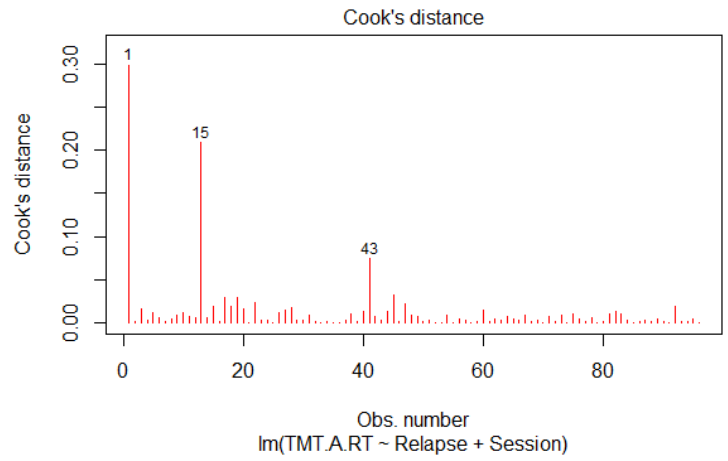


Figure 4.18: Graph of outliers for the TMT-A, time to completion across sessions

Cooks Distance – outliers	Study Status	Value	Time session 2	Session 1
CM173_1 (17 on bar graph)		0.10	91.80	356.14
CM215_1 (20 on bar graph)		0.19	124.30	433.60
CM260_2 (56 on bar graph)		0.09	342.30	103.32

Table 4.19: Outliers details for the TMT-B, time to completion across sessions

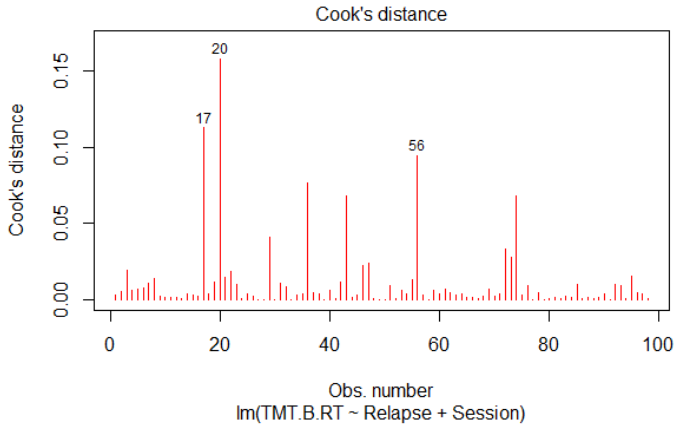


Figure 4.19: Graph of outliers for the TMT-B, time to completion across sessions

The Stroop Word Task

Cooks Distance – outliers	Study Status	Value	Accuracy
CM008_2 (29 on bar graph)		0.35	10.32

Table 4.20: Outliers details for Stroop accuracy across sessions

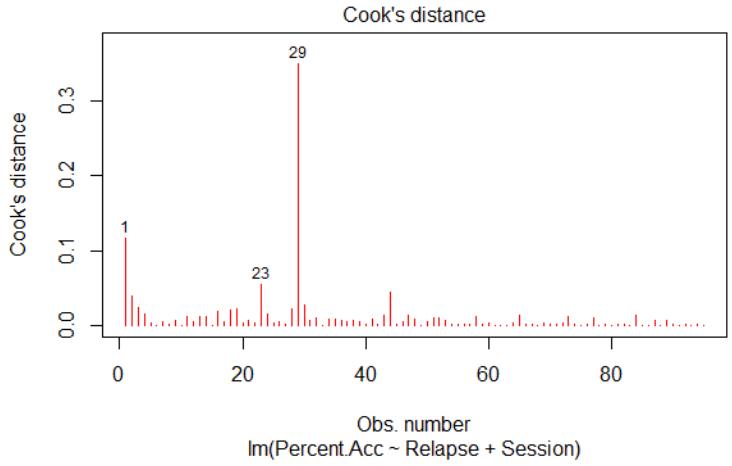


Figure 4.20: Graph of outliers for the Stroop, accuracy across sessions

Cooks Distance – outliers	Study Status	Value	Accuracy
CM026_1 (4 on bar graph)		0.16	32.96
HC010_1 (58 on bar graph)		0.07	22.03
HC088_1 (65 on bar graph)		0.11	26.76

Table 4.21: Outliers details for Stroop effect, accuracy across sessions

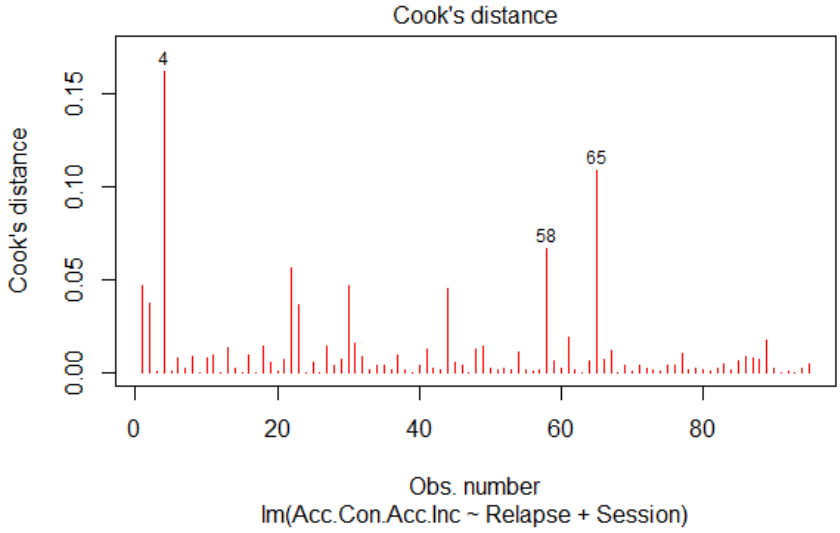


Figure 4.21: Graph of outliers for the Stroop effect, accuracy across sessions

Cooks Distance – outliers	Study Status	Value	RT
CM424_2 (49 on bar graph)		0.39	-19.41

Table 4.22: Outliers details for Stroop effect, reaction time across sessions

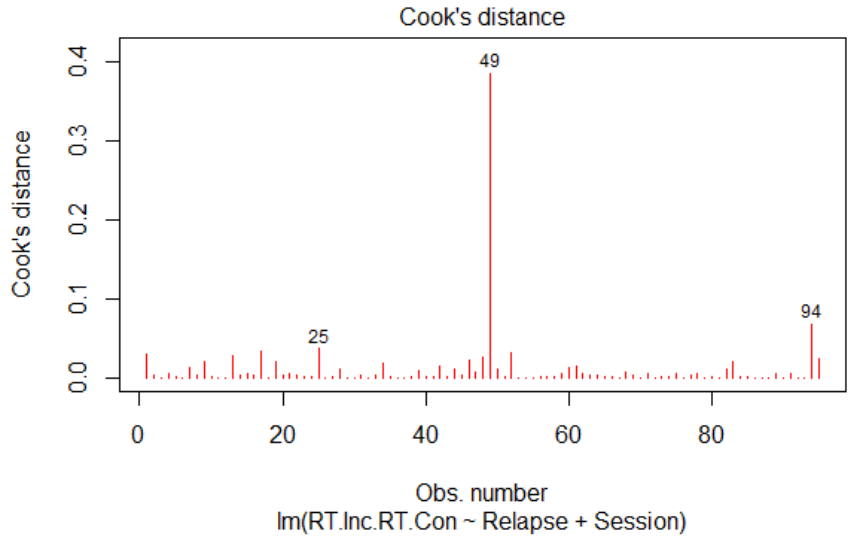


Figure 4.22: Graph of outliers for the Stroop effect, reaction timer across sessions

Cooks Distance – outliers	Study Status	Value	Accuracy
CM021_1 (3 on bar graph)		0.08	-26.04
CM242_1 (23 on bar graph)		0.10	-40.58
CM253_2 (52 on bar graph)		0.19	-49.34

Table 4.23: Outliers details for Stroop Lamming Rabbit effect, accuracy across sessions

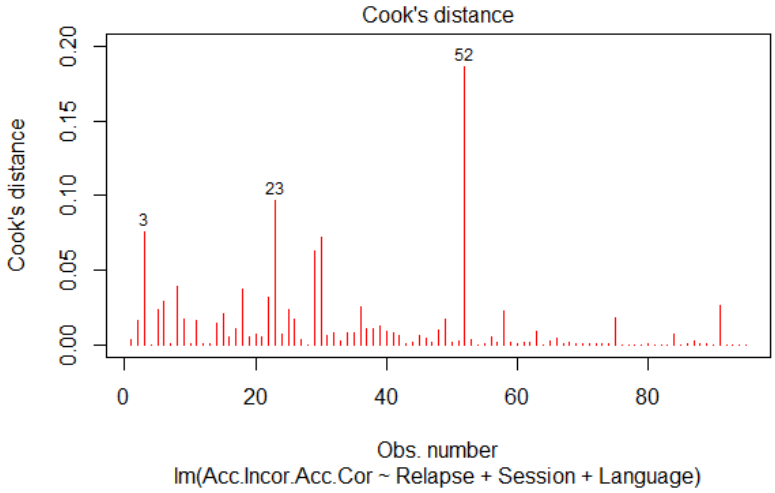


Figure 4.23: Graph of outliers for the Stroop Lamming Rabbit effect, accuracy across sessions

Cooks Distance – outliers	Study Status	Value	Accuracy
CM222_2 (47 on bar graph)		0.06	0.66
HC037_1 (58 on bar graph)		0.08	-19.23
HC040_1 (60 on bar graph)		0.11	0.66

Table 4.24: Outliers details for Stroop Lamming Rabbit effect, reaction time across sessions

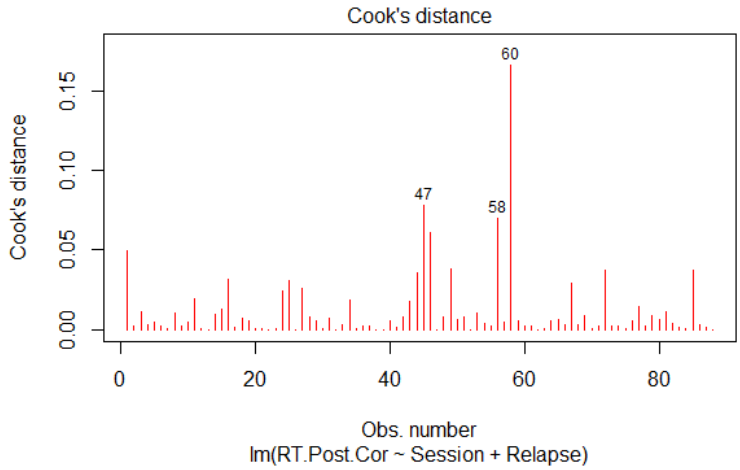


Figure 4.24: Graph of outliers for the Stroop Lamming Rabbit effect, reaction time across sessions

Cooks Distance – outliers	Study Status	Value	Accuracy
HC033_1 (58 on bar graph)		0.13	-316.69

Table 4.25: Outliers details for Stroop Kerns effect, across sessions

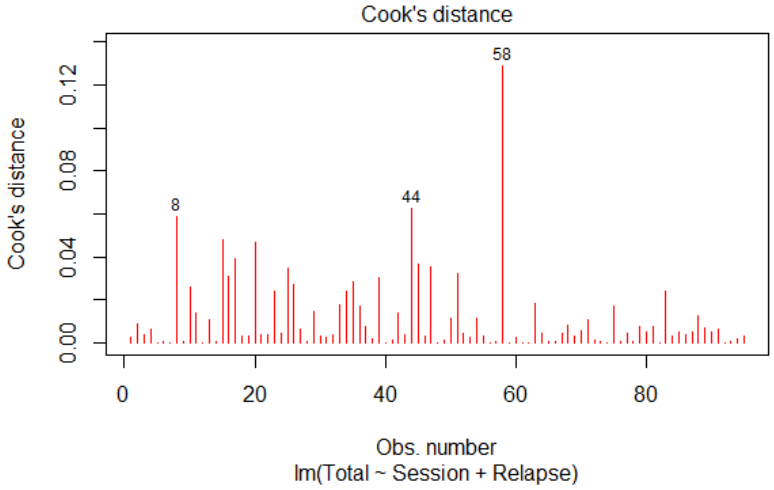


Figure 4.25: Graph of outliers for the Stroop Kerns effect, across sessions

The Continuous Performance Task

Cooks Distance – outliers	Study Status	Value	Accuracy
CM021_1 (3 on bar graph)		0.12	49
CM075_1 (13 on bar graph)		0.11	52
CM145_1 (16 on bar graph)		0.07	42

Table 4.26: Outliers details for CPT accuracy, across sessions

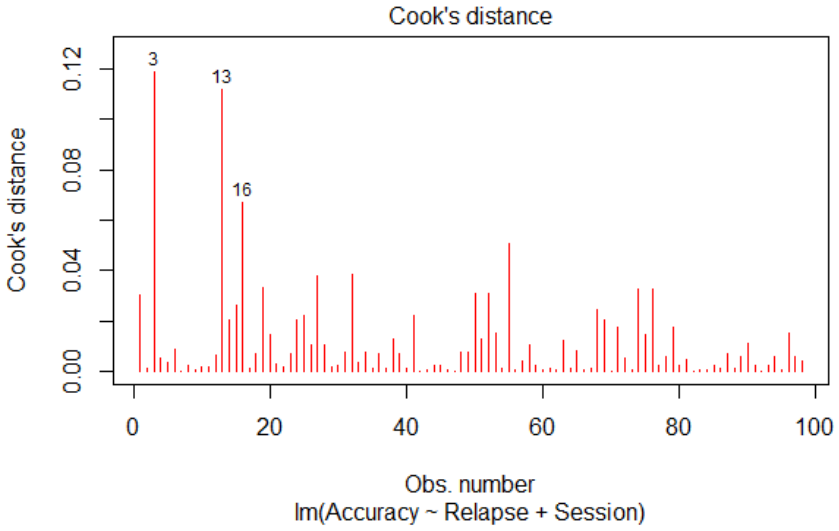
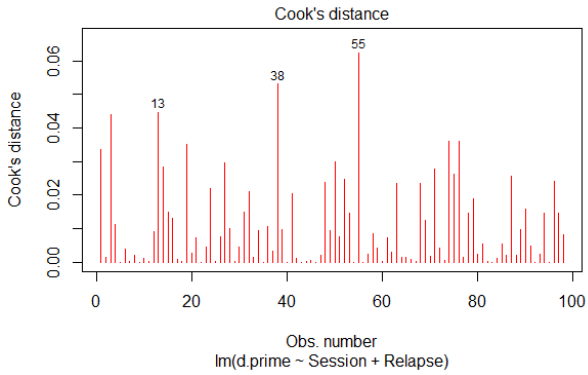


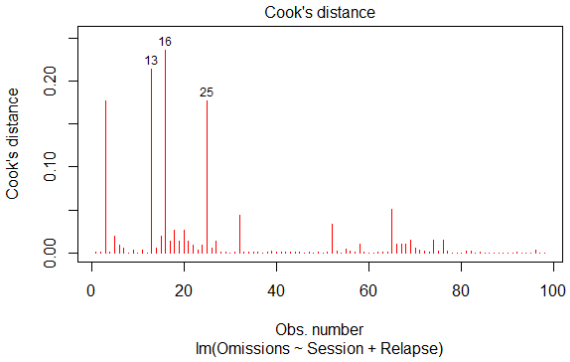
Figure 4.26: Graph of outliers for the CPT accuracy, across sessions

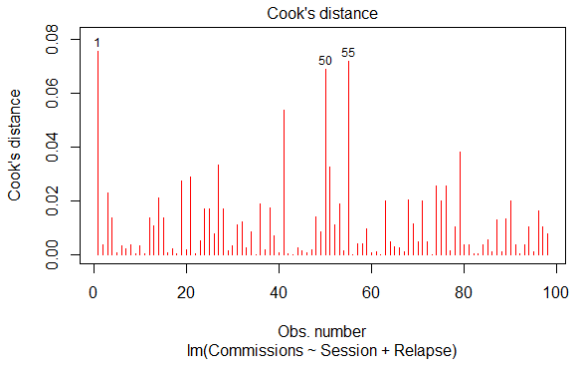
Cooks Distance – outliers	Study Status	Value	d'prime
CM075_1 (13 on bar graph)		0.05	2,82
HC085_1 (38 on bar graph)		0.05	4.05
CM030_2 (55 on bar graph)		0.06	2.16
Cooks Distance – outliers	**Study Status**	**Value**	**Omissions**
CM075_1 (13 on bar graph)		0.21	31
CM145_1 (16 on bar graph)		0.24	30
CM243_1 (25 on bar graph)		0.18	27
Cooks Distance – outliers	**Study Status**	**Value**	**Commissions**
CM003_1 (1 on bar graph)		0.08	29
CM003_2 (50 on bar graph)		0.07	28

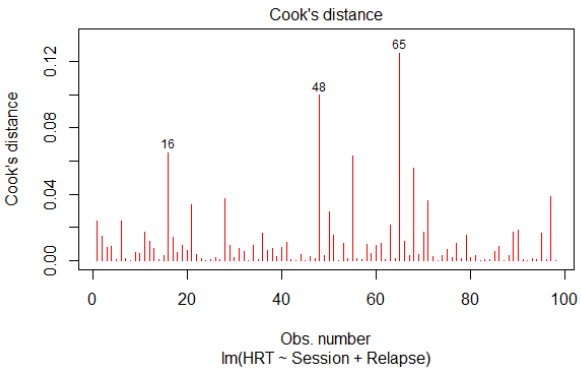
CM030_2 (55 on bar graph)		0.07	31
Cooks Distance – outliers	**Study Status**	**Value**	**HRT**
CM145_1 (16 on bar graph) HC128_1 (48 on bar graph) CM145_2 (65 on bar graph)		0.07 0.10 0.13	512.84 586.53 259.18
Cooks Distance – outliers	**Study Status**	**Value**	**Variability**
CM003_1 (1 on bar graph) CM075_1 (13 on bar graph) CM145_2 (65 on bar graph)		0.23 0.32 0.16	157.54 193.53 131.93

Table 4.27: Outliers details for CPT inattentiveness, across sessions









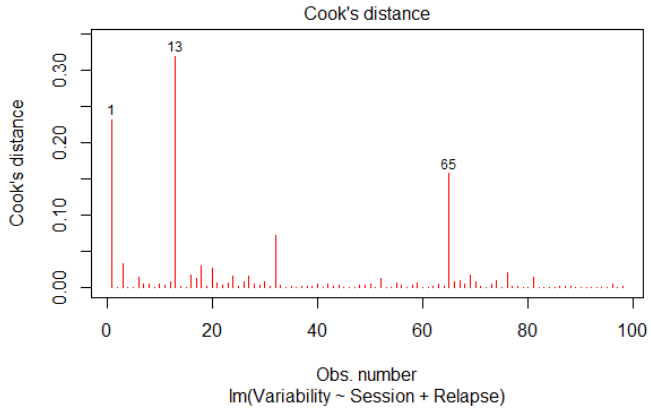
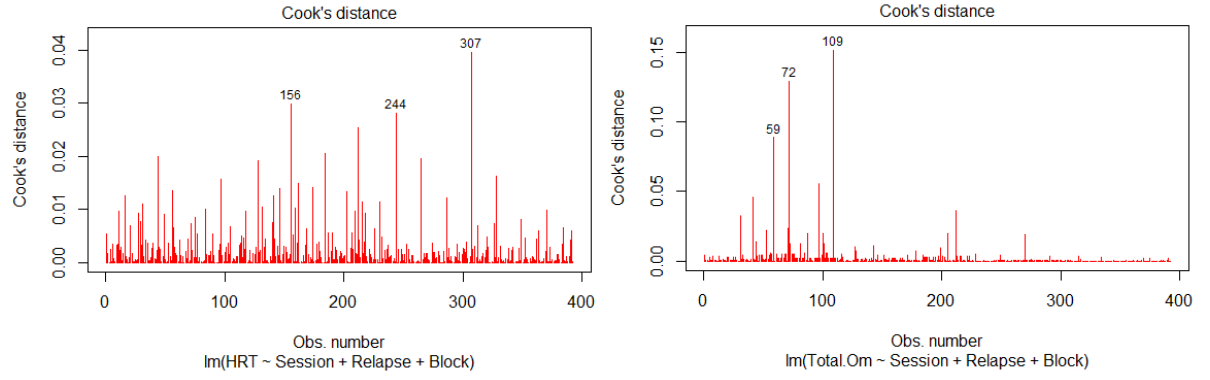


Figure 4.27 : Graphs of outliers for the CPT inattentiveness, across sessions

Cooks Distance – outliers	**Study Status**	**Value**	**HRT**
CM145_2_B2 (156 on bar graph)		0.03	584.06
HC128_1 B1 (244 on bar graph)		0.03	617.69
HC128_1 B4 (307 on bar graph)		0.04	653.49
Cooks Distance – outliers	**Study Status**	**Value**	**Omissions**
CM021_1 B3 (59 on bar graph)		0.089	12
CM145_1 B3 (72 on bar graph)		0.13	14
CM222_1 B4 (109 on bar graph)		0.15	1
Cooks Distance – outliers	**Study Status**	**Value**	**Commissions**
CM021_1 B4 (87 on bar graph)		0.02	9
CM003_2 B2 (141 on bar graph)		0.02	9
CM173_2 B2 (157 on bar graph)		0.03	10

Table 4.28: Outliers details for CPT sustained attention, across sessions



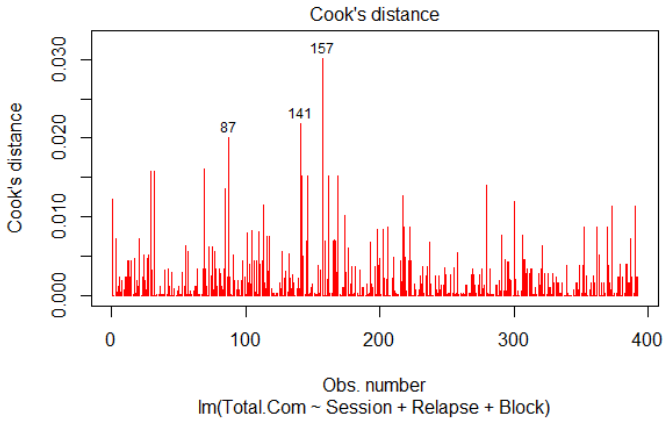


Figure 4.28: Graphs of outliers for the CPT sustained attention, across sessions

Appendix M

Chapter 4: Tests for Heteroscedacity Hypothesis One

Trail Making Task –B minus –A Accuracy

Independent variable	Koenker-Bassett Test	Degrees of freedom	p value
Education	0.61	1	0.44
Sex	0.18	1	0.67
Income	1.02	1	0.31

Table 4.30: test for heteroscedasticity

Stroop Reaction Time

Independent variable	Koenker-Bassett Test	Degrees of freedom	p value
Education	0.41	1	0.52
Sex	2.00	1	0.16
Income	1.02	1	0.31

Table 4.31: test for heteroscedasticity

Stroop Kerns Effect

Independent variable	Koenker-Bassett Test	Degrees of freedom	p value
Education	0.03	1	0.86
Sex	0.88	1	0.35
Income	2.33	1	0.13

Table 4.32: test for heteroscedasticity

CPT Reaction Time

Independent variable	Koenker-Bassett Test	Degrees of freedom	p value
Education	0.59	1	0.44
Sex	2.23	1	0.14
Income	7.55	4	0.11

Table 4.33: test for heteroscedasticity

CPT Inattentiveness

Independent variable	Koenker-Bassett Test	Degrees of freedom	p value
d' Prime			
Education	2.17	1	0.14
Sex	1.69	1	0.19
Income	0.35	1	0.56
Omissions			
Education	0.05	1	0.83
Sex	0.02	1	0.90
Income	0.13	1	0.72
Commissions			
Education	0.79	1	0.38
Sex	0.37	1	0.55
Income	0.42	1	0.52
HRT			
Education	0.62	1	0.43
Sex	2.22	1	0.14
Income	3.84	1	0.05
Variability			

Education	1.42	1	0.23
Sex	0.78	1	0.38
Income	0.54	1	0.47

Table 4.34: test for heteroscedasticity

CPT Sustained Attention

Independent variable	Koenker-Bassett Test	Degrees of freedom	p value
HRT			
Education	2.19	1	0.14
Sex	4.85	1	0.03
Income	7.36	1	0.01
Omissions			
Education	0.01	1	0.95
Sex	1.17	1	0.28
Income	0.10	1	0.76
Commissions			
Education	0.74	1	0.39
Sex	0.70	1	0.40
Income	0.06	1	0.81

Table 4.35: test for heteroscedasticity

Chapter 4: Tests for Heteroscedacity Hypothesis Two

TMT Time to Completion between Sessions

Independent variable	Koenker-Bassett Test	Degrees of freedom	p value
Education	4.09	1	0.04
Sex	2.14	1	0.14
Income	0.05	1	0.82

Table 4.36: test for heteroscedasticity

Stroop Accuracy between Sessions

Independent variable	Koenker-Bassett Test	Degrees of freedom	p value
Education	0.02	1	0.89
Sex	1.77	1	0.18
Income	0.06	1	0.80

Table 4.37: test for heteroscedasticity

Stroop Effect Accuracy between Sessions

Independent variable	Koenker-Bassett Test	Degrees of freedom	p value
Education	1.33	1	0.25
Sex	0.20	1	0.66
Income	1.02	1	0.31

Table 4.38: test for heteroscedasticity

Stroop Lamming Rabbit Effect Accuracy between Sessions

Independent variable	Koenker-Bassett Test	Degrees of freedom	p value
Education	0.85	1	0.36
Sex	0.04	1	0.85

Income	1.48	1	0.22

Table 4.39: test for heteroscedasticity

Stroop Kerns Effect Accuracy between Sessions

Independent variable	Koenker-Bassett Test	Degrees of freedom	p value
Education	0.01	1	0.97
Sex	1.64	1	0.20
Income	2.83	1	0.09

Table 4.40: test for heteroscedasticity

CPT Accuracy between Sessions

Independent variable	Koenker-Bassett Test	Degrees of freedom	p value
Education	0.24	1	0.63
Sex	0.13	1	0.72
Income	0.71	1	0.40

Table 4.41: test for heteroscedasticity

CPT Inattentiveness Accuracy between Sessions

Independent variable	Koenker-Bassett Test	Degrees of freedom	p value
d' Prime			
Education	4.07	1	0.04
Sex	0.07	1	0.79
Income	0.37	1	0.54
Omissions			
Education	0.01	1	0.96
Sex	0.14	1	0.71
Income	0.09	1	0.77

Commissions			
Education	0.81	1	0.37
Sex	3.30	1	0.07
Income	0.06	1	0.81
HRT			
Education	0.79	1	0.38
Sex	4.37	1	0.04
Income	2.65	1	0.10
Variability			
Education	1.79	1	0.18
Sex	0.31	1	0.58
Income	0.11	1	0.75

Table 4.42: test for heteroscedasticity

CPT Sustained Attention Accuracy between Sessions

Independent variable	Koenker-Bassett Test	Degrees of freedom	p value
HRT			
Education	1.53	1	0.22
Sex	12.11	1	0.01
Income	6.06	1	0.01
Omissions			
Education	0.11	1	0.74
Sex	2.11	1	0.15
Income	0.07	1	0.79
Commissions			
Education	0.02	1	0.89
Sex	6.02	1	0.01
Income	0.48	1	0.49

Table 4.43: test for homoscedasticity

Appendix N

Chapter 4: Results

Demographics

Responders (n = 17)	Non-Responders (n = 13)	Healthy Controls (n = 23)	Linear Regression
25.82 ± 2.01	24.46 ± 2.82	25.30 ± 2.70	p = 0.22

Table 4.45: MoCA, total score

	Responders (n = 17)	Non-Responders (n = 13)	Wilcoxon Rank Sum
Medical (means ± std.dev.)	0.06 ± 0.14	0.15 ± 0.32	p = 0.59
Employment (means ± std.dev.)	0.88 ± 0.13	0.87 ± 0.17	p = 1
Alcohol (means ± std.dev.)	0.09 ± 0.02	0.10 ± 0.01	p = 0.17
Drug (means ± std.dev.)	0.26 ± 0.1	0.25 ± 0.08	p = 0.69
Legal (means ± std.dev.)	0.07 ± 0.17	0.08 ± 0.14	p = 0.58
Family/ social (means ± std.dev.)	0.35 ± 0.23	0.38 ± 0.24	p = 1
Psychiatric (means ± std.dev.)	0.16 ± 0.21	0.13 ± 0.26	p = 0.40

Table 4.46: Sections of the ASI

	Responders (n = 17)	**Non-Responders (n = 13)**	**Wilcoxon Rank Sum**
Physical neglect (means ± std.dev.)	8.24 ± 3.05 low	8.39 ± 2.87 low	p = 0.8
Physical abuse (means ± std.dev.)	9.0 ± 3.08 moderate	11.69 ± 4.68 moderate	p = 0.15
Emotional abuse (means ± std.dev.)	11.59 ± 5.1 low	13.15 ± 7.09 moderate	p = 0.61
Emotional neglect (means ± std.dev.)	11.47 ± 4.42 low	11.0 ± 3.14 low	p = 0.83
Sexual abuse (means ± std.dev.)	6.94 ± 4.279 low	8.46 ± 7.25 moderate	p = 0.65
Denial (means ± std.dev.)	0.41 ± 0.71	0.69 ± 0.95	p = 0.38
Total score (means ± std.dev.)	54.18 ± 10.82	59.69 ± 18.66	p = 0.63

Table 4.47: CTQ within treatment group

	MA group (n = 30)	**Healthy Controls (n = 23)**	**Wilcoxon Rank Sum**
Physical neglect (means ± std.dev.)	8.30 ± 2.93 low	7.04 ± 2.53 low	p = 0.08
Physical abuse (means ± std.dev.)	10.17 ± 4.018 moderate	9.5 ± 2.92 moderate	p = 0.69
Emotional abuse (means ± std.dev.)	12.27 ± 5.98 moderate	8.29 ± 3.64 low	p = 0.02*
Emotional neglect (means ± std.dev.)	11.27 ± 3.86 low	9.79 ± 3.86 low	p = 0.16

Sexual abuse (means ± std.dev.)	7.600± 5.70 moderate	8.13 ± 6.07 moderate	p = 0.83
Denial (means ± std.dev.)	0.53 ± 0.82	0.71 ± 0.86	p = 0.37
Total score (means ± std.dev.)	56.57 ± 14.71	51.33 ± 14.03	p = 0.17

Table 4.48: CTQ MA to HC (stars (*) flag levels of significance with one star denoting a p value below 0.05)

Hypothesis one

Results – MA Group Effects

Trail Making Task B minus A – Accuracy **Responders to treatment n = 17, Non-responders to treatment n = 13**	
Wilcox Rank Sum	**Benjamini Hochberg**
p = 0.73	0.88
Trail Making Task B minus A – Time to completion **Responders to treatment n = 17, Non-responders to treatment n = 13**	
Wilcox Rank Sum	**Benjamini Hochberg**
p = 0.01*	0.07+
Stroop Word Task – Accuracy **Responders to treatment n = 17, Non-responders to treatment n = 12**	
Wilcox Rank Sum	**Benjamini Hochberg**
p = 0.23	0.88
Stroop Word Task – Reaction Time **Responders to treatment n = 17, Non-responders to treatment n = 12**	
T Test	**Benjamini Hochberg**
p = 0.66	0.88
Conner's Continuous Performance Task – Accuracy **Responders to treatment n = 17, Non-responders to treatment n = 13**	
Wilcox Rank Sum	**Benjamini Hochberg**
p = 0.41	0.88
Conner's Continuous Performance Task – Reaction Tine **Responders to treatment n = 17, Non-responders to treatment n = 13**	
T Test	**Benjamini Hochberg**
p = 0.88	0.88

Table 4.49: – significance for all tasks responders to treatment vs non-responders to treatment (Benjamini Hochberg n = 6 tests, TMT accuracy, speed of completion, Stroop accuracy and reaction time, CPT accuracy & reaction time)

Exploratory Analysis for CPT Inattentiveness

	Responders Means + SD **(n = 17)**	**Non-Responders** Means + SD **(n = 13)**	**Controls** Means + SD **(n = 23)**	**Linear regression Group Effect**	**Covariate**	**F statistic**	**Degrees of freedom**
d' prime	2.99 ± 0.34	2.93 ± 0.34	3.21 ± 0.34	p = 0.02*	Sex p = 0.04* Education p = 0.09+ Income p = 0.02*	3.64	2 and 50
Omissions	4.77 ± 7.47	8.08 ± 11.51	2.20 ± 4.19	p = 0.03*	Sex p = 0.04* Education p = 0.02* Income p = 0.03*	2.43	2 and 50

Table 4.50: Linear regression (Inattentiveness variable ~ group + sex/ education/ income) (covariates entered separately)with contrast test and Cohen's d for baseline CPT Inattentiveness (stars (*) flag levels of significance with one star denoting a p value below 0.05)

Exploratory Analysis for CPT Sustained Attention

Omissions	**Responders** Means + SD **(n = 17)**	**Non-Responders** Means + SD **(n = 12)**	**Controls** Means + SD **(n = 23)**	**Linear regression – Group effect**	**Covariate**	**F statistic**	**Degrees of freedom**
Block 1	0.53 ± 1.01	1 ± 1.29	0.47 ± 1.56	p = 0.36	Sex p = 0.33 Education p = 0.22 Income p = 0.44	0.56	2 and 50
Block 2	1.41 ± 2.27	2.39 ± 2.93	0.48 ± 0.90	p = 0.01**	Sex p = 0.01* Education p = 0.02* Income p = 0.01**	3.80	2 and 50
Block 3	1.47 ± 2.07	3.31 ± 4.80	0.65 ± 1.50	p = 0.01**	Sex p = 0.01* Education p = 0.01** Income p = 0.01*	3.73	2 and 50
Block 4	1.18 ± 2.53	3.23 ± 4.45	0.61 ± 0.84	p = 0.01**	Sex p = 0.01** Education p = 0.01** Income p = 0.01**	4.078	2 and 50

Table 4.51: Linear regression (CPT sustained attention omissions by block ~ group + sex/ education/income) (covariates entered separately) with contrast test and Cohen's d for baseline (, stars (*) flag levels of significance with one star denoting a p value below 0.05 and two if the p value is less than 0.01)

Hypothesis two – Baseline and Post-Treatment

Trail Making Task B minus A – Time to Completion **Responders to treatment n = 17, Non-responders to treatment n = 11, Healthy controls = n = 21**							
Baseline	**Mean & Std. dev.**	**Linear regression group effects**	**Contrast test t**	**Contrast test p**	**Cohens d**	**CI range**	**Benjamini Hochberg**
Responders to treatment	114.75 ± 90.23	p = 0.08*	R-NR -1.96	0.13	0.75	[-0.22 – 1.48]	p = 0.08+
Non-responders to treatment	84.15 ± 49.45		R-C 1.03	0.56	0.41	[-0.21 – 0.93]	
Healthy controls	153.16 ± 134.02		NR-C -1.13	0.50	-0.36	[-1.17 – 0.45]	
Post-treatment	**Mean & Std. dev.**	**Linear regression group effects**	**Contrast test t**	**Contrast test p**	**Cohens d**	**CI range**	**Benjamini Hochberg**
Responders to treatment	127.27 ± 99.57	p = 0.22	R-NR 0.40	0.92	-0.13	[-0.81 – 0.67]	0.30
Non-responders to treatment	115.81 ± 65.43		R-C -1.90	0.16	-0.59	[-1.21 – 0.08]	
Healthy controls	81.86 ± 51.82		NR-C -1.23	0.45	-0.60	[-1.37 – 0.23]	
Stroop Word Task – Accuracy **Responders to treatment n = 17, Non-responders to treatment n = 10, Healthy controls = n = 21**							
Baseline	**Mean & Std. dev.**	**Linear regression group effects**	**Contrast test t**	**Contrast test p**	**Cohens d**	**CI range**	**Benjamini Hochberg**
Responders to treatment	81.49 ±13.24	p = 0.06+	R-NR -0.92	0.63	0.23	[-0.64 – 1.12]	0.08+
Non-responders to treatment	84.80 ±15.83		R-C 2.83	0.02*	1.03	[0.34 – 1.59]	
Healthy controls	92.26 ±7.4		NR-C 1.41	0.35	0.69	[-0.39 – 1.51]	

Post-treatment	**Mean & Std. dev.**	**Linear regression group effects**	**Contrast test t**	**Contrast test p**	**Cohens d**	**CI range**	**Benjamini Hochberg**
Responders to treatment	84.44 ± 20.69	p = 0.3	R-NR -0.54	0.85	0.17	[-0.63 – 0.88]	0.30
Non-responders to treatment	87.54 ± 12.41		R-C 1.88	0.16	0.60	[-0.09 – 0.97]	
Healthy controls	93.39 ± 6.86		NR-C 1.05	0.55	0.65	[-0.30 – 1.54]	
Continuous Performance Task – Accuracy **Responders to treatment n = 17, Non-responders to treatment n = 11, Healthy controls = n = 21**							
Baseline	**Mean & Std. dev.**	**Linear regression group effects**	**Contrast test t**	**Contrast test p**	**Cohens d**	**CI range**	**Benjamini Hochberg**
Responders to treatment	18.53 ± 11.93	p = 0.02*	R-NR -1.04	0.56	0.35	[-0.58 – 1.15]	0.05*
Non-responders to treatment	23.09 ± 14.82		R-C -1.66	0.23	-0.60	[-1.22 – 0.14]	
Healthy controls	12.38 ± 8.63		NR-C -2.53	0.04*	-0.97	[-1.91 - -0.15]	
Post-treatment	**Mean & Std. dev.**	**Linear regression group effects**	**Contrast test t**	**Contrast test p**	**Cohens d**	**CI range**	**Benjamini Hochberg**
Responders to treatment	17.47 ± 9.51	p = 0.21	R-NR 0.30	0.95	-0.10	[-0.96 – 0.71]	0.30
Non-responders to treatment	16.46 ± 10.75		R-C -2.01	0.12	-0.70	[-1.37 – 0.03]	
Healthy controls	11.62 ± 7.24		NR-C -1.46	0.32	-0.56	[-1.42 – 0.32]	

Table 4.52: Baseline and post-treatment outcomes for all tasks with regards to accuracy and time (R = Responder to treatment, NR = Non-responder to treatment, C = Healthy control)

The Stroop Exploratory Analyses

	Responders to Treatment	Non-Responders to Treatment	Healthy Controls	Linear Regression	Covariates	F Statistic	DF
	Means ± Std.dev. **(n = 17)**	**Means ± Std.dev.** **(n = 10)**	**Means ± Std.dev.** **(n = 20)**				
The Stroop Effect							
Baseline							
Accuracy	9.93 ± 9.11	2.15 ± 4.18	4.60 ± 7.34	p = 0.01**			
RT	-182.45 ± 95.37	-188.27 ± 88.72	-161.21 ± 72.14	p = 0.77			
Post-Treatment							
Accuracy	5.10 ± 4.84	3.22 ±5.15	3.60 ± 4.31	p = 0.25			
RT	-129.60 ± 186.84	-137.95 ± 75.47	-125.13 ± 98.64	p = 0.96			
Between Sessions							
Accuracy				p = 0.01**	Sex p = 0.01** Education p = 0.01** Income p = 0.01*** Language p = 0.01**	3.67	3 and 91

RT				p = 0.90	Sex p = 0.91 Education p = 0.93 Income p = 0.90 Language p = 0.44		
The Lamming/ Rabbit Effect							
Baseline							
Accuracy	-10.66 ± 13.92	-6.85 ± 11.83	-0.71 ± 6.73	p = 0.05*			
RT	-44.47 ± 99.54	14.91 ± 273.19	-18.11 ± 337.46	p = 0.05*			
Post-Treatment							
Accuracy	-6.75 ± 6.73	-1.74 ± 13.92	0.16 ± 11.83	p = 0.05*			
RT	-31.45 ± 337.46	-45.45 ± 99.54	67.85 ± 273.19	p = 0.29			
Between Sessions							
Accuracy				p = 0.01**	Sex p = 0.01** Education p = 0.01* Income p = 0.01**	4.545	3 and 91

					Language p = 0.01**		
RT				p = 0.47	Sex p = 0.46 Education p = 0.51 Income p = 0.89 Language = 0.34		

Table 4.53: exploratory analysis between sessions, linear regression (accuracy/ reaction time of congruent targets minus accuracy/ reaction time of incongruent targets ~ group + session + sex/ education/income) (covariates entered separately) (stars (*) flag levels of significance with one star denoting a p value below 0.05, two if the p value is less than 0.01 and three for less that p = 0.001)

The Continuous Performance Task Exploratory Analyses

	Responders to Treatment	**Non-Responders to Treatment**	**Healthy Controls**	**Linear Regression**	**Covariates**	**F Statistic**	**DF**
	Means ± Std.dev. **(n = 17)**	**Means ± Std.dev.** **(n = 11)**	**Means ± Std.dev.** **(n = 21)**				
The Continuous Performance Task - Inattentiveness							
Baseline							
d' Prime	2.99 ± 0.34	2.96 ± 0.34	3.23 ± 0.35	p = 0.05*			

Omissions	4.77 ± 7.47	9.00 ± 7.47	1.81 ± 3.28	p = 0.32			
Variability	46.64 ± 39.98	58.34 ± 39.98	35.51 ± 20.50	p = 0.07+			
Post-Treatment							
d' Prime	2.99 ± 0.38	3.08 ± 0.36	3.22 ± 0.33	p = 0.01*			
Omissions	0.81 ± 2.51	4.09 ± 5.70	0.91 ± 1.19	p = 0.01*			
Variability	45.14 ± 10.91	45.48 ± 33.34	26.30 ± 9.41	p = 0.01**			
Between Sessions							
d' Prime				p = 0.03*	Sex p = 0.05 Education p = 0.08 Income p = 0.01**	3.149	3 and 94
Omissions				p = 0.01***	Sex p = 0.01** Education p = 0.01*** Income p = 0.01***	4.975	3 and 94
Variability				p = 0.01**	Sex p = 0.01** Education p = 0.01** Income p = 0.01**	4.358	3 and 94

Table 4.54: CPT inattentiveness, linear regression (d' prime/ omissions/ commissions/ HRT/ variability ~ group + session + sex/ education/income) (covariates entered separately) (stars (*) flag levels of significance with one star denoting a p value below 0.05, two if the p value is less than 0.01 and three for less that p = 0.001*)*

	Responders to Treatment	Non-Responders to Treatment	Healthy Controls	Linear Regression	Block	Covariates	F Statistic	DF
	Means ± Std.dev. (n = 17)	**Means ± Std.dev. (n = 11)**	**Means ± Std.dev. (n = 21)**					
	The Continuous Performance Task – Sustained Attention (between blocks)							
Baseline								
Omissions - Baseline	1.15 ± 2.04	2.80 ± 3.90	0.45 ± 0.95	p = 0.01***				
Omissions – Post Treatment	0.91 ± 1.22	1.02 ± 1.84	0.23 ± 0.55	p = 0.01***				
Omissions Across Sessions				p = 0.01***	Block 2 - p = 0.19 Block 3 - p = 0.03* Block 4 - p =0.02*	Sex p = 0.01*** Education p = 0.01*** Income p = 0.01***	9.91	6 and 385

Table 4.55: CPT sustained attention between sessions and blocks, linear regression (HRT/ omissions/ commissions ~ group + session + block + sex/ education/income) (covariates entered separately) (stars (*) flag levels of significance with one star denoting a p value below 0.05, two if the p value is less than 0.01 and three for less that p = 0.001)

Appendix O

No post hoc testing done as no significant differences were discovered in rsFC.

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Appendix P

Chapter 5: Structural Analysis

Surface Average for the left hemisphere of the brain Session 1

	Mean & Std.dev.	Mean & Std.dev.	T.test	T.stat	Degrees of Freedom
	Responders	**Non-Responders**			
L_bankssts_surfavg	1016.235 ± 151.5027	1003.692 ± 143.1697	0,8184	0,23184	26,6779
L_caudalanteriorcingulate_surfavg	568.9412 ± 119.1572	565.1538 ± 113.0743	0,9299	0,088807	26,631
L_caudalmiddlefrontal_surfavg	2108.529 ± 439.1833	2071.692 ± 354.8329	0,8013	0,25401	27,884
L_cuneus_surfavg	1587.176 ± 182.7181	1576.000 ± 236.6527	0,8891	0,14113	22,005
L_entorhinal_surfavg	427.4706 ± 88.33750	457.2308 ± 93.09597	0,3835	-0,887	25,24
L_fusiform_surfavg	3033.176 ± 371.4282	3064.615 ± 288.6548	0,7961	-0,26086	27,982
L_inferiorparietal_surfavg	4482.176 ± 676.0303	4196.385 ± 628.8083	0,2429	1,1939	26,854
L_inferiortemporal_surfavg	3319.176 ± 436.9269	3276.615 ± 536.4388	0,8178	0,233	22,853
L_isthmuscingulate_surfavg	1003.882 ± 168.4399	1021.308 ± 179.9122	0,7892	0,27021	25,041
L_lateraloccipital_surfavg	5141.941 ± 503.1019	5026.538 ± 674.1696	0,6105	0,51587	21,476
L_lateralorbitofrontal_surfavg	2502.412 ± 275.2799	2643.846 ± 229.2956	0,1364	-1,5339	27,748
L_lingual_surfavg	3045.353 ± 322.7414	3003.231 ± 515.3518	0,7988	0,25848	18,996
L_medialorbitofrontal_surfavg	1826.882 ± 238.4816	1850.077 ± 209.2357	0,7792	-0,28309	27,402
L_middletemporal_surfavg	3164.235 ± 421.2040	3110.000 ± 407.9111	0,7248	0,3558	26,389
L_parahippocampal_surfavg	658.6471 ± 55.18372	665.7692 ± 89.39720	0,8032	-0,25277	18,814
L_paracentral_surfavg	1243.941 ± 126.0989	1220.769 ± 168.8911	0,6828	0,41421	21,484
L_parsopercularis_surfavg	1569.294 ± 265.9309	1507.231 ± 261.7506	0,5283	0,63911	26,185
L_parsorbitalis_surfavg	650.7059 ± 77.20732	708.3846 ± 95.86496	0,08956	-1,7736	22,673
L_parstriangularis_surfavg	1298.588 ± 188.4732	1287.538 ± 181.8743	0,8723	0,16232	26,432
L_pericalcarine_surfavg	1455.471 ± 241.1882	1474.077 ± 287.1107	0,8523	0,18831	23,347

L_postcentral_surfavg	3893.588 ± 460.7670	3834.231 ± 677.2545	0,7887	0,27158	20,109
L_posteriorcingulate_surfavg	1099.176 ± 165.1428	1092.154 ± 151.0898	0,9045	0,12115	27,025
L_precentral_surfavg	4603.000 ± 607.3929	4345.692 ± 501.6633	0,2147	1,2698	27,791
L_precuneus_surfavg	3739.647 ± 478.5196	3585.308 ± 441.7392	0,3685	0,91455	26,933
L_rostralanteriorcingulate_surfavg	769.2353 ± 210.9317	815.3077 ± 133.4144	0,4718	-0,72971	27,196
L_rostralmiddlefrontal_surfavg	5713.882 ± 997.5916	5810.692 ± 743.5741	0,763	-0,30451	27,993
L_superiorfrontal_surfavg	6887.647 ± 922.3255	6824.692 ± 781.2112	0,8413	0,20215	27,653
L_superiorparietal_surfavg	5177.412 ± 645.9646	4952.615 ± 584.1057	0,3273	0,99747	27,139
L_superiortemporal_surfavg	3881.765 ± 545.6670	3776.846 ± 393.6477	0,5458	0,61154	27,936
L_supramarginal_surfavg	3926.824 ± 601.9162	3787.615 ± 788.4725	0,6018	0,52944	21,828
L_frontalpole_surfavg	244.1765 ± 34.3279	255.3077 ± 17.6181	0,2598	-1,153	24,971
L_temporalpole_surfavg	472.1765 ± 52.73547	483.3077 ± 56.07641	0,5853	-0,55279	25,107
L_transversetemporal_surfavg	441.5882 ± 62.58800	433.6923 ± 53.05247	0,7116	0,37349	27,648
L_insula_surfavg	2256.235 ± 231.2784	2380.308 ± 261.1246	0,1881	-1,3544	24,187

Table 5.13: Surface Average for the left hemisphere of the brain Session 1

Surface Average for the right hemisphere of the brain Session 1

	Mean & Std.dev.	Mean & Std.dev.	T.test	T stat	Degrees of Freedom
Relapse	**Responders**	**Non-Responders**			
R_bankssts_surfavg	890.5882 ± 127.0222	878.4615 ± 161.1974	0,8253	0,22335	22,326
R_caudalanteriorcingulate_surfavg	677.4706 ± 145.5868	664.8462 ± 104.4795	0,7843	0,27638	27,922
R_caudalmiddlefrontal_surfavg	2013.647 ± 408.0467	1970.462 ± 424.8307	0,7812	0,2065	25,417
R_cuneus_surfavg	1663.000 ± 209.0631	1697.385 ± 334.7398	0,7487	-0,32504	18,961
R_entorhinal_surfavg	366.2941 ± 58.87037	391.0000 ± 82.43381	0,3835	-0,887	25,24
R_fusiform_surfavg	2964.765 ± 265.7034	3043.769 ± 371.3092	0,5226	-0,65033	20,841
R_inferiorparietal_surfavg	5025.118 ± 823.9938	4819.000 ± 562.9782	0,4233	0,81273	27,722
R_inferiortemporal_surfavg	3149.118 ± 388.0067	3066.923 ± 436.8408	0,597	0,53578	24,232
R_isthmuscingulate_surfavg	889.8235 ± 149.6564	897.0000 ± 158.5996	0,9009	-0,12584	25,157
R_lateraloccipital_surfavg	5118.118 ± 626.2762	5216.692 ± 821.9309	0,7224	-0,35985	21,798
R_lateralorbitofrontal_surfavg	2499.706 ± 324.8470	2579.385 ± 213.5176	0,4258	-0,80842	27,488
R_lingual_surfavg	3253.471 ± 469.2035	3100.385 ± 586.3590	0,4486	0,77126	22,57
R_medialorbitofrontal_surfavg	1888.824 ± 295.3249	1912.769 ± 166.3681	0,7809	-0,28104	26,053
R_middletemporal_surfavg	3402.588 ± 391.6041	3383.846 ± 478.5875	0,9096	0,11483	22,926
R_parahippocampal_surfavg	646.2353 ± 48.18652	641.8462 ± 103.40764	0,8891	0,14172	15,986

R_paracentral_surfavg	1390.882 ± 150.7730	1345.615 ± 192.4589	0,4914	0,69961	22,234
R_parsopercularis_surfavg	1253.471 ± 182.7718	1222.769 ± 166.1897	0,635	0,48009	27,086
R_parsorbitalis_surfavg	800.2353 ± 112.40247	835.5385 ± 64.25291	0,2883	-1,0839	26,213
R_parstriangularis_surfavg	1447.647 ± 279.7682	1541.462 ± 162.0492	0,2594	-1,1527	26,355
R_pericalcarine_surfavg	1648.059 ± 313.6988	1612.923 ± 329.0601	0,7699	0,29571	25,308
R_postcentral_surfavg	3893.353 ± 433.5206	3741.077 ± 460.7672	0,3662	0,92016	25,114
R_posteriorcingulate_surfavg	1142.235 ± 182.2202	1148.846 ± 156.8018	0,9159	-0,10662	27,548
R_precentral_surfavg	4647.353 ± 601.3999	4522.231 ± 567.6794	0,5648	0,58298	26,692
R_precuneus_surfavg	3890.765 ± 448.3211	3674.077 ± 472.7484	0,2149	1,2721	25,231
R_rostralanteriorcingulate_surfavg	509.3529 ± 108.2387	562.8462 ± 116.4659	0,2106	-1,2852	24,93
R_rostralmiddlefrontal_surfavg	5780.529 ± 1135.4421	5854.000 ± 449.1878	0,8102	-0,24308	21,991
R_superiorfrontal_surfavg	6640.000 ± 941.7490	6784.231 ± 817.9954	0,6577	-0,44802	27,48
R_superiorparietal_surfavg	5093.294 ± 484.6345	4825.846 ± 596.6044	0,2007	1,3177	22,81
R_superiortemporal_surfavg	3655.118 ± 330.7932	3533.385 ± 327.6175	0,3245	1,0043	26,104
R_supramarginal_surfavg	3691.412 ± 431.5277	3507.846 ± 723.0596	0,4275	0,81149	18,403
R_frontalpole_surfavg	299.5294 ± 50.48529	313.4615 ± 41.60652	0,4147	-0,82805	27,801
R_temporalpole_surfavg	458.8235 ± 54.14706	475.1538 ± 55.51553	0,4271	-0,80695	25,635
R_transversetemporal_surfavg	349.3529 ±	333.4615 ±	0,3852	0,88719	20,56

	38.63926	55.03880			
R_insula_surfavg	2282.647 ± 276.6304	2418.538 ± 248.9339	0,1694	-1,4115	27,184

Table 5.14: Surface Average for the right hemisphere of the brain Session 1

Overview of Surface average Session 1

	Means & Std.dev.	Means & Std.dev.	T.test	T.stat	Degrees of Freedom
	Responders	**Non-Responders**			
LThickness	2.448185 ± 0.09079755	2.463763 ± 0.11018156	0,686	-0,41357	23,04
RThickness	2.438207 ± 0.09413068	2.454942 ± 0.11773965	0,6785	-0,42	22,556
LSurfArea	83199.24 ± 8588.406	82087.93 ± 7461.007	0,708	0,37849	27,479
RSurfArea	83313.24 ± 8408.055	82507.23 ± 7295.904	0,7811	0,28056	27,488
ICV	1493211 ± 196560.3	1467952 ± 217336.9	0.7452	0.32868	24.514

Table 5.15

Cortical Thickness for the left hemisphere of the brain Session 1

	Responders	**Non-Responders**			
	Means & Std.dev.	**Means & Std.dev.**	**T.Test**	**T.stat**	**Degrees of Freedom**
L_bankssts_thickavg	2.419706 ± 0.1342985	2.478615 ± 0.1820378	0,3379	-0,98046	21,3
L_caudalanteriorcingulate_thickavg	2.609529 ± 0.2577004	2.666923 ± 0.2103590	0,5076	-0,67127	27,844
L_caudalmiddlefrontal_thickavg	2.489118 ± 0.1573419	2.544538 ± 0.1669354	0,3644	-0,92369	25,14
L_cuneus_thickavg	1.865176 ± 0.1263543	1.964923 ± 0.1138884	0,03159	-2,2665	27,169
L_entorhinal_thickavg	3.290176 ± 0.3093736	3.353923 ± 0.1972276	0,4982	-0,68651	27,26
L_fusiform_thickavg	2.634235 ± 0.1219265	2.655385 ± 0.0851269	0,5807	-0,55891	27,825
L_inferiorparietal_thickavg	2.388353 ± 0.09098966	2.396538 ± 0.15207872	0,8653	-0,17195	18,433
L_inferiortemporal_thickavg	2.683353 ± 0.1622717	2.651846 ± 0.1515029	0,5887	0,54726	26,813
L_isthmuscingulate_thickavg	2.376882 ± 0.1094406	2.354615 ± 0.1200524	0,6057	0,52292	24,636
L_lateraloccipital_thickavg	2.102059 ± 0.08916801	2.074154 ± 0.10618447	0,4527	0,76373	23,241
L_lateralorbitofrontal_thickavg	2.669059 ± 0.1344561	2.673538 ± 0.1015058	0,9179	-0,10398	28
L_lingual_thickavg	2.071294 ± 0.07696977	2.043154 ± 0.16941018	0,5856	0,55659	15,792
L_medialorbitofrontal_thickavg	2.475765 ± 0.1007047	2.517846 ± 0.1613923	0,4195	-0,82525	18,95
L_middletemporal_thickavg	2.779118 ± 0.1892059	2.788615 ± 0.1739370	0,8876	-0,14265	26,976
L_parahippocampal_thickavg	2.652059 ± 0.2636305	2.714462 ± 0.3318576	0,5832	-0,55682	22,455

L_paracentral_thickavg	2.389706 ± 0.1488413	2.381077 ± 0.1851853	0,8919	0,13745	22,641
L_parsopercularis_thickavg	2.582176 ± 0.1915507	2.730538 ± 0.1471896	0,02335	-2,3989	27,994
L_parsorbitalis_thickavg	2.668824 ± 0.1816570	2.706769 ± 0.1894444	0,5848	-0,55339	25,392
L_parstriangularis_thickavg	2.524882 ± 0.1547889	2.449308 ± 0.1089666	0,1281	1,5681	27,858
L_pericalcarine_thickavg	1.697529 ± 0.08584733	1.697308 ± 0.10930491	0,9952	0,00603	22,274
L_postcentral_thickavg	2.013118 ± 0.1059881	2.072846 ± 0.1894865	0,3211	-1,0209	17,67
L_posteriorcingulate_thickavg	2.472059 ± 0.1752489	2.457615 ± 0.1820977	0,8285	0,21881	25,445
L_precentral_thickavg	2.535882 ± 0.1662505	2.562231 ± 0.2475618	0,7442	-0,3309	19,927
L_precuneus_thickavg	2.349765 ± 0.1212588	2.350231 ± 0.1231281	0,9918	-0,01034	25,77
L_rostralanteriorcingulate_thickavg	2.731882 ± 0.2953646	2.763692 ± 0.1910346	0,7238	-0,35701	27,372
L_rostralmiddlefrontal_thickavg	2.364882 ± 0.1076754	2.399231 ± 0.1081574	0,3957	-0,86362	25,917
L_superiorfrontal_thickavg	2.712824 ± 0.1387125	2.713692 ± 0.1731215	0,9883	-0,01482	22,591
L_superiorparietal_thickavg	2.147294 ± 0.09002414	2.152000 ± 0.14262363	0,9181	-0,10415	19,097
L_superiortemporal_thickavg	2.803529 ± 0.1938979	2.787077 ± 0.1542225	0,7977	0,25881	27,933
L_supramarginal_thickavg	2.514000 ± 0.1272571	2.498692 ± 0.1381300	0,7583	0,31115	24,798
L_frontalpole_thickavg	2.744235 ± 0.2843386	2.679077± 0.2463153	0,5077	0,67124	27,5
L_temporalpole_thickavg	3.490353 ± 0.3196494	3.544923 ± 0.3584656	0,6689	-0,43284	24,294
L_transversetemporal_thickavg	2.389706 ±	2.401769 ±	0,8745	-0,15971	22,368

	0.1770303	0.2240607			
L_insula_thickavg	2.946353 ± 0.1632988	2.971462 ± 0.1881580	0,7049	-0,38326	23,866

Table 5.16: Cortical Thickness for the left hemisphere of the brain Session 1

Cortical Thickness for the right hemisphere of the brain Session 1

	Responders	Non-Responders			
	Mean & Std.dev.	Mean & Std.dev.	T.test	T.stat	Degrees of Freedom
R_bankssts_thickavg	2.539529 ± 0.1546981	2.578077 ± 0.1890148	0,5557	-0,59795	22,93
R_caudalanteriorcingulate_thickavg	2.485588 ± 0.2265555	2.432308 ± 0.1713235	0,4694	0,73345	28
R_caudalmiddlefrontal_thickavg	2.448412 ± 0.1547769	2.476385 ± 0.1667396	0,6427	-0,46963	24,912
R_cuneus_thickavg	1.892647 ± 0.09652975	1.936000 ± 0.09900168	0,2406	-1,2014	25,63
R_entorhinal_thickavg	3.491294 ± 0.2911702	3.505923 ± 0.3381327	0,9019	-0,12461	23,742
R_fusiform_thickavg	2.676765 ± 0.1202422	2.730615 ± 0.1113452	0,2157	-1,2678	26,901
R_inferiorparietal_thickavg	2.435882 ± 0.1326640	2.467077 ± 0.1655403	0,5834	-0,5564	22,594
R_inferiortemporal_thickavg	2.734706 ± 0.1785979	2.797077 ± 0.1945642	0,3761	-0,90135	24,742
R_isthmuscingulate_thickavg	2.394647 ± 0.1669375	2.367615 ± 0.2045994	0,7018	0,38778	22,881
R_lateraloccipital_thickavg	2.155059 ± 0.0965275	2.186077 ± 0.0935463	0,3828	-0,8876	26,38
R_lateralorbitofrontal_thickavg	2.497529 ± 0.1414006	2.496077 ± 0.1388077	0,9777	0,028172	26,219
R_lingual_thickavg	2.052588 ± 0.09843339	2.055385 ± 0.12529135	0,9477	-0,06633	22,279
R_medialorbitofrontal_thickavg	2.509824 ± 0.1936270	2.391231 ± 0.1089925	0,04338	2,1234	26,044
R_middletemporal_thickavg	2.788059 ± 0.1592869	2.829462 ± 0.1860930	0,5269	-0,6422	23,646
R_parahippocampal_thickavg	2.675294 ± 0.2061285	2.639692 ± 0.2006026	0,638	0,47597	26,328

R_paracentral_thickavg	2.438471 ± 0.1921822	2.467077 ± 0.1801904	0,6789	-0,4186	26,767
R_parsopercularis_thickavg	2.598412 ± 0.2242630	2.638385 ± 0.1575154	0,5713	-0,57297	27,849
R_parsorbitalis_thickavg	2.660765 ± 0.1737637	2.639000 ± 0.1500850	0,7161	0,36743	27,522
R_parstriangularis_thickavg	2.512471 ± 0.1173825	2.450692 ± 0.1834532	0,3024	1,0596	19,273
R_pericalcarine_thickavg	1.704765 ± 0.2056823	1.675077 ± 0.1252640	0,6293	0,48836	26,86
R_postcentral_thickavg	1.999235 ± 0.1114936	2.040769 ± 0.1493124	0,4103	-0,83977	21,485
R_posteriorcingulate_thickavg	2.418647 ± 0.09782698	2.407615 ± 0.16353264	0,8317	0,21552	18,431
R_precentral_thickavg	2.464412 ± 0.1725196	2.528462 ± 0.2143201	0,3875	-0,88112	22,665
R_precuneus_thickavg	2.385000 ± 0.1289385	2.402308 ± 0.1427634	0,7345	-0,34303	24,492
R_rostralanteriorcingulate_thickavg	2.824059 ± 0.292586	2.797154 ± 0.162356	0,7514	0,32013	25,884
R_rostralmiddlefrontal_thickavg	2.290941 ± 0.08534889	2.271154 ± 0.12100127	0,6211	0,50183	20,629
R_superiorfrontal_thickavg	2.681765 ± 0.1374557	2.651308 ± 0.1643646	0,5948	0,53929	23,275
R_superiorparietal_thickavg	2.131824 ± 0.09967524	2.163692 ± 0.16455616	0,5447	-0,61705	18,581
R_superiortemporal_thickavg	2.835294 ± 0.1831976	2.846385 ± 0.1657913	0,8636	-0,17345	27,131
R_supramarginal_thickavg	2.491235 ± 0.1310160	2.521538 ± 0.1563621	0,5784	-0,56365	23,306
R_frontalpole_thickavg	2.764000 ± 0.2055338	2.541308 ± 0.2233657	0,009743	2,8006	24,779
R_temporalpole_thickavg	3.687706 ± 0.3454019	3.706231 ± 0.3150791	0,8795	-0,15303	27,054
R_transversetemporal_thickavg	2.373882 ±	2.427154 ±	0,5758	-0,56728	24,102

	0.2362818	0.2682284			
R_insula_thickavg	2.940824 ± 0.1589266	2.939692 ± 0.1628923	0,985	0,019048	25,639

Table 5.16: Cortical Thickness for the right hemisphere of the brain Session 1

Overview of Cortical Thickness Session 1

	Responders	**Non-responders**			
	Mean & Std.dev.	**Mean & Std.dev.**	**T.Test**	**T.tsat**	**Degrees of Freedom**
LThickness	2.448185 ± 0.09079755	2.463763 ± 0.11018156	0,683	-0,41357	23,04
RThickness	2.438207 ± 0.09413068	2.454942 ± 0.11773965	0,6785	-0,42	22,556
LSurfArea	83199.24 ± 8588.406	82087.93 ± 7461.007	0,708	0,37849	27,479
RSurfArea	83313.24 ± 8408.055	82507.23 ± 7295.904	0,7811	0,28056	27,488
ICV	1493211 ± 196560.3	1467952 ± 217336.9	7452	0,32868	24,514

Table 5.17: Overview

Surface Average for the left hemisphere of the brain Session 2

	Responders	**Non-responders**			
	Mean & Std.dev.	**Mean & Std.dev.**	**T.test**	**T.stat**	**Degrees of Freedom**
L_bankssts_surfavg	1012.9412 ± 137.8008	978.7273 ± 120.1300	0,4943	0,69422	23,59
L_caudalanteriorcingulate_surfavg	562.7059 ± 128.5077	557.0000 ± 126.3186	0,9088	0,11594	21,775
L_caudalmiddlefrontal_surfavg	2097.353 ± 480.1942	2014.818 ± 363.6220	0,6103	0,516	25,226
L_cuneus_surfavg	1600 ± 194.9808	1583 ± 240.2836	0,8464	0,19649	18,264
L_entorhinal_surfavg	400.7647 ± 85.50404	441.9091 ± 70.62925	0,1789	-1,3842	24,301
L_fusiform_surfavg	3054.824 ± 354.8953	2965.818 ± 254.8662	0,4475	0,77137	25,624
L_inferiorparietal_surfavg	4459.941 ± 717.1052	4105.364 ± 602.5141	0,1714	1,4099	24,086
L_inferiortemporal_surfavg	3332.000 ± 442.6679	3281.727 ± 541.5642	0,7998	0,25725	18,37
L_isthmuscingulate_surfavg	986.7647 ± 194.6916	1028.2727 ± 202.1802	0,5961	-0,5383	20,898
L_lateraloccipital_surfavg	5176.176 ± 526.1301	4881.636 ± 600.2505	0,1989	1,3301	19,415
L_lateralorbitofrontal_surfavg	2516.118 ± 301.1146	2634.818 ± 257.9992	0,277	-1,1125	23,827
L_lingual_surfavg	3093.471 ± 358.3572	3042.455 ± 603.7076	0,8039	0,25292	14,605
L_medialorbitofrontal_surfavg	1785.176 ± 307.3539	1841.455 ± 132.2364	0,5121	-0,66572	23,4
L_middletemporal_surfavg	3180.471 ± 429.6489	3065.091 ± 399.9129	0,4765	0,72399	22,627
L_parahippocampal_surfavg	656.2353 ± 51.53704	659.0909 ± 87.23469	0,9232	-0,098059	14,563
L_paracentral_surfavg	1248.235 ± 153.4966	1199.909 ±	0,4184	0,82484	21,863

		150.0456			
L_parsopercularis_surfavg	1586.941 ± 285.5391	1395.455 ± 146.7006	0,02814	2,3303	25,047
L_parsorbitalis_surfavg	654.3529 ± 87.3391	686.7273 ± 105.9435	0,4091	-0,84465	18,494
L_parstriangularis_surfavg	1296.529 ± 202.8713	1289.364 ± 189.2143	0,9251	0,095116	22,596
L_pericalcarine_surfavg	1472.176 ± 243.3278	1493.091 ± 290.0698	0,845	-0,19823	18,75
L_postcentral_surfavg	3877.882 ± 514.8020	3877.182 ± 513.8842	0,9972	0,0035205	21,53
L_posteriorcingulate_surfavg	1085.882 ± 208.0507	1058.364 ± 145.8954	0,6844	0,41108	25,758
L_precentral_surfavg	4541.176 ± 625.9176	4290.455 ± 485.6796	0,2457	1,1887	24,998
L_precuneus_surfavg	3755.765 ± 548.1677	3577.818 ± 446.5601	0,3562	0,94042	24,469
L_rostralanteriorcingulate_surfavg	774.4118 ± 197.8090	803.7273 ±	0,6631	-0,44085	25,048
L_rostralmiddlefrontal_surfavg	5614.765 ± 1093.856	5743.182 ± 821.507	0,7264	-0,35381	25,297
L_superiorfrontal_surfavg	6809.059 ± 1015.021	6563.818 ± 809.410	0,4859	0,70747	24,713
L_superiorparietal_surfavg	5175.706 ± 764.0343	5088.000 ± 453.4569	0,7064	0,38086	25,887
L_superiortemporal_surfavg	3882.000 ± 575.2140	3782.091 ± 429.9675	0,6044	0,52461	25,336
L_supramarginal_surfavg	3912.471 ± 625.2110	3887.364 ± 656.7531	0,9208	0,10067	22,715
L_frontalpole_surfavg	246.2941 ± 33.38369	260.0909 ± 27.72888	0,2473	-1,1854	24,232
L_temporalpole_surfavg	468.8235 ± 54.53352	496.9091 ± 53.86363	0,1938	-1,3409	21,698
L_transversetemporal_surfavg	433.5882 ± 67.47227	429.8182 ± 58.97765	0,8774	0,156	23,552
L_insula_surfavg	2293.118 ± 296.0794	2262.636 ± 174.1099	0,7346	0,34267	25,856

Table 5.18: Surface Average for the left hemisphere of the brain Session 2

Surface Average for the right hemisphere of the brain Session 2

	Responder	**Non-responder**			
	Mean & Std.dev.	**Mean & Std.dev.**	**T.Test**	**T.stat**	**Degrees of Freedom**
R_bankssts_surfavg	886.2353 ± 114.1553	896.5455 ± 172.5928	0,8634	-0,1749	15,678
R_caudalanteriorcingulate_surfavg	685.8235 ± 146.6694	643.3636 ± 128.9203	0,4284	0,80583	23,474
R_caudalmiddlefrontal_surfavg	1998.412 ± 466.7368	1830.818 ± 407.9401	0,3263	1,0026	23,553
R_cuneus_surfavg	1679.588 ± 212.5727	1628.000 ± 398.5820	0,6993	0,3945	13,729
R_entorhinal_surfavg	357.5294 ± 59.14402	388.1818 ± 60.17444	0,1992	-1,3253	21,226
R_fusiform_surfavg	2958.765 ± 269.5588	2920.182 ± 257.5554	0,7075	0,38008	22,222
R_inferiorparietal_surfavg	5019.059 ± 869.9479	4772.455 ± 602.5986	0,384	0,88566	26,815
R_inferiortemporal_surfavg	3125.588 ± 407.9986	3080.909 ± 405.5965	0,7791	0,28402	21,596
R_isthmuscingulate_surfavg	906.5294 ± 160.1137	903.5455 ± 167.4648	0,9631	0,04685	20,784
R_lateraloccipital_surfavg	5102.824 ± 619.4063	5041.000 ± 732.8348	0,8195	0,23138	18,863
R_lateralorbitofrontal_surfavg	2505.706 ± 272.1754	2562.182 ± 297.8647	0,6179	-0,5067	20,064
R_lingual_surfavg	3286.882 ± 499.2796	3107.727 ± 479.6797	0,3525	0,94977	22,136
R_medialorbitofrontal_surfavg	1883.118 ± 249.1696	1881.636 ± 223.5286	9871	0,01636	23,18
R_middletemporal_surfavg	3422.176 ± 412.6809	3359.545 ± 493.0865	0,7306	0,34946	18,716
R_parahippocampal_surfavg	653.5294 ± 56.6272	641.6364 ± 108.6741	0,7429	0,33475	13,561

R_paracentral_surfavg	1362.529 ± 154.3268	1372.273 ± 258.4442	0,9118	-0,1127	14,659
R_parsopercularis_surfavg	1245.294 ± 185.8675	1207.818 ± 167.7622	0,5855	0,55311	23,09
R_parsorbitalis_surfavg	810.7059 ± 110.41669	823.7273 ± 60.51792	0,6912	-0,4018	25,508
R_parstriangularis_surfavg	1447.941 ± 279.7402	1505.636 ± 180.1190	0,5126	-0,6639	25,996
R_pericalcarine_surfavg	1692.529 ± 279.6697	1560.909 ± 297.5864	0,2553	1,1702	20,509
R_postcentral_surfavg	3871.529 ± 478.4860	3821.636 ± 463.3239	0,7861	0,27472	22,012
R_posteriorcingulate_surfavg	1138.706 ± 205.4391	1157.000 ± 152.2097	0,7893	-0,2701	25,406
R_precentral_surfavg	4579.765 ± 611.1506	4522.000 ± 855.8291	0,8484	0,19411	16,561
R_precuneus_surfavg	3879.471 ± 496.7277	3745.000 ± 522.4931	0,5053	0,67804	20,693
R_rostralanteriorcingulate_surfavg	526.5882 ± 102.6761	539.4545 ± 114.7217	0,7659	-0,3019	19,739
R_rostralmiddlefrontal_surfavg	5704.059 ± 1204.521	5840.273 ± 491.910	0,6815	-0,4158	22,879
R_superiorfrontal_surfavg	6564.706 ± 1010.2616	6572.364 ± 905.3605	0,9835	-0,0209	23,195
R_superiorparietal_surfavg	5099.706 ± 590.2120	4929.364 ± 493.4473	0,4174	0,82505	24,15
R_superiortemporal_surfavg	3645.000 ± 347.9195	3508.727 ± 346.3369	0,3213	1,015	21,574
R_supramarginal_surfavg	3656.471 ± 430.3171	3514.182 ± 695.3346	0,5526	0,60757	14,995
R_frontalpole_surfavg	296.8235 ± 49.10351	310.1818 ± 36.98058	0,4205	-0,8188	25,273
R_temporalpole_surfavg	462.7059 ± 71.53475	476.6364 ± 55.25083	0,5676	-0,5792	25,044
R_transversetemporal_surfavg	341.8824 ± 40.93269	338.9091 ± 55.90788	0,881	0,15198	16,871

R_insula_surfavg	2319.765 ± 307.8676	2287.091 ± 178.7246	0,7256	0,35483	25,806

Table 5.19: Surface Average for the right hemisphere of the brain Session 2

Overview of Surface Average Session 2

	Responder	**Non-responder**			
	Mean & Std.dev.	**Mean & Std.dev.**	**T.Test**	**T.stat**	**Degrees of Freedom**
LThickness	2.45400 ± 0.08621358	2.43347 ± 0.11837572	0,6261	0,49631	16,805
RThickness	2.435669 ± 0.09018338	2.421881 ± 0.11252400	0,7366	0,34157	18,087
LSurfArea	83027.25 ± 9661.042	81234.89 ± 7662.778	0,5908	0,54468	24,771
RSurfArea	83104.65 ± 9230.03	81685.09 ± 7621.56	0,662	0,44249	24,305
ICV	1464956 ± 211379.6	1462865 ± 217963.2	0,9802	0,025081	21,011

Table 5.20: Overview

Cortical Thickness for the left hemisphere of the brain Session 2

	Responders	Non-responders			
	Means & Std.dev.	**Means & Std.dev.**	**T.Test**	**T.stat**	**Degrees of Freedom**
L_bankssts_thickavg	2.445765 ± 0.1211216	2.427455 ± 0.1817858	0,7723	0,29444	15,758
L_caudalanteriorcingulate_thickavg	2.608176 ± 0.2506343	2.648455 ± 0.1626575	0,6104	-0,51569	25,99
L_caudalmiddlefrontal_thickavg	2.498588 ± 0.1422617	2.515455 ± 0.1192697	0,738	-0,3343	24,114
L_cuneus_thickavg	1.874588 ± 0.1318565	1.965273 ± 0.1344887	0,09354	-1,756	21,186
L_entorhinal_thickavg	3.425353 ± 0.2677417	3.334000 ± 0.2355453	0,3521	0,9493	23,461
L_fusiform_thickavg	2.679235 ± 0.08930253	2.620545 ± 0.08263094	0,08883	1,7778	22,717
L_inferiorparietal_thickavg	2.386235 ± 0.06242248	2.371545 ± 0.14319313	0,7535	0,32108	12,492
L_inferiortemporal_thickavg	2.733353 ± 0.1280590	2.628364 ± 0.1003277	0,02307	2,4216	24,901
L_isthmuscingulate_thickavg	2.387882 ± 0.1299610	2.342000 ± 0.1630135	0,4422	0,7858	18,013
L_lateraloccipital_thickavg	2.114588 ± 0.09105909	2.037273 ± 0.12314064	0,09133	1,7897	16,998
L_lateralorbitofrontal_thickavg	2.666294 ± 0.1696860	2.643364 ± 0.1318266	0,692	0,40078	24,986
L_lingual_thickavg	2.060412 ± 0.09845942	2.013455 ± 0.16691936	0,4129	0,84295	14,549
L_medialorbitofrontal_thickavg	2.477353 ± 0.1244488	2.459545 ± 0.1600096	0,758	0,31291	17,668
L_middletemporal_thickavg	2.809647 ± 0.1554248	2.743455 ± 0.1675120	0,3059	1,0503	20,306
L_parahippocampal_thickavg	2.695471 ± 0.3116108	2.666000 ± 0.3859982	0,8342	0,21237	18,19
L_paracentral_thickavg	2.367706 ± 0.1735878	2.361727 ± 0.1474382	0,923	0,097647	23,944
L_parsopercularis_thickavg	2.579824 ± 0.1626231	2.691273 ± 0.2112350	0,1546	-1,4877	17,53
L_parsorbitalis_thickavg	2.678412 ± 0.1677949	2.680455 ± 0.2708868	0,9824	-0,02239	15,004
L_parstriangularis_thickavg	2.528 ± 0.1865814	2.413 ± 0.1372465	0,07225	1,8754	25,461
L_pericalcarine_thickavg	1.661059 ± 0.08439599	1.700182 ± 0.11359473	0,3405	-0,98051	17,059
L_postcentral_thickavg	1.997059 ± 0.1032022	2.013727 ± 0.1359604	0,7327	-0,34703	17,34

L_posteriorcingulate_thickavg	2.450412 ± 0.1370055	2.412455 ± 0.1697347	0,5416	0,62206	18,188
L_precentral_thickavg	2.494412 ± 0.1668252	2.576818 ± 0.1656984	0,2135	-1,2818	21,61
L_precuneus_thickavg	2.341765 ± 0.1014523	2.334545 ± 0.1306303	0,3562	0,94042	24,469
L_rostralanteriorcingulate_thickavg	2.820235 ± 0.2273952	2.742000 ± 0.1541940	0,2881	1,0846	25,896
L_rostralmiddlefrontal_thickavg	2.393000 ± 0.1368672	2.367909 ± 0.1270641	0,6254	0,49497	22,667
L_superiorfrontal_thickavg	2.720118 ± 0.1443662	2.684000 ± 0.1899405	0,5974	0,53807	17,357
L_superiorparietal_thickavg	2.124941 ± 0.09384527	2.125455 ± 0.13093919	0,9911	-0,01127	16,606
L_superiortemporal_thickavg	2.843471 ± 0.1700118	2.744455 ± 0.1840752	0,1674	1,4321	20,233
L_supramarginal_thickavg	2.505412 ± 0.08540642	2.482000 ± 0.13476201	0,6151	0,51333	15,23
L_frontalpole_thickavg	2.808706 ± 0.3685330	2.663182 ± 0.3062093	0,2685	1,1324	24,228
L_temporalpole_thickavg	3.634882 ± 0.2628607	3.533000 ± 0.2770960	0,3435	0,96944	20,658
L_transversetemporal_thickavg	2.408647 ± 0.1594008	2.431727 ± 0.2272220	0,7729	-0,2934	16,347
L_insula_thickavg	2.932412 ± 0.1603645	2.953091 ± 0.1833055	0,7629	-0,30598	19,386

Table 5.21: Cortical Thickness for the left hemisphere of the brain Session 2

Cortical Thickness for the right hemisphere of the brain Session 2

	Responders	**Non-Responders**			
	Mean & Std.dev.	**Mean & Std.dev.**	**T.test**	**T.stat**	**Degrees of Freedom**
R_bankssts_thickavg	2.554647 ± 0.1292270	2.579909 ± 2.579909	0,7278	-0,35466	14,844
R_caudalanteriorcingulate_thickavg	2.433353 ± 0.1634415	2.347909 ± 2.347909	0,1791	1,3873	22,205
R_caudalmiddlefrontal_thickavg	2.454412 ± 0.1485741	2.436091 ± 2.436091	0,7558	0,315	21,199
R_cuneus_thickavg	1.877882 ± 0.07617651	1.908455 ± 1.908455	0,5018	-0,68921	14,246
R_entorhinal_thickavg	3.543118 ± 0.2545297	3.402091 ± 3.402091	0,1551	1,4717	22,229
R_fusiform_thickavg	2.712118 ± 0.07858744	2.713545 ± 2.713545	0,971	-0,03688	16,375
R_inferiorparietal_thickavg	2.440059 ± 0.1032373	2.446727 ± 2.446727	0,8972	-0,1312	16,384
R_inferiortemporal_thickavg	2.788529 ± 0.1296255	2.764000 ± 2.764000	0,6856	0,41162	17,568
R_isthmuscingulate_thickavg	2.392176 ± 0.1523837	2.353091 ± 2.353091	0,5202	0,65393	21,148
R_lateraloccipital_thickavg	2.158235 ± 0.1052571	2.150909 ± 2.150909	0,8606	0,1777	21,184
R_lateralorbitofrontal_thickavg	2.468647 ± 0.1873593	2.486545 ± 2.486545	0,7786	-0,28414	25,046
R_lingual_thickavg	2.053882 ± 0.0965912	2.042000 ± 2.042000	0,8188	0,2331	15,383
R_medialorbitofrontal_thickavg	2.431059 ± 0.1941010	2.423000 ± 2.423000	0,899	0,12818	25,676
R_middletemporal_thickavg	2.822882 ± 0.1294893	2.784364 ± 2.784364	0,5232	0,65129	17,691
R_parahippocampal_thickavg	2.716765 ± 0.2006192	2.599727 ± 2.599727	0,1658	1,4376	20,288
R_paracentral_thickavg	2.421647 ± 0.20648909	2.382545 ± 2.382545	0,4988	0,68708	23,49
R_parsopercularis_thickavg	2.598059 ± 0.2416137	2.570636 ± 2.570636	0,7179	0,36519	25,996
R_parsorbitalis_thickavg	2.664294 ± 0.1913876	2.585818 ± 2.585818	0,2944	1,0743	21,864
R_parstriangularis_thickavg	2.477824 ± 0.1836941	2.418455 ± 2.418455	0,4296	0,80575	20,577
R_pericalcarine_thickavg	1.627471 ± 0.1069171	1.665455 ± 1.665455	0,4583	-0,75875	17,231
R_postcentral_thickavg	1.985059 ± 0.09955932	2.010000 ± 2.010000	0,6611	-0,44743	14,664

R_posteriorcingulate_thickavg	2.417235 ± 0.1199065	2.409273 ± 2.409273	0,8808	0,15204	18,595
R_precentral_thickavg	2.448588 ± 0.1233724	2.472273 ± 2.472273	0,6763	-0,42441	17,879
R_precuneus_thickavg	2.374235 ± 0.1117399	2.351727 ± 2.351727	0,5053	0,67804	20,693
R_rostralanteriorcingulate_thickavg	2.770176 ± 0.2292156	2.739000 ± 2.739000	0,6759	0,42284	25,761
R_rostralmiddlefrontal_thickavg	2.296824 ± 0.1265564	2.258455 ± 2.258455	0,456	0,75971	20,705
R_superiorfrontal_thickavg	2.664235 ± 0.1557263	2.617000 ± 2.617000	0,4018	0,8537	23,759
R_superiorparietal_thickavg	2.121471 ± 0.09080619	2.117636 ± 2.117636	0,9335	0,084693	16,189
R_superiortemporal_thickavg	2.841294 ± 0.1565778	2.795364 ± 2.795364	0,538	0,6283	17,283
R_supramarginal_thickavg	2.473765 ± 0.09359589	2.501909 ± 2.501909	0,627	-0,497	13,878
R_frontalpole_thickavg	2.798941 ± 0.2666856	2.530909 ± 2.530909	0,01683	2,5923	21,451
R_temporalpole_thickavg	3.657941 ± 0.2640337	3.641545 ± 3.641545	0,8985	0,1295	16,816
R_transversetemporal_thickavg	2.418118 ± 0.2388208	2.404091 ± 2.404091	0,8795	0,15335	21,772
R_insula_thickavg	2.966765 ± 0.1365524	2.931364 ± 2.931364	0,5262	0,64481	20,517

Table 5.22: Cortical Thickness for the right hemisphere of the brain Session 2

Overview of Cortical Thickness for Session 2

	Responders	**Non-Responders**			
	Mean & Std.dev.	**Mean & Std.dev.**	**T.test**	**T.stat**	**Degrees of Freedom**
LThickness	2.45400 ± 0.08621358	2.43347 ± 2.43347	0,6261	0,49631	16,805
RThickness	2.435669 ± 0.09018338	2.421881 ± 2.421881	0,7366	0,34157	18,087
LSurfArea	83027.25 ± 9661.042	81234.89 ± 81234.89	0,5908	0,54468	24,771
RSurfArea	83104.65 ± 9230.03	81685.09 ± 81685.09	0,662	0,44249	24,305
ICV	1464956 ± 211379.6	1462865 ± 1462865	0,9802	0,025081	21,011

Table 5.23: Overview

Post-Treatment

	RTT (n = 17)	**NRTT (n = 11)**				
	Means & Std.dev.	**Means & Std.dev.**	**T.Test**	**T.stat**	**Degrees of Freedom**	**Benjamini Hochberg**
L_parsopercularis_surfavg	1586.941 ± 285.5391	1395.455 ± 146.7006	0,028*	2,3303	25,047	0.094+
L_cuneus_thickavg	1.874588 ± 0.1318565	1.965273 ± 0.1344887	0,094+	-1,756	21,186	0.094+
L_fusiform_thickavg	2.679235 ± 0.08930253	2.620545 ± 0.08263094	0,089+	1,7778	22,717	0.094+
L_inferiortemporal_thickavg	2.733353 ± 0.1280590	2.628364 ± 0.1003277	0,023*	2,4216	24,901	0.094+
L_lateraloccipital_thickavg	2.114588 ± 0.09105909	2.037273 ± 0.12314064	0,091+	1,7897	16,998	0.094+
L_parstriangularis_thickavg	2.528 ± 0.1865814	2.413 ± 0.1372465	0,072+	1,8754	25,461	0.094+
R_frontalpole_thickavg	2.799 ± 0.267	2.531 ± 2.531	0,016*	2,5923	21,451	0.094+

Table 5.24: Cortical Thickness for the left hemisphere of the brain Post-treatment

RTT (n = 17) NRTT (n = 11)	**Ancova - Relapse**	**Relapse & ICV**	**Relapse & Number of years of education**	**Relapse & household income**	**Relapse & Sex**
L_parsopercularis_surfavg	0.051+	0.009**	0.054+	0.039*	0.047*
L_cuneus_thickavg	0.09+	0.083+	0.095+	0.085+	0.094+
L_fusiform_thickavg	0.092+	0.099+	0.098+	0.07+	0.097+
L_inferiortemporal_thickavg	0.03*	0.025*	0.033*	0.019*	0.033*
L_lateraloccipital_thickavg	0.03*	0.025*	0.033*	0.019*	0.033*
L_parstriangularis_thickavg	0.091+	0.092+	0.095+	0.074+	0.094+
R_frontalpole_thickavg	0.016*	0.017*	0.016*	0.015*	0.014*

Table 5.25: ANCOVA

Appendix Q

Chapter 5 - Post-Treatment results for between regions (exploratory analysis)

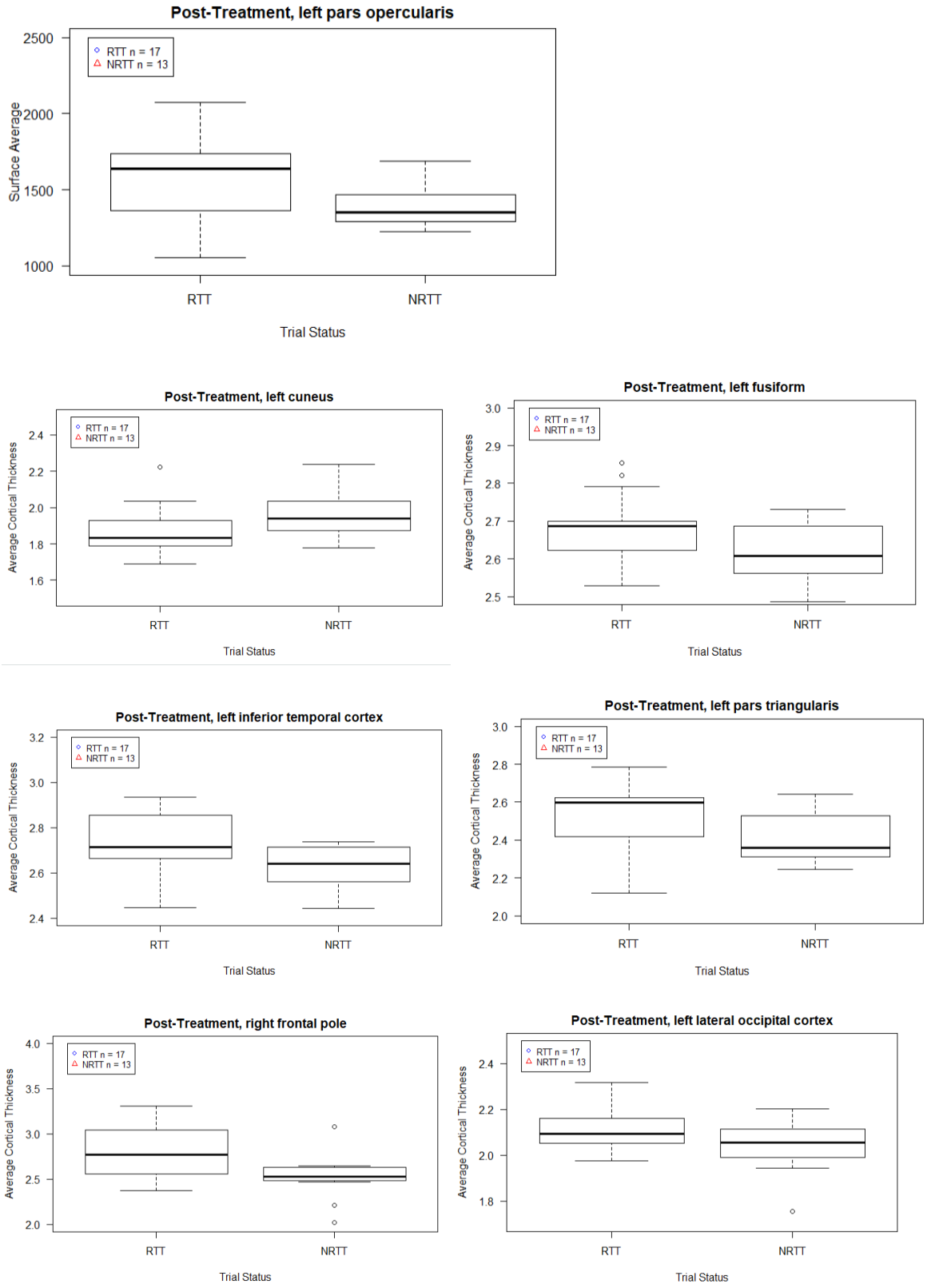

Figure 5.1 : Session two whisker and box plot of surface average and cortical thickness

Appendix R

Chapter 2 – PubMed Search for Systematic Review

1. Biol Psychiatry Cogn Neurosci Neuroimaging. 2017 Oct;2(7):626-635. doi: 10.1016/j.bpsc.2017.03.011.

Brain Volume Correlates with Duration of Abstinence from Substance Abuse in a Region-Specific and Substance-Specific Manner.

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Background: Human neuroimaging studies indicate that the loss of brain volume

associated with substance abuse may be recovered during abstinence. Subcortical and prefrontal cortical regions involved in reward and decision-making are among the regions most consistently implicated in damage and recovery from substance abuse, but the relative capacities of these different brain regions to recover volume during abstinence remains unclear, and it is unknown whether recovery capacities depend on the substance that was abused.

Methods: Voxel-based morphometry in a prison inmate sample (n=107) of long-term abstinent former regular users (FRUs) and former light users (FLUs) of alcohol, cocaine, and/or cannabis. Cross-sectional indicators of volume recovery were operationalized as 1) positive correlation between abstinence duration and volume in FRUs and 2) absence of lower volume in FRUs compared to FLUs.

Results: In FRUs of alcohol, abstinence duration positively correlated with volume in subcortical regions (particularly the putamen and amygdala) but not prefrontal regions; lower prefrontal but not subcortical volume was observed in FRUs compared to FLUs. In FRUs of cocaine, abstinence duration positively correlated with volume in both subcortical regions (particularly the nucleus accumbens) and prefrontal regions; lower volume was not observed in either subcortical or prefrontal regions in FRUs. In FRUs of cannabis, abstinence duration positively correlated with subcortical but not prefrontal volume; lower prefrontal but not subcortical volume was observed in FRUs.

Conclusions: Subcortical structures displayed indicators of volume recovery across FRUs of all three substances, whereas prefrontal regions displayed indicators of volume recovery only in FRUs of cocaine.

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2. Basic Clin Neurosci. 2017 Sep-Oct;8(5):371-385. doi: 10.18869/nirp.bcn.8.5.371.

Analysis of Resting-State fMRI Topological Graph Theory Properties in Methamphetamine Drug Users Applying Box-Counting Fractal Dimension.

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Introduction: Graph theoretical analysis of functional Magnetic Resonance Imaging (fMRI) data has provided new measures of mapping human brain in vivo. Of all methods to measure the functional connectivity between regions, Linear Correlation (LC) calculation of activity time series of the brain regions as a linear measure is considered the most ubiquitous one. The strength of the

dependence obligatory for graph construction and analysis is consistently underestimated by LC, because not all the bivariate distributions, but only the marginals are Gaussian. In a number of studies, Mutual Information (MI) has been employed, as a similarity measure between each two time series of the brain regions, a pure nonlinear measure. Owing to the complex fractal organization of the brain indicating self-similarity, more information on the brain can be revealed by fMRI Fractal Dimension (FD) analysis.

Methods: In the present paper, Box-Counting Fractal Dimension (BCFD) is introduced for graph theoretical analysis of fMRI data in 17 methamphetamine drug users and 18 normal controls. Then, BCFD performance was evaluated compared to those of LC and MI methods. Moreover, the global topological graph properties of the brain networks inclusive of global efficiency, clustering coefficient and characteristic path length in addict subjects were investigated too.

Results: Compared to normal subjects by using statistical tests ($P<0.05$), topological graph properties were postulated to be disrupted significantly during the resting-state fMRI.

Conclusion: Based on the results, analyzing the graph topological properties (representing the brain networks) based on BCFD is a more reliable method than LC and MI.

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to declare.

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Left frontoparietal network activity is modulated by drug stimuli in cocaine addiction.

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Cocaine addicts present reduced activity in the left frontoparietal network, a brain network associated with cognitive control, during the processing of non-drug reward related stimuli (Costumero et al., Addiction Biology 22:479-489,

2015). However, the involvement of this network in drug-related stimuli processing remains unclear. Here, fifteen cocaine-dependent men and fifteen healthy matched controls viewed cocaine-related, erotic, aversive, and neutral pictures during an fMRI session. Group independent component analysis was then performed to investigate how functional networks were modulated by the different emotional images. The results showed that the cocaine-dependent group showed stronger left frontoparietal network activity during the processing of cocaine-related pictures than the control group. Furthermore, the activity of this network during cocaine image processing was positively associated with the years of cocaine use in addicted subjects. In conclusion, our results indicate that the left frontoparietal network is affected in cocaine-dependent men, and may be related to the cognitive control deficits shown in addiction.

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Callous-Unemotional Traits Modulate Brain Drug Craving Response in High-Risk Young Offenders.

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Adults with psychopathy have a high propensity for substance abuse, generally starting from a young age. This investigation tested hypotheses about differences in the neural responses associated with drug craving among high-risk young offenders with histories of abuse of stimulants and other drugs as a function of psychopathic traits. Fifty-four male adolescents (44 with a history of stimulant abuse and 10 controls) incarcerated at a maximum-security facility (M age = 17.08 years) completed a drug-cue exposure task while brain hemodynamic activity was monitored using functional magnetic resonance imaging (fMRI) with a mobile MRI scanner stationed at the facility. Psychopathic traits were assessed using the Hare Psychopathy Checklist: Youth Version (PCL:YV). In the stimulant abuser group, drug cues elicited activity in classic reward circuitry. Consistent with studies of adult psychopathic traits and substance abuse, there was a

negative association between PCL-YV scores and hemodynamic response related to drug craving in the amygdala and ACC in youth with a history of stimulant abuse. However, there were considerably more negative associations between the PCL:YV and hemodynamic response among youth than adults and this was primarily due to callous-unemotional traits rather than interpersonal or behavioral traits. The implications for how personality traits modulate motivations for drug-seeking behavior among adolescent offenders are discussed.

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5. Psychiatry Res. 2018 Jan 30;271:59-66. doi: 10.1016/j.pscychresns.2017.10.012. Epub 2017 Oct 27.

Altered anterior cingulate cortex to hippocampus effective connectivity in response to drug cues in men with cocaine use disorder.

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Drug-related attentional bias may have significant implications for the treatment of cocaine use disorder (CocUD). However, the neurobiology of attentional bias is not completely understood. This study employed dynamic causal modeling (DCM) to conduct an analysis of effective (directional) connectivity involved in drug-related attentional bias in treatment-seeking CocUD subjects. The DCM analysis was conducted based on functional magnetic resonance imaging (fMRI) data acquired from fifteen CocUD subjects while performing a cocaine-word Stroop task, during which blocks of Cocaine Words (CW) and Neutral Words (NW) alternated. There was no significant attentional bias at group level. Although no significant brain activation was found, the DCM analysis found that, relative to the NW, the CW caused a significant increase in the strength of the right (R) anterior cingulate cortex (ACC) to R hippocampus effective connectivity. Greater increase of this connectivity was associated with greater CW reaction time (relative to NW

reaction time). The increased strength of R ACC to R hippocampus connectivity may reflect ACC activation of hippocampal memories related to drug use, which was triggered by the drug cues. This circuit could be a potential target for therapeutics in CocUD patients. No significant change was found in the other modeled connectivities.

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Prenatal methamphetamine exposure is associated with corticostriatal white matter changes in neonates.

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Diffusion tensor imaging (DTI) studies have shown that prenatal exposure to methamphetamine is associated with alterations in white matter microstructure, but to date no tractography studies have been performed in neonates. The striato-thalamo-orbitofrontal circuit and its associated limbic-striatal areas, the primary circuit responsible for reinforcement, has been postulated to be dysfunctional in drug addiction. This study investigated potential white matter changes in the striatal-orbitofrontal circuit in neonates with prenatal methamphetamine exposure. Mothers were recruited antenatally and interviewed regarding methamphetamine use during pregnancy, and DTI sequences were acquired in the first postnatal month. Target regions of interest were manually

delineated, white matter bundles connecting pairs of targets were determined using probabilistic tractography in AFNI-FATCAT, and fractional anisotropy (FA) and diffusion measures were determined in white matter connections. Regression analysis showed that increasing methamphetamine exposure was associated with reduced FA in several connections between the striatum and midbrain, orbitofrontal cortex, and associated limbic structures, following adjustment for potential confounding variables. Our results are consistent with previous findings in older children and extend them to show that these changes are already evident in neonates. The observed alterations are likely to play a role in the deficits in attention and inhibitory control frequently seen in children with prenatal methamphetamine exposure.

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7. J Alcohol Drug Depend. 2017 Aug;5(4). pii: 279. doi: 10.4172/2329-6488.1000279. Epub 2017 Aug 31.

Modeling Causal Relationships among Brain Areas in the Mesocorticolimbic System during Resting-State in Cocaine Users Utilizing a Graph Theoretic Approach.

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OBJECTIVE: While effective connectivity (EC, causal interaction) between brain areas has been investigated in chronic users of cocaine as they view cocaine pictures cues, no study has examined EC while they take part in a resting-state scan. This resting-state fMRI study aims to investigate the causal interaction among brain areas in the mesocorticolimbic system (MCLS), which is involved in reward and motivation, in cocaine users (vs. controls).
METHOD: Twenty cocaine users and 17 healthy controls finished a structural and a resting-state scan. Mean voxel-based time series data were obtained from brain regions of interest (ROIs) from the MCLS, and were input into a Bayesian search algorithm called IMaGES.
RESULTS: The causal interaction pattern was different between the two groups. The feed-forward pattern found in cocaine smokers, between 7 ROIs of the MCLS during resting-state [ventral tegmental area (VTA)→hippocampus (HIPP)→ventral striatum (VenStri)→orbital frontal cortex (OFC), medial frontal cortex (MFC), anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC)], was absent in controls. That is, the subcortical VenStri area had a causal influence on four cortical brain areas only in cocaine users.
CONCLUSIONS: During the resting-state scan, the VTA of cocaine smokers abstinent for at least 72 hours, but not controls, begins causal connections to limbic, midbrain, and frontal regions in the MCLS in a feed-forward manner. Following replication, further studies may assess if changes over time in EC during

resting-state predict cocaine treatment efficacy and outcome.

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Reward Sensitivity and Waiting Impulsivity: Shift towards Reward Valuation away from Action Control.

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Background: Impulsivity and reward expectancy are commonly interrelated. Waiting

impulsivity, measured using the rodent 5-Choice Serial Reaction Time task, predicts compulsive cocaine seeking and sign (or cue) tracking. Here, we assess human waiting impulsivity using a novel translational task, the 4-Choice Serial Reaction Time task, and the relationship with reward cues.

Methods: Healthy volunteers (n=29) performed the monetary incentive delay task as a functional MRI study where subjects observe a cue predicting reward (cue) and wait to respond for high (£5), low (£1), or no reward. Waiting impulsivity was tested with the 4-Choice Serial Reaction Time task.

Results: For high reward prospects (£5, no reward), greater waiting impulsivity on the 4-CSRT correlated with greater medial orbitofrontal cortex and lower supplementary motor area activity to cues. In response to high reward cues, greater waiting impulsivity was associated with greater subthalamic nucleus connectivity with orbitofrontal cortex and greater subgenual cingulate connectivity with anterior insula, but decreased connectivity with regions implicated in action selection and preparation.

Conclusion: These findings highlight a shift towards regions implicated in reward valuation and a shift towards compulsivity away from higher level motor preparation and action selection and response. We highlight the role of reward sensitivity and impulsivity, mechanisms potentially linking human waiting impulsivity with incentive approach and compulsivity, theories highly relevant to disorders of addiction.

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Reduced interhemispheric executive control network coupling in men during early cocaine abstinence: A pilot study.

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BACKGROUND: Individuals who use cocaine have fewer cognitive resources needed to maintain abstinence. This is evidenced by blunted brain function during cognitive control tasks and reduced communication between brain regions associated with cognitive function. For instance, relapse vulnerability is heightened in individuals with less communication between the right and left frontoparietal executive control network (ECN). Given that recent cocaine use enhances such communication, it is plausible that recency of cocaine use influences interhemispheric ECN communication. However, it is unclear whether ECN communication weakens over the course of early cocaine abstinence, which may then enhance relapse risk.

METHODS: In ten men with cocaine use disorder, we conducted a preliminary assessment of the relationship between the number of days since last cocaine use (1-3days) and interhemispheric ECN coupling using resting state functional magnetic resonance imaging (fMRI).

RESULTS: Reduced interhemispheric ECN coupling was associated with increasing days since last cocaine use; weaker coupling was also associated with lower urine cocaine metabolite concentrations. This association was more prominent in prefrontal than parietal ECN-subregions.

CONCLUSIONS: Preliminary results indicate that resting state interhemispheric ECN coupling weakens within the first few days following last cocaine use. Because of the known link between reduced ECN interhemispheric coupling and relapse vulnerability, these results suggest that relapse risk may increase the longer an individual abstains during an early quit attempt. Treatments focused on reversing this coupling deficit may facilitate abstinence.

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10. Front Psychiatry. 2017 Sep 25;8:182. doi: 10.3389/fpsyt.2017.00182. eCollection 2017.

Executive Control and Striatal Resting-State Network Interact with Risk Factors to Influence Treatment Outcomes in Alcohol-Use Disorder.

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Alterations within mesocorticolimbic terminal regions commonly occur with alcohol

use disorder (AUD). As pathological drug-seeking behavior may arise as a consequence of alcohol-induced neuroadaptations, it is critical to understand how such changes increase the likelihood of relapse. This report examined resting-state functional connectivity (RSFC) using both a seed-based and model-free approach in individuals in treatment for AUD and how dysregulation of network connectivity contributes to treatment outcomes. In order to provide a mechanism by which neural networks promote relapse, interactive effects of mesocorticolimbic connectivity and AUD risk factors in treatment completers and non-completers were examined. AUD group showed stronger RSFC between striatum, insula, and anterior cingulate cortex than controls. Within the AUD group, non-completers compared to completers showed enhanced RSFC between (1) striatum-insula, (2) executive control network (ECN)-amygdala, and (3) basal ganglia/salience network and striatum, precuneus, and insula. Completers showed enhanced RSFC between striatum-right dorsolateral prefrontal cortex. Furthermore, completers and non-completers differed in relationships between RSFC and relapse risk factors, where non-completers exhibited positive associations between craving intensity and RSFC of striatum-insula and ECN-amygdala. These findings provide evidence for interactions between corticolimbic connectivity in AUD and craving and establish an important link between network connectivity and dynamic risk factors that contribute to relapse. Results demonstrate that relapse vulnerability is attributed to craving dysregulation manifested by enhanced connectivity in striato-limbic regions and diminished corticostriatal connectivity.

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Unseen scars: Cocaine patients with prior trauma evidence heightened resting state functional connectivity (RSFC) between the amygdala and limbic-striatal regions.

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BACKGROUND: Substance use disorder (SUD) patients with a history of trauma exhibit poorer treatment outcome, greater functional impairment and higher risk for relapse. Endorsement of prior trauma has, in several SUD populations, been linked to abnormal functional connectivity (FC) during task-based studies. We examined amygdala FC in the resting state (RS), testing for differences between cocaine patients with and without prior trauma.

METHODS: Patients with cocaine use disorder (CUD; n=34) were stabilized in an inpatient setting prior to a BOLD fMRI scan. Responses to Addiction Severity Index and the Mini-International Neuropsychiatric Interview were used to characterize the No-Trauma (n=16) and Trauma (n=18) groups. Seed-based RSFC was conducted using the right and left amygdala as regions of interest. Examination of amygdala RSFC was restricted to an a priori anatomical mask that incorporated nodes of the limbic-striatal motivational network.

RESULTS: RSFC was compared for the Trauma versus No-Trauma groups. The Trauma group evidenced greater connectivity between the amygdala and the a priori limbic-striatal mask. Peaks within the statistically significant limbic-striatal mask included the amygdala, putamen, pallidum, caudate, thalamus, insula, hippocampus/parahippocampus, and brain stem.

CONCLUSIONS: Results suggest that cocaine patients with prior trauma (versus without) have heightened communication within nodes of the motivational network, even at rest. To our knowledge, this is the first fMRI study to examine amygdala RSFC among those with CUD and trauma history. Heightened RSFC intralimbic connectivity for the Trauma group may reflect a relapse-relevant brain vulnerability and a novel treatment target for this clinically-challenging population.

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Altered functional connectivity to stressful stimuli in prenatally cocaine-exposed adolescents.

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BACKGROUND: Prenatal cocaine exposure (PCE) is linked to addiction and obesity vulnerability. Neural responses to stressful and appetitive cues in adolescents with PCE versus those without have been differentially linked to substance-use initiation. However, no prior studies have assessed cue-reactivity responses among PCE adolescents using a connectivity-based approach.

METHODS: Twenty-two PCE and 22 non-prenatally drug-exposed (NDE) age-, sex-, IQ- and BMI-matched adolescents participated in individualized guided imagery with appetitive (favorite-food), stressful and neutral-relaxing cue scripts during functional magnetic resonance imaging. Subjective favorite-food craving scores were collected before and after script exposure. A data-driven voxel-wise intrinsic connectivity distribution analysis was used to identify between-group differences and examine relationships with craving scores.

RESULTS: A group-by-cue interaction effect identified a parietal lobe cluster where PCE versus NDE adolescents showed less connectivity during stressful and more connectivity during neutral-relaxing conditions. Follow-up seed-based connectivity analyses revealed that, among PCE adolescents, the parietal seed was positively connected to inferior parietal and sensory areas and negatively connected to corticolimbic during both stress and neutral-relaxing conditions. For NDE, greater parietal connectivity to parietal, cingulate and sensory areas

and lesser parietal connectivity to medial prefrontal areas were found during stress compared to neutral-relaxing cueing. Craving scores inversely correlated with corticolimbic connectivity in PCE, but not NDE adolescents, during the favorite-food condition.
CONCLUSIONS: Findings from this first data-driven intrinsic connectivity analysis of PCE influences on adolescent brain function indicate differences relating to PCE status and craving. These findings provide insight into the developmental impact of in utero drug exposure.

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Effects of sex and HIV serostatus on spatial navigational learning and memory among cocaine users.

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Spatial learning and memory are critically dependent on the integrity of hippocampal systems. Functional MRI and neuropathological studies show that hippocampal circuitry is prominently affected among HIV-seropositive individuals, but potential spatial learning and memory deficits have not been studied in detail in this population. We investigated the independent and interactive effects of sex and HIV serostatus on performance of a spatial learning and memory task in a sample of 181 individuals with a history of cocaine dependence. We found that men showed faster times to completion on immediate recall trials compared with women and that delayed recall was significantly poorer among HIV-infected compared with HIV-uninfected participants. Additionally, a sex × serostatus effect was found on the total number of completed learning trials. Specifically, HIV-infected men successfully completed more learning trials compared with HIV-infected women. Results are discussed in the context of recent reports of sex and HIV serostatus effects on episodic memory performance.

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Cocaine dependence modulates the effect of HIV infection on brain activation during intertemporal decision making.

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BACKGROUND: Both HIV infection and chronic cocaine use alter the neural circuitry of decision making, but the interactive effects of these commonly comorbid conditions have not been adequately examined. This study tested how cocaine moderates HIV-related neural activation during an intertemporal decision-making task.

METHODS: The sample included 73 participants who differed on cocaine and HIV status (18 COC+/HIV+, 19 COC+/HIV-, 19 COC-/HIV+, 17 COC-/HIV-). Participants made choices between smaller, sooner and larger, delayed rewards while undergoing functional MRI. Choices varied in difficulty based on subjective value: hard (equivalently valued), easy (disparately valued), and control choices. A mixed-effects model controlling for education and smoking identified main and interactive effects of HIV and COC during hard relative to easy choices (difficulty contrast).

RESULTS: COC+ status was associated with lower activation in bilateral frontal gyri and right insular and posterior parietal cortices. HIV+ status was associated with higher activation in the visual cortex, but lower activation in bilateral prefrontal cortices and cerebellum and left posterior parietal cortex. COC moderated the effects of HIV in several clusters centered in the bilateral prefrontal cortices and cerebellum. In post-hoc analyses, there were significant effects of HIV status on activation for COC+, but not COC-, participants; interaction effects remained after controlling for polysubstance use.

CONCLUSION: Cocaine use may diminish the compensatory neural activation often seen among HIV+ samples during decision making. Our results highlight the importance of examining the neuropsychiatric effects of comorbid medical conditions to identify potential neural targets for cognitive remediation interventions.

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Alterations in functional brain networks associated with loss-chasing in gambling disorder and cocaine-use disorder.

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BACKGROUND: Continued, persistent gambling to recover accumulating losses, or

'loss-chasing', is a behavioral pattern linked particularly closely to gambling disorder (GD) but may reflect impaired decision-making processes relevant to drug addictions like cocaine-use disorder (CUD). However, little is known regarding the neurocognitive mechanisms of this complex, maladaptive behavior, particularly in individuals with addictive disorders.

METHODS: Seventy participants (25 GD, 18 CUD, and 27 healthy comparison (HC)) completed a loss-chase task during fMRI. Engagement of functional brain networks in response to losing outcomes and during decision-making periods preceding choices to loss-chase or to quit chasing losses were investigated using independent component analysis (ICA). An exploratory factor analysis was performed to examine patterns of coordinated engagement across identified networks.

RESULTS: In GD relative to HC and CUD participants, choices to quit chasing were associated with greater engagement of a medial frontal executive-processing network. By comparison, CUD participants exhibited altered engagement of a striato-amygdala motivational network in response to losing outcomes as compared to HC, and during decision-making as compared to GD. Several other networks were differentially engaged during loss-chase relative to quit-chasing choices, but did not differ across participant groups. Exploratory factor analysis identified a system of coordinated activity across prefrontal executive-control networks that was greater in GD and CUD relative to HC participants and was associated with increased chasing persistence across all participants.

CONCLUSIONS: Results provide evidence of shared and distinct neurobiological mechanisms in substance and behavioral addictions, and lend insight into potential cognitive interventions targeting loss-chasing behavior in GD.

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Left frontal pole theta burst stimulation decreases orbitofrontal and insula activity in cocaine users and alcohol users.

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BACKGROUND: Preclinical research has demonstrated a causal relationship between medial prefrontal cortex activity and cocaine self-administration. As a step towards translating those data to a neural circuit-based intervention for patients, this study sought to determine if continuous theta burst stimulation (cTBS) to the left frontal pole (FP), would attenuate frontal-striatal activity in two substance-dependent populations.
METHODS: Forty-nine substance dependent individuals (25 cocaine, 24 alcohol) completed a single-blind, sham-controlled, crossover study wherein they received 6 trains of real or sham cTBS (110% resting motor threshold, FP1) each visit. Baseline evoked BOLD signal was measured immediately before and after real and sham cTBS (interleaved TMS/BOLD imaging: single pulses to left FP; scalp-to-cortex distance covariate, FWE correction $p<0.05$) RESULTS: Among cocaine users, real cTBS significantly decreased evoked BOLD signal in the caudate, accumbens, anterior cingulate, orbitofrontal (OFC) and parietal cortex relative to sham cTBS. Among alcohol users, real cTBS significantly decreased evoked BOLD signal in left OFC, insula, and lateral sensorimotor cortex. There was no significant difference between the groups.
CONCLUSIONS: These data suggest that 6 trains of left FP cTBS delivered in a

single day decreases TMS-evoked BOLD signal in the OFC and several cortical nodes which regulate salience and are typically activated by drug cues. The reliability of this pattern across cocaine- and alcohol-dependent individuals suggests that cTBS may be an effective tool to dampen neural circuits typically engaged by salient drug cues. Multiday studies are required to determine it this has a sustainable effect on the brain or drug use behavior.

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Cocaine and HIV are independently associated with neural activation in response to gain and loss valuation during economic risky choice.

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Stimulant abuse is disproportionately common in HIV-positive persons. Both HIV and stimulants are independently associated with deficits in reward-based decision making, but their interactive and/or additive effects are poorly understood despite their prevalent co-morbidity. Here, we examined the effects of cocaine dependence and HIV infection in 69 adults who underwent functional magnetic resonance imaging while completing an economic loss aversion task. We identified two neural networks that correlated with the evaluation of the favorable characteristics of the gamble (i.e. higher gains/lower losses: ventromedial prefrontal cortex, anterior cingulate, anterior and posterior precuneus and visual cortex) versus unfavorable characteristics of the gamble (i.e. lower gains/higher losses: dorsal prefrontal, lateral orbitofrontal, posterior parietal cortex, anterior insula and dorsal caudate). Behaviorally, cocaine and HIV had additive effects on loss aversion scores, with HIV-positive cocaine users being the least loss averse. Cocaine users had greater activation in brain regions that tracked the favorability of gamble characteristics (i.e. increased activation to gains, but decreased activation to losses). In contrast, HIV infection was independently associated with lesser activation in regions that tracked the unfavorability of gamble characteristics. These results suggest that cocaine is associated with an overactive reward-seeking system, while HIV is associated with an underactive cognitive control system. Together, these alterations may leave HIV-positive cocaine users particularly vulnerable to making unfavorable decisions when outcomes are uncertain.

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Contribution of Clinical Neuroimaging to the Understanding of the Pharmacology of Methylphenidate.

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Methylphenidate (MPH) is currently the most widely used molecule in the pharmacologic treatment of attention-deficit hyperactivity disorder (ADHD). Although experience of its application now extends over several decades, its psychotropic nature, prolonged use in children, and chemical relation to amphetamines still raise doubts in the minds of prescribers and the families of

the patients. Brain imaging has shed considerable light on the neuropharmacology of MPH. The two main in vivo neuroimaging techniques are positron-emission tomography (PET) and magnetic resonance imaging (MRI), and these can be applied in both animal models and humans. The present review seeks to show how human molecular and functional imaging has contributed to determining not only the molecular targets of MPH, and the action kinetics of the various pharmaceutical forms available, but also the connectivity and brain networks activated by treatment. We also discuss the perspectives opened up by new hybrid PET-MRI techniques that enable multimodal tracking of the impact of methylphenidate on neurotransmission.

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Salience and default mode network dysregulation in chronic cocaine users predict treatment outcome.

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While chronic cocaine use is associated with abnormalities in both brain structure and function within and interactions between regions, previous studies have been limited to interrogating structure and function independently, and the detected neural differences have not been applied to independent samples to assess the clinical relevance of results. We investigated consequences of structural differences on resting-state functional connectivity in cocaine addiction and tested whether resting-state functional connectivity of the identified circuits predict relapse in an independent cohort. Subjects included 64 non-treatment-seeking cocaine users (NTSCUs) and 67 healthy control subjects and an independent treatment-completed cohort (n = 45) of cocaine-dependent individuals scanned at the end of a 30-day residential treatment programme. Differences in cortical thickness and related resting-state functional connectivity between NTSCUs and healthy control subjects were identified. Survival analysis, applying cortical thickness of the identified regions, resting-state functional connectivity of the identified circuits and clinical characteristics to the treatment cohort, was used to predict relapse. Lower cortical thickness in bilateral insula and higher thickness in bilateral temporal pole were found in NTSCUs versus healthy control subjects. Whole brain

resting-state functional connectivity analyses with these four different anatomical regions as seeds revealed eight weaker circuits including within the salience network (insula seeds) and between temporal pole and elements of the default mode network in NTSCUs. Applying these circuits and clinical characteristics to the independent cocaine-dependent treatment cohort, functional connectivity between right temporal pole and medial prefrontal cortex, combined with years of education, predicted relapse status at 150 days with 88% accuracy. Deficits in the salience network suggest an impaired ability to process physiologically salient events, while abnormalities in a temporal pole-medial prefrontal cortex circuit might speak to the social-emotional functional alterations in cocaine addiction. The involvement of the temporal pole-medial prefrontal cortex circuit in a model highly predictive of relapse highlights the importance of social-emotional functions in cocaine dependence, and provides a potential underlying neural target for therapeutic interventions, and for identifying those at high risk of relapse.

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20. Med Sci Sports Exerc. 2017 Jul;49(7):1443-1451. doi: 10.1249/MSS.0000000000001252.

Methylphenidate Enhances Grip Force and Alters Brain Connectivity.

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INTRODUCTION: A central fatigue theory proposes that force output during fatiguing exercise is limited to maintain homeostasis. The self-awareness of the body's homeostatic state is known as interoception. Brain regions thought to play a role in interoception, such as the insular and orbital frontal cortex, have been proposed as sites for the upstream regulation of fatiguing exercise. Methylphenidate (MPH) can improve force output during exercise and may alter central processes during fatiguing exercise. However, the ergogenic neural underpinnings of MPH are unknown. This study examines the effect of MPH on force output and brain functional connectivity during a muscle-fatiguing handgrip task.
METHODS: In a double-blind, crossover design, 15 subjects (mean age = 28.4 ± 5.2; 9 males and 6 females) ingested MPH or placebo before performing a muscle-fatiguing handgrip task during functional magnetic resonance imaging. We examined force output and brain connectivity (psychophysiological interactions and functional connectivity) throughout the task as well as in the few seconds just before releasing the grip dynamometer (i.e., pretask failure).
RESULTS: We show that in the MPH condition, subjects increased grip force

throughout but not during pretask failure. Brain connectivity was altered throughout the task between the insular and the hand motor cortex, as well as between the insular and the orbital frontal cortex. There were no differences in connectivity during pretask failure.
CONCLUSION: For the first time, we show that brain connectivity can be influenced by MPH during muscle-fatiguing exercise. This study provides additional support that the CNS acts to regulate motor drive subservient to homeostasis.

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21. Transl Psychiatry. 2017 Mar 7;7(3):e1054. doi: 10.1038/tp.2017.34.

Effects of naltrexone are influenced by childhood adversity during negative emotional processing in addiction recovery.

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Naltrexone is an opioid receptor antagonist used in the management of alcohol dependence. Although the endogenous opioid system has been implicated in emotion regulation, the effects of mu-opioid receptor blockade on brain systems underlying negative emotional processing are not clear in addiction. Individuals meeting criteria for alcohol dependence alone (n=18, alcohol) and in combination with cocaine and/or opioid dependence (n=21, alcohol/drugs) and healthy individuals without a history of alcohol or drug dependence (n=21) were recruited. Participants were alcohol and drug abstinent before entered into this double-blind, placebo-controlled, randomized, crossover study. Functional magnetic resonance imaging was used to investigate brain response while viewing aversive and neutral images relative to baseline on 50 mg of naltrexone and placebo. We found that naltrexone modulated task-related activation in the medial prefrontal cortex and functional connectivity between the anterior cingulate cortex and the hippocampus as a function of childhood adversity (for aversive versus neutral images) in all groups. Furthermore, there was a group-by-treatment-by-condition interaction in the right amygdala, which was mainly driven by a normalization of response for aversive relative to neutral images under naltrexone in the alcohol/drugs group. We conclude that early

childhood adversity is one environmental factor that influences pharmacological response to naltrexone. Pharmacotherapy with naltrexone may also have some ameliorative effects on negative emotional processing in combined alcohol and drug dependence, possibly due to alterations in endogenous opioid transmission or the kappa-opioid receptor antagonist actions of naltrexone.

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The effect of task difficulty on motor performance and frontal-striatal connectivity in cocaine users.

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BACKGROUND: There is growing recognition that chronic cocaine users have alterations in sensorimotor control that are positively related to low

frontal-striatal connectivity within the motor system. These frontal-striatal motor circuits however, are modulated by circuits governing attention, which are also disrupted in cocaine users. This study's aim was to determine if sensorimotor control deficits are positively related to the difficulty of a motor task or exist independent of the increasing cognitive demand.

METHODS: Functional MRI data was collected from 40 individuals (20 non-treatment seeking chronic cocaine users, 20 age and gender matched non-drug using controls) as they mimicked an unpredictable finger-tapping sequence at various speeds. Dependent measures included task accuracy, percent BOLD signal change in sensorimotor regions of interest (ROIs), and functional connectivity (temporal correlations) between ROIs.

RESULTS: In both groups, as speed increased, the BOLD signal change increased in the primary motor cortex, supplementary motor area (SMA), cerebellum, and anterior cingulate cortex. Compared to controls, cocaine user SMA-Caudate and ACC-Putamen connectivity was lower at all speeds in the contralateral hemisphere. Furthermore, as speed increased there was a decrease in connectivity between additional ROI pairs among users.

CONCLUSIONS: These data support previous observations of sensorimotor performance deficits and dorsal frontal-striatal connectivity impairments among cocaine users. While previous studies demonstrate these deficits when performing a finger-tapping task at a single speed, we show that these same impairments exist at multiple levels of task difficulty. These data suggest that previously observed frontal-striatal connectivity in cocaine users during sensorimotor task performance are stable and not directly related to cognitive demands of the task.

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Naltrexone ameliorates functional network abnormalities in alcohol-dependent individuals.

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Naltrexone, an opioid receptor antagonist, is commonly used as a relapse prevention medication in alcohol and opiate addiction, but its efficacy and the

mechanisms underpinning its clinical usefulness are not well characterized. In the current study, we examined the effects of 50-mg naltrexone compared with placebo on neural network changes associated with substance dependence in 21 alcohol and 36 poly-drug-dependent individuals compared with 36 healthy volunteers. Graph theoretic and network-based statistical analysis of resting-state functional magnetic resonance imaging (MRI) data revealed that alcohol-dependent subjects had reduced functional connectivity of a dispersed network compared with both poly-drug-dependent and healthy subjects. Higher local efficiency was observed in both patient groups, indicating clustered and segregated network topology and information processing. Naltrexone normalized heightened local efficiency of the neural network in alcohol-dependent individuals, to the same levels as healthy volunteers. Naltrexone failed to have an effect on the local efficiency in abstinent poly-substance-dependent individuals. Across groups, local efficiency was associated with substance, but no alcohol exposure implicating local efficiency as a potential premorbid risk factor in alcohol use disorders that can be ameliorated by naltrexone. These findings suggest one possible mechanism for the clinical effects of naltrexone, namely, the amelioration of disrupted network topology.

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Cocaine differentially affects synaptic activity in memory and midbrain areas of female and male rats: an in vivo MEMRI study.

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Manganese enhanced magnetic resonance imaging (MEMRI) has been previously used to determine the effect of acute cocaine on calcium-dependent synaptic activity in male rats. However, there have been no MEMRI studies examining sex differences in the functional neural circuits affected by repeated cocaine. In the present study, we used MEMRI to investigate the effects of repeated cocaine on brain activation in female and male rats. Adult female and male rats were scanned at 4.7 Tesla three days after final treatment with saline, a single cocaine injection (15 mg kg-1, i.p. × 1 day) or repeated cocaine injections (15 mg kg-1, i.p. × 10 days). A day before imaging rats were provided with an i.p. injection of manganese chloride (70 mg kg-1). Cocaine produced effects on MEMRI activity

that were dependent on sex. In females, we observed that a single cocaine injection reduced MEMRI activity in hippocampal CA3, ventral tegmental area (VTA), and median Raphé, whereas repeated cocaine increased MEMRI activity in dentate gyrus and interpeduncular nucleus. In males, repeated cocaine reduced MEMRI activity in VTA. Overall, it appeared that female rats showed a general trend towards increase MEMRI activity with single cocaine and reduced activity with repeated exposure, while male rats showed a trend towards opposite effects. Our results provide evidence for sex differences in the in vivo neural response to cocaine, which involves primarily hippocampal, amygdala and midbrain areas.

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25. Acta Radiol. 2017 Nov;58(11):1378-1385. doi: 10.1177/0284185117692170. Epub 2017 Feb 9.

Microstructures in striato-thalamo-orbitofrontal circuit in methamphetamine users.

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Background Striato-thalamo-orbitofrontal (STO) circuit plays a key role in the development of drug addiction. Few studies have investigated its microstructural abnormalities in methamphetamine (MA) users. Purpose To evaluate the microstructural changes and relevant clinical relevance of the STO circuit in MA users using diffusion tensor imaging (DTI). Material and Methods Twenty-eight MA users and 28 age-matched normal volunteers were enrolled. 3T magnetic resonance imaging (MRI) was employed to obtain structural T1-weighted (T1W) imaging and diffusion-tensor imaging (DTI) data. Freesurfer software was used for automated segmentation of the bilateral nucleus accumbens (NAc), thalami, and orbitofrontal cortex (OFC). Four DTI measures maps, fractional anisotropy (FA), mean diffusivity (MD), axial diffusion (AD), and radial diffusion (RD) were generated and non-linearly co-registered to structural space. Comparisons of DTI measures of the STO circuit were carried out between MA and controls using repeated measures analysis of variance. Correlation analyses were performed between STO circuit DTI measures and clinical characteristics. Results The MA group had significant FA reduction in the bilateral NAc, OFC, and right thalamus ($P < 0.05$). Lower left OFC FA and right NAc FA/AD were associated with longer duration of MA use. Lower right OFC FA was associated with younger age at first MA use. Higher FA and lower MD/RD in the thalamus, as well as higher left OFC RD, were associated with increased psychiatric symptoms. Conclusion The STO circuit has reduced microstructural integrity in MA users. Microstructural changes in the thalamus may compensate for dysfunction in functionally connected cortices, which needs further investigation.

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Doubling down: increased risk-taking behavior following a loss by individuals with cocaine use disorder is associated with striatal and anterior cingulate dysfunction.

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BACKGROUND: Cocaine use disorders (CUDs) have been associated with increased

risk-taking behavior. Neuroimaging studies have suggested that altered activity in reward and decision-making circuitry may underlie cocaine user's heightened risk-taking. It remains unclear if this behavior is driven by greater reward salience, lack of appreciation of danger, or another deficit in risk-related processing.

METHODS: Twenty-nine CUD participants and forty healthy comparison participants completed the Risky Gains Task during a functional magnetic resonance imaging scan. During the Risky Gains Task, participants choose between a safe option for a small, guaranteed monetary reward and risky options with larger rewards but also the chance to lose money. Frequency of risky choice overall and following a win versus a loss were compared. Neural activity during the decision and outcome phase were examined using linear mixed effects models.

RESULTS: Although the groups did not differ in overall risk-taking frequency, the CUD group chose a risky option more often following a loss. Neuroimaging analyses revealed that the comparison group showed increasing activity in the bilateral ventral striatum as they chose higher-value, risky options, but the CUD group failed to show this increase. During the outcome phase, the CUD group showed a greater decrease in bilateral striatal activity relative to the comparison group when losing the large amount, and this response was correlated with risk-taking frequency after a loss.

CONCLUSIONS: The brains of CUD individuals are hypersensitive to losses, leading to increased risk-taking behaviors, and this may help explain why these individuals take drugs despite aversive outcomes.

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Resting state brain connectivity patterns before eventual relapse into cocaine abuse.

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According to recent theories, drug addicted patients suffer of an impaired response inhibition and salience attribution (I-RISA) together with a perturbed connectivity between the nuclei accumbens (NAcs) and the orbito-prefrontal (oPFC) and dorsal prefrontal (dPFC) cortices, brain regions associated with motivation and cognitive control. To empirically test these assumptions, we evaluated the (neuro)psychological trait and the functional organization of the resting state brain networks associated with the NAcs in 18 former cocaine abusers (FCAs), while being in drug abstinence since 5 months. The psychological data were grouped into three empirical variables related with emotion regulation, emotion awareness and strategic and controlled behaviour. Comparison of the resting state patterns between the entire sample of FCAs and 19 controls revealed a reduction of functional connectivity between the NAcs and the dPFC and enhanced connectivity between the NAcs and the dorsal-striatum. In the 8 FCAs who relapsed into cocaine use after 3 months, the level of functional connectivity between the NAcs and dPFC was lower than the functional connectivity estimated in the group of patients that did not relapsed. Finally, in the entire sample of FCAs, the higher the connectivity between the NAc and the oPFC the lower was the level of strategic and controlled behaviour. Taken together, these results are compatible with models of the interactions between the NAcs, the dorsal striatum and frontal cortices in the I-RISA syndrome, showing that such interactions are particularly perturbed in patients at greater risk of relapse into cocaine abuse.

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Anything goes? Regulation of the neural processes underlying response inhibition in TBI patients.

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Despite evidence for beneficial use of methylphenidate in response inhibition, no studies so far have investigated the effects of this drug in the neurobiology of inhibitory control in traumatic brain injury (TBI), even though impulsive behaviours are frequently reported in this patient group. We investigated the neural basis of response inhibition in a group of TBI patients using functional magnetic resonance imaging and a stop-signal paradigm. In a randomised double-blinded crossover study, the patients received either a single 30mg dose

of methylphenidate or placebo and performed the stop-signal task. Activation in the right inferior frontal gyrus (RIFG), an area associated with response inhibition, was significantly lower in patients compared to healthy controls. Poor response inhibition in this group was associated with greater connectivity between the RIFG and a set of regions considered to be part of the default mode network (DMN), a finding that suggests the interplay between DMN and frontal executive networks maybe compromised. A single dose of methylphenidate rendered activity and connectivity profiles of the patients RIFG near normal. The results of this study indicate that the neural circuitry involved in response inhibition in TBI patients may be partially restored with methylphenidate. Given the known mechanisms of action of methylphenidate, the effect we observed may be due to increased dopamine and noradrenaline levels.

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Epigenetics of amphetamine-induced sensitization: HDAC5 expression and microRNA in neural remodeling.

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BACKGROUND: Histone deacetylase (HDAC) activities modify chromatin structure and play a role in learning and memory during developmental processes. Studies of adult mice suggest HDACs are involved in neural network remodeling in brain repair, but its function in drug addiction is less understood. We aimed to examine in vivo HDAC5 expression in a preclinical model of amphetamine-induced sensitization (AIS) of behavior. We generated specific contrast agents to measure HDAC5 levels by in vivo molecular contrast-enhanced (MCE) magnetic resonance imaging (MRI) in amphetamine-naïve mice as well as in mice with AIS. To validate the MRI results we used ex vivo methods including in situ hybridization, RT-PCR, immunohistochemistry, and transmision electron microscopy.
METHODS: We compared the expression of HDAC5 mRNA in an acute exposure paradigm (in which animals experienced a single drug exposure [A1]) and in a chronic-abstinence-challenge paradigm (in which animals were exposed to the drug once every other day for seven doses, then underwent 2 weeks of abstinence followed by a challenge dose [A7WA]). Control groups for each of these exposure paradigms were given saline. To delineate how HDAC5 expression was related to AIS, we compared the expression of HDAC5 mRNA at sequences where no known microRNA (miR) binds (hdac5AS2) and at sequences where miR-2861 is known to bind

(miD2861). We synthesized and labeled phosphorothioated oligonucleic acids (sODN) of hdac5AS2 or miD2861 linked to superparamagentic iron oxide nanoparticles (SPION), and generated HDAC5-specific contrast agents (30 ± 20 nm, diameter) for MCE MRI; the same sequences were used for primers for TaqMan® analysis (RT-qPCR) in ex vivo validation. In addition, we used subtraction R2* maps to identify regional HDAC5 expression.

RESULTS: Naïve C57black6 mice that experience acute exposure to amphetamine (4 mg/kg, by injection intraperitoneally) show expression of both total and phosphorylated (S259) HDAC5 antigens in GFAP+ and GFAP- cells, but the appearance of these cells was attenuated in the chronic paradigm. We found that MCE MRI reports HDAC5 mRNA with precision in physiological conditions because the HDAC5 mRNA copy number reported by TaqMan analysis was positively correlated (with a linear coefficient of 1.0) to the ΔR2* values (the frequency of signal reduction above background, 1/s) measured by MRI. We observed SPION-mid2861 as electron dense nanoparticles (EDNs) of less than 30 nm in the nucleus of the neurons, macrophages, and microglia, but not in glia and endothelia. We found no preferential distribution in any particular type of neural cells, but observed scattered EDNs of 60-150 nm (dia) in lysosomes. In the acute paradigm, mice pretreated with miD2861 (1.2 mmol/kg, i.p./icv) exhibited AIS similar to that exibited by mice in the chronic exposure group, which exhibited null response to mid2861 pretreatment. Moreover, SPION-miD2861 identified enhanced HDAC5 expression in the lateral septum and the striatum after amphetamine, where we found neurprogenitor cells coexpressing NeuN and GFAP.

CONCLUSIONS: We conclude that miD2681 targets HDAC5 mRNA with precision similar to that of RT-PCR. Our MCE MRI detects RNA-bound nanoparticles (NPs) in vivo, and ex vivo validation methods confirm that EDNs do not accumulate in any particular cell type. As HDAC5 expression may help nullify AIS and identify progenitor

cells, the precise delivery of miD2861 may serve as a vehicle for monitoring network remodeling with target specificity and signal sensitivity after drug exposure that identifies brain repair processes in adult animals.

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Distinct intrinsic functional brain network abnormalities in methamphetamine-dependent patients with and without a history of psychosis.

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Chronic methamphetamine use is associated with executive functioning deficits that suggest dysfunctional cognitive control networks (CCNs) in the brain. Likewise, abnormal connectivity between intrinsic CCNs and default mode networks (DMNs) has also been associated with poor cognitive function in clinical populations. Accordingly, we tested the extent to which methamphetamine use predicts abnormal connectivity between these networks, and whether, as predicted, these abnormalities are compounded in patients with a history of methamphetamine-associated psychosis (MAP). Resting-state fMRI data were acquired from 46 methamphetamine-dependent patients [19 with MAP, 27 without (MD)], as well as 26 healthy controls (CTRL). Multivariate network modelling and whole-brain voxel-wise connectivity analyses were conducted to identify group differences in intrinsic connectivity across four cognitive control and three DMN networks identified using an independent components analysis approach (meta-ICA). The relationship of network connectivity and psychotic symptom severity, as well as antipsychotic treatment and methamphetamine use variables, was also investigated. Robust evidence of hyper-connectivity was observed between the right frontoparietal and anterior DMN networks in MAP patients, and 'normalized' with increased duration of treatment with antipsychotics. Attenuation of anticorrelated anterior DMN-dorsal attention network activity was also restricted to this group. Elevated coupling detected in MD participants between anterior and posterior DMN networks became less apparent with increasing duration of abstinence from methamphetamine. In summary, we observed both alterations of RSN connectivity between DMN networks with chronic methamphetamine exposure, as well as DMN-CCN coupling abnormalities consistent with possible MAP-specific frontoparietal deficits in the biasing of task-appropriate network activity.

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eCollection 2016.

Reward Contingencies Improve Goal-Directed Behavior by Enhancing Posterior Brain Attentional Regions and Increasing Corticostriatal Connectivity in Cocaine Addicts.

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The dopaminergic system provides the basis for the interaction between motivation

and cognition. It is triggered by the possibility of obtaining rewards to initiate the neurobehavioral adaptations necessary to achieve them by directing the information from motivational circuits to cognitive and action circuits. In drug addiction, the altered dopamine (DA) modulation of the meso-cortico-limbic reward circuitry, such as the prefrontal cortex (PFC), underlies the disproportionate motivational value of drug use at the expense of other non-drug reinforcers and the user's loss of control over his/her drug intake. We examine how the magnitude of the reward affects goal-directed processes in healthy control (HC) subjects and abstinent cocaine dependent (ACD) patients by using functional magnetic resonance imaging (fMRI) during a counting Stroop task with blocked levels of monetary incentives of different magnitudes (€0, €0.01, €0.5, €1 or €1.5). Our results showed that increasing reward magnitude enhances (1) performance facilitation in both groups; (2) left dorsolateral prefrontal cortex (DLPFC) activity in HC and left superior occipital cortex activity in ACD; and (3) left DLPFC and left putamen connectivity in ACD compared to HC. Moreover, we observed that (4) dorsal striatal and pallidum activity was associated with craving and addiction severity during the parametric increases in the monetary reward. In conclusion, the brain response to gradients in monetary value was different in HC and ACD, but both groups showed improved task performance due to the possibility of obtaining greater monetary rewards.

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Conflict of interest statement: The authors have declared that no competing interests exist.

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Effective Connectivity within the Mesocorticolimbic System during Resting-State in Cocaine Users.

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Objective: Although effective connectivity between brain regions has been examined in cocaine users during tasks, no effective connectivity study has been conducted on cocaine users during resting-state. In the present functional magnetic resonance imaging study, we examined effective connectivity in resting-brain, between the brain regions within the mesocorticolimbic dopamine system, implicated in reward and motivated behavior, while the chronic cocaine users and controls took part in a resting-state scan by using a spectral Dynamic causal modeling (spDCM) approach. Method: As part of a study testing cocaine cue reactivity in cocaine users (Ray et al., 2015b), 20 non-treatment seeking cocaine-smoking (abstinent for at least 3 days) and 17 control participants completed a resting state scan and an anatomical scan. A mean voxel-based time series data extracted from four key brain areas (ventral tegmental area, VTA; nucleus accumbens, NAc; hippocampus, medial frontal cortex) within the

mesocorticolimbic dopamine system during resting-state from the cocaine and control participants were used as input to the spDCM program to generate spDCM analysis outputs. Results: Compared to the control group, the cocaine group had higher effective connectivity from the VTA to NAc, hippocampus and medial frontal cortex. In contrast, the control group showed a higher effective connectivity from the medial frontal cortex to VTA, from the NAc to medial frontal cortex, and on the hippocampus self-loop. Conclusions: The present study is the first to show that during resting-state in abstaining cocaine users compared to controls, the VTA initiates an enhanced effective connectivity to NAc, hippocampus and medial frontal cortex areas within the mesocorticolimbic dopamine system, the brain's reward system. Future studies of effective connectivity analysis during resting-state may eventually be used to monitor treatment outcome.

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33. Neuroimage Clin. 2016 Oct 4;12:691-697. eCollection 2016.

Pharmaco fMRI: Determining the functional anatomy of the effects of medication.

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Functional MRI studies have helped to elucidate underlying mechanisms in complex neurological and neuropsychiatric disorders. Disease processes often involve complex large-scale network interactions, extending beyond the presumed main disease focus. Given both the complexity of the clinical phenotype and the underlying dysfunctional brain circuits, so called pharmaco-fMRI (ph-MRI) studies probe pharmacological effects on functional neuro-anatomy, and can help to determine early treatment response, mechanisms of drug efficacy and side effects, and potentially advance CNS drug development. In this review, we discuss recent ph-MRI research in three major neuropsychiatric and neurological disorders and associated network alterations, namely selective serotonin and noradrenergic reuptake inhibitors in affective disorders and emotional processing circuits; antiepileptic drugs in epilepsy and cognitive networks; and stimulants in attention-deficit/hyperactivity disorder and networks of attention control. We conclude that ph-MRI studies show consistent and reproducible changes on disease relevant networks, and prove sensitive to early pharmacological effects on functional anatomy associated with disease. Further CNS drug research and development would benefit greatly from improved disease phenotyping, or biomarkers, using advanced imaging techniques.

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Midbrain functional connectivity and ventral striatal dopamine D2-type receptors: link to impulsivity in methamphetamine users.

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Stimulant use disorders are associated with deficits in striatal dopamine receptor availability, abnormalities in mesocorticolimbic resting-state functional connectivity (RSFC) and impulsivity. In methamphetamine-dependent research participants, impulsivity is correlated negatively with striatal D2-type receptor availability, and mesocorticolimbic RSFC is stronger than that in controls. The extent to which these features of methamphetamine dependence are

interrelated, however, is unknown. This question was addressed in two studies. In Study 1, 19 methamphetamine-dependent and 26 healthy control subjects underwent [18F]fallypride positron emission tomography to measure ventral striatal dopamine D2-type receptor availability, indexed by binding potential (BPND), and functional magnetic resonance imaging (fMRI) to assess mesocorticolimbic RSFC, using a midbrain seed. In Study 2, an independent sample of 20 methamphetamine-dependent and 18 control subjects completed the Barratt Impulsiveness Scale in addition to fMRI. Study 1 showed a significant group by ventral striatal BPND interaction effect on RSFC, reflecting a negative relationship between ventral striatal BPND and RSFC between the midbrain and striatum, orbitofrontal cortex and insula in methamphetamine-dependent participants, but a positive relationship in the control group. In Study 2, an interaction of the group with RSFC on impulsivity was observed. Methamphetamine-dependent users exhibited a positive relationship of midbrain RSFC to the left ventral striatum with cognitive impulsivity, whereas a negative relationship was observed in healthy controls. The results indicate that ventral striatal D2-type receptor signaling may affect the system-level activity within the mesocorticolimbic system, providing a functional link that may help explain high impulsivity in methamphetamine-dependent individuals.

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Assessing the effects of cocaine dependence and pathological gambling using group-wise sparse representation of natural stimulus FMRI data.

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Assessing functional brain activation patterns in neuropsychiatric disorders such as cocaine dependence (CD) or pathological gambling (PG) under naturalistic stimuli has received rising interest in recent years. In this paper, we propose and apply a novel group-wise sparse representation framework to assess differences in neural responses to naturalistic stimuli across multiple groups of participants (healthy control, cocaine dependence, pathological gambling). Specifically, natural stimulus fMRI (N-fMRI) signals from all three groups of subjects are aggregated into a big data matrix, which is then decomposed into a

common signal basis dictionary and associated weight coefficient matrices via an effective online dictionary learning and sparse coding method. The coefficient matrices associated with each common dictionary atom are statistically assessed for each group separately. With the inter-group comparisons based on the group-wise correspondence established by the common dictionary, our experimental results demonstrated that the group-wise sparse coding and representation strategy can effectively and specifically detect brain networks/regions affected by different pathological conditions of the brain under naturalistic stimuli.

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Emotional, physical and sexual abuse are associated with a heightened limbic response to cocaine cues.

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Drug-reward cues trigger motivational circuitry, a response linked to drug-seeking in animals and in humans. Adverse life events have been reported to increase sensitivity to drug rewards and to bolster drug reward signaling. Therefore, we hypothesized that cocaine-dependent individuals with prior emotional, physical and sexual abuse might have a heightened mesolimbic brain response to cues for drug reward in a new brief-cue probe. Cocaine-dependent human individuals (N = 68) were stabilized in an inpatient setting and then completed an event-related blood-oxygen-level dependent functional magnetic resonance imaging task featuring 500-ms evocative (cocaine, sexual, aversive) and comparator (neutral) cues. Responses to three questions about emotional, physical and sexual abuse from the Addiction Severity Index were used to divide the patients into subgroups (history of Abuse [n = 40] versus No Abuse [n = 28]). When subjects were grouped by the historical presence or absence of emotional, physical or sexual abuse, the Abuse group showed a heightened midbrain, thalamic, caudate, and caudal orbitofrontal cortex response to cocaine cues; a similar result was found in other evocative cues, as well. These findings are the first reported for a 500-ms cocaine-cue probe, and they highlight the ability of very brief evocative cues to activate the brain's motivational circuitry. Although all participants had severe cocaine use disorders, individuals reporting prior abuse had a heightened mesolimbic response to evocative cues. To our knowledge, this is the first study in humans linking a history of abuse to a brain vulnerability (heightened mesolimbic response to drug cues) previously shown to contribute to drug-seeking.

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37. J Neurosci. 2016 Sep 14;36(37):9547-57. doi: 10.1523/JNEUROSCI.1746-16.2016.

Methylphenidate Modulates Functional Network Connectivity to Enhance Attention.

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Recent work has demonstrated that human whole-brain functional connectivity

patterns measured with fMRI contain information about cognitive abilities, including sustained attention. To derive behavioral predictions from connectivity patterns, our group developed a connectome-based predictive modeling (CPM) approach (Finn et al., 2015; Rosenberg et al., 2016). Previously using CPM, we defined a high-attention network, comprising connections positively correlated with performance on a sustained attention task, and a low-attention network, comprising connections negatively correlated with performance. Validating the networks as generalizable biomarkers of attention, models based on network strength at rest predicted attention-deficit/hyperactivity disorder (ADHD) symptoms in an independent group of individuals (Rosenberg et al., 2016). To investigate whether these networks play a causal role in attention, here we examined their strength in healthy adults given methylphenidate (Ritalin), a common ADHD treatment, compared with unmedicated controls. As predicted, individuals given methylphenidate showed patterns of connectivity associated with better sustained attention: higher high-attention and lower low-attention network strength than controls. There was significant overlap between the high-attention network and a network with greater strength in the methylphenidate group, and between the low-attention network and a network with greater strength in the control group. Network strength also predicted behavior on a stop-signal task, such that participants with higher go response rates showed higher high-attention and lower low-attention network strength. These results suggest that methylphenidate acts by modulating functional brain networks related to sustained attention, and that changing whole-brain connectivity patterns may help improve attention.SIGNIFICANCE STATEMENT: Recent work identified a promising neuromarker of sustained attention based on whole-brain functional connectivity networks. To investigate the causal role of these networks in attention, we examined their response to a dose of methylphenidate, a common and effective treatment for

attention-deficit/hyperactivity disorder, in healthy adults. As predicted, individuals on methylphenidate showed connectivity signatures of better sustained attention: higher high-attention and lower low-attention network strength than controls. These results suggest that methylphenidate acts by modulating strength in functional brain networks related to attention, and that changing whole-brain connectivity patterns may improve attention.

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Psychological intervention with working memory training increases basal ganglia volume: A VBM study of inpatient treatment for methamphetamine use.

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BACKGROUND: Protracted methamphetamine (MA) use is associated with decreased control over drug craving and altered brain volume in the frontostriatal network. However, the nature of volumetric changes following a course of psychological intervention for MA use is not yet known.
METHODS: 66 males (41 MA patients, 25 healthy controls, HC) between the ages of 18-50 were recruited, the MA patients from new admissions to an in-patient drug rehabilitation centre and the HC via public advertisement, both in Cape Town, South Africa. 17 MA patients received 4 weeks of treatment as usual (TAU), and 24 MA patients completed TAU plus daily 30-minute cognitive training (CT) using an N-back working memory task. Magnetic resonance imaging (MRI) at baseline and 4-week follow-up was acquired and voxel-based morphometry (VBM) was used for analysis.
RESULTS: TAU was associated with larger bilateral striatum (caudate/putamen) volume, whereas CT was associated with more widespread increases of the bilateral basal ganglia (incorporating the amygdala and hippocampus) and reduced bilateral cerebellum volume coinciding with improvements in impulsivity scores.
CONCLUSIONS: While psychological intervention is associated with larger volume in mesolimbic reward regions, the utilisation of additional working memory training as an adjunct to treatment may further normalize frontostriatal structure and function.

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Executive control network connectivity strength protects against relapse to cocaine use.

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Cocaine addiction is characterized by notoriously high relapse rates following treatment. Recent efforts to address poor treatment outcomes have turned to potential neural markers of relapse risk. Accordingly, the present study examined resting state functional connectivity (rsFC) within and between three large-scale

cortical networks: the default mode network (DMN), salience network (SN) and executive control network (ECN). All three have been implicated in relapse-related phenomena including craving, withdrawal and executive control deficits. Forty-five cocaine-dependent individuals and 22 healthy controls completed 6-min resting fMRI scans, The Wisconsin Card Sorting Task, Continuous Performance Test and Cocaine Craving Questionnaire. Cocaine-dependent individuals completed all measures in the final week of a residential treatment episode. Ten control and 9 abstinent cocaine-dependent individuals returned for 3-6 month follow-up scan visits. A group-level independent component analysis was employed to generate ECN, DMN and SN components. For individuals abstinent up to day 30 post-treatment (n = 21), we found enhanced pre-discharge rsFC between the left ECN and both the right ECN and SN as well as between the right ECN and left ECN. Left ECN rsFC effects remained elevated 3-6 months later among abstinent cocaine-dependent individuals. Relapse was related to fewer years of education and more years smoking but no other demographic, clinical, treatment and neurocognitive characteristics. Findings suggest that interhemispheric ECN and ECN-SN connectivity strength may protect against relapse to cocaine use following treatment. These patterns of enhanced interhemispheric network connectivity may reflect a greater capacity to engage executive control processes when faced with opportunities to use cocaine post-treatment.

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Cocaine dependence and thalamic functional connectivity: a multivariate pattern analysis.

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Cocaine dependence is associated with deficits in cognitive control. Previous

studies demonstrated that chronic cocaine use affects the activity and functional connectivity of the thalamus, a subcortical structure critical for cognitive functioning. However, the thalamus contains nuclei heterogeneous in functions, and it is not known how thalamic subregions contribute to cognitive dysfunctions in cocaine dependence. To address this issue, we used multivariate pattern analysis (MVPA) to examine how functional connectivity of the thalamus distinguishes 100 cocaine-dependent participants (CD) from 100 demographically matched healthy control individuals (HC). We characterized six task-related networks with independent component analysis of fMRI data of a stop signal task and employed MVPA to distinguish CD from HC on the basis of voxel-wise thalamic connectivity to the six independent components. In an unbiased model of distinct training and testing data, the analysis correctly classified 72% of subjects with leave-one-out cross-validation ($p < 0.001$), superior to comparison brain regions with similar voxel counts ($p < 0.004$, two-sample t test). Thalamic voxels that form the basis of classification aggregate in distinct subclusters, suggesting that connectivities of thalamic subnuclei distinguish CD from HC. Further, linear regressions provided suggestive evidence for a correlation of the thalamic connectivities with clinical variables and performance measures on the stop signal task. Together, these findings support thalamic circuit dysfunction in cognitive control as an important neural marker of cocaine dependence.

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Biomarkers for Success: Using Neuroimaging to Predict Relapse and Develop Brain Stimulation Treatments for Cocaine-Dependent Individuals.

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Cocaine dependence is one of the most difficult substance use disorders to treat. While the powerful effects of cocaine use on behavior were documented in the 19th century, it was not until the late 20th century that we realized cocaine use was affecting brain tissue and function. Following a brief introduction (Section 1), this chapter will summarize our current knowledge regarding alterations in neural circuit function typically observed in chronic cocaine users (Section 2) and highlight an emerging body of literature which suggests that pretreatment limbic circuit activity may be a reliable predictor of clinical outcomes among individuals seeking treatment for cocaine (Section 3). Finally, as the field of addiction research strives to translate this neuroimaging data into something clinically meaningful, we will highlight several new brain stimulation approaches which utilize functional brain imaging data to design noninvasive brain stimulation interventions for individuals seeking treatment for substance dependence disorders (Section 4).

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Abnormal fronto-limbic engagement in incarcerated stimulant users during moral processing.

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RATIONALE: Stimulant use is a significant and prevalent problem, particularly in criminal populations. Previous studies found that cocaine and methamphetamine use is related to impairment in identifying emotions and empathy. Stimulant users also have abnormal neural structure and function of the ventromedial prefrontal cortex (vmPFC), amygdala, and anterior (ACC) and posterior cingulate (PCC), regions implicated in moral decision-making. However, no research has studied the neural correlates of stimulant use and explicit moral processing in an incarcerated population.

OBJECTIVES: Here, we examine how stimulant use affects sociomoral processing that might contribute to antisocial behavior. We predicted that vmPFC, amygdala, PCC, and ACC would show abnormal neural response during a moral processing task in incarcerated methamphetamine and cocaine users.

METHODS: Incarcerated adult males (N = 211) were scanned with a mobile MRI system while completing a moral decision-making task. Lifetime drug use was assessed. Neural responses during moral processing were compared between users and non-users. The relationship between duration of use and neural function was also examined.

RESULTS: Incarcerated stimulant users showed less amygdala engagement than non-users during moral processing. Duration of stimulant use was negatively associated with activity in ACC and positively associated with vmPFC response during moral processing.

CONCLUSIONS: These results suggest a dynamic pattern of fronto-limbic moral processing related to stimulant use with deficits in both central motive and cognitive integration elements of biological moral processes theory. This increases our understanding of how drug use relates to moral processing in the brain in an ultra-high-risk population.

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43. Neuropsychopharmacology. 2016 Dec;41(13):3032-3041. doi: 10.1038/npp.2016.114. Epub 2016 Jul 4.

Mobilization of Medial and Lateral Frontal-Striatal Circuits in Cocaine Users and Controls: An Interleaved TMS/BOLD Functional Connectivity Study.

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The integrity of frontal-striatal circuits is an area of great interest in substance dependence literature, particularly as the field begins to develop neural circuit-specific brain stimulation treatments for these individuals. Prior research indicates that frontal-striatal connectivity is disrupted in chronic

cocaine users in a baseline (resting) state. It is unclear, however, if this is also true when these circuits are mobilized by an external source. In this study, we measured the functional and structural integrity of frontal-striatal circuitry involved in limbic arousal and executive control in 36 individuals-18 cocaine-dependent individuals with a history of failed quit attempts and 18 age-matched controls. This was achieved by applying a transcranial magnetic stimulation to the medial prefrontal cortex (Brodmann area 10) and the dorsolateral prefrontal cortex (lateral Brodmann 9) while participants rested in the MRI scanner (TMS/BOLD imaging). Relative to the controls, cocaine users had a lower ventral striatal BOLD response to MPFC stimulation. The dorsal striatal BOLD response to DLPFC stimulation however was not significantly different between the groups. Among controls, DLPFC stimulation led to a reciprocal attenuation of MPFC activity (BA 10), but this pattern did not exist in cocaine users. No relationship was found between regional diffusion metrics and functional activity. Considered together these data suggest that, when engaged, cocaine users can mobilize their executive control system similar to controls, but that the 'set point' for mobilizing their limbic arousal system has been elevated-an interpretation consistent with opponent process theories of addiction.

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44. Neuropsychopharmacology. 2016 Nov;41(12):2872-2881. doi: 10.1038/npp.2016.99. Epub 2016 Jun 17.

The Effects of Pharmacological Opioid Blockade on Neural Measures of Drug Cue-Reactivity in Humans.

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Interactions between dopaminergic and opioidergic systems have been implicated in the reinforcing properties of drugs of abuse. The present study investigated the effects of opioid blockade, via naltrexone, on functional magnetic resonance imaging (fMRI) measures during methamphetamine cue-reactivity to elucidate the role of endogenous opioids in the neural systems underlying drug craving. To investigate this question, non-treatment seeking individuals with methamphetamine use disorder (N=23; 74% male, mean age=34.70 (SD=8.95)) were recruited for a randomized, placebo controlled, within-subject design and underwent a visual methamphetamine cue-reactivity task during two blood-oxygen-level dependent (BOLD) fMRI sessions following 3 days of naltrexone (50 mg) and matched time for placebo. fMRI analyses tested naltrexone-induced differences in BOLD activation and functional connectivity during cue processing. The results showed that naltrexone administration reduced cue-reactivity in sensorimotor regions and related to altered functional connectivity of dorsal striatum, ventral tegmental area, and precuneus with frontal, visual, sensory, and motor-related regions. Naltrexone also weakened the associations between subjective craving and

precuneus functional connectivity with sensorimotor regions and strengthened the associations between subjective craving and dorsal striatum and precuneus connectivity with frontal regions. In conclusion, this study provides the first evidence that opioidergic blockade alters neural responses to drug cues in humans with methamphetamine addiction and suggests that naltrexone may be reducing drug cue salience by decreasing the involvement of sensorimotor regions and by engaging greater frontal regulation over salience attribution.

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Power spectrum scale invariance as a neural marker of cocaine misuse and altered cognitive control.

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BACKGROUND: Magnetic resonance imaging (MRI) has highlighted the effects of chronic cocaine exposure on cerebral structures and functions, and implicated the prefrontal cortices in deficits of cognitive control. Recent investigations suggest power spectrum scale invariance (PSSI) of cerebral blood oxygenation level dependent (BOLD) signals as a neural marker of cerebral activity. We examined here how PSSI is altered in association with cocaine misuse and impaired cognitive control.
METHODS: Eighty-eight healthy (HC) and seventy-five age and gender matched cocaine dependent (CD) adults participated in functional MRI of a stop signal task (SST). BOLD images were preprocessed using standard procedures in SPM, including detrending, band-pass filtering (0.01-0.25 Hz), and correction for head motions. Voxel-wise PSSI measures were estimated by a linear fit of the power spectrum with a log-log scale. In group analyses, we examined differences in PSSI between HC and CD, and its association with clinical and behavioral variables using a multiple regression. A critical component of cognitive control is post-signal behavioral adjustment, which is compromised in cocaine dependence. Therefore, we examined the PSSI changes in association with post-signal slowing (PSS) in the SST.
RESULTS: Compared to HC, CD showed decreased PSS and PSSI in multiple frontoparietal regions. PSSI was positively correlated with PSS in HC in multiple

regions, including the left inferior frontal gyrus (IFG) and right supramarginal gyrus (SMG), which showed reduced PSSI in CD.
CONCLUSIONS: These findings suggest disrupted connectivity dynamics in the fronto-parietal areas in association with post-signal behavioral adjustment in cocaine addicts. These new findings support PSSI as a neural marker of impaired cognitive control in cocaine addiction.

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46. Neurotoxicol Teratol. 2016 Jul-Aug;56:16-25. doi: 10.1016/j.ntt.2016.05.009. Epub 2016 May 27.

Thalamocortical functional connectivity and behavioral disruptions in neonates with prenatal cocaine exposure.

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Prenatal cocaine exposure (PCE) affects neurobehavioral development, however, disentangling direct drug-related mechanisms from contextual effects (e.g., socioeconomic status) has proven challenging in humans. The effects of environmental confounds are minimal immediately after birth thus we aimed to delineate neurobehavioral correlates of PCE in a large cohort of neonates (2-6weeks of age, N=152) with and without drug exposure using resting state functional magnetic resonance imaging (rsfMRI) and developmental assessments at 3months with the Bayley Scales of Infant & Toddler Development, 3rd edition. The cohort included healthy controls and neonates with similar poly-drug exposure±cocaine. We focused on the thalamus given its critical importance in early brain development and its unique positioning in the dopamine system. Our results revealed PCE-related hyper-connectivity between the thalamus and frontal regions and a drug-common hypo-connective signature between the thalamus and motor-related regions. PCE-specific neonatal thalamo-frontal connectivity was inversely related to cognitive and fine motor scores and thalamo-motor connectivity showed a positive relationship with composite (gross plus fine) motor scores. Finally, cocaine by selective-serotonin-reuptake-inhibitor (SSRI) interactions were detected, suggesting the combined use of these drugs during pregnancy could have additional consequences on fetal development. Overall, our

findings provide the first delineation of PCE-related disruptions of thalamocortical functional connectivity, neurobehavioral correlations, and drug-drug interactions during infancy.

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Amphetamine alters neural response to sucrose in healthy women.

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Amphetamine, likely via action on the brain's dopaminergic systems, induces anorectic eating behavior and blunts dopaminergic midbrain activation to rewards. Past work has hypothesized that this blunted reward responsivity is a result of increasing tonic over phasic DA activity. We sought to extend past findings to sweet taste during fMRI following single-blind administration of dextroamphetamine and placebo in 11 healthy women. We hypothesized that neural response in both limbic and cognitive sweet taste circuits would mirror past work with monetary rewards by effectively blunting sweet taste reward, and 'equalizing' it's rewarding taste with receipt of water. Behavioral results showed that amphetamine reduced self-reported hunger (supporting the existence of amphetamine anorexia) and increased self-report euphoria. In addition, region of Interest analysis revealed significant treatment by taste interactions in the middle insula and dorsal anterior cingulate confirming the 'equalizing' hypothesis in the cingulate, but unlike monetary reinforcers, the insula actually evinced enhanced separation between tastes on the amphetamine day. These results suggest a divergence from prior research using monetary reinforcers when extended

to primary reinforcers, and may hint that altering dopaminergic signaling in the insula and anterior cingulate may be a target for pharmacological manipulation of appetite, and the treatment of obesity.

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Candidate gene networks and blood biomarkers of methamphetamine-associated psychosis: an integrative RNA-sequencing report.

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The clinical presentation, course and treatment of methamphetamine (METH)-associated psychosis (MAP) are similar to that observed in schizophrenia (SCZ) and subsequently MAP has been hypothesized as a pharmacological and environmental model of SCZ. However, several challenges currently exist in diagnosing MAP accurately at the molecular and neurocognitive level before the MAP model can contribute to the discovery of SCZ biomarkers. We directly assessed subcortical brain structural volumes and clinical parameters of MAP within the framework of an integrative genome-wide RNA-Seq blood transcriptome analysis of subjects diagnosed with MAP (N=10), METH dependency without psychosis (MA; N=10) and healthy controls (N=10). First, we identified discrete groups of co-expressed genes (that is, modules) and tested them for functional annotation and phenotypic relationships to brain structure volumes, life events and psychometric measurements. We discovered one MAP-associated module involved in ubiquitin-mediated proteolysis downregulation, enriched with 61 genes previously found implicated in psychosis and SCZ across independent blood and post-mortem brain studies using convergent functional genomic (CFG) evidence. This module demonstrated significant relationships with brain structure volumes including the anterior corpus callosum (CC) and the nucleus accumbens. Furthermore, a second MAP and psychoticism-associated module involved in circadian clock upregulation was also enriched with 39 CFG genes, further associated with the CC. Subsequently, a machine-learning analysis of differentially expressed genes identified single blood-based biomarkers able to differentiate controls from methamphetamine dependents with 87% accuracy and MAP from MA subjects with 95% accuracy. CFG evidence validated a significant proportion of these putative MAP

biomarkers in independent studies including CLN3, FBP1, TBC1D2 and ZNF821 (RNA degradation), ELK3 and SINA3 (circadian clock) and PIGF and UHMK1 (ubiquitin-mediated proteolysis). Finally, focusing analysis on brain structure volumes revealed significantly lower bilateral hippocampal volumes in MAP subjects. Overall, these results suggest similar molecular and neurocognitive mechanisms underlying the pathophysiology of psychosis and SCZ regardless of substance abuse and provide preliminary evidence supporting the MAP paradigm as an exemplar for SCZ biomarker discovery.

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High estrogen and chronic haloperidol lead to greater amphetamine-induced BOLD activation in awake, amphetamine-sensitized female rats.

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The ovarian hormone estrogen has been implicated in schizophrenia symptomatology. Low levels of estrogen are associated with an increase in symptom severity, while exogenous estrogen increases the efficacy of antipsychotic medication, pointing at a possible interaction between estrogen and the dopaminergic system. The aim of this study is to further investigate this interaction in an animal model of some aspects of schizophrenia using awake functional magnetic resonance imaging. Animals receiving 17β-estradiol and haloperidol were scanned and BOLD activity was assessed in response to amphetamine. High 17β-estradiol replacement and chronic haloperidol treatment showed increased BOLD activity in regions of interest and neural networks associated with schizophrenia (hippocampal formations, habenula, amygdala, hypothalamus etc.), compared with low, or no 17β-estradiol. These data show that chronic haloperidol treatment has a sensitizing effect, possibly on the dopaminergic system, and this effect is dependent on hormonal status, with high 17β-estradiol showing the greatest BOLD increase. Furthermore, these experiments further support the use of imaging techniques in studying schizophrenia, as modeled in the rat, but can be extended to addiction and other disorders.

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Abnormal response to methylphenidate across multiple fMRI procedures in cocaine use disorder: feasibility study.

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RATIONALE: The indirect dopamine agonist methylphenidate remediates cognitive deficits in psychopathology, but the individual characteristics that determine its effects on the brain are not known.
OBJECTIVES: We aimed to determine whether targeted dopaminergically modulated traits and individual differences could predict neural response to methylphenidate across multiple functional magnetic resonance imaging (fMRI) procedures.
METHODS: We combined neural measures from three separate procedures (two inhibitory control tasks differing in their degree of emotional salience and resting-state functional connectivity) during methylphenidate (20 mg oral, versus randomized and counterbalanced placebo) and correlated these aggregated responses with cocaine use disorder diagnosis (22 cocaine abusers, 21 controls), symptoms of attention deficit hyperactivity disorder, and working memory capacity.
RESULTS: Cocaine abusers, relative to controls, had a lower response in the dorsolateral prefrontal cortex to methylphenidate across all three procedures, driven by responses to the two inhibitory control tasks; reduced methylphenidate fMRI response in this region further correlated with more frequent cocaine use.
CONCLUSIONS: Cocaine abuse (and its frequency), associated with lower tonic dopamine levels, correlated with a reduction in activation to methylphenidate (versus placebo). These initial results provide feasibility to the idea that multimodal fMRI tasks can be meaningfully aggregated, and that these aggregated procedures show a common disruption in addiction in a highly anticipated region

relevant to cognitive control. Results also suggest that drug use frequency may represent an important modulatory variable in interpreting the efficacy of pharmacologically enhanced cognitive interventions in addiction.

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51. Neurosci Biobehav Rev. 2016 Jul;66:15-32. doi: 10.1016/j.neubiorev.2016.03.030. Epub 2016 Apr 23.

A place for the hippocampus in the cocaine addiction circuit: Potential roles for adult hippocampal neurogenesis.

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Cocaine addiction is a chronic brain disease in which the drug seeking habits and profound cognitive, emotional and motivational alterations emerge from drug-induced neuroadaptations on a vulnerable brain. Therefore, a 'cocaine addiction brain circuit' has been described to explain this disorder. Studies in both cocaine patients and rodents reveal the hippocampus as a main node in the cocaine addiction circuit. The contribution of the hippocampus to cocaine craving and the associated memories is essential to understand the chronic relapsing nature of addiction, which is the main obstacle for the recovery. Interestingly, the hippocampus holds a particular form of plasticity that is rare in the adult brain: the ability to generate new functional neurons. There is an active scientific debate on the contributions of these new neurons to the addicted brain. This review focuses on the potential role(s) of adult hippocampal neurogenesis (AHN) in cocaine addiction. Although the current evidence primarily originates from animal research, these preclinical studies support AHN as a relevant component for the hippocampal effects of cocaine.

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52. Brain Res. 2016 Jul 1;1642:497-504. doi: 10.1016/j.brainres.2016.04.040. Epub 2016 Apr 18.

Cocaine and methamphetamine induce opposing changes in BOLD signal response in rats.

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BACKGROUND: Neuroimaging studies in psychostimulant addicts have reported functional neural activity changes in brain regions involved in relapse. However, the difference between the effects of the psychostimulants methamphetamine and cocaine on neuronal activity in a similar setting not been clarified. Since studies in humans are limited by the inability to study the initial impact of psychostimulant drugs, we addressed this issue in a rat model.
OBJECTIVE: Here, we report methamphetamine and cocaine-induced blood-oxygen-level dependent (BOLD) signal change using functional magnetic resonance imaging (fMRI) in rats receiving drug for the first time during the imaging session.
METHODS: Twenty-three male Long Evans rats underwent fMRI imaging and received an intravenous infusion of methamphetamine, cocaine, or saline. Anatomical and pharmacological fMRI (pfMRI) were performed on a 7T BioSpec dedicated research MR scanner under isoflurane gas (1.5-2%). After collecting baseline data for 10min, rats received drug over the next 10min for a total 40min scan time. Data were

then preprocessed and statistically analyzed in anatomically defined regions of interest (ROIs) that have been implicated in persistent drug seeking and relapse.
RESULTS: Methamphetamine during the imaging session resulted in a sustained negative BOLD signal change in key regions of the relapse circuit, except for the prefrontal cortex. In contrast, cocaine evoked a positive or unchanged BOLD signal in these same regions. In all of the investigated ROIs, there were no changes in BOLD signal following saline.
CONCLUSION: Acute methamphetamine and cocaine have distinct patterns of functional activity as measured by pfMRI.

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53. Am J Psychiatry. 2016 Oct 1;173(10):1033-1042. Epub 2016 Apr 15.

Hyperresponsiveness of the Neural Fear Network During Fear Conditioning and Extinction Learning in Male Cocaine Users.

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OBJECTIVE: The authors investigated whether cocaine use disorder is associated with abnormalities in the neural underpinnings of aversive conditioning and extinction learning, as these processes may play an important role in the development and persistence of drug abuse.

METHOD: Forty male regular cocaine users and 51 male control subjects underwent a fear conditioning and extinction protocol during functional MRI. Skin conductance response was measured throughout the experiment as an index of conditioned responses.

RESULTS: Cocaine users showed hyperresponsiveness of the amygdala and insula during fear conditioning, as well as hyporesponsiveness of the dorsomedial prefrontal cortex during extinction learning. In cocaine users, but not in control subjects, skin conductance responses were positively correlated with responsiveness of the insula, amygdala, and dorsomedial prefrontal cortex during fear conditioning but negatively correlated with responsiveness of the ventromedial prefrontal cortex during extinction learning.

CONCLUSIONS: Increased sensitivity to aversive conditioned cues in cocaine users might be a risk factor for stress-relief craving in cocaine use disorder. These results support the postulated role of altered aversive conditioning in cocaine use disorder and may be an important step in understanding the role of aversive learning in the pathology of cocaine use disorder.

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54. J Neurosci. 2016 Apr 6;36(14):4038-49. doi: 10.1523/JNEUROSCI.3206-15.2016.

Individual Differences in Cognitive Control Circuit Anatomy Link Sensation Seeking, Impulsivity, and Substance Use.

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Individuals vary widely in their tendency to seek stimulation and act impulsively, early developing traits with genetic origins. Failures to regulate these behaviors increase risk for maladaptive outcomes including substance abuse. Here, we explored the neuroanatomical correlates of sensation seeking and impulsivity in healthy young adults. Our analyses revealed links between sensation seeking and reduced cortical thickness that were preferentially localized to regions implicated in cognitive control, including anterior cingulate and middle frontal gyrus (n = 1015). These associations generalized to self-reported motor impulsivity, replicated in an independent group (n = 219), and correlated with heightened alcohol, tobacco, and caffeine use. Critically, the relations between sensation seeking and brain structure were evident in participants without a history of alcohol or tobacco use, suggesting that observed associations with anatomy are not solely a consequence of substance use. These results demonstrate that individual differences in the tendency to seek stimulation, act on impulse, and engage in substance use are correlated with the anatomical structure of cognitive control circuitry. Our findings suggest that, in healthy populations, covariation across these complex multidimensional behaviors may in part originate from a common underlying biology.SIGNIFICANCE STATEMENT: Impaired cognitive control may result in a tendency to seek

stimulation impulsively and an increased risk for maladaptive outcomes, including substance abuse. Here, we examined the structural correlates of sensation seeking and impulsivity in a large cohort of healthy young adults. Our analyses revealed links between sensation seeking and reduced cortical thickness that were preferentially localized to regions implicated in cognitive control, including anterior cingulate and middle frontal gyrus. The observed associations generalized to motor impulsivity, replicated in an independent group, and predicted heightened alcohol, tobacco, and caffeine use. These data indicate that normal variability in cognitive control system anatomy predicts sensation seeking and motor impulsivity in the healthy populations, potentially increasing risk for substance use disorders.

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55. Addict Biol. 2017 Sep;22(5):1378-1390. doi: 10.1111/adb.12396. Epub 2016 Apr 2.

Distress tolerance among substance users is associated with functional connectivity between prefrontal regions during a distress tolerance task.

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Distress tolerance (DT), defined as the ability to persist in goal directed behavior while experiencing affective distress, is implicated in the development and maintenance of substance use disorders. While theory and evidence indicate that cortico-limbic neural dysfunction may account for deficits in goal directed behavior while experiencing distress, the neurobiological mechanisms of DT have yet to be examined. We modified a computerized DT task for use in functional magnetic resonance imaging (fMRI), the Paced Auditory Serial Addition Task (PASAT-M), and examined the neural correlates and functional connectivity of DT among a cohort of substance users (n = 21; regular cocaine and nicotine users) and healthy controls (n = 25). In response to distress during the PASAT-M, we found greater activation in a priori cortico-limbic network ROIs, namely the right insula, anterior cingulate cortex (ACC), bilateral medial frontal gyrus (MFG), right inferior frontal gyrus (IFG) and right ventromedial prefrontal cortex (vmPFC) significantly predicted higher DT among substance users, but not healthy controls. In addition, greater task-specific functional connectivity during distress between the right MFG and bilateral vmPFC/sgACC was associated with higher DT among substance users, but not healthy controls. The observed positive relationship between DT and neural activation in cortico-limbic structures, as well as functional connectivity between the rMFG and vmPFC/sgACC, is in line with theory and research suggesting the importance of these structures for persisting in goal directed behavior while experiencing affective distress.

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56. J Child Adolesc Psychopharmacol. 2016 Aug;26(6):527-36. doi:

10.1089/cap.2015.0243. Epub 2016 Mar 30.

Neural Correlates of Symptom Improvement Following Stimulant Treatment in Adults with Attention-Deficit/Hyperactivity Disorder.

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OBJECTIVE: The purposes of this study were to examine the impact of 3 weeks of amphetamine administration on intrinsic connectome-wide connectivity patterns in adults with attention-deficit/hyperactivity disorder (ADHD) and explore the association between stimulant-induced symptom improvement and functional

connectivity alteration.

METHODS: Participants included 19 adults (age 20-55 years) diagnosed with ADHD using the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) criteria per the Adult Clinician Diagnostic Scale taking part in amphetamine trials. For each patient, two 6-minute resting-state functional magnetic resonance imaging (R-fMRI) scans were acquired at baseline and after treatment. A fully data-driven multivariate analytic approach (i.e., multivariate distance matrix regression [MDMR]) was applied to R-fMRI data to characterize the distributed pharmacological effects in the entire functional connectome. Clinical efficacy was assessed using ADHD rating scale with adult prompts and the Adult Self-Report Scale v1.1 Symptom Checklist. We linked stimulant-induced functional connectivity changes to symptom amelioration using Spearman's correlation.

RESULTS: Three weeks of administration of a stimulant significantly reduced ADHD symptoms. MDMR-based analyses on R-fMRI data highlighted the left dorsolateral prefrontal cortex (DLPFC, a key cognitive control region) and the medial prefrontal cortex (MPFC, the anterior core of default network) whose distributed patterns of functional connectivity across the entire brain were altered by psychostimulants. Follow-up intrinsic functional connectivity revealed that stimulants specifically decreased the positive functional connectivity between DLPFC-insula, DLPFC-anterior cingulate cortex, and MPFC-insula. Importantly, these functional connectivity changes are associated with symptom improvement.

CONCLUSION: These results suggested that ADHD is associated with increased functional integration or decreased functional segregation between core regions of cognitive control, default, and salience networks. The apparent normalization of intrinsic functional interaction in these circuits (i.e., increased functional segregation) may underlie the clinical benefits produced by 3 weeks of

amphetamine treatment.

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57. J Child Adolesc Psychopharmacol. 2016 Aug;26(6):555-61. doi:
10.1089/cap.2015.0221. Epub 2016 Mar 30.

Intrinsic Brain Connectivity Following Long-Term Treatment with Methylphenidate in Children with Attention-Deficit/Hyperactivity Disorder.

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INTRODUCTION: Although widely used for the treatment of attention-deficit/hyperactivity disorder (ADHD) across the life span, the effects of methylphenidate (MPH) on the brain are not completely understood. Functional

neuroimaging techniques may help increase knowledge about the mechanisms of MPH action.

OBJECTIVE: To evaluate changes in functional connectivity patterns of the default mode network (DMN) in children with ADHD following long-term treatment with MPH.

METHODS: Twenty-three right-handed treatment-naïve boys with ADHD underwent a protocol of intrinsic functional connectivity before and after 6 months of treatment with MPH. Functional connectivity was analyzed using a region of interest (ROI) approach and independent component analysis (ICA).

RESULTS: ROI analyses showed no significant changes in connectivity between regions of the DMN following treatment, with a relatively small increase in the anterior-posterior connectivity of the network. ICA revealed a significant increase in connectivity between the left putamen and the DMN ($p < 0.001$, corrected). There was a correlation between the reduction of symptoms and the increased connectivity between the putamen and the DMN after treatment ($rho = -0.65$, $p = 0.017$).

CONCLUSION: Dysfunctions in cortical-subcortical circuits have often been associated with the pathophysiology of ADHD. Our findings suggest that effective treatment with MPH in children with ADHD may affect brain functioning by increasing connectivity between the DMN and subcortical nuclei.

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58. Am J Addict. 2016 Apr;25(3):210-4. doi: 10.1111/ajad.12362. Epub 2016 Mar 22.

Anterior cingulum white matter is altered in tobacco smokers.

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BACKGROUND AND OBJECTIVES: The anterior cingulate cortex (ACC) is hypothesized to be involved in decision making and emotion regulation. Previous observations of drug dependent individuals indicate that substance dependence may be associated with cingulum white matter abnormalities. The present study evaluated cingulum white matter in cigarette smokers.

METHODS: Diffusion tensor imaging (DTI) in adult tobacco smokers and healthy non-smoker controls (total N = 70) was performed in a 3T Siemens Trio MRI scanner.

RESULTS: Analyses of DTI tractography of the cingulum in tobacco-smoking individuals and controls indicated that tobacco abusers have significantly reduced fractional anisotropy (FA) in the right cingulum. In addition, FA in the left cingulum white matter was negatively associated with the number of cigarettes smoked per day and the Fagerstrom test for nicotine dependence, a self-report measure of tobacco dependence severity.

CONCLUSIONS: The white matter of the cingulum is altered in a non-symmetrical way in tobacco smokers. An inverse relationship between FA and reported number of cigarettes per day was observed. Previous studies have also noted altered neural connectivity in cigarette smokers using similar methods. Similar white matter differences in the cingulum have been observed in methamphetamine dependent individuals and patients with dementia, which suggests that the cingulum may be altered by mechanisms not specific to tobacco exposure.
SCIENTIFIC SIGNIFICANCE: By better understanding the effects of tobacco abuse on the brain, we hope to gain insight into how drug dependence influences the neurological foundations of behavior.

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59. Eur Neuropsychopharmacol. 2016 Apr;26(4):674-83. doi: 10.1016/j.euroneuro.2016.02.007. Epub 2016 Feb 10.

Stimulant treatment history predicts frontal-striatal structural connectivity in adolescents with attention-deficit/hyperactivity disorder.

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Diffusion tensor imaging (DTI) has revealed white matter abnormalities in individuals with attention-deficit/hyperactivity disorder (ADHD). Stimulant treatment may affect such abnormalities. The current study investigated associations between long-term stimulant treatment and white matter integrity within the frontal-striatal and mesolimbic pathways, in a large sample of children, adolescents and young adults with ADHD. Participants with ADHD (N=172; mean age 17, range 9-26) underwent diffusion-weighted MRI scanning, along with an age- and gendermatched group of 96 control participants. Five study-specific white matter tract masks (orbitofrontal-striatal, orbitofrontal-amygdalar, amygdalar-striatal, dorsolateral-prefrontal-striatal and medialprefrontal-striatal) were created. First we analyzed case-control differences in fractional anisotropy (FA) and mean diffusivity (MD) within each

tract. Second, FA and MD in each tract was predicted from cumulative stimulant intake within the ADHD group. After correction for multiple testing, participants with ADHD showed reduced FA in the orbitofrontal-striatal pathway (p=0.010, effect size=0.269). Within the ADHD group, higher cumulative stimulant intake was associated with lower MD in the same pathway (p=0.011, effect size=-0.164), but not with FA. The association between stimulant treatment and orbitofrontal-striatal MD was of modest effect size. It fell short of significance after adding ADHD severity or ADHD type to the model (p=0.036 and p=0.094, respectively), while the effect size changed little. Our findings are compatible with stimulant treatment enhancing orbitofrontal-striatal white matter connectivity, and emphasize the importance of the orbitofrontal cortex and its connections in ADHD. Longitudinal studies including a drug-naïve baseline assessment are needed to distinguish between-subject variability in ADHD severity from treatment effects.

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60. Psychiatry Res. 2016 Feb 28;248:110-8. doi: 10.1016/j.pscychresns.2016.01.001. Epub 2016 Jan 8.

Converging effects of cocaine addiction and sex on neural responses to monetary rewards.

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There is some evidence that cocaine addiction manifests as more severe in women than men. Here, we examined whether these sex-specific differences in the clinical setting parallel differential neurobehavioral sensitivity to rewards in the laboratory setting. Twenty-eight (14 females/14 males) cocaine-dependent and 25 (11 females/14 males) healthy individuals completed a monetary reward task during fMRI. Results showed that the effects of cocaine dependence and sex overlapped in regions traditionally considered part of the mesocorticolimbic brain circuits including the hippocampus and posterior cingulate cortex (PCC), as well as those outside of this circuit (e.g., the middle temporal gyrus). The nature of this 'overlap' was such that both illness and female sex were associated with lower activations in these regions in response to money. Diagnosis-by-sex interactions instead emerged in the frontal cortex, such that cocaine-dependent females exhibited lower precentral gyrus and greater inferior

frontal gyrus (IFG) activations relative to cocaine-dependent males and healthy females. Within these regions modulated both by diagnosis and sex, lower activation in the hippocampus and PCC, and higher IFG activations, correlated with increased subjective craving during the task. Results suggest sex-specific differences in addiction extend to monetary rewards and may contribute to core symptoms linked to relapse.

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61. Addict Biol. 2017 May;22(3):844-856. doi: 10.1111/adb.12356. Epub 2016 Jan 19.

Cocaine addiction is associated with abnormal prefrontal function, increased striatal connectivity and sensitivity to monetary incentives, and decreased connectivity outside the human reward circuit.

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Cocaine addiction has been associated with increased sensitivity of the human reward circuit to drug-related stimuli. However, the capacity of non-drug incentives to engage this network is poorly understood. Here, we characterized the functional sensitivity to monetary incentives and the structural integrity of the human reward circuit in abstinent cocaine-dependent (CD) patients and their matched controls. We assessed the BOLD response to monetary gains and losses in 30 CD patients and 30 healthy controls performing a lottery task in a magnetic

resonance imaging scanner. We measured brain gray matter volume (GMV) using voxel-based morphometry and white matter microstructure using voxel-based fractional anisotropy (FA). Functional data showed that, after monetary incentives, CD patients exhibited higher activation in the ventral striatum than controls. Furthermore, we observed an inverted BOLD response pattern in the prefrontal cortex, with activity being highest after unexpected high gains and lowest after losses. Patients showed increased GMV in the caudate and the orbitofrontal cortex, increased white matter FA in the orbito-striatal pathway but decreased FA in antero-posterior association bundles. Abnormal activation in the prefrontal cortex correlated with GMV and FA increases in the orbitofrontal cortex. While functional abnormalities in the ventral striatum were inversely correlated with abstinence duration, structural alterations were not. In conclusion, results suggest abnormal incentive processing in CD patients with high salience for rewards and punishments in subcortical structures but diminished prefrontal control after adverse outcomes. They further suggest that hypertrophy and hyper-connectivity within the reward circuit, to the expense of connectivity outside this network, characterize cocaine addiction.

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62. Addict Biol. 2017 May;22(3):857-863. doi: 10.1111/adb.12361. Epub 2016 Jan 11.

Posterior hippocampal regional cerebral blood flow predicts abstinence: a

replication study.

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The posterior hippocampus (pHp) plays a major role in the processing and storage of drug-related cues and is linked to striatal-limbic brain circuits involved with craving and drug salience. We have recently reported that increased basal regional cerebral blood flow (rCBF) in a pHp loci, as measured by pseudo-continuous arterial spin labeling magnetic resonance imaging, predicted days to cocaine relapse following residential treatment. In this secondary analysis, we explored whether rCBF in this same pHp region would successfully predict 30-day point prevalence abstinence 60 days following residential treatment in an independent group of previously studied participants with cocaine dependence. rCBF was assessed with single photon emission computerized tomography during a saline infusion in 21 cocaine dependence and 22 healthy control participants. pHp rCBF was significantly higher in those endorsing substance use ($n = 10$) relative to both abstinent ($n = 11$) ($p < 0.001$) and control ($p < 0.05$) participants. There were no significant differences in measured demographic or clinical variables between the actively using and non-using participants. This replicative finding suggests that heightened pHp activation is a significant

predictor of substance use in cocaine-dependent individuals, possibly reflecting a neural susceptibility to continued drug cues.

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63. Brain Imaging Behav. 2016 Dec;10(4):1254-1263.

Cannabis and cocaine decrease cognitive impulse control and functional corticostriatal connectivity in drug users with low activity DBH genotypes.

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The dopamine β-hydroxylase (DβH) enzyme transforms dopamine into noradrenaline. We hypothesized that individuals with low activity DBH genotypes (rs1611115 CT/TT) are more sensitive to the influence of cannabis and cocaine on cognitive impulse control and functional connectivity in the limbic 'reward' circuit because they experience a drug induced hyperdopaminergic state compared to individuals with high activity DBH genotypes (rs1611115 CC). Regular drug users (N = 122) received acute doses of cannabis (450 µg/kg THC), cocaine HCl 300 mg and placebo. Cognitive impulse control was assessed by means of the Matching Familiar Figures Test (MFFT). Resting state fMRI was measured in a subset of participants to determine functional connectivity between the nucleus accumbens (NAc) and (sub)cortical areas. The influence of cannabis and cocaine on impulsivity and functional connectivity significantly interacted with DBH genotype. Both drugs increased cognitive impulsivity in participants with CT/TT genotypes but not in CC participants. Both drugs also reduced functional connectivity between the NAc and the limbic lobe, prefrontal cortex, striatum and thalamus and primarily in individuals with CT/TT genotypes. Correlational analysis indicated a significant negative association between cognitive impulsivity and functional connectivity in subcortical areas of the brain. It is concluded that interference of cannabis and cocaine with cognitive impulse

control and functional corticostriatal connectivity depends on DBH genotype. The present data provide a neural substrate and behavioral mechanism by which drug users can progress to drug seeking and may also offer a rationale for targeted pharmacotherapy in chronic drug users with high risk DBH genotypes.

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64. Addict Biol. 2017 Mar;22(2):479-489. doi: 10.1111/adb.12329. Epub 2015 Nov 27.

Reduced activity in functional networks during reward processing is modulated by abstinence in cocaine addicts.

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Cocaine addiction is characterized by alterations in motivational and cognitive processes. Recent studies have shown that some alterations present in cocaine users may be related to the activity of large functional networks. The aim of this study was to investigate how these functional networks are modulated by non-drug rewarding stimuli in cocaine-dependent individuals. Twenty abstinent cocaine-dependent and 21 healthy matched male controls viewed erotic and neutral pictures while undergoing a functional magnetic resonance imaging scan. Group independent component analysis was then performed in order to investigate how functional networks were modulated by reward in cocaine addicts. The results showed that cocaine addicts, compared with healthy controls, displayed diminished modulation of the left frontoparietal network in response to erotic pictures, specifically when they were unpredicted. Additionally, a positive correlation between the length of cocaine abstinence and the modulation of the left frontoparietal network by unpredicted erotic images was found. In agreement with current addiction models, our results suggest that cocaine addiction contributes to reduce sensitivity to rewarding stimuli and that abstinence may mitigate this effect.

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Longitudinal changes of amygdala and default mode activation in adolescents prenatally exposed to cocaine.

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Prenatal cocaine exposure (PCE) is associated with long-term and negative effect on arousal regulation. Recent neuroimaging studies have examined brain mechanisms related to arousal dysregulation with cross-sectional experimental designs; but longitudinal changes in the brain, reflecting group differences in

neurodevelopment, have never been directly examined. To directly assess the interaction of PCE and neurodevelopment, the present study used a longitudinal design to analyze functional magnetic resonance imaging (fMRI) data collected from 33 adolescents (21 with PCE and 12 non-exposed controls) while they performed the same working memory task with emotional distracters at two points in time. The mean age of participants was 14.3 years at time_1 and 16.7 years at time_2. With confounding factors statistically controlled, the fMRI data revealed significant exposure-by-time interaction in the activations of the amygdala and default mode network (DMN). For the control adolescents, brain activations associated with emotional arousal (amygdala) and cognitive effort (DMN) were both reduced at time_2 as compared to that at time_1. However, these activation reductions were not observed in the PCE group, indicating persistently high levels of emotional arousal and cognitive effort. In addition, correlations between longitudinal changes in the brain and in behavior have shown that adolescents with persistently high emotional arousal were more likely in need of high cognitive effort; and their cognitive performance was more likely to be affected by distractive challenges. The present results complement and extend previous findings from cross-sectional studies with further evidence supporting the view of PCE associated long-term teratogenic effects on arousal regulation.

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A comprehensive study of sensorimotor cortex excitability in chronic cocaine users: Integrating TMS and functional MRI data.

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BACKGROUND: Disruptions in motor control are often overlooked features of chronic cocaine users. During a simple sensorimotor integration task, for example, cocaine users activate a larger area of cortex than controls but have lower functional connectivity between the cortex and dorsal striatum, which is further correlated with poor performance. The purpose of this study was to determine whether abnormal cortical excitability in cocaine users was related to disrupted inhibitory or excitatory mechanisms, as measured by transcranial magnetic stimulation (TMS).
METHODS: A battery of TMS measures were acquired from 87 individuals (50 cocaine

dependent, 37 controls). Functional MRI data were acquired from a subset of 28 individuals who performed a block-design finger tapping task.
RESULTS: TMS measures revealed that cocaine users had significantly higher resting motor thresholds and higher intracortical cortical facilitation (ICF) than controls. There was no between-group difference in either measure of cortical inhibition. Task-evoked BOLD signal in the motor cortex was significantly correlated with ICF in the cocaine users. There was no significant difference in brain-skull distance between groups.
CONCLUSION: These data demonstrated that cocaine users have disrupted cortical facilitation (as measured with TMS), which is related to elevated BOLD signal. Cortical inhibition, however, is largely intact. Given the relationship between ICF and glutamatergic agents, this may be a potentially fruitful and treatable target in addiction. Finally, among controls the distance from the scalp to the cortex was correlated with the motor threshold which may be a useful parameter to integrate into therapeutic TMS protocols in the future.

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Abnormal frontostriatal activity in recently abstinent cocaine users during

implicit moral processing.

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Investigations into the neurobiology of moral cognition are often done by examining clinical populations characterized by diminished moral emotions and a proclivity toward immoral behavior. Psychopathy is the most common disorder studied for this purpose. Although cocaine abuse is highly co-morbid with psychopathy and cocaine-dependent individuals exhibit many of the same abnormalities in socio-affective processing as psychopaths, this population has received relatively little attention in moral psychology. To address this issue, the authors used functional magnetic resonance imaging (fMRI) to record hemodynamic activity in 306 incarcerated male adults, stratified into regular cocaine users (n = 87) and a matched sample of non-cocaine users (n = 87), while viewing pictures that did or did not depict immoral actions and determining whether each depicted scenario occurred indoors or outdoors. Consistent with

expectations, cocaine users showed abnormal neural activity in several frontostriatial regions during implicit moral picture processing compared to their non-cocaine using peers. This included reduced moral/non-moral picture discrimination in the vACC, vmPFC, lOFC, and left vSTR. Additionally, psychopathy was negatively correlated with activity in an overlapping region of the ACC and right lateralized vSTR. These results suggest that regular cocaine abuse may be associated with affective deficits which can impact relatively high-level processes like moral cognition.

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Effect of cocaine dependence on brain connections: clinical implications.

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Cocaine dependence (CD) is associated with several cognitive deficits. Accumulating evidence, based on human and animal studies, has led to models for interpreting the neural basis of cognitive functions as interactions between functionally related brain regions. In this review, we focus on magnetic resonance imaging (MRI) studies using brain connectivity techniques as related to CD. The majority of these brain connectivity studies indicated that cocaine use is associated with altered brain connectivity between different structures, including cortical-striatal regions and default mode network. In cocaine users some of the altered brain connectivity measures are associated with behavioral performance, history of drug use, and treatment outcome. The implications of these brain connectivity findings to the treatment of CD and the pros and cons of the major brain connectivity techniques are discussed. Finally potential future directions in cocaine use disorder research using brain connectivity techniques are briefly described.

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69. Transl Psychiatry. 2015 Oct 27;5:e667. doi: 10.1038/tp.2015.158.

Transcriptomic and genetic studies identify NFAT5 as a candidate gene for cocaine dependence.

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Cocaine reward and reinforcing effects are mediated mainly by dopaminergic neurotransmission. In this study, we aimed at evaluating gene expression changes induced by acute cocaine exposure on SH-SY5Y-differentiated cells, which have been widely used as a dopaminergic neuronal model. Expression changes and a concomitant increase in neuronal activity were observed after a 5 µM cocaine exposure, whereas no changes in gene expression or in neuronal activity took place at 1 µM cocaine. Changes in gene expression were identified in a total of 756 genes, mainly related to regulation of transcription and gene expression, cell cycle, adhesion and cell projection, as well as mitogen-activeated protein kinase (MAPK), CREB, neurotrophin and neuregulin signaling pathways. Some genes displaying altered expression were subsequently targeted with predicted functional single-nucleotide polymorphisms (SNPs) in a case-control association study in a sample of 806 cocaine-dependent patients and 817 controls. This study highlighted associations between cocaine dependence and five SNPs predicted to alter microRNA binding at the 3'-untranslated region of the NFAT5 gene. The association of SNP rs1437134 with cocaine dependence survived the Bonferroni correction for multiple testing. A functional effect was confirmed for this variant by a luciferase reporter assay, with lower expression observed for the rs1437134G allele, which was more pronounced in the presence of hsa-miR-509. However, brain volumes in regions of relevance to addiction, as assessed with

magnetic resonance imaging, did not correlate with NFAT5 variation. These results suggest that the NFAT5 gene, which is upregulated a few hours after cocaine exposure, may be involved in the genetic predisposition to cocaine dependence.

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70. J Psychopharmacol. 2015 Sep;29(9):943-60. doi: 10.1177/0269881115596155. Epub 2015 Aug 5.

The Imperial College Cambridge Manchester (ICCAM) platform study: An experimental medicine platform for evaluating new drugs for relapse prevention in addiction. Part A: Study description.

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Drug and alcohol dependence are global problems with substantial societal costs. There are few treatments for relapse prevention and therefore a pressing need for further study of brain mechanisms underpinning relapse circuitry. The Imperial College Cambridge Manchester (ICCAM) platform study is an experimental medicine approach to this problem: using functional magnetic resonance imaging (fMRI) techniques and selective pharmacological tools, it aims to explore the neuropharmacology of putative relapse pathways in cocaine, alcohol, opiate dependent, and healthy individuals to inform future drug development. Addiction studies typically involve small samples because of recruitment difficulties and attrition. We established the platform in three centres to assess the feasibility of a multisite approach to address these issues. Pharmacological modulation of reward, impulsivity and emotional reactivity were investigated in a monetary incentive delay task, an inhibitory control task, and an evocative images task, using selective antagonists for μ-opioid, dopamine D3 receptor (DRD3) and neurokinin 1 (NK1) receptors (naltrexone, GSK598809, vofopitant/aprepitant), in a placebo-controlled, randomised, crossover design. In two years, 609 scans were performed, with 155 individuals scanned at baseline. Attrition was low and the majority of individuals were sufficiently motivated to complete all five sessions (n=87). We describe herein the study design, main aims, recruitment numbers, sample characteristics, and explain the test hypotheses and anticipated study outputs.

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71. Hum Brain Mapp. 2015 Oct;36(10):4222-30. doi: 10.1002/hbm.22913. Epub 2015 Jul 28.

Dysfunctional amygdala activation and connectivity with the prefrontal cortex in current cocaine users.

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OBJECTIVES: Stimulant use is associated with increased anxiety and a single administration of dexamphetamine increases amygdala activation to biologically

salient stimuli in healthy individuals. Here, we investigate how current cocaine use affects amygdala activity and amygdala connectivity with the prefrontal cortex in response to biologically salient stimuli in an emotional face matching task (EFMT).

EXPERIMENTAL DESIGN: Amygdala activity and amygdala connectivity during the EFMT were assessed in 51 cocaine using males and 32 non-drug-using healthy males using functional magnetic resonance imaging (fMRI). Within the cocaine use group, we explored whether amygdala activation was associated with age of first use of cocaine and duration of cocaine use to distinguish between amygdala activation alterations as a cause or a consequence of cocaine use.

PRINCIPAL OBSERVATIONS: We observed hyperactivity of the amygdala, thalamus, and hippocampus and reduced amygdala connectivity with the anterior cingulate gyrus in response to angry and fearful facial expressions in current cocaine users compared to controls. Increased amygdala activation was independently associated with earlier age of first cocaine use and with longer exposure to cocaine.

CONCLUSIONS: Our findings suggest that amygdala hyperactivity to biologically salient stimuli may represent a risk factor for an early onset of cocaine use and that prolonged cocaine use may further sensitize amygdala activation. High amygdala activation to emotional face processing in current cocaine users may result from low prefrontal control of the amygdala response to such stimuli.

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Cocaine-specific neuroplasticity in the ventral striatum network is linked to delay discounting and drug relapse.

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AIMS: To contrast functional connectivity on ventral and dorsal striatum networks in cocaine dependence relative to pathological gambling, via a resting-state functional connectivity approach; and to determine the association between cocaine dependence-related neuroadaptations indexed by functional connectivity and impulsivity, compulsivity and drug relapse.
DESIGN: Cross-sectional study of 20 individuals with cocaine dependence (CD), 19 individuals with pathological gambling (PG) and 21 healthy controls (HC), and a prospective cohort study of 20 CD followed-up for 12 weeks to measure drug relapse.

SETTING AND PARTICIPANTS: CD and PG were recruited through consecutive admissions to a public clinic specialized in substance addiction treatment (Centro Provincial de Drogodependencias) and a public clinic specialized in gambling treatment (AGRAJER), respectively; HC were recruited through community advertisement in the same area in Granada (Spain).

MEASUREMENTS: Seed-based functional connectivity in the ventral striatum (ventral caudate and ventral putamen) and dorsal striatum (dorsal caudate and dorsal putamen), the Kirby delay-discounting questionnaire, the reversal-learning task and a dichotomous measure of cocaine relapse indicated with self-report and urine tests.

FINDINGS: CD relative to PG exhibit enhanced connectivity between the ventral caudate seed and subgenual anterior cingulate cortex, the ventral putamen seed and dorsomedial pre-frontal cortex and the dorsal putamen seed and insula (P≤0.001, kE=108). Connectivity between the ventral caudate seed and subgenual anterior cingulate cortex is associated with steeper delay discounting (P≤0.001, kE=108) and cocaine relapse (P≤0.005, kE=34).

CONCLUSIONS: Cocaine dependence-related neuroadaptations in the ventral striatum of the brain network are associated with increased impulsivity and higher rate of cocaine relapse.

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Effects of dexamphetamine-induced dopamine release on resting-state network connectivity in recreational amphetamine users and healthy controls.

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Dexamphetamine (dAMPH) is not only used for the treatment of attention deficit hyperactivity disorder (ADHD), but also as a recreational drug. Acutely, dAMPH induces release of predominantly dopamine (DA) in the striatum, and in the cortex both DA and noradrenaline. Recent animal studies have shown that chronic dAMPH administration can induce changes in the DA system following long-term exposure, as evidenced by reductions in DA transporters, D2/3 receptors and endogenous DA levels. However, only a limited number of studies have investigated the effects of dAMPH in the human brain. We used a combination of resting-state functional magnetic resonance imaging (rs-fMRI) and [(123)I]IBZM single-photon emission computed tomography (SPECT) (to assess baseline D2/3 receptor binding and DA release) in 15 recreational AMPH users and 20 matched healthy controls to investigate the short-, and long-term effects of AMPH before and after an acute intravenous challenge with dAMPH. We found that acute dAMPH administration reduced functional connectivity in the cortico-striatal-thalamic network. dAMPH-induced DA release, but not DA D2/3 receptor binding, was positively associated with connectivity changes in this network. In addition, acute dAMPH reduced connectivity in default mode networks and salience-executive-networks networks in both groups. In contrast to our hypothesis, no significant group differences were found in any of the rs-fMRI networks investigated, possibly due to lack of sensitivity or compensatory mechanisms. Our findings thus support the use of ICA-based resting-state functional connectivity as a tool to investigate acute, but not chronic, alterations induced by dAMPH on dopaminergic processing in the striatum.

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Inhibitory behavioral control: A stochastic dynamic causal modeling study comparing cocaine dependent subjects and controls.

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Cocaine dependence is associated with increased impulsivity in humans. Both cocaine dependence and impulsive behavior are under the regulatory control of cortico-striatal networks. One behavioral laboratory measure of impulsivity is response inhibition (ability to withhold a prepotent response) in which altered patterns of regional brain activation during executive tasks in service of normal performance are frequently found in cocaine dependent (CD) subjects studied with functional magnetic resonance imaging (fMRI). However, little is known about aberrations in specific directional neuronal connectivity in CD subjects. The present study employed fMRI-based dynamic causal modeling (DCM) to study the effective (directional) neuronal connectivity associated with response inhibition in CD subjects, elicited under performance of a Go/NoGo task with two levels of NoGo difficulty (Easy and Hard). The performance on the Go/NoGo task was not significantly different between CD subjects and controls. The DCM analysis revealed that prefrontal-striatal connectivity was modulated (influenced) during the NoGo conditions for both groups. The effective connectivity from left (L) anterior cingulate cortex (ACC) to L caudate was similarly modulated during the Easy NoGo condition for both groups. During the Hard NoGo condition in controls, the effective connectivity from right (R) dorsolateral prefrontal cortex (DLPFC) to L caudate became more positive, and the effective connectivity from R ventrolateral prefrontal cortex (VLPFC) to L caudate became more negative. In CD subjects, the effective connectivity from L ACC to L caudate became more negative during the Hard NoGo conditions. These results indicate that during Hard NoGo trials in CD subjects, the ACC rather than DLPFC or VLPFC influenced caudate during response inhibition.

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75. Transl Psychiatry. 2015 May 26;5:e570. doi: 10.1038/tp.2015.58.

In the face of threat: neural and endocrine correlates of impaired facial emotion recognition in cocaine dependence.

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The ability to recognize facial expressions of emotion in others is a cornerstone of human interaction. Selective impairments in the recognition of facial expressions of fear have frequently been reported in chronic cocaine users, but the nature of these impairments remains poorly understood. We used the multivariate method of partial least squares and structural magnetic resonance imaging to identify gray matter brain networks that underlie facial affect processing in both cocaine-dependent (n = 29) and healthy male volunteers (n = 29). We hypothesized that disruptions in neuroendocrine function in cocaine-dependent individuals would explain their impairments in fear recognition by modulating the relationship with the underlying gray matter networks. We found that cocaine-dependent individuals not only exhibited significant impairments in the recognition of fear, but also for facial expressions of anger. Although recognition accuracy of threatening expressions co-varied in all participants with distinctive gray matter networks implicated in fear and anger processing, in cocaine users it was less well predicted by these networks than in controls. The weaker brain-behavior relationships for threat processing were also mediated by distinctly different factors. Fear recognition impairments were influenced by variations in intelligence levels, whereas anger recognition impairments were associated with comorbid opiate dependence and related reduction in testosterone levels. We also observed an inverse relationship between testosterone levels and the duration of crack and opiate use. Our data provide novel insight into the neurobiological basis of abnormal threat processing in cocaine dependence, which may shed light on new opportunities facilitating the psychosocial integration of these patients.

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76. Neuropsychopharmacology. 2015 Dec;40(13):2960-8. doi: 10.1038/npp.2015.150. Epub 2015 Jun 3.

Modeling Causal Relationship Between Brain Regions Within the Drug-Cue Processing Network in Chronic Cocaine Smokers.

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The cues associated with drugs of abuse have an essential role in perpetuating problematic use, yet effective connectivity or the causal interaction between brain regions mediating the processing of drug cues has not been defined. The aim of this fMRI study was to model the causal interaction between brain regions within the drug-cue processing network in chronic cocaine smokers and matched control participants during a cocaine-cue exposure task. Specifically, cocaine-smoking (15M; 5F) and healthy control (13M; 4F) participants viewed cocaine and neutral cues while in the scanner (a Siemens 3 T magnet). We examined whole brain activation, including activation related to drug-cue processing. Time

series data extracted from ROIs determined through our General Linear Model (GLM) analysis and prior publications were used as input to IMaGES, a computationally powerful Bayesian search algorithm. During cocaine-cue exposure, cocaine users showed a particular feed-forward effective connectivity pattern between the ROIs of the drug-cue processing network (amygdala → hippocampus → dorsal striatum → insula → medial frontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex) that was not present when the controls viewed the cocaine cues. Cocaine craving ratings positively correlated with the strength of the causal influence of the insula on the dorsolateral prefrontal cortex in cocaine users. This study is the first demonstration of a causal interaction between ROIs within the drug-cue processing network in cocaine users. This study provides insight into the mechanism underlying continued substance use and has implications for monitoring treatment response.

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Interactions between the salience and default-mode networks are disrupted in cocaine addiction.

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Cocaine dependence is a complex neuropsychiatric disorder manifested as dysregulation of multiple behavioral, emotional, and cognitive constructs. Neuroimaging studies have begun to identify specific neurobiological circuit impairments in cocaine-dependent (CD) individuals that may underlie these symptoms. However, whether, where, and how the interactions within and between these circuits are disrupted remain largely unknown. We used resting-state fMRI and modularity network analysis to identify brain modules of a priori interest (default-mode network [DMN], salience network [SN], executive control network [ECN], medial temporal lobe [MTL], and striatum) in 47 CD and 47 matched healthy control (HC) participants and explored alterations within and between these brain modules as a function of addiction. At the module level, intermodule connectivity decreased between DMN and SN in CD. At the nodal level, several regions showed decreased connections with multiple modules in CD: the rostral anterior cingulate connection strength was reduced with SN and MTL; the posterior cingulate had reduced connections with ECN; and the bilateral insula demonstrated decreased

connections with DMN. Furthermore, alexithymia, a personality trait previously associated with addiction, correlated negatively with intramodule connectivity within SN only in cocaine users. Our results indicate that cocaine addiction is associated with disrupted interactions among DMN, MTL, and SN, which have been implicated, respectively, in self-referential functions, emotion and memory, and coordinating between internal and external stimuli, providing novel and important insights into the neurobiological mechanisms of cocaine addiction.

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78. Brain Connect. 2015 Oct;5(8):476-86. doi: 10.1089/brain.2014.0240. Epub 2015 Aug 6.

Altered Functional Connectivity Strength in Abstinent Chronic Cocaine Smokers Compared to Healthy Controls.

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Past research involving cocaine and resting-state functional connectivity (RSFC) has shown altered functional connectivity within the frontal and between the frontal and other cortical and subcortical brain regions in chronic users of cocaine. However, there have been discrepancies in literature regarding the relationship between RSFC between brain regions and cocaine use behavior. This study explored the RSFC between brain regions in cocaine smokers abstinent from cocaine use for 72 h and healthy controls. Also, the relationship between RSFC between brain regions and various cocaine use measures (cocaine use duration; frequency, and money spent on cocaine/week) was examined. Twenty chronic cocaine users and 17 controls completed a resting-state scan and an anatomical MPRAGE scan. Group independent component analysis performed on functional magnetic resonance imaging data identified 13 ICs pertaining to distinct resting-state networks, and group-level differences were examined. To examine inter-network functional connectivity between brain regions, these 13 ICs were divided into 61 distinct regions of interest (ROIs). Correlations were calculated between 61 ROI time series. For the ROI pairs that significantly differed from controls in connectivity strength, correlations were computed between connectivity strength and cocaine use measures. Results showed an enhanced RSFC within the sensory motor cortex and the left frontal-parietal network in cocaine users than controls. An increased inter-network RSFC between frontal-temporal and frontal-parietal brain regions, and a decreased RSFC between parietal-parietal, occipital-limbic, occipital-occipital, and occipital-parietal brain regions was found in cocaine users. This study demonstrated that intra-network connectivity strength of sensory motor cortex was negatively correlated with years of cocaine use. Inter-network connectivity strength between occipital-limbic brain regions was positively correlated with years of cocaine use, while connectivity strength within occipital brain regions was negatively related to cocaine use frequency

and money spent on cocaine per week in abstinent cocaine users.

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79. Drug Alcohol Depend. 2015 Jul 1;152:102-8. doi: 10.1016/j.drugalcdep.2015.04.015. Epub 2015 May 1.

A hyper-connected but less efficient small-world network in the substance-dependent brain.

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BACKGROUND: The functional interconnections of the addicted brain may differ from the non-addicted population in important ways, but prioranalytic approaches were usually limited to the study of connections between a few number of selected brain regions. Recent approaches enable examination of the vast functional interactions within the entire brain, the functional connectome (FCM). The purpose of this study was to characterize FCM alterations in addiction using resting state functional Magnetic Resonance Imaging (rsfMRI) and to assess their relations to addiction-related symptoms.

METHODS: rsfMRI data were acquired from 20 chronic polydrug users whose primary diagnosis was cocaine dependence (DRUG) and 19 age-matched non-drug using healthy controls (CTL). FCM was assessed using graph theoretical analysis.

RESULTS: Among the assessed 90 brain subdivisions, DRUG showed stronger functional connectivity. After controlling functional connectivity difference and the resultant network density, DRUG showed reduced communication efficiency and reduced small-worldness.

CONCLUSIONS: The increased connection strength in drug users' brain suggests an elevated dynamic resting state that may enable a rapid, semi-automatic, execution of behaviors directed toward drug-related goals.The reduced FCM communication efficiency and reduced small-worldness suggest a loss of normal inter-regional communications and topology features that makes it difficult to inhibit the drug seeking behavior.

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80. Neuroscience. 2015 Nov 19;309:243-58. doi: 10.1016/j.neuroscience.2015.04.044. Epub 2015 Apr 28.

Effects of long-term methylphenidate treatment in adolescent and adult rats on hippocampal shape, functional connectivity and adult neurogenesis.

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Methylphenidate (MPH) is a widely prescribed stimulant drug for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents. Its use in this age group raises concerns regarding the potential interference with ongoing neurodevelopmental processes. Particularly the hippocampus is a highly plastic brain region that continues to develop postnatally and is involved in cognition and emotional behavior, functions known to be affected by MPH. In this study, we assessed whether hippocampal structure and function were affected by chronic oral MPH treatment and whether its effects were different in adolescent or adult rats. Using behavioral testing, resting-state functional MRI, post-mortem structural magnetic resonance imaging (MRI), and immunohistochemistry, we assessed MPH's effects on recognition memory, depressive-like behavior, topological features of functional connectivity networks, hippocampal shape and markers for hippocampal neurogenesis and proliferation. Object recognition memory was transiently impaired in adolescent treated rats, while in animals treated during adulthood, increased depressive-like behavior was observed. Neurogenesis was increased in adolescent treated rats, whereas cell proliferation was decreased following adult treatment. Adolescent treated rats showed inward shape deformations adjacent to ventral parahippocampal regions known to be involved in recognition memory, whereas such deformations were not observed in adult treated animals. Irrespective of the age of treatment, MPH affected topological features of ventral hippocampal functional networks. Thus, chronic oral treatment with a therapeutically relevant dose of MPH preferentially affected the ventral part of the hippocampus and induced contrasting effects in adolescent and adult rats. The differences in behavior

were paralleled by opposite effects on adult neurogenesis and granule cell proliferation.

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81. Mol Psychiatry. 2015 Jun;20(6):764-71. doi: 10.1038/mp.2015.47. Epub 2015 Apr 21.

Gray-matter volume, midbrain dopamine D2/D3 receptors and drug craving in methamphetamine users.

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Dysfunction of the mesocorticolimbic system has a critical role in clinical features of addiction. Despite evidence suggesting that midbrain dopamine receptors influence amphetamine-induced dopamine release and that dopamine is involved in methamphetamine-induced neurotoxicity, associations between dopamine receptors and gray-matter volume have been unexplored in methamphetamine users. Here we used magnetic resonance imaging and [(18)F]fallypride positron emission tomography, respectively, to measure gray-matter volume (in 58 methamphetamine users) and dopamine D2/D3 receptor availability (binding potential relative to nondisplaceable uptake of the radiotracer, BPnd) (in 31 methamphetamine users and 37 control participants). Relationships between these measures and self-reported drug craving were examined. Although no difference in midbrain D2/D3 BPnd was detected between methamphetamine and control groups, midbrain D2/D3 BPnd was positively correlated with gray-matter volume in the striatum, prefrontal cortex, insula, hippocampus and temporal cortex in methamphetamine users, but not in control participants (group-by-midbrain D2/D3 BPnd interaction, $P<0.05$ corrected for multiple comparisons). Craving for methamphetamine was negatively associated with gray-matter volume in the insula, prefrontal cortex, amygdala, temporal cortex, occipital cortex, cerebellum and thalamus ($P<0.05$ corrected for multiple

comparisons). A relationship between midbrain D2/D3 BPnd and methamphetamine craving was not detected. Lower midbrain D2/D3 BPnd may increase vulnerability to deficits in gray-matter volume in mesocorticolimbic circuitry in methamphetamine users, possibly reflecting greater dopamine-induced toxicity. Identifying factors that influence prefrontal and limbic volume, such as midbrain BPnd, may be important for understanding the basis of drug craving, a key factor in the maintenance of substance-use disorders.

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82. J Neurosci. 2015 Apr 8;35(14):5860-9. doi: 10.1523/JNEUROSCI.4333-14.2015.

Prenatal drug exposure affects neonatal brain functional connectivity.

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Prenatal drug exposure, particularly prenatal cocaine exposure (PCE), incurs great public and scientific interest because of its associated neurodevelopmental consequences. However, the neural underpinnings of PCE remain essentially uncharted, and existing studies in school-aged children and adolescents are confounded greatly by postnatal environmental factors. In this study, leveraging a large neonate sample (N = 152) and non-invasive resting-state functional magnetic resonance imaging, we compared human infants with PCE comorbid with other drugs (such as nicotine, alcohol, marijuana, and antidepressant) with infants with similar non-cocaine poly drug exposure and drug-free controls. We aimed to characterize the neural correlates of PCE based on functional connectivity measurements of the amygdala and insula at the earliest stage of development. Our results revealed common drug exposure-related connectivity disruptions within the amygdala-frontal, insula-frontal, and insula-sensorimotor circuits. Moreover, a cocaine-specific effect was detected within a subregion of the amygdala-frontal network. This pathway is thought to play an important role in arousal regulation, which has been shown to be irregular in PCE infants and adolescents. These novel results provide the earliest human-based functional delineations of the neural-developmental consequences of prenatal drug exposure and thus open a new window for the advancement of effective strategies aimed at early risk identification and intervention.

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83. JAMA Psychiatry. 2015 Jun;72(6):584-92. doi: 10.1001/jamapsychiatry.2015.1.

Impaired functional connectivity within and between frontostriatal circuits and its association with compulsive drug use and trait impulsivity in cocaine addiction.

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IMPORTANCE: Converging evidence has long identified both impulsivity and compulsivity as key psychological constructs in drug addiction. Although dysregulated striatal-cortical network interactions have been identified in cocaine addiction, the association between these brain networks and addiction is poorly understood.
OBJECTIVES: To test the hypothesis that cocaine addiction is associated with disturbances in striatal-cortical communication as captured by resting-state functional connectivity (rsFC), measured from coherent spontaneous fluctuations in the blood oxygenation level-dependent functional magnetic resonance imaging signal, and to explore the relationships between striatal rsFC, trait impulsivity, and uncontrolled drug use in cocaine addiction.
DESIGN, SETTING, AND PARTICIPANTS: A case-control, cross-sectional study was

conducted at the National Institute on Drug Abuse Intramural Research Program outpatient magnetic resonance imaging facility. Data used in the present study were collected between December 8, 2005, and September 30, 2011. Participants included 56 non-treatment-seeking cocaine users (CUs) (52 with cocaine dependence and 3 with cocaine abuse) and 56 healthy individuals serving as controls (HCs) matched on age, sex, years of education, race, estimated intelligence, and smoking status.

MAIN OUTCOMES AND MEASURES: Voxelwise statistical parametric analysis testing the rsFC strength differences between CUs and HCs in brain regions functionally connected to 6 striatal subregions defined a priori.

RESULTS: Increased rsFC strength was observed predominantly in striatal-frontal circuits; decreased rsFC was found between the striatum and cingulate, striatal, temporal, hippocampal/amygdalar, and insular regions in the CU group compared with the HCs. Increased striatal-dorsal lateral prefrontal cortex connectivity strength was positively correlated with the amount of recent cocaine use (uncorrected $P < .046$) and elevated trait impulsivity in the CUs (uncorrected $P < .012$), and an index reflecting the balance between striatal-dorsal anterior cingulate cortex and striatal-anterior prefrontal/orbitofrontal cortex circuits was significantly associated with loss of control over cocaine use (corrected $P < .012$).

CONCLUSIONS AND RELEVANCE: Cocaine addiction is associated with disturbed rsFC in several specific striatal-cortical circuits. Specifically, compulsive cocaine use, a defining characteristic of dependence, was associated with a balance of increased striatal-anterior prefrontal/orbitofrontal and decreased striatal-dorsal anterior cingulate connectivity; trait impulsivity, both a risk factor for and a consequence of cocaine use, was associated with increased dorsal striatal-dorsal lateral prefrontal cortex connectivity uniquely in CUs. These

findings provide new insights toward the neurobiological mechanisms of addiction and suggest potential novel therapeutic targets for treatment.

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84. Drug Alcohol Depend. 2015 Jun 1;151:84-91. doi: 10.1016/j.drugalcdep.2015.03.004. Epub 2015 Mar 18.

Denial in methamphetamine users: Associations with cognition and functional connectivity in brain.

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BACKGROUND: Despite harmful consequences of drug addiction, it is common for individuals with substance use disorders to deny having problems with drugs. Emerging evidence suggests that some drug users lack insight into their behavior due to neurocognitive dysfunction, but little research has examined potential neurocognitive contributions to denial.

METHODS: This study explored the relationship between denial, cognitive performance and functional connectivity in brain. The participants were 58 non-treatment-seeking, methamphetamine-dependent participants who completed the URICA precontemplation scale, a self-report measure of denial of drug problems warranting change, as well as a cognitive test battery. A subset of participants (N = 21) had functional MRI scans assessing resting-state functional connectivity. Given literature indicating roles of the rostral anterior cingulate (rACC), anterior insula and precuneus in self-awareness, relationships between denial and resting-state connectivity were tested using seeds placed in these regions.

RESULTS: The results revealed a negative relationship between denial and an overall cognitive battery score ($p = 0.001$), the effect being driven particularly by performance on tests of memory and executive function. Denial was negatively associated with strength of connectivity between the rACC and regions of the frontal lobe (precentral gyri, left ventromedial prefrontal cortex, left orbitofrontal cortex), limbic system (left amygdala, left hippocampus and left parahippocampal gyrus), occipital lobes and cerebellum; and between the precuneus and the midbrain and cerebellum. Anterior insula connectivity was unrelated to denial.

CONCLUSIONS: These findings suggest that denial by methamphetamine users is linked with a cognitive and neural phenotype that may impede the development of

insight into their behavior.

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Integration of neural networks activated by amphetamine in females with different estrogen levels: a functional imaging study in awake rats.

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Previous studies demonstrate that schizophrenia symptomatology in women is dependent upon estrogen levels. Estrogen has beneficial properties when administered in conjunction with antipsychotics, and estrogen also alters, in rats, dopamine neurotransmission, which is a common target of all antipsychotic medications, suggesting a possible interaction between the two. The aim of the current study was to investigate this possible interaction using functional magnetic resonance imaging in awake, female rats. Amphetamine-sensitized, ovariectomized rats receiving no, chronic low, or phasic high levels of estradiol replacement were used, and changes in blood-oxygen-level-dependent (BOLD) signal were recorded over time in response to an acute amphetamine injection. Increasing levels of estradiol enhanced BOLD activation in pathways previously known to be implicated in schizophrenia symptomatology, such as the mesocorticolimbic, habenular and olfactory pathways, as well as more widespread areas. We propose here the first comprehensive "amphetamine activation map" integrating brain regions where amphetamine-related BOLD activity is influenced by estrogen levels in sensitized female rats.

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86. J Int Neuropsychol Soc. 2015 Mar;21(3):203-13. doi: 10.1017/S1355617715000156. Epub 2015 Mar 31.

HIV infection is associated with attenuated frontostriatal intrinsic

connectivity: a preliminary study.

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HIV-associated cognitive impairments are prevalent, and are consistent with injury to both frontal cortical and subcortical regions of the brain. The current study aimed to assess the association of HIV infection with functional connections within the frontostriatal network, circuitry hypothesized to be highly vulnerable to HIV infection. Fifteen HIV-positive and 15 demographically matched control participants underwent 6 min of resting-state functional magnetic resonance imaging (RS-fMRI). Multivariate group comparisons of age-adjusted

estimates of connectivity within the frontostriatal network were derived from BOLD data for dorsolateral prefrontal cortex (DLPFC), dorsal caudate and mediodorsal thalamic regions of interest. Whole-brain comparisons of group differences in frontostriatal connectivity were conducted, as were pairwise tests of connectivity associations with measures of global cognitive functioning and clinical and immunological characteristics (nadir and current CD4 count, duration of HIV infection, plasma HIV RNA). HIV - associated reductions in connectivity were observed between the DLPFC and the dorsal caudate, particularly in younger participants (<50 years, N=9). Seropositive participants also demonstrated reductions in dorsal caudate connectivity to frontal and parietal brain regions previously demonstrated to be functionally connected to the DLPFC. Cognitive impairment, but none of the assessed clinical/immunological variables, was also associated with reduced frontostriatal connectivity. In conclusion, our data indicate that HIV is associated with attenuated intrinsic frontostriatal connectivity. Intrinsic connectivity of this network may therefore serve as a marker of the deleterious effects of HIV infection on the brain, possibly via HIV-associated dopaminergic abnormalities. These findings warrant independent replication in larger studies.

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87. Front Hum Neurosci. 2015 Mar 9;9:116. doi: 10.3389/fnhum.2015.00116. eCollection 2015.

Alterations in interhemispheric functional and anatomical connectivity are associated with tobacco smoking in humans.

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Abnormal interhemispheric functional connectivity correlates with several neurologic and psychiatric conditions, including depression, obsessive-compulsive disorder, schizophrenia, and stroke. Abnormal interhemispheric functional connectivity also correlates with abuse of cannabis and cocaine. In the current report, we evaluated whether tobacco abuse (i.e., cigarette smoking) is associated with altered interhemispheric connectivity. To that end, we examined resting state functional connectivity (RSFC) using magnetic resonance imaging (MRI) in short term tobacco deprived and smoking as usual tobacco smokers, and in non-smoker controls. Additionally, we compared diffusion tensor imaging (DTI) in the same subjects to study differences in white matter. The data reveal a significant increase in interhemispheric functional connectivity in sated tobacco smokers when compared to controls. This difference was larger in frontal regions, and was positively correlated with the average number of cigarettes smoked per

day. In addition, we found a negative correlation between the number of DTI streamlines in the genual corpus callosum and the number of cigarettes smoked per day. Taken together, our results implicate changes in interhemispheric functional and anatomical connectivity in current cigarette smokers.

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88. Neuroimage. 2015 Jun;113:26-36. doi: 10.1016/j.neuroimage.2015.03.022. Epub 2015 Mar 18.

Risky decision-making and ventral striatal dopamine responses to amphetamine: a positron emission tomography [(11)C]raclopride study in healthy adults.

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Comment in

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Recent functional magnetic resonance imaging (fMRI) studies have provided compelling evidence that corticolimbic brain regions are integrally involved in human decision-making. Although much less is known about molecular mechanisms, there is growing evidence that the mesolimbic dopamine (DA) neurotransmitter system may be an important neural substrate. Thus far, direct examination of DA signaling in human risk-taking has centered on gambling disorder. Findings from several positron emission tomography (PET) studies suggest that dysfunctions in mesolimbic DA circuits may play an important role in gambling behavior. Nevertheless, interpretation of these findings is currently hampered by a need for better understanding of how individual differences in regional DA function influence normative decision-making in humans. To further our understanding of these processes, we used [(11)C]raclopride PET to examine associations between

ventral striatal (VS) DA responses to amphetamine (AMPH) and risky decision-making in a sample of healthy young adults with no history of psychiatric disorder, Forty-five male and female subjects, ages 18-29 years, completed a computerized version of the Iowa Gambling Task. Participants then underwent two 90-minute PET studies with high specific activity [(11)C]raclopride. The first scan was preceded by intravenous saline; the second, by intravenous AMPH (0.3mg/kg). Findings of primary analyses showed that less advantageous decision-making was associated with greater right VS DA release; the relationship did not differ as a function of gender. No associations were observed between risk-taking and left VS DA release or baseline D2/D3 receptor availability in either hemisphere. Overall, the results support notions that variability in striatal DA function may mediate inter-individual differences in risky decision-making in healthy adults, further suggesting that hypersensitive DA circuits may represent a risk pathway in this population.

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89. Brain Res. 2015 Dec 2;1628(Pt A):199-209. doi: 10.1016/j.brainres.2015.02.053. Epub 2015 Mar 11.

What goes up, can come down: Novel brain stimulation paradigms may attenuate craving and craving-related neural circuitry in substance dependent individuals.

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Vulnerability to drug related cues is one of the leading causes for continued use and relapse among substance dependent individuals. Using drugs in the face of cues may be associated with dysfunction in at least two frontal-striatal neural circuits: (1) elevated activity in medial and ventral areas that govern limbic arousal (including the medial prefrontal cortex (MPFC) and ventral striatum) or (2) depressed activity in dorsal and lateral areas that govern cognitive control (including the dorsolateral prefrontal cortex (DLPFC) and dorsal striatum). Transcranial magnetic stimulation (TMS) is emerging as a promising new tool for

the attenuation of craving among multiple substance dependent populations. To date however, nearly all repetitive TMS studies in addiction have focused on amplifying activity in frontal-striatal circuits that govern cognitive control.
This manuscript reviews recent work using TMS as a tool to decrease craving for multiple substances and provides a theoretical model for how clinical researchers might approach target and frequency selection for TMS of addiction. To buttress this model, preliminary data from a single-blind, sham-controlled, crossover study of 11 cocaine-dependent individuals is also presented. These results suggest that attenuating MPFC activity through theta burst stimulation decreases activity in the striatum and anterior insula. It is also more likely to attenuate craving than sham TMS. Hence, while many TMS studies are focused on applying LTP-like stimulation to the DLPFC, the MPFC might be a new, efficacious, and treatable target for craving in cocaine dependent individuals.

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90. Biol Psychiatry. 2015 Oct 1;78(7):496-504. doi: 10.1016/j.biopsych.2014.12.027. Epub 2015 Jan 30.

Basal Hippocampal Activity and Its Functional Connectivity Predicts Cocaine Relapse.

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BACKGROUND: Cocaine-induced neuroplastic changes may result in a heightened propensity for relapse. Using regional cerebral blood flow (rCBF) as a marker of basal neuronal activity, this study assessed alterations in rCBF and related resting state functional connectivity (rsFC) to prospectively predict relapse in patients following treatment for cocaine use disorder (CUD).

METHODS: Pseudocontinuous arterial spin labeling functional magnetic resonance imaging and resting blood oxygen level-dependent functional magnetic resonance imaging data were acquired in the same scan session in abstinent participants with CUD before residential treatment discharge and in 20 healthy matched control subjects. Substance use was assessed twice weekly following discharge. Relapsed

participants were defined as those who used stimulants within 30 days following treatment discharge (n = 22); early remission participants (n = 18) did not.
RESULTS: Voxel-wise, whole-brain analysis revealed enhanced rCBF only in the left posterior hippocampus (pHp) in the relapsed group compared with the early remission and control groups. Using this pHp as a seed, increased rsFC strength with the posterior cingulate cortex (PCC)/precuneus was seen in the relapsed versus early remission subgroups. Together, both increased pHp rCBF and strengthened pHp-PCC rsFC predicted relapse with 75% accuracy at 30, 60, and 90 days following treatment.
CONCLUSIONS: In CUD participants at risk of early relapse, increased pHp basal activity and pHp-PCC circuit strength may reflect the propensity for heightened reactivity to cocaine cues and persistent cocaine-related ruminations. Mechanisms to mute hyperactivated brain regions and delink dysregulated neural circuits may prove useful to prevent relapse in patients with CUD.

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Effects of chronic and acute stimulants on brain functional connectivity hubs.

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The spatial distribution and strength of information processing 'hubs' are essential features of the brain's network topology, and may thus be particularly susceptible to neuropsychiatric disease. Despite growing evidence that drug addiction alters functioning and connectivity of discrete brain regions, little is known about whether chronic drug use is associated with abnormalities in this network-level organization, and if such abnormalities could be targeted for intervention. We used functional connectivity density (FCD) mapping to evaluate how chronic and acute stimulants affect brain hubs (i.e., regions with many short-range or long-range functional connections). Nineteen individuals with cocaine use disorders (CUD) and 15 healthy controls completed resting-state fMRI scans following a randomly assigned dose of methylphenidate (MPH; 20mg) or placebo. Short-range and long-range FCD maps were computed for each participant and medication condition. CUD participants had increased short-range and long-range FCD in the ventromedial prefrontal cortex, posterior

cingulate/precuneus, and putamen/amygdala, which in areas of the default mode network correlated with years of use. Across participants, MPH decreased short-range FCD in the thalamus/putamen, and decreased long-range FCD in the supplementary motor area and postcentral gyrus. Increased density of short-range and long-range functional connections to default mode hubs in CUD suggests an overrepresentation of these resource-expensive hubs. While the effects of MPH on FCD were only partly overlapping with those of CUD, MPH-induced reduction in the density of short-range connections to the putamen/thalamus, a network of core relevance to habit formation and addiction, suggests that some FCD abnormalities could be targeted for intervention.

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92. Neurotoxicol Teratol. 2015 Mar-Apr;48:69-77. doi: 10.1016/j.ntt.2015.02.002. Epub 2015 Feb 12.

Prenatal drug exposure to illicit drugs alters working memory-related brain activity and underlying network properties in adolescence.

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Comment in

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The persistence of effects of prenatal drug exposure (PDE) on brain functioning during adolescence is poorly understood. We explored neural activation to a visuospatial working memory (VSWM) versus a control task using functional magnetic resonance imaging (fMRI) in adolescents with PDE and a community comparison group (CC) of non-exposed adolescents. We applied graph theory metrics to resting state data using a network of nodes derived from the VSWM task activation map to further explore connectivity underlying WM functioning. Participants (ages 12-15 years) included 47 adolescents (27 PDE and 20 CC). All analyses controlled for potentially confounding differences in birth characteristics and postnatal environment. Significant group by task differences in brain activation emerged in the left middle frontal gyrus (BA 6) with the CC group, but not the PDE group, activating this region during VSWM. The PDE group deactivated the culmen, whereas the CC group activated it during the VSWM task.

The CC group demonstrated a significant relation between reaction time and culmen activation, not present in the PDE group. The network analysis underlying VSWM performance showed that PDE group had lower global efficiency than the CC group and a trend level reduction in local efficiency. The network node corresponding to the BA 6 group by task interaction showed reduced nodal efficiency and fewer direct connections to other nodes in the network. These results suggest that adolescence reveals altered neural functioning related to response planning that may reflect less efficient network functioning in youth with PDE.

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Pharmacological MRI response to a selective dopamine transporter inhibitor, GBR12909, in awake and anesthetized rats.

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Pharmacological magnetic resonance imaging (phMRI) is a powerful tool for imaging the effects of drugs on brain activity. In preclinical phMRI studies, general anesthesia used for minimizing head movements is thought to influence the phMRI responses to drugs. In this study we investigated the phMRI responses to a selective dopamine transporter (DAT) inhibitor, GBR12909, and a dopamine (DA) releaser, d-amphetamine (AMPH), in the isoflurane anesthetized and awake rats using a relative cerebral blood volume (rCBV) method. AMPH (1 mg/kg i.p.) caused an increase in rCBV in the dopaminergic circuitry in the both anesthetized and awake rats. The striatal rCBV change was correlated with the change of the striatal DA concentration induced by AMPH in the both anesthetized and awake rats. GBR12909 (10 mg/kg i.p.) caused a positive rCBV response and showed a similar regional pattern of rCBV response to AMPH in the awake rats, and the correlation between the change of the striatal rCBV and the striatal DA concentration was observed. However, in the anesthetized rats, GBR12909 induced a widespread negative rCBV response, whereas an increase in striatal DA concentration was observed. These findings indicate that phMRI responses to activation of DA neurotransmission by GBR12909 or AMPH are overall identical in the awake state, while the phMRI response to a DAT inhibitor, GBR12909 but not to AMPH was changed by isoflurane anesthesia. For the evaluation of neuroactive drugs using phMRI, isoflurane anesthesia might be complicated the interpretation of pharmacodynamic effects of drugs in preclinical studies.

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94. Neuropharmacology. 2015 May;92:63-8. doi: 10.1016/j.neuropharm.2014.12.030. Epub 2015 Jan 12.

Interhemispheric insular and inferior frontal connectivity are associated with substance abuse in a psychiatric population.

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Substance abuse is highly comorbid with major psychiatric disorders. While the neural underpinnings of drug abuse have been studied extensively, most existing

studies compare drug users without comorbidities and healthy, non-user controls. Such studies do not generalize well to typical patients with substance abuse disorders. Therefore, we studied a population of psychiatric inpatients (n = 151) with a range of mental illnesses. Psychiatric disorders were diagnosed via structured interviews. Sixty-five percent of patients met criteria for at least one substance use disorder. Patients were recruited for resting state functional connectivity (RSFC) and diffusion tensor imaging (DTI) experiments to examine the interhemispheric connectivity between brain regions hypothesized to be involved in drug addiction, namely: the inferior, medial, and superior frontal gyri; insula; striatum; and anterior cingulate cortex. The World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test (WHOA) questionnaire was used to further assess drug use. An association between use of tobacco, alcohol, cocaine, sedatives, and hallucinogens with increased insular interhemispheric connectivity was observed. In addition, increased inferior frontal gyrus interhemispheric connectivity was associated with amphetamine and inhalant use. Our results suggest that increased inter-hemispheric insula connectivity is associated with the use of several drugs of abuse. Importantly, psychiatric inpatients without a history of drug dependence were used as an ecologically valid control group rather than the more typical comparison between "mentally ill vs. healthy control" populations. We suggest that dysfunction of interhemispheric connectivity of the insula and to a lesser extent of the inferior frontal gyrus, are related to drug abuse in psychiatric populations.

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rsfMRI effects of KB220Z™ on neural pathways in reward circuitry of abstinent genotyped heroin addicts.

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Recently, Willuhn et al. reported that cocaine use and even non-substance-related addictive behavior increases as dopaminergic function is reduced. Chronic cocaine exposure has been associated with decreases in D2/D3 receptors and was also associated with lower activation of cues in occipital cortex and cerebellum, in a recent PET study by Volkow's et al. Therefore, treatment strategies, like dopamine agonist therapy, that might conserve dopamine function may be an interesting approach to relapse prevention in psychoactive drug and behavioral addictions. To this aim, we evaluated the effect of KB220Z™ on reward circuitry of 10 heroin addicts undergoing protracted abstinence (average 16.9 months). In a randomized placebo-controlled crossover study of KB220Z, five subjects completed a triple-blinded experiment in which the subject, the person administering the treatment, and the person evaluating the response to treatment were blinded to the treatment that any particular subject was receiving. In addition, nine

subjects were genotyped utilizing the GARSDX™ test. We preliminarily report that KB220Z induced an increase in BOLD activation in caudate-accumbens-dopaminergic pathways compared to placebo following 1-hour acute administration. Furthermore, KB220Z also reduced resting-state activity in the putamen of abstinent heroin addicts. In the second phase of this pilot study of all 10 abstinent heroin-dependent subjects, we observed that three brain regions of interest were significantly activated from resting state by KB220Z compared to placebo ($p < 0.05$). Increased functional connectivity was observed in a putative network that included the dorsal anterior cingulate, medial frontal gyrus, nucleus accumbens, posterior cingulate, occipital cortical areas, and cerebellum. These results and other quantitative electroencephalogy (qEEG) study results suggest a putative anti-craving/anti-relapse role of KB220Z in addiction by direct or indirect dopaminergic interaction. Due to small sample size, we caution definitive interpretation of these preliminary results, and confirmation with additional research and ongoing rodent and human studies of KB220Z is required.

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Chronic methamphetamine abuse and corticostriatal deficits revealed by neuroimaging.

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Despite aggressive efforts to contain it, methamphetamine use disorder continues to be major public health problem; and with generic behavioral therapies still the mainstay of treatment for methamphetamine abuse, rates of attrition and relapse remain high. This review summarizes the findings of structural, molecular, and functional neuroimaging studies of methamphetamine abusers, focusing on cortical and striatal abnormalities and their potential contributions to cognitive and behavioral phenotypes that can serve to promote compulsive drug use. These studies indicate that individuals with a history of chronic methamphetamine abuse often display several signs of corticostriatal dysfunction, including abnormal gray- and white-matter integrity, monoamine neurotransmitter system deficiencies, neuroinflammation, poor neuronal integrity, and aberrant patterns of brain connectivity and function, both when engaged in cognitive tasks and at rest. More importantly, many of these neural abnormalities were found to be linked with certain addiction-related phenotypes that may influence treatment response (e.g., poor self-control, cognitive inflexibility, maladaptive

decision-making), raising the possibility that they may represent novel therapeutic targets.

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Altered neural correlates of reward and loss processing during simulated slot-machine fMRI in pathological gambling and cocaine dependence.

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BACKGROUND: Individuals with gambling or substance-use disorders exhibit similar functional alterations in reward circuitry suggestive of a shared underlying vulnerability in addictive disorders. Additional research into common and unique alterations in reward-processing in substance-related and non-substance-related addictions may identify neural factors that could be targeted in treatment development for these disorders.

METHODS: To investigate contextual reward-processing in pathological gambling, a slot-machine fMRI task was performed by three groups (with pathological gambling, cocaine dependence and neither disorder; N = 24 each) to determine the extent to which two groups with addictions (non-substance-related and substance-related) showed similarities and differences with respect to each other and a non-addicted group during anticipatory periods and following the delivery of winning, losing and 'near-miss' outcomes.

RESULTS: Individuals with pathological gambling or cocaine dependence compared to those with neither disorder exhibited exaggerated anticipatory activity in mesolimbic and ventrocortical regions, with pathological-gambling participants displaying greater positive possible-reward anticipation and cocaine-dependent participants displaying more negative certain-loss anticipation. Neither clinical sample exhibited medial frontal or striatal responses that were observed following near-miss outcomes in healthy comparison participants.

CONCLUSIONS: Alterations in anticipatory processing may be sensitive to the valence of rewards and content-disorder-specific. Common and unique findings in pathological gambling and cocaine dependence with respect to anticipatory reward and near-miss loss processing suggest shared and unique elements that might be

targeted through behavioral or pharmacological interventions in the treatment of addictions.

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Childhood maltreatment and amygdala connectivity in methamphetamine dependence: a pilot study.

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INTRODUCTION: Childhood maltreatment, a well-known risk factor for the development of substance abuse disorders, is associated with functional and structural abnormalities in the adult brain, particularly in the limbic system. However, almost no research has examined the relationship between childhood maltreatment and brain function in individuals with drug abuse disorders.
METHODS: We conducted a pilot study of the relationship between childhood maltreatment (evaluated with the Childhood Trauma Questionnaire; Bernstein and Fink 1998) and resting-state functional connectivity of the amygdala (bilateral region of interest) with functional magnetic resonance imaging in 15 abstinent, methamphetamine-dependent research participants. Within regions that showed connectivity with the amygdala as a function of maltreatment, we also evaluated whether amygdala connectivity was associated positively with negative affect and negatively with healthy emotional processing.
RESULTS: The results indicated that childhood maltreatment was positively associated with resting-state connectivity between the amygdala and right hippocampus, right parahippocampal gyrus, right inferior temporal gyrus, right orbitofrontal cortex, cerebellum, and brainstem. Furthermore, connectivity between the amygdala and hippocampus was positively related to measures of depression, trait anxiety, and emotion dysregulation, and negatively related to self-compassion and dispositional mindfulness.
CONCLUSIONS: These findings suggest that childhood maltreatment may contribute to increased limbic connectivity and maladaptive emotional processing in

methamphetamine-dependent adults, and that healthy emotion regulation strategies may serve as a therapeutic target to ameliorate the associated behavioral phenotype. Childhood maltreatment warrants further investigation as a potentially important etiological factor in the neurobiology and treatment of substance use disorders.

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PMCID: PMC4178299
PMID: 25365801 [Indexed for MEDLINE]

99. Front Psychol. 2014 Sep 17;5:919. doi: 10.3389/fpsyg.2014.00919. eCollection 2014.

Dopamine and glucose, obesity, and reward deficiency syndrome.

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Obesity as a result of overeating as well as a number of well described eating disorders has been accurately considered to be a world-wide epidemic. Recently a

number of theories backed by a plethora of scientifically sound neurochemical and genetic studies provide strong evidence that food addiction is similar to psychoactive drug addiction. Our laboratory has published on the concept known as Reward Deficiency Syndrome (RDS) which is a genetic and epigenetic phenomena leading to impairment of the brain reward circuitry resulting in a hypo-dopaminergic function. RDS involves the interactions of powerful neurotransmitters and results in abnormal craving behavior. A number of important facts which could help translate to potential therapeutic targets espoused in this focused review include: (1) consumption of alcohol in large quantities or carbohydrates binging stimulates the brain's production of and utilization of dopamine; (2) in the meso-limbic system the enkephalinergic neurons are in close proximity, to glucose receptors; (3) highly concentrated glucose activates the calcium channel to stimulate dopamine release from P12 cells; (4) a significant correlation between blood glucose and cerebrospinal fluid concentrations of homovanillic acid the dopamine metabolite; (5) 2-deoxyglucose (2DG), the glucose analog, in pharmacological doses is associated with enhanced dopamine turnover and causes acute glucoprivation. Evidence from animal studies and fMRI in humans support the hypothesis that multiple, but similar brain circuits are disrupted in obesity and drug dependence and for the most part, implicate the involvement of DA-modulated reward circuits in pathologic eating behaviors. Based on a consensus of neuroscience research treatment of both glucose and drug like cocaine, opiates should incorporate dopamine agonist therapy in contrast to current theories and practices that utilizes dopamine antagonistic therapy. Considering that up until now clinical utilization of powerful dopamine D2 agonists have failed due to chronic down regulation of D2 receptors newer targets based on novel less powerful D2 agonists that up-regulate D2 receptors seems prudent. We encourage new strategies targeted at improving DA function in the treatment and prevention

of obesity a subtype of reward deficiency.

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PMID: 25278909

100. J Psychiatry Neurosci. 2015 Jan;40(1):46-57.

Functional dysconnectivity of corticostriatal circuitry and differential response to methylphenidate in youth with attention-deficit/hyperactivity disorder.

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BACKGROUND: Brain frontostriatal circuits have been implicated in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD). However, effects of methylphenidate on circuit-level functional connectivity are as yet unclear. The aim of the present study was to comprehensively investigate the functional connectivity of major striatal subregions in children with ADHD, including subanalyses directed at mapping cognitive and treatment response characteristics.
METHODS: Using a comprehensive seeding strategy, we examined resting-state functional connectivity of dorsal and ventral subdivisions of the caudate nucleus and putamen in children and adolescents with ADHD and in age- and sex-matched healthy controls.
RESULTS: We enrolled 83 patients with ADHD and 22 controls in our study. Patients showed significantly reduced dorsal caudate functional connectivity with the superior and middle prefrontal cortices as well as reduced dorsal putamen connectivity with the parahippocampal cortex. These connectivity measures were correlated in opposite directions in patients and controls with attentional performance, as assessed using the Continuous Performance Test. Patients showing a good response to methylphenidate had significantly reduced ventral caudate/nucleus accumbens connectivity with the inferior frontal cortices compared with poor responders.
LIMITATIONS: Possible confounding effects of age-related functional connectivity change were not excluded owing to the wide age range of participants.
CONCLUSION: We observed a region-specific effect of methylphenidate on

resting-state functional connectivity, suggesting the pretreatment level of ventral frontostriatal functional connectivity as a possible methylphenidate response biomarker of ADHD.

PMCID: PMC4275331

PMID: 25266402 [Indexed for MEDLINE]

101. Rev Neurol. 2014 Feb 24;58 Suppl 1:S3-16.

Brain abnormalities in attention-deficit hyperactivity disorder: a review.

[Article in English, Spanish; Abstract available in Spanish from the publisher]

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AIM: To review the magnetic resonance imaging findings in child and adult attention-deficit hyperactivity disorder (ADHD).

DEVELOPMENT: Studies have shown that ADHD is characterised by multiple functional and structural neural network abnormalities including most prominently fronto-striatal, but also fronto-parieto-temporal, fronto-cerebellar and even fronto-limbic networks. Evidence from longitudinal structural imaging studies has shown that ADHD is characterised by a delay in structural brain maturation. This

is reinforced by indirect evidence from cross-sectional imaging studies for more immature brain function as well as structural and functional connectivity patterns, which, however, needs corroboration by longitudinal studies. Dysfunction of the ventrolateral prefrontal cortex seems to be more pronounced in ADHD relative to other pediatric disorders and there is some evidence for differential abnormalities in the basal ganglia. A meta-analysis of stimulant effects on brain function shows that the most consistent mechanism of action of acute psychostimulant medication is the increased activation of the inferior prefrontal cortex and the basal ganglia. First attempts to use neuroimaging data to make individual diagnostic classifications of ADHD children based on pattern recognition techniques are promising but need replication across centres and scanners.
CONCLUSIONS: The last two decades of neuroimaging have shaped out biomarkers of ADHD. Future studies will need to focus on using this information for clinical translation such as using neuroimaging for individual diagnostic and prognostic classification or by using neuroimaging as a neurotherapy to reverse those brain function abnormalities that have been established over the last two decades of neuroimaging.

Publisher: Anomalias cerebrales en el trastorno por deficit de atencion/hiperactividad: una revision.Objetivo. Revisar los hallazgos de los estudios con resonancia magnetica en el trastorno por deficit de atencion/hiperactividad (TDAH) infantil y adulto. Desarrollo. Dichos estudios han demostrado que el TDAH se caracteriza por la presencia de multiples anomalias de caracter estructural y funcional, primordialmente en los circuitos frontoestriatales, pero tambien en los circuitos frontoparietotemporales, frontocerebelares e, incluso, frontolimbicos. Los datos aportados por los

estudios longitudinales de resonancia magnetica estructural demuestran que el TDAH se caracteriza por un retraso en la maduracion estructural del cerebro. Esta conclusion se ve reforzada por los indicios indirectos ofrecidos por los estudios de cortes transversales, que indican la existencia de una inmadurez sustancial tanto en la funcion cerebral como en los patrones de conectividad estructural y funcional, indicios que, sin embargo, estan pendientes de confirmar en estudios longitudinales. La alteracion funcional de la corteza prefrontal ventrolateral parece estar mas afectada en el TDAH que en otros trastornos pediatricos, y existen algunos indicios de anomalias distintivas en los ganglios basales. Un metaanalisis sobre los efectos de los estimulantes en la funcion cerebral demuestra que el mecanismo de accion agudo mas congruente de los farmacos psicoestimulantes consiste en el aumento de la activacion de la corteza prefrontal inferior y los ganglios basales. Los primeros intentos por utilizar los datos de los estudios de neuroimagen para elaborar clasificaciones diagnosticas individuales de los niños con TDAH a partir de tecnicas de reconocimiento de patrones han cosechado resultados alentadores, pero todavia deben ser replicados por mas centros y aparatos de resonancia magnetica. Conclusiones. Durante los ultimos 20 años, las tecnicas de neuroimagen han perfilado los biomarcadores del TDAH, pero es necesario que nuevos estudios descubran la utilidad clinica de esa informacion, como el uso de tales tecnicas como instrumento de clasificacion diagnostica y pronostica individualizada o como terapia para revertir las anomalias de la funcion cerebral que han sido confirmadas durante los dos decenios anteriores.

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102. Neuroimage. 2014 Dec;103:492-501. doi: 10.1016/j.neuroimage.2014.08.051. Epub 2014 Sep 2.

Ultrasensitive detection of 3D cerebral microvascular network dynamics in vivo.

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Despite widespread applications of multiphoton microscopy in microcirculation, its small field of view and inability to instantaneously quantify cerebral blood flow velocity (CBFv) in vascular networks limit its utility in investigating the heterogeneous responses to brain stimulations. Optical Doppler tomography (ODT) provides 3D images of CBFv networks, but it suffers poor sensitivity for measuring capillary flows. Here we report on a new method, contrast-enhanced ODT with Intralipid that significantly improves quantitative CBFv imaging of capillary networks by obviating the errors from long latency between flowing red blood cells (low hematocrit ~20% in capillaries). This enhanced sensitivity allowed us to measure the ultraslow microcirculation surrounding a brain tumor and the abnormal ingrowth of capillary flows in the tumor as well as in ischemia triggered by chronic cocaine in the mouse brain that could not be detected by

regular ODT. It also enabled significantly enhanced sensitivity for quantifying the heterogeneous CBFv responses of vascular networks to acute cocaine exposure. Inasmuch as lipid emulsions are widely used for parenteral nutrition the Intralipid contrast method has translational potential for clinical applications.

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103. Hum Brain Mapp. 2015 Jan;36(1):120-36. doi: 10.1002/hbm.22617. Epub 2014 Aug 21.

Overlapping patterns of brain activation to food and cocaine cues in cocaine abusers: association to striatal D2/D3 receptors.

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Cocaine, through its activation of dopamine (DA) signaling, usurps pathways that process natural rewards. However, the extent to which there is overlap between the networks that process natural and drug rewards and whether DA signaling associated with cocaine abuse influences these networks have not been

investigated in humans. We measured brain activation responses to food and cocaine cues with fMRI, and D2/D3 receptors in the striatum with [11C]raclopride and Positron emission tomography in 20 active cocaine abusers. Compared to neutral cues, food and cocaine cues increasingly engaged cerebellum, orbitofrontal, inferior frontal, and premotor cortices and insula and disengaged cuneus and default mode network (DMN). These fMRI signals were proportional to striatal D2/D3 receptors. Surprisingly cocaine and food cues also deactivated ventral striatum and hypothalamus. Compared to food cues, cocaine cues produced lower activation in insula and postcentral gyrus, and less deactivation in hypothalamus and DMN regions. Activation in cortical regions and cerebellum increased in proportion to the valence of the cues, and activation to food cues in somatosensory and orbitofrontal cortices also increased in proportion to body mass. Longer exposure to cocaine was associated with lower activation to both cues in occipital cortex and cerebellum, which could reflect the decreases in D2/D3 receptors associated with chronicity. These findings show that cocaine cues activate similar, though not identical, pathways to those activated by food cues and that striatal D2/D3 receptors modulate these responses, suggesting that chronic cocaine exposure might influence brain sensitivity not just to drugs but also to food cues.

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104. Psychopharmacology (Berl). 2015 Feb;232(4):745-54. doi:
10.1007/s00213-014-3709-9. Epub 2014 Aug 21.

Functional connectivity in frontal-striatal brain networks and cocaine self-administration in female rhesus monkeys.

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RATIONALE: Cocaine addiction is characterized by alternating cycles of abstinence and relapse and loss of control of drug use despite severe negative life consequences associated with its abuse.
OBJECTIVE: The objective of the present study was to elucidate critical neural circuits involved in individual vulnerabilities to resumption of cocaine self-administration following prolonged abstinence.
METHODS: The subjects were three female rhesus monkeys in prolonged abstinence following a long history of cocaine self-administration. Initial experiments examined the effects of acute cocaine administration (0.3 mg/kg, IV) on functional brain connectivity across the whole brain and in specific brain networks related to behavioral control using functional magnetic resonance imaging in fully conscious subjects. Subsequently, these subjects were allowed to resume cocaine self-administration to determine whether loss of basal connectivity within specific brain networks predicted the magnitude of resumption of cocaine intake following prolonged abstinence.

RESULTS: Acute cocaine administration robustly decreased global functional connectivity and selectively impaired top-down prefrontal circuits that control behavior, while sparing connectivity of striatal areas within limbic circuits. Importantly, impaired connectivity between prefrontal and striatal areas during abstinence predicted cocaine intake when these subjects were provided renewed access to cocaine.
CONCLUSIONS: Based on these findings, loss of prefrontal to striatal functional connectivity may be a critical mechanism underlying the negative downward spiral of cycles of abstinence and relapse that characterizes cocaine addiction.

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PMID: 25138647 [Indexed for MEDLINE]

105. Neuropharmacology. 2014 Dec;87:104-14. doi: 10.1016/j.neuropharm.2014.07.011. Epub 2014 Jul 29.

New perspectives on using brain imaging to study CNS stimulants.

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While the recent application of brain imaging to study CNS stimulants has offered new insights into the fundamental factors that contribute to their use and abuse, many gaps remain. Brain circuits that mediate pleasure, dependence, craving and relapse are anatomically, neurophysiologically and neurochemically distinct from one another, which has guided the search for correlates of stimulant-seeking and taking behavior. However, unlike other drugs of abuse, metrics for tolerance and physical dependence on stimulants are not obvious. The dopamine theory of stimulant abuse does not sufficiently explain this disorder as serotonergic, GABAergic and glutamagergic circuits are clearly involved in stimulant pharmacology and so tracking the source of the "addictive" processes must adopt a more multimodal, multidisciplinary approach. To this end, both anatomical and functional magnetic resonance imaging (MRI), MR spectroscopy (MRS) and positron emission tomography (PET) are complementary and have equally contributed to our understanding of how stimulants affect the brain and behavior. New vistas in this area include nanotechnology approaches to deliver small molecules to receptors and use MRI to resolve receptor dynamics. Anatomical and blood flow imaging has yielded data showing that cognitive enhancers might be useful adjuncts in treating CNS stimulant dependence, while MRS has opened opportunities to examine the brain's readiness to accept treatment as GABA tone normalizes after detoxification. A desired outcome of the above approaches is being able to offer evidence-based rationales for treatment approaches that can be implemented in a more broad geographic area, where access to brain imaging facilities may be limited. This article is part of the Special Issue entitled 'CNS Stimulants'.

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106. Brain Connect. 2014 Sep;4(7):499-510. doi: 10.1089/brain.2014.0264.

Abstinence from cocaine and sucrose self-administration reveals altered mesocorticolimbic circuit connectivity by resting state MRI.

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Previous preclinical studies have emphasized that drugs of abuse, through actions within and between mesocorticolimbic (MCL) regions, usurp learning and memory processes normally involved in the pursuit of natural rewards. To distinguish MCL circuit pathobiological neuroadaptations that accompany addiction from general learning processes associated with natural reward, we trained two groups of rats to self-administer either cocaine (IV) or sucrose (orally) followed by an identically enforced 30 day abstinence period. These procedures are known to induce behavioral changes and neuroadaptations. A third group of sedentary animals served as a negative control group for general handling effects. We examined low-frequency spontaneous fluctuations in the functional magnetic resonance imaging (fMRI) signal, known as resting-state functional connectivity

(rsFC), as a measure of intrinsic neurobiological interactions between brain regions. Decreased rsFC was seen in the cocaine-SA compared with both sucrose-SA and housing control groups between prelimbic (PrL) cortex and entopeduncular nucleus and between nucleus accumbens core (AcbC) and dorsomedial prefrontal cortex (dmPFC). Moreover, individual differences in cocaine SA escalation predicted connectivity strength only in the Acb-dmPFC circuit. These data provide evidence of fronto-striatal plasticity across the addiction trajectory, which are consistent with Acb-PFC hypoactivity seen in abstinent human drug addicts, indicating potential circuit level biomarkers that may inform therapeutic interventions. They further suggest that available data from cross-sectional human studies may reflect the consequence of rather a predispositional predecessor to their dependence.

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PMCID: PMC4146381
PMID: 24999822 [Indexed for MEDLINE]

107. Dev Neurosci. 2014;36(3-4):316-28. doi: 10.1159/000362685. Epub 2014 Jul 1.

Structural brain imaging in children and adolescents following prenatal cocaine exposure: preliminary longitudinal findings.

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The brain morphometry of 21 children, who were followed from birth and underwent structural brain magnetic resonance imaging at 8-10 years, was studied. This cohort included 11 children with prenatal cocaine exposure (CE) and 10 noncocaine-exposed children (NCE). We compared the CE versus NCE groups using FreeSurfer to automatically segment and quantify the volume of individual brain structures. In addition, we created a pediatric atlas specifically for this population and demonstrate the enhanced accuracy of this approach. We found an overall trend towards smaller brain volumes among CE children. The volume differences were significant for cortical gray matter, the thalamus and the putamen. Here, reductions in thalamic and putaminal volumes showed a robust inverse correlation with exposure levels, thus highlighting effects on dopamine-rich brain regions that form key components of brain circuitry known to play important roles in behavior and attention. Interestingly, head circumferences (HCs) at birth as well as at the time of imaging showed a tendency for smaller size among CE children. HCs at the time of imaging correlated well with the cortical volumes for all subjects. In contrast, HCs at birth were predictive of the cortical volume only for the CE group. A subgroup of these subjects (6 CE, 4 NCE) was also scanned at 13-15 years of age. In subjects who were scanned twice, we found that the trend for smaller structures continued into teenage years. We found that the differences in structural volumes between the CE and NCE groups are largely diminished when the HCs are controlled for or matched by study design. Participants in this study were drawn from a unique longitudinal cohort and, while the small sample size precludes strong conclusions regarding the longitudinal findings reported, the results point to reductions in HCs and in

specific brain structures that persist through teenage years in children who were exposed to cocaine in utero.

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108. Neuropharmacology. 2014 Oct;85:461-70. doi: 10.1016/j.neuropharm.2014.05.011. Epub 2014 Jun 18.

Neural correlates of craving and impulsivity in abstinent former cocaine users: Towards biomarkers of relapse risk.

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A significant hindrance to effective treatment of addiction is identifying those most likely to relapse. Cocaine addiction is characterized by deficits in inhibitory control and elevated reactivity to cocaine cues, both hypothesized to be integral to development of addiction and propensity to relapse. It follows that reduction of both impulsivity and cue-reactivity following abstinence is protective against relapse, and that persistence of these factors increases vulnerability. Using functional magnetic resonance imaging, we examined neural activation patterns in dorsal and ventral striatum in abstinent cocaine dependent (CD) individuals (N=20) and non-using controls (N=19) as they performed a cocaine craving task. We also examined activations in nodes of the response inhibition circuit (RIC) as they performed an inhibition task. At the between-groups level, no differences in RIC or striatal activation were seen in former users, in contrast to previous investigations in current users, suggesting large-scale functional recovery with abstinence. However, at the individual participant-level, abstinent CD individuals displayed an association between

cocaine cue-related neural activations in the right ventral striatum and compulsive cocaine craving scores. Compulsive craving scores were also negatively correlated with duration of abstinence. Further, there was an association between motor impulsivity scores and inhibition-related activations in the right inferior frontal gyrus and pre-supplementary motor area in abstinent CD individuals. Thus, while former users as a group did not show deficits in inhibitory function or cocaine-cue reactivity, participant-level results pointed to activation patterns in a minority of these individuals that likely contributes to enduring relapse vulnerability.

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109. Neuroimage Clin. 2014 Feb 7;4:585-92. doi: 10.1016/j.nicl.2014.01.015. eCollection 2014.

Error-related functional connectivity of the thalamus in cocaine dependence.

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Error processing is a critical component of cognitive control, an executive function that has been widely implicated in substance misuse. In previous studies we showed that error related activations of the thalamus predicted relapse to drug use in cocaine addicted individuals (Luo et al., 2013). Here, we investigated whether the error-related functional connectivity of the thalamus is altered in cocaine dependent patients (PCD, n = 54) as compared to demographically matched healthy individuals (HC, n = 54). The results of a generalized psychophysiological interaction analysis showed negative thalamic connectivity with the ventral medial prefrontal cortex (vmPFC), in the area of perigenual and subgenual anterior cingulate cortex, in HC but not PCD ($p < 0.05$, corrected, two-sample t test). This difference in functional connectivity was not observed for task-residual signals, suggesting that it is specific to task-related processes during cognitive control. Further, the thalamic-vmPFC connectivity is positively correlated with the amount of cocaine use in the prior month for female but not for male PCD. These findings add to recent literature and provide additional evidence for circuit-level biomarkers of cocaine dependence.

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PMID: 24936409 [Indexed for MEDLINE]

110. Hum Brain Mapp. 2014 Nov;35(11):5379-88. doi: 10.1002/hbm.22557. Epub 2014 May 23.

The effects of methylphenidate on whole brain intrinsic functional connectivity.

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Methylphenidate (MPH) is an indirect dopaminergic and noradrenergic agonist that is used to treat attention deficit hyperactivity disorder and that has shown therapeutic potential in neuropsychiatric diseases such as depression, dementia, and Parkinson's disease. While effects of MPH on task-induced brain activation have been investigated, little is known about how MPH influences the resting brain. To investigate the effects of 40 mg of oral MPH on intrinsic functional connectivity, we used resting state fMRI in 54 healthy male subjects in a double-blind, randomized, placebo-controlled study. Functional connectivity analysis employing ICA revealed seven resting state networks (RSN) of interest. Connectivity strength between the dorsal attention network and the thalamus was increased after MPH intake. Other RSN located in association cortex areas, such as the left and right frontoparietal networks and the executive control network, showed MPH-induced connectivity increase to sensory-motor and visual cortex regions and connectivity decrease to cortical and subcortical components of cortico-striato-thalamo-cortical circuits (CST). RSN located in sensory-motor

cortex areas showed the opposite pattern with MPH-induced connectivity increase to CST components and connectivity decrease to sensory-motor and visual cortex regions. Our results provide evidence that MPH does not only alter intrinsic connectivity between brain areas involved in sustained attention, but that it also induces significant changes in the cortico-cortical and cortico-subcortical connectivity of many other cognitive and sensory-motor RSN.

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111. JAMA Psychiatry. 2014 Jul 1;71(7):812-20. doi: 10.1001/jamapsychiatry.2014.399.

Risky decision making, prefrontal cortex, and mesocorticolimbic functional connectivity in methamphetamine dependence.

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IMPORTANCE: Various neuropsychiatric disorders, especially addictions, feature impairments in risky decision making; clarifying the neural mechanisms underlying this problem can inform treatment.

OBJECTIVE: To determine how methamphetamine-dependent and control participants differ in brain activation during a risky decision-making task, resting-state functional connectivity within mesolimbic and executive control circuits, and the relationships between these measures.

DESIGN, SETTING, AND PARTICIPANTS: A case-control, functional magnetic resonance imaging study of methamphetamine-dependent and healthy comparison participants at rest and when performing the Balloon Analogue Risk Task, which involves the choice to pump a balloon or to cash out in the context of uncertain risk. Conducted at a clinical research center at an academic institution, this study involved 25 methamphetamine-dependent and 27 control participants.

MAIN OUTCOMES AND MEASURES: Parametric modulation of activation in the striatum and right dorsolateral prefrontal cortex (rDLPFC; ie, the degree to which activation changed as a linear function of risk and potential reward), both indexed by pump number, and resting-state functional connectivity, measured in the whole brain with seeds in the midbrain and rDLPFC. Relationships between these outcomes were also tested.

RESULTS: Parametric modulation of cortical and striatal activation by pump number during risk taking differed with group. It was stronger in the ventral striatum but weaker in the rDLPFC in methamphetamine-dependent participants than control individuals. Methamphetamine-dependent participants also exhibited greater resting-state functional connectivity of the midbrain with the putamen, amygdala, and hippocampus ($P < .05$, whole brain, cluster corrected). This connectivity was negatively related to modulation of rDLPFC activation by risk level during risky

decision making. In control participants, parametric modulation of rDLPFC activation by risk during decision making was positively related to resting-state functional connectivity of the rDLPFC with the striatum.
CONCLUSIONS AND RELEVANCE: Maladaptive decision making by methamphetamine users may reflect circuit-level dysfunction, underlying deficits in task-based activation. Heightened resting-state connectivity within the mesocorticolimbic system, coupled with reduced prefrontal cortical connectivity, may create a bias toward reward-driven behavior over cognitive control in methamphetamine users. Interventions to improve this balance may enhance treatments for stimulant dependence and other disorders that involve maladaptive decision making.

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112. Int J Neuropsychopharmacol. 2014 Aug;17(8):1177-91. doi: 10.1017/S1461145714000674. Epub 2014 May 13.

The effects of methylphenidate on resting-state striatal, thalamic and global functional connectivity in healthy adults.

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By blocking dopamine and norepinephrine transporters, methylphenidate affects cognitive performance and regional brain activation in healthy individuals as well as those with neuropsychiatric disorders. Resting-state connectivity evaluates the functional integrity of a network of brain regions. Here, we examined how methylphenidate effects resting-state functional connectivity of the dorsal striatum and thalamus, areas each with dense dopaminergic and noradrenergic innervations, as well as global cerebral connectivity. We administered a single, oral dose (45 mg) to 24 healthy adults and compared resting-state connectivity to 24 demographically matched adults who did not receive any medication. The results showed that methylphenidate alters seed-based and global connectivity between the thalamus/dorsal striatum with primary motor cortex, amygdala/hippocampus and frontal executive areas ($p < 0.05$, corrected). Specifically, while methylphenidate at this dosage enhances connectivity to the motor cortex and memory circuits, it dampens prefrontal cortical connectivity perhaps by increasing catecholaminergic signalling past the 'optimal' level. These findings advance our understanding of a critical aspect of the multifaceted effects of methylphenidate on brain functions. The results may also facilitate future studies of the aetiology and treatment of neurological and psychiatric disorders that implicate catecholaminergic dysfunction.

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MRI assessment of cerebral oxygen metabolism in cocaine-addicted individuals: hypoactivity and dose dependence.

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Long-term cocaine use is known to negatively impact neural and cerebrovascular systems. However, the use of imaging markers to separately assess these parameters remains challenging. The primary reason is that most functional imaging markers, such as cerebral blood flow, functional connectivity, and task-evoked functional MRI, are known to reflect a complex interplay between neural and vascular components, thus the interpretation of the results is not straightforward. The goal of the present study is to examine neural-activity-specific changes in cocaine addiction, using cerebral metabolic rate of oxygen (CMRO2) as a surrogate marker of aggregated neural activity. We applied a recently developed CMRO2 technique in 13 cocaine-addicted subjects and 13 age- and gender-matched control subjects, and examined the impact of long-term cocaine use on CMRO2. Our results showed that CMRO2 in cocaine-addicted subjects (152 ± 16 μmol/100 g/min) is significantly lower (p = 0.031) than that in

controls (169 ± 20 µmol/100 g/min). Furthermore, the severity of this decreased metabolism is associated with lifetime cocaine use (p = 0.05). Additionally, the CMRO2 reduction was accompanied by a trend of decrease in cerebral blood flow (p = 0.058), but venous oxygenation was unaffected (p = 0.96), which suggested that the CMRO2 change may be attributed to a vascular deficiency in chronic cocaine users. To our knowledge, this is the first study to measure CMRO2 in cocaine-addicted individuals. Our findings suggest that CMRO2 may be a promising approach for assessing the long-term effects of cocaine use on the brain.

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Changes in resting functional connectivity during abstinence in stimulant use disorder: a preliminary comparison of relapsers and abstainers.

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BACKGROUND: Previously identified resting functional connectivity (FC) differences in individuals with stimulant use disorder (SUD) suggest an imbalance in neural regions that mediate behavioral aspects relevant to addiction such as emotion regulation and reward processing. There is a need to further investigate these differences across time between those that relapse and those that do not. This is the first longitudinal study of recently abstinent SUD (SUD-RA) that identifies specific FC changes in subsequent relapsers (vs abstainers). We hypothesized that (1) subsequent relapsers (vs abstainers) will show lower FC of emotion regulation regions and higher FC of reward processing regions and (2) FC differences would be more evident across time.

METHODS: We examined resting FC in 18 SUD-RAs (8 females, age: M=22.05 ± 2.64) and 15 non-substance abusing controls (NSAC; 5 females, age: M=24.21 ± 5.76) at Time 1 (abstinent ~5 weeks). Fourteen NSAC and 12 SUD-RAs were re-examined at Time 2 (abstinent ~13 weeks). With seed-based FC measures, we examined FC differences between SUD-RAs that abstained or relapsed over the subsequent 6 months.

RESULTS: Relapsers (vs abstainers) had higher FC between (1) nucleus accumbens (NAcc) and left frontopolar cortex (FPC), (2) NAcc and posterior cingulate gyrus and (3) subgenual anterior cingulate and left FPC at Time 1. Relapsers (vs

abstainers) showed larger reduction in FC strength within these regions across time.

CONCLUSIONS: Resting FC reduction found in relapsers (vs. abstainers) from 5 to 13 weeks of abstinence may be a biological marker of relapse vulnerability. These preliminary findings require replication with larger sample sizes.

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Amphetamine sensitization alters reward processing in the human striatum and amygdala.

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Dysregulation of mesolimbic dopamine transmission is implicated in a number of psychiatric illnesses characterised by disruption of reward processing and goal-directed behaviour, including schizophrenia, drug addiction and impulse control disorders associated with chronic use of dopamine agonists. Amphetamine sensitization (AS) has been proposed to model the development of this aberrant dopamine signalling and the subsequent dysregulation of incentive motivational processes. However, in humans the effects of AS on the dopamine-sensitive neural circuitry associated with reward processing remains unclear. Here we describe the effects of acute amphetamine administration, following a sensitising dosage regime, on blood oxygen level dependent (BOLD) signal in dopaminoceptive brain

regions during a rewarded gambling task performed by healthy volunteers. Using a randomised, double-blind, parallel-groups design, we found clear evidence for sensitization to the subjective effects of the drug, while rewarded reaction times were unchanged. Repeated amphetamine exposure was associated with reduced dorsal striatal BOLD signal during decision making, but enhanced ventromedial caudate activity during reward anticipation. The amygdala BOLD response to reward outcomes was blunted following repeated amphetamine exposure. Positive correlations between subjective sensitization and changes in anticipation- and outcome-related BOLD signal were seen for the caudate nucleus and amygdala, respectively. These data show for the first time in humans that AS changes the functional impact of acute stimulant exposure on the processing of reward-related information within dopaminoceptive regions. Our findings accord with pathophysiological models which implicate aberrant dopaminergic modulation of striatal and amygdala activity in psychosis and drug-related compulsive disorders.

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Nipping cue reactivity in the bud: baclofen prevents limbic activation elicited by subliminal drug cues.

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Relapse is a widely recognized and difficult to treat feature of the addictions. Substantial evidence implicates cue-triggered activation of the mesolimbic dopamine system as an important contributing factor. Even drug cues presented outside of conscious awareness (i.e., subliminally) produce robust activation within this circuitry, indicating the sensitivity and vulnerability of the brain to potentially problematic reward signals. Because pharmacological agents that prevent these early cue-induced responses could play an important role in relapse prevention, we examined whether baclofen-a GABAB receptor agonist that reduces mesolimbic dopamine release and conditioned drug responses in laboratory animals-could inhibit mesolimbic activation elicited by subliminal cocaine cues in cocaine-dependent individuals. Twenty cocaine-dependent participants were randomized to receive baclofen (60 mg/d; 20 mg t.i.d.) or placebo. Event-related BOLD fMRI and a backward-masking paradigm were used to examine the effects of baclofen on subliminal cocaine (vs neutral) cues. Sexual and aversive cues were included to examine specificity. We observed that baclofen-treated participants displayed significantly less activation in response to subliminal cocaine (vs neutral) cues, but not sexual or aversive (vs neutral) cues, than placebo-treated participants in a large interconnected bilateral cluster spanning the ventral

striatum, ventral pallidum, amygdala, midbrain, and orbitofrontal cortex (voxel threshold $p < 0.005$; cluster corrected at $p < 0.05$). These results suggest that baclofen may inhibit the earliest type of drug cue-induced motivational processing-that which occurs outside of awareness-before it evolves into a less manageable state.

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Coupled Intrinsic Connectivity Distribution analysis: a method for exploratory connectivity analysis of paired FMRI data.

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We present a novel voxel-based connectivity approach for paired functional magnetic resonance imaging (fMRI) data collected under two different conditions labeled the Coupled Intrinsic Connectivity Distribution (coupled-ICD). Our proposed method jointly models both conditions to incorporate additional paired information into the connectivity metric. Voxel-based connectivity holds promise as a clinical tool to characterize a wide range of neurological and psychiatric diseases, and monitor their treatment. As such, examining paired connectivity data such as scans acquired pre- and post-intervention is an important application for connectivity methodologically. When presented with data from paired conditions, conventional voxel-based methods analyze each condition separately. However, summarizing each connection separately can misrepresent patterns of changes in connectivity. We show that commonly used methods can underestimate functional changes and subsequently introduce and evaluate our solution to this problem, the coupled-ICD metric, using two studies: 1) healthy controls scanned awake and under anesthesia, and 2) cocaine-dependent subjects and healthy controls scanned while being presented with relaxing or drug-related imagery cues. The coupled-ICD approach detected differences between paired

conditions in similar brain regions as the conventional approaches while also revealing additional changes in regions not identified using conventional voxel-based connectivity analyses. Follow-up seed-based analyses on data independent from the voxel-based results also showed connectivity differences between conditions in regions detected by coupled-ICD. This approach of jointly analyzing paired resting-state scans provides a new and important tool with many applications for clinical and basic neuroscience research.

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118. Front Psychiatry. 2014 Feb 27;5:16. doi: 10.3389/fpsyt.2014.00016. eCollection 2014.

Cortico-amygdala coupling as a marker of early relapse risk in cocaine-addicted individuals.

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Addiction to cocaine is a chronic condition characterized by high rates of early relapse. This study builds on efforts to identify neural markers of relapse risk by studying resting-state functional connectivity (rsFC) in neural circuits arising from the amygdala, a brain region implicated in relapse-related processes including craving and reactivity to stress following acute and protracted withdrawal from cocaine. Whole-brain resting-state functional magnetic resonance imaging connectivity (6 min) was assessed in 45 cocaine-addicted individuals and 22 healthy controls. Cocaine-addicted individuals completed scans in the final week of a residential treatment episode. To approximate preclinical models of relapse-related circuitry, separate seeds were derived for the left and right basolateral (BLA) and corticomedial (CMA) amygdala. Participants also completed the Iowa Gambling Task, Wisconsin Card Sorting Test, Cocaine Craving Questionnaire, Obsessive-Compulsive Cocaine Use Scale and Personality Inventory. Relapse within the first 30 days post-treatment (n = 24) was associated with reduced rsFC between the left CMA and ventromedial prefrontal cortex/rostral anterior cingulate cortex (vmPFC/rACC) relative to cocaine-addicted individuals who remained abstinent (non-relapse, n = 21). Non-relapse participants evidenced reduced rsFC between the bilateral BLA and visual processing regions (lingual gyrus/cuneus) compared to controls and relapsed participants. Early relapse was associated with fewer years of education but unrelated to trait reactivity to stress, neurocognitive and clinical characteristics or cocaine use history. Findings suggest that rsFC within neural circuits implicated in preclinical models of relapse may provide a promising marker of relapse risk in cocaine-addicted individuals. Future efforts to replicate the current findings and alter connectivity within these circuits may yield novel interventions and

improve treatment outcomes.

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119. J Alzheimers Dis. 2014;41(1):101-12. doi: 10.3233/JAD-132360.

Acute caffeine administration effect on brain activation patterns in mild cognitive impairment.

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Previous studies showed that acute caffeine administration enhances task-related brain activation in elderly individuals with preserved cognition. To explore the effects of this widely used agent on cognition and brain activation in early phases of cognitive decline, we performed a double-blinded, placebo-controlled functional magnetic resonance imaging (fMRI) study during an n-back working memory task in 17 individuals with mild cognitive impairment (MCI) compared to 17

age-matched healthy controls (HC). All individuals were regular caffeine consumers with an overnight abstinence and given 200 mg caffeine versus placebo tablets 30 minutes before testing. Analyses included assessment of task-related activation (general linear model), functional connectivity (tensorial-independent component analysis, TICA), baseline perfusion (arterial spin labeling, ASL), grey matter density (voxel-based morphometry, VBM), and white matter microstructure (tract-based spatial statistics, TBSS). Acute caffeine administration induced a focal activation of the prefrontal areas in HC with a more diffuse and posteromedial activation pattern in MCI individuals. In MCI, TICA documented a significant caffeine-related enhancement in the prefrontal cortex, supplementary motor area, ventral premotor and parietal cortex as well as the basal ganglia and cerebellum. The absence of significant group differences in baseline ASL perfusion patterns supports a neuronal rather than a purely vascular origin of these differences. The VBM and TBSS analyses excluded potentially confounding differences in grey matter density and white matter microstructure between MCI and HC. The present findings suggest a posterior displacement of working memory-related brain activation patterns after caffeine administration in MCI that may represent a compensatory mechanism to counterbalance a frontal lobe dysfunction.

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120. Psychiatry Res. 2014 Mar 30;221(3):220-30. doi: 10.1016/j.pscychresns.2014.01.005. Epub 2014 Jan 23.

Chronic cocaine administration causes extensive white matter damage in brain: diffusion tensor imaging and immunohistochemistry studies.

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The effect of chronic cocaine exposure on multiple white matter structures in rodent brain was examined using diffusion tensor imaging (DTI), locomotor behavior, and end point histology. The animals received either cocaine at a dose of 100mg/kg (N=19), or saline (N=17) for 28 days through an implanted osmotic minipump. The animals underwent serial DTI scans, locomotor assessment, and end point histology for determining the expressions of myelin basic protein (MBP), neurofilament-heavy protein (NF-H), proteolipid protein (PLP), Nogo-A, aquaporin-4 (AQP-4), and growth associated protein-43 (GAP-43). Differences in the DTI measures were observed in the splenium (scc) and genu (gcc) of the corpus callosum (cc), fimbria (fi), and the internal capsule (ic). A significant increase in the activity in the fine motor movements and a significant decrease in the number of rearing events were observed in the cocaine-treated animals.

Reduced MBP and Nogo-A and increased GAP-43 expressions were most consistently observed in these structures. A decrease in the NF-H expression was observed in fi and ic. The reduced expression of Nogo-A and the increased expression of GAP-43 may suggest destabilization of axonal connectivity and increased neurite growth with aberrant connections. Increased GAP-43 suggests drug-induced plasticity or a possible repair mechanism response. The findings indicated that multiple white matter tracts are affected following chronic cocaine exposure.

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Pharmaco-MEG evidence for attention related hyper-connectivity between auditory and prefrontal cortices in ADHD.

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The ability to attend to particular stimuli while ignoring others is crucial in goal-directed activities and has been linked with prefrontal cortical regions, including the dorsolateral prefrontal cortex (DLPFC). Both hyper- and hypo-activation in the DLPFC has been reported in patients with attention-deficit/hyperactivity disorder (ADHD) during many different cognitive tasks, but the network-level effects of such aberrant activity remain largely unknown. Using magnetoencephalography (MEG), we examined functional connectivity between regions of the DLPFC and the modality-specific auditory cortices during an auditory attention task in medicated and un-medicated adults with ADHD, and those without ADHD. Participants completed an attention task in two separate sessions (medicated/un-medicated), and each session consisted of two blocks

(attend and no-attend). All MEG data were coregistered to structural MRI, corrected for head motion, and projected into source space. Subsequently, we computed the phase coherence (i.e., functional connectivity) between DLPFC regions and the auditory cortices. We found that un-medicated adults with ADHD exhibited greater phase coherence in the beta (14-30Hz) and gamma frequency (30-56Hz) range in attend and no-attend conditions compared to controls. Stimulant medication attenuated these differences, but did not fully eliminate them. These results suggest that aberrant bottom-up processing may engulf executive resources in ADHD.

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The Effects of Acutely Administered 3,4-Methylenedioxymethamphetamine on Spontaneous Brain Function in Healthy Volunteers Measured with Arterial Spin Labeling and Blood Oxygen Level-Dependent Resting State Functional Connectivity.

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Comment in

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BACKGROUND: The compound 3,4-methylenedioxymethamphetamine (MDMA) is a potent monoamine releaser that produces an acute euphoria in most individuals.
METHODS: In a double-blind, placebo-controlled, balanced-order study, MDMA was orally administered to 25 physically and mentally healthy individuals. Arterial spin labeling and seed-based resting state functional connectivity (RSFC) were used to produce spatial maps displaying changes in cerebral blood flow (CBF) and RSFC after MDMA administration. Participants underwent two arterial spin labeling and two blood oxygen level-dependent scans in a 90-minute scan session; MDMA and placebo study days were separated by 1 week.
RESULTS: Marked increases in positive mood were produced by MDMA. Decreased CBF only was observed after MDMA, and this was localized to the right medial temporal lobe (MTL), thalamus, inferior visual cortex, and the somatosensory cortex. Decreased CBF in the right amygdala and hippocampus correlated with ratings of the intensity of global subjective effects of MDMA. The RSFC results complemented the CBF results, with decreases in RSFC between midline cortical regions, the medial prefrontal cortex, and MTL regions, and increases between the amygdala and hippocampus. There were trend-level correlations between these effects and ratings of intense and positive subjective effects.
CONCLUSIONS: The MTLs appear to be specifically implicated in the mechanism of action of MDMA, but further work is required to elucidate how the drug's characteristic subjective effects arise from its modulation of spontaneous brain activity.

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Methylphenidate and brain activity in a reward/conflict paradigm: role of the insula in task performance.

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Psychostimulants, such as methylphenidate, are thought to improve information processing in motivation-reward and attention-activation networks by enhancing the effects of more relevant signals and suppressing those of less relevant ones; however the nature of such reciprocal influences remains poorly understood. To explore this question, we tested the effect of methylphenidate on performance and associated brain activity in the Anticipation, Conflict, Reward (ACR) task.
Sixteen healthy adult volunteers, ages 21-45, were scanned twice using functional magnetic resonance imaging (fMRI) as they performed the ACR task under placebo and methylphenidate conditions. A three-way repeated measures analysis of variance, with cue (reward vs. non-reward), target (congruent vs. incongruent) and medication condition (methylphenidate vs. placebo) as the factors, was used to analyze behaviors on the task. Blood oxygen level dependent (BOLD) signals, reflecting task-related neural activity, were evaluated using linear contrasts.
Participants exhibited significantly greater accuracy in the methylphenidate condition than the placebo condition. Compared with placebo, the methylphenidate condition also was associated with lesser task-related activity in components of attention-activation systems irrespective of the reward cue, and less task-related activity in components of the reward-motivation system, particularly the insula, during reward trials irrespective of target difficulty. These results

suggest that methylphenidate enhances task performance by improving efficiency of information processing in both reward-motivation and in attention-activation systems.

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Functional changes of the reward system underlie blunted response to social gaze in cocaine users.

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Comment in

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Social interaction deficits in drug users likely impede treatment, increase the

burden of the affected families, and consequently contribute to the high costs for society associated with addiction. Despite its significance, the neural basis of altered social interaction in drug users is currently unknown. Therefore, we investigated basal social gaze behavior in cocaine users by applying behavioral, psychophysiological, and functional brain-imaging methods. In study I, 80 regular cocaine users and 63 healthy controls completed an interactive paradigm in which the participants' gaze was recorded by an eye-tracking device that controlled the gaze of an anthropomorphic virtual character. Valence ratings of different eye-contact conditions revealed that cocaine users show diminished emotional engagement in social interaction, which was also supported by reduced pupil responses. Study II investigated the neural underpinnings of changes in social reward processing observed in study I. Sixteen cocaine users and 16 controls completed a similar interaction paradigm as used in study I while undergoing functional magnetic resonance imaging. In response to social interaction, cocaine users displayed decreased activation of the medial orbitofrontal cortex, a key region of reward processing. Moreover, blunted activation of the medial orbitofrontal cortex was significantly correlated with a decreased social network size, reflecting problems in real-life social behavior because of reduced social reward. In conclusion, basic social interaction deficits in cocaine users as observed here may arise from altered social reward processing. Consequently, these results point to the importance of reinstatement of social reward in the treatment of stimulant addiction.

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125. Neuropsychopharmacology. 2014 Jun;39(7):1578-93. doi: 10.1038/npp.2014.2. Epub 2014 Jan 20.

Antipsychotic drug-like effects of the selective M4 muscarinic acetylcholine receptor positive allosteric modulator VU0152100.

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Accumulating evidence suggests that selective M4 muscarinic acetylcholine receptor (mAChR) activators may offer a novel strategy for the treatment of psychosis. However, previous efforts to develop selective M4 activators were unsuccessful because of the lack of M4 mAChR subtype specificity and off-target muscarinic adverse effects. We recently developed VU0152100, a highly selective M4 positive allosteric modulator (PAM) that exerts central effects after systemic administration. We now report that VU0152100 dose-dependently reverses amphetamine-induced hyperlocomotion in rats and wild-type mice, but not in M4 KO mice. VU0152100 also blocks amphetamine-induced disruption of the acquisition of contextual fear conditioning and prepulse inhibition of the acoustic startle reflex. These effects were observed at doses that do not produce catalepsy or peripheral adverse effects associated with non-selective mAChR agonists. To further understand the effects of selective potentiation of M4 on region-specific brain activation, VU0152100 alone and in combination with amphetamine were evaluated using pharmacologic magnetic resonance imaging (phMRI). Key neural substrates of M4-mediated modulation of the amphetamine response included the nucleus accumbens (NAS), caudate-putamen (CP), hippocampus, and medial thalamus. Functional connectivity analysis of phMRI data, specifically assessing correlations in activation between regions, revealed several brain networks involved in the M4 modulation of amphetamine-induced brain activation, including the NAS and retrosplenial cortex with motor cortex, hippocampus, and medial thalamus. Using in vivo microdialysis, we found that VU0152100 reversed amphetamine-induced increases in extracellular dopamine levels in NAS and CP. The present data are consistent with an antipsychotic drug-like profile of activity

for VU0152100. Taken together, these data support the development of selective M4 PAMs as a new approach to the treatment of psychosis and cognitive impairments associated with psychiatric disorders such as schizophrenia.

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126. Neuropsychopharmacology. 2014 May;39(6):1379-87. doi: 10.1038/npp.2013.333. Epub 2013 Dec 6.

Attenuated insular processing during risk predicts relapse in early abstinent methamphetamine-dependent individuals.

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There is some evidence that neuroimaging can be used to predict relapse among

abstinent methamphetamine-dependent (MD) individuals. However, it remains unclear what cognitive and neural processes contribute to relapse. This investigation examined whether insula activation during risk-taking decisions-a process shown to be disrupted in MD-is able to predict susceptibility for relapse. Sixty-eight MD enrolled in a treatment program during early abstinence completed a risk-taking task during functional magnetic resonance imaging. Sixty-three of the sixty-eight individuals were followed up 1 year after the study. Of these, 18 MD reported relapse. The 45 abstinent MD showed patterns of insula activation during risky decisions that resembled those found in prior studies of healthy controls, consisting of lower insula activation during safe decisions paired with higher activation during risky decisions. In contrast, the 18 relapsed MD showed similar insula activation during safe and risky decisions. An increase in one standard deviation in the difference in insula activation between risky and safe choices was associated with a 0.34 odds ratio for relapse at any given time. A median split of insula activation (difference between risky and safe) showed that individuals in the bottom half were two times more likely to relapse. In addition, a model that included several other brain regions increased prediction accuracy compared with insula-based model alone. These results suggest that failure to differentially activate the insula as a function of risk is a part of an altered risk-processing network associated with an increased susceptibility to relapse.

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127. Biol Psychiatry. 2014 Oct 15;76(8):616-28. doi: 10.1016/j.biopsych.2013.10.016. Epub 2013 Oct 24.

Effects of stimulants on brain function in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis.

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Comment in

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BACKGROUND: Psychostimulant medication, most commonly the catecholamine agonist methylphenidate, is the most effective treatment for attention-deficit/hyperactivity disorder (ADHD). However, relatively little is

known on the mechanisms of action. Acute effects on brain function can elucidate underlying neurocognitive effects. We tested methylphenidate effects relative to placebo in functional magnetic resonance imaging (fMRI) during three disorder-relevant tasks in medication-naïve ADHD adolescents. In addition, we conducted a systematic review and meta-analysis of the fMRI findings of acute stimulant effects on ADHD brain function.

METHODS: The fMRI study compared 20 adolescents with ADHD under either placebo or methylphenidate in a randomized controlled trial while performing stop, working memory, and time discrimination tasks. The meta-analysis was conducted searching PubMed, ScienceDirect, Web of Knowledge, Google Scholar, and Scopus databases. Peak coordinates of clusters of significant effects of stimulant medication relative to placebo or off medication were extracted for each study.

RESULTS: The fMRI analysis showed that methylphenidate significantly enhanced activation in bilateral inferior frontal cortex (IFC)/insula during inhibition and time discrimination but had no effect on working memory networks. The meta-analysis, including 14 fMRI datasets and 212 children with ADHD, showed that stimulants most consistently enhanced right IFC/insula activation, which also remained for a subgroup analysis of methylphenidate effects alone. A more lenient threshold also revealed increased putamen activation.

CONCLUSIONS: Psychostimulants most consistently increase right IFC/insula activation, which are key areas of cognitive control and also the most replicated neurocognitive dysfunction in ADHD. These neurocognitive effects may underlie their positive clinical effects.

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128. Neurosci Biobehav Rev. 2014 Jan;38:1-16. doi: 10.1016/j.neubiorev.2013.10.013. Epub 2013 Nov 6.

Factors modulating neural reactivity to drug cues in addiction: a survey of human neuroimaging studies.

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Human neuroimaging studies suggest that neural cue reactivity is strongly associated with indices of drug use, including addiction severity and treatment success. However, little is known about factors that modulate cue reactivity. The

goal of this review, in which we survey published fMRI and PET studies on drug cue reactivity in cocaine, alcohol, and tobacco cigarette users, is to highlight major factors that modulate brain reactivity to drug cues. First, we describe cue reactivity paradigms used in neuroimaging research and outline the brain circuits that underlie cue reactivity. We then discuss major factors that have been shown to modulate cue reactivity and review specific evidence as well as outstanding questions related to each factor. Building on previous model-building reviews on the topic, we then outline a simplified model that includes the key modulatory factors and a tentative ranking of their relative impact. We conclude with a discussion of outstanding challenges and future research directions, which can inform future neuroimaging studies as well as the design of treatment and prevention programs.

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Striatal-insula circuits in cocaine addiction: implications for impulsivity and relapse risk.

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BACKGROUND: Dysregulated striatal functioning coupled with executive control deficits arising from abnormal frontal cortical function are considered key mechanisms in the development and maintenance of cocaine addiction. The same features are thought to underlie high trait impulsivity observed in cocaine-addicted populations.

OBJECTIVES: Employing resting state functional connectivity, the current study sought to identify cortico-striatal circuit alterations in cocaine addiction and examine the degree to which circuit connectivity contributes to relapse risk and impulsivity among cocaine-addicted individuals.

METHODS: Whole-brain resting-state functional magnetic resonance imaging connectivity was assessed in 45 cocaine-addicted individuals relative to 22 healthy controls using seed volumes in the left and right caudate, putamen and nucleus accumbens. Cocaine-addicted individuals completed scans in the final week of a 2-4 weeks residential treatment episode. Relapse by day 30 post-discharge served to separate cocaine-addicted individuals into relapse and non-relapse groups. All participants completed the Barratt Impulsivity Scale (BIS-11a).

RESULTS: Cocaine-addicted individuals exhibited reduced positive connectivity between the bilateral putamen and posterior insula and right postcentral gyrus. Group differences were primarily driven by reduced connectivity in relapse individuals relative to controls. No relapse versus non-relapse differences emerged. Impulsivity (BIS-11a) was higher in cocaine-addicted participants, an effect that was partially mediated by reduced putamen-posterior insula

connectivity in this group.

CONCLUSION: Cocaine addiction, relapse risk and impulsivity were associated with reduced connectivity in putamen-posterior insula/postcentral gyrus circuits implicated in temporal discounting and habitual responding. Findings provide new insight into the neurobiological mechanisms underlying impulsivity and relapse in cocaine addiction.

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130. Am J Drug Alcohol Abuse. 2013 Nov;39(6):403-13. doi: 10.3109/00952990.2013.848211.

An intrinsic connectivity network approach to insula-derived dysfunctions among cocaine users.

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BACKGROUND: Addiction is a complex phenotype, though it consistently includes characteristics of impulsivity. A number of brain regions are suggested to be involved in cocaine addiction, including the insula, which serves diverse functions including interoceptive awareness and integration of neural signals

from sensory, subcortical and frontal regions. Malfunction of this integration links impulsive behavior to the insula.

OBJECTIVES: This study examines intrinsic connectivity of the insula in chronic cocaine users to investigate abnormal insular circuitry, its role in cocaine addiction, and relationships to measure of impulsivity.

METHODS: Cocaine-dependent individuals (n = 33) and healthy controls (n = 32) completed a resting-state fMRI scan. An intrinsic connectivity network (ICN) approach generated metrics of mean network connectivity and inter-network connectivity from fMRI data. Metrics pertaining to ICNs involving insula and other structures repeatedly involved in addiction (e.g. striatum) were selected for analysis, which included the capacity to discriminate groups. Relationships between group discriminating connectivity metrics and behavioral impulsivity were examined.

RESULTS: Models demonstrated group prediction accuracy up to 75%. Accuracy of 69% was obtained by a parsimonious model of six inter-network connectivity metrics. The inter-network connectivity between an ICN involving the anterior insula and ACC, and an ICN involving the striatum, was significantly weaker in cocaine users relative to controls. The degree of reduced inter-network connectivity was significantly related to greater non-planning impulsivity in cocaine users.

CONCLUSIONS: Aberrant insula-derived intrinsic connectivity patterns are observed in cocaine users and include dysfunctions in insula to striatal connectivity, which is furthermore linked to increased impulsivity pertaining to forethought.

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131. Am J Drug Alcohol Abuse. 2013 Nov;39(6):392-402. doi:
10.3109/00952990.2013.841711.

A preliminary investigation of Stroop-related intrinsic connectivity in cocaine dependence: associations with treatment outcomes.

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BACKGROUND: Cocaine-dependent individuals demonstrate neural and behavioral differences compared to healthy comparison subjects when performing the Stroop color-word interference test. Stroop measures also relate to treatment outcome for cocaine dependence. Intrinsic connectivity analyses assess the extent to which task-related regional brain activations are related to each other in the absence of defining a priori regions of interest.
OBJECTIVE: This study examined 1) the extent to which cocaine-dependent and non-addicted individuals differed on measures of intrinsic connectivity during fMRI Stroop performance; and 2) the relationships between fMRI Stroop intrinsic connectivity and treatment outcome in cocaine dependence.
METHODS: Sixteen treatment-seeking cocaine-dependent patients and matched non-addicted comparison subjects completed an fMRI Stroop task. Between-group differences in intrinsic connectivity were assessed and related to self-reported and urine-toxicology-based cocaine-abstinence measures.

RESULTS: Cocaine-dependent patients vs. comparison subjects showed less intrinsic connectivity in cortical and subcortical regions. When adjusting for individual degree of intrinsic connectivity, cocaine-dependent vs. comparison subjects showed relatively greater intrinsic connectivity in the ventral striatum, putamen, inferior frontal gyrus, anterior insula, thalamus and substantia nigra. Non-mean-adjusted intrinsic-connectivity measures in the midbrain, thalamus, ventral striatum, substantia nigra, insula and hippocampus negatively correlated with measures of cocaine abstinence.
CONCLUSION: The diminished intrinsic connectivity in cocaine-dependent vs. comparison subjects suggests poorer communication across brain regions during cognitive-control processes. In mean-adjusted analyses, the cocaine-dependent group displayed relatively greater Stroop-related connectivity in regions implicated in motivational processes in addictions. The relationships between treatment outcomes and connectivity in the midbrain and basal ganglia suggest that connectivity represents a potential treatment target.

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132. Neuropsychopharmacology. 2014 Apr;39(5):1135-47. doi: 10.1038/npp.2013.314. Epub 2013 Nov 7.

Individual differences in attentional bias associated with cocaine dependence are related to varying engagement of neural processing networks.

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Cocaine and other drug dependencies are associated with significant attentional bias for drug use stimuli that represents a candidate cognitive marker of drug dependence and treatment outcomes. We explored, using fMRI, the role of discrete neural processing networks in the representation of individual differences in the drug attentional bias effect associated with cocaine dependence (AB-coc) using a word counting Stroop task with personalized cocaine use stimuli (cocStroop). The cocStroop behavioral and neural responses were further compared with those associated with a negative emotional word Stroop task (eStroop) and a neutral word counting Stroop task (cStroop). Brain-behavior correlations were explored using both network-level correlation analysis following independent component analysis (ICA) and voxel-level, brain-wide univariate correlation analysis. Variation in the attentional bias effect for cocaine use stimuli among cocaine-dependent men and women was related to the recruitment of two separate neural processing networks related to stimulus attention and salience attribution (inferior frontal-parietal-ventral insula), and the processing of the negative affective properties of cocaine stimuli (frontal-temporal-cingulate). Recruitment of a sensory-motor-dorsal insula network was negatively correlated with AB-coc and suggested a regulatory role related to the sensorimotor processing of cocaine stimuli. The attentional bias effect for cocaine stimuli and for negative affective word stimuli were significantly correlated across individuals, and both

were correlated with the activity of the frontal-temporal-cingulate network. Functional connectivity for a single prefrontal-striatal-occipital network correlated with variation in general cognitive control (cStroop) that was unrelated to behavioral or neural network correlates of cocStroop- or eStroop-related attentional bias. A brain-wide mass univariate analysis demonstrated the significant correlation of individual attentional bias effect for cocaine stimuli with distributed activations in the frontal, occipitotemporal, parietal, cingulate, and premotor cortex. These findings support the involvement of multiple processes and brain networks in mediating individual differences in risk for relapse associated with drug dependence.

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133. Front Neuroinform. 2013 Oct 18;7:21. doi: 10.3389/fninf.2013.00021. eCollection 2013.

The Cerebral Blood Flow Biomedical Informatics Research Network (CBFBIRN) database and analysis pipeline for arterial spin labeling MRI data.

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Arterial spin labeling (ASL) is a magnetic resonance imaging technique that provides a non-invasive and quantitative measure of cerebral blood flow (CBF). After more than a decade of active research, ASL is now emerging as a robust and reliable CBF measurement technique with increased availability and ease of use. There is a growing number of research and clinical sites using ASL for neuroscience research and clinical care. In this paper, we present an online CBF Database and Analysis Pipeline, collectively called the Cerebral Blood Flow Biomedical Informatics Research Network (CBFBIRN) that allows researchers to upload and share ASL and clinical data. In addition to serving the role as a central data repository, the CBFBIRN provides a streamlined data processing infrastructure for CBF quantification and group analysis, which has the potential to accelerate the discovery of new scientific and clinical knowledge. All capabilities and features built into the CBFBIRN are accessed online using a web browser through a secure login. In this work, we begin with a general description of the CBFBIRN system data model and its architecture, then devote the remainder of the paper to the CBFBIRN capabilities. The latter part of our work is divided into two processing modules: (1) Data Upload and CBF Quantification Module; (2) Group Analysis Module that supports three types of analysis commonly used in neuroscience research. To date, the CBFBIRN hosts CBF maps and associated clinical data from more than 1,300 individual subjects. The data have been contributed by more than 20 different research studies, investigating the effect of various conditions on CBF including Alzheimer's, schizophrenia, bipolar disorder, depression, traumatic brain injury, HIV, caffeine usage, and methamphetamine abuse. Several example results, generated by the CBFBIRN processing modules, are presented. We conclude with the lessons learned during implementation and deployment of the CBFBIRN and our experience in promoting data

sharing.

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134. Neuropsychology. 2013 Nov;27(6):654-65. doi: 10.1037/a0034032. Epub 2013 Sep 16.

Estimating the passage of minutes: deviant oscillatory frontal activity in medicated and unmedicated ADHD.

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OBJECTIVE: Attention-deficit/hyperactivity disorder (ADHD) is a common and extensively treated psychiatric disorder in children, which often persists into adulthood. The core diagnostic symptoms include inappropriate levels of hyperactivity, impulsivity, and/or pervasive inattention. Another crucial aspect of the disorder involves aberrations in temporal perception, which have been well documented in behavioral studies and, recently, have been the focus of neuroimaging studies. These functional magnetic resonance imaging studies have shown reduced activation in anterior cingulate and prefrontal cortices in ADHD using a time-interval discrimination task, whereby participants distinguish intervals differing by only hundreds of milliseconds.

METHOD: We used magnetoencephalography (MEG) to evaluate the cortical network serving temporal perception during a continuous, long-duration (in minutes) time estimation experiment. Briefly, medicated and unmedicated persons with ADHD, and a control group responded each time they estimated 60 s had elapsed for an undisclosed amount of time in two separate MEG sessions. All MEG data were transformed into regional source activity, and subjected to spectral analyses to derive amplitude estimates of gamma-band activity.
RESULTS: Compared to controls, unmedicated patients were less accurate time estimators and had weaker gamma activity in the anterior cingulate, supplementary motor area, and left prefrontal cortex. After medication, these patients exhibited small but significant increases in gamma across these same neural regions and significant improvements in time estimation accuracy, which correlated with the gamma activity increases.
CONCLUSION: We found deficient gamma activity in brain areas known to be crucial for timing functions, which may underlie the day-to-day abnormalities in time perception that are common in ADHD.

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135. J Neuropsychiatry Clin Neurosci. 2013 Summer;25(3):222-8. doi: 10.1176/appi.neuropsych.12050121.

White-matter connectivity and methylphenidate-induced changes in attentional performance according to α2A-adrenergic receptor gene polymorphisms in Korean children with attention-deficit hyperactivity disorder.

Park S, Hong SB, Kim JW, Yang YH, Park MH, Kim BN, Shin MS, Yoo HJ, Cho SC.

The authors examined the association between the MspI C/G and DraI C/T genotypes of the α2A-adrenergic receptor gene and white-matter connectivity and attentional performance before and after medication in 53 children with attention-deficit hyperactivity disorder. Subjects who carried the T allele at the DraI polymorphism showed fewer changes in the mean commission error scores after 8 weeks of medication and decreased fractional anisotropy (FA) values in the right middle frontal cortex than subjects without the T allele. Subjects with the C allele at the MspI polymorphism showed decreased FA values in the right postcentral gyrus than subjects without.

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136. Neuropharmacology. 2014 Sep;84:79-89. doi: 10.1016/j.neuropharm.2013.08.023. Epub 2013 Sep 4.

Resting state functional connectivity: its physiological basis and application in neuropharmacology.

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Brain structures do not work in isolation; they work in concert to produce sensory perception, motivation and behavior. Systems-level network activity can be investigated by resting state magnetic resonance imaging (rsMRI), an emerging neuroimaging technique that assesses the synchrony of the brain's ongoing spontaneous activity. Converging evidence reveals that rsMRI is able to consistently identify distinct spatiotemporal patterns of large-scale brain networks. Dysregulation within and between these networks has been implicated in a number of neurodegenerative and neuropsychiatric disorders, including Alzheimer's disease and drug addiction. Despite wide application of this approach in systems neuroscience, the physiological basis of these fluctuations remains incompletely understood. Here we review physiological studies in electrical, metabolic and hemodynamic fluctuations that are most pertinent to the rsMRI signal. We also review recent applications to neuropharmacology - specifically drug effects on resting state fluctuations. We speculate that the mechanisms governing spontaneous fluctuations in regional oxygenation availability likely give rise to the observed rsMRI signal. We conclude by identifying several open questions surrounding this technique. This article is part of the Special Issue Section entitled 'Neuroimaging in Neuropharmacology'.

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Methylphenidate remediates error-preceding activation of the default mode brain regions in cocaine-addicted individuals.

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Many previous studies suggest the potential of psychostimulants in improving cognitive functioning. Our earlier pharmacological brain imaging study showed that intravenous methylphenidate (MPH) improves inhibitory control by altering cortico-striato-thalamic activations in cocaine-dependent (CD) individuals. Here we provide additional evidence for the effects of MPH in restoring cerebral activations during cognitive performance. Ten CD individuals performed a stop signal task (SST) during functional magnetic resonance imaging (fMRI) in two sessions, in which either MPH (0.5mg/kg body weight) or saline was administered intravenously. In the SST, a frequent go signal instructs participants to make a speeded response and a less frequent stop signal instructs them to withhold the response. Our previous work described increased activation of the

precuneus/posterior cingulate cortex and ventromedial prefrontal cortex-regions of the default mode network (DMN)-before participants committed a stop error in healthy control but not CD individuals (Bednarski et al., 2011). The current results showed that, compared to saline, MPH restored error-preceding activations of DMN regions in CD individuals. The extent of the changes in precuneus activity was correlated with MPH-elicited increase in systolic blood pressure. These findings suggest that the influence of MPH on cerebral activations may extend beyond cognitive control and provide additional evidence warranting future studies to investigate the neural mechanisms and physiological markers of the efficacy of agonist therapy in cocaine dependence.

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138. JAMA Psychiatry. 2013 Oct;70(10):1.

Reward signals, attempted suicide, and impulsivity in late-life depression.

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IMPORTANCE—Suicide can be viewed as an escape from unendurable punishment at the cost of any future rewards. Could faulty estimation of these outcomes predispose to suicidal behavior? In behavioral studies, many of those who have attempted suicide misestimate expected rewards on gambling and probabilistic learning tasks.OBJECTIVES—To describe the neural circuit abnormalities that underlie disadvantageous choices in people at risk for suicide and to relate these abnormalities to impulsivity, which is one of the components of vulnerability to suicide.DESIGN—Case-control functional magnetic resonance imaging study of reward learning using are inforcement learning model.SETTING—University hospital and outpatient clinic.PATIENTS—Fifty-three participants 60 years or older, including 15 depressed patients who had attempted suicide, 18 depressed patients who had never attempted suicide (depressed control subjects), and 20 psychiatrically healthy controls.MAIN OUTCOMES AND MEASURES—Components of the cortical blood oxygenation level–dependent response tracking expected and unpredicted rewards.RESULTS—Depressed elderly participants displayed 2 distinct disruptions of control over reward-guided behavior. First, impulsivity and a history of suicide attempts (particularly poorly planned ones) were associated with a weakened expected reward signal in the paralimbic cortex,which in turn predicted the behavioral insensitivity to contingency change. Second, depression was associated with disrupted corticostriatothalamic encoding of unpredicted rewards, which in turn predicted the behavioral over sensitivity to punishment. These results were robust to the effects of possible brain damage from suicide attempts, depressive severity, co-occurring substance use and anxiety disorders, antidepressant and anticholinergic exposure, lifetime exposure to electroconvulsive therapy, vascular illness, and incipient dementia.CONCLUSIONS AND RELEVANCE—Altered paralimbic reward signals and impulsivity and/or

carelessness may facilitate unplanned suicidal acts. This pattern, also seen in gambling and cocaine use, may reflect a primary deficit in the paralimbic cortex or in its mesolimbic input. The over reactivity to punishment in depression may be caused in part by a disruption of appetitive learning in the corticostriatothalamic circuits.

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PMID: 23925710 [Indexed for MEDLINE]

139. Neuropsychopharmacology. 2014 Feb;39(3):545-55. doi: 10.1038/npp.2013.189. Epub 2013 Aug 6.

Neural correlates of reward-based spatial learning in persons with cocaine dependence.

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Dysfunctional learning systems are thought to be central to the pathogenesis of and impair recovery from addictions. The functioning of the brain circuits for episodic memory or learning that support goal-directed behavior has not been studied previously in persons with cocaine dependence (CD). Thirteen abstinent CD and 13 healthy participants underwent MRI scanning while performing a task that requires the use of spatial cues to navigate a virtual-reality environment and find monetary rewards, allowing the functional assessment of the brain systems for spatial learning, a form of episodic memory. Whereas both groups performed similarly on the reward-based spatial learning task, we identified disturbances in brain regions involved in learning and reward in CD participants. In particular, CD was associated with impaired functioning of medial temporal lobe (MTL), a brain region that is crucial for spatial learning (and episodic memory) with concomitant recruitment of striatum (which normally participates in stimulus-response, or habit, learning), and prefrontal cortex. CD was also associated with enhanced sensitivity of the ventral striatum to unexpected rewards but not to expected rewards earned during spatial learning. We provide evidence that spatial learning in CD is characterized by disturbances in functioning of an MTL-based system for episodic memory and a striatum-based system for stimulus-response learning and reward. We have found additional abnormalities in distributed cortical regions. Consistent with findings from animal studies, we provide the first evidence in humans describing the disruptive

effects of cocaine on the coordinated functioning of multiple neural systems for learning and memory.

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PMID: 23917430 [Indexed for MEDLINE]

140. Neuroimage. 2013 Dec;83:983-90. doi: 10.1016/j.neuroimage.2013.07.057. Epub 2013 Jul 27.

The amplitude of the resting-state fMRI global signal is related to EEG vigilance measures.

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In resting-state functional magnetic resonance imaging (fMRI), functional connectivity measures can be influenced by the presence of a strong global component. A widely used pre-processing method for reducing the contribution of this component is global signal regression, in which a global mean time series signal is projected out of the fMRI time series data prior to the computation of

connectivity measures. However, the use of global signal regression is controversial because the method can bias the correlation values to have an approximately zero mean and may in some instances create artifactual negative correlations. In addition, while many studies treat the global signal as a non-neural confound that needs to be removed, evidence from electrophysiological and fMRI measures in primates suggests that the global signal may contain significant neural correlates. In this study, we used simultaneously acquired fMRI and electroencephalographic (EEG) measures of resting-state activity to assess the relation between the fMRI global signal and EEG measures of vigilance in humans. We found that the amplitude of the global signal (defined as the standard deviation of the global signal) exhibited a significant negative correlation with EEG vigilance across subjects studied in the eyes-closed condition. In addition, increases in EEG vigilance due to the ingestion of caffeine were significantly associated with both a decrease in global signal amplitude and an increase in the average level of anti-correlation between the default mode network and the task-positive network.

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141. Neuropharmacology. 2013 Dec;75:246-54. doi: 10.1016/j.neuropharm.2013.06.034. Epub 2013 Jul 24.

Neurodegeneration of lateral habenula efferent fibers after intermittent cocaine administration: implications for deep brain stimulation.

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Deep brain stimulation (DBS) is an emerging technique for effective, non-pharmacological intervention in the course of neurological and neuropsychiatric diseases. Several brain targets have been suggested as suitable for DBS treatment of drug addiction. Previously, we showed that DBS of the lateral habenula (LHb) can reduce cocaine intake, facilitate extinction and attenuate drug-induced relapse in rats trained to self-administrate cocaine. Herein, we demonstrated that cocaine self-administration dose-dependently decreased connectivity between the LHb and midbrain, as shown by neurodegeneration of the main LHb efferent fiber, the fasciculus retroflexus

(FR). FR degeneration, in turn, may have caused lack of response to LHb stimulation in rats trained to self-administer high-dose cocaine (1.5 mg/kg; i.v.). Furthermore, we show that the micro-structural changes caused by cocaine can be non-invasively detected using magnetic resonance imaging and diffusion tensor imaging. Detection of cocaine-induced alterations in FR anatomy can aid the selection of potential responders to LHb stimulation for treatment of drug addiction.

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142. Neuroscience. 2013 Oct 10;250:364-71. doi: 10.1016/j.neuroscience.2013.07.021. Epub 2013 Jul 19.

Acute caffeine administration impact on working memory-related brain activation and functional connectivity in the elderly: a BOLD and perfusion MRI study.

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In young individuals, caffeine-mediated blockade of adenosine receptors and vasoconstriction has direct repercussions on task-related activations, changes in functional connectivity, as well as global vascular effects. To date, no study has explored the effect of caffeine on brain activation patterns during highly demanding cognitive tasks in the elderly. This prospective, placebo-controlled crossover design comprises 24 healthy elderly individuals (mean age 68.8 ± 4.0 years, 17 females) performing a 2-back working memory (WM) task in functional magnetic resonance imaging (fMRI). Analyses include complimentary assessment of task-related activations (general linear model, GLM), functional connectivity (tensorial independent component analysis, TICA), and baseline perfusion (arterial spin labeling). Despite a reduction in whole-brain global perfusion (-22.7%), caffeine-enhanced task-related GLM activation in a local and distributed network is most pronounced in the bilateral striatum and to a lesser degree in the right middle and inferior frontal gyrus, bilateral insula, left superior and inferior parietal lobule as well as in the cerebellum bilaterally. TICA was significantly enhanced (+8.2%) in caffeine versus placebo in a distributed and task-relevant network including the pre-frontal cortex, the supplementary motor area, the ventral premotor cortex and the parietal cortex as well as the occipital cortex (visual stimuli) and basal ganglia. The inverse comparison of placebo versus caffeine had no significant difference. Activation strength of the task-relevant-network component correlated with response accuracy for caffeine yet not for placebo, indicating a selective cognitive effect of caffeine. The present findings suggest that acute caffeine intake enhances WM-related brain activation as well as functional connectivity of blood oxygen level-dependent fMRI in elderly individuals.

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143. Neuropsychopharmacology. 2014 Jan;39(2):263-73. doi: 10.1038/npp.2013.169. Epub 2013 Jul 15.

Long-term oral methylphenidate treatment in adolescent and adult rats: differential effects on brain morphology and function.

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Methylphenidate is a widely prescribed psychostimulant for treatment of attention

deficit hyperactivity disorder (ADHD) in children and adolescents, which raises questions regarding its potential interference with the developing brain. In the present study, we investigated effects of 3 weeks oral methylphenidate (5 mg/kg) vs vehicle treatment on brain structure and function in adolescent (post-natal day [P]25) and adult (P65) rats. Following a 1-week washout period, we used multimodal magnetic resonance imaging (MRI) to assess effects of age and treatment on independent component analysis-based functional connectivity (resting-state functional MRI), D-amphetamine-induced neural activation responses (pharmacological MRI), gray and white matter tissue volumes and cortical thickness (postmortem structural MRI), and white matter structural integrity (postmortem diffusion tensor imaging (DTI)). Many age-related differences were found, including cortical thinning, white matter development, larger dopamine-mediated activation responses and increased striatal functional connectivity. Methylphenidate reduced anterior cingulate cortical network strength in both adolescents and adults. In contrast to clinical observations from ADHD patient studies, methylphenidate did not increase white matter tissue volume or cortical thickness in rat. Nevertheless, DTI-based fractional anisotropy was higher in the anterior part of the corpus callosum following adolescent treatment. Furthermore, methylphenidate differentially affected adolescents and adults as evidenced by reduced striatal volume and myelination upon adolescent treatment, although we did not observe adverse treatment effects on striatal functional activity. Our findings of small but significant age-dependent effects of psychostimulant treatment in the striatum of healthy rats highlights the importance of further research in children and adolescents that are exposed to methylphenidate.

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144. J Stroke Cerebrovasc Dis. 2013 Nov;22(8):1432-5. doi: 10.1016/j.jstrokecerebrovasdis.2013.05.038. Epub 2013 Jul 4.

123I-IMP-SPECT in a patient with cerebral proliferative angiopathy: a case report.

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Cerebral proliferative angiopathy (CPA) is a new clinical entity demonstrating a diffuse network of densely enhanced vascular abnormalities with intermingled normal brain parenchyma and is distinguishable from classical arteriovenous malformations by specific clinical and imaging markers. However, the pathophysiological nature of this disease is unclear, and there is no consensus on the treatment. We describe cerebral perfusion abnormalities in a patient with CPA by using N-isopropyl-p-[123I] iodoamphetamine single-photon emission computed tomography (123I-IMP-SPECT) and perfusion-weighted magnetic resonance imaging. The patient, a 13-year-old boy, had reversible focal neurological deficits unrelated to cerebral hemorrhage. 123I-IMP-SPECT at resting state showed preserved uptake within the vascular lesion, yet lower uptake in the area

adjacent to the lesion. In addition, acetazolamide-stressed 123I-IMP-SPECT exhibited severely impaired cerebrovascular reactivity over the affected hemisphere, suggesting that his focal neurological deficits were related to the cerebral ischemia. The perfusion abnormalities on 123I-IMP-SPECT in a CPA patient have never been previously reported. The concept of vascular malformation-related hypoperfusion is discussed.

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145. JAMA Psychiatry. 2013 Aug;70(8):857-68. doi: 10.1001/jamapsychiatry.2013.1129.

Effects of methylphenidate on resting-state functional connectivity of the mesocorticolimbic dopamine pathways in cocaine addiction.

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IMPORTANCE: Cocaine addiction is associated with altered resting-state functional connectivity among regions of the mesocorticolimbic dopamine pathways.

Methylphenidate hydrochloride, an indirect dopamine agonist, normalizes task-related regional brain activity and associated behavior in cocaine users; however, the neural systems-level effects of methylphenidate in this population have not yet been described.

OBJECTIVE: To use resting-state functional magnetic resonance imaging to examine changes in mesocorticolimbic connectivity with methylphenidate and how connectivity of affected pathways relates to severity of cocaine addiction.

DESIGN: Randomized, placebo-controlled, before-after, crossover study.

SETTING: Clinical research center.

PARTICIPANTS: Eighteen nonabstaining individuals with cocaine use disorders.

INTERVENTIONS: Single doses of oral methylphenidate (20 mg) or placebo were administered at each of 2 study sessions. At each session, resting scans were acquired twice: immediately after drug administration (before the onset of effects [baseline]) and 120 minutes later (within the window of peak effects).

MAIN OUTCOMES AND MEASURES: Functional connectivity strength was evaluated using a seed voxel correlation approach. Changes in this measure were examined to characterize the neural systems-level effects of methylphenidate; severity of cocaine addiction was assessed by interview and questionnaire.

RESULTS: Short-term methylphenidate administration reduced an abnormally strong connectivity of the ventral striatum with the dorsal striatum (putamen/globus pallidus), and lower connectivity between these regions during placebo administration uniquely correlated with less severe addiction. In contrast, methylphenidate strengthened several corticolimbic and corticocortical connections.

CONCLUSIONS AND RELEVANCE: These findings help elucidate the neural systems-level effects of methylphenidate and suggest that short-term methylphenidate can, at least transiently, remodel abnormal circuitry relevant to the pathophysiologic

characteristics of cocaine addiction. In particular, the effects of methylphenidate within striatal and cortical pathways constitute a potentially viable mechanism by which methylphenidate could facilitate control of behavior in cocaine addiction.

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PMID: 23803700 [Indexed for MEDLINE]

146. Biol Psychiatry. 2013 Oct 1;74(7):529-37. doi: 10.1016/j.biopsych.2013.04.029. Epub 2013 Jun 15.

Robust changes in reward circuitry during reward loss in current and former cocaine users during performance of a monetary incentive delay task.

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BACKGROUND: Abnormal function in reward circuitry in cocaine addiction could predate drug use as a risk factor, follow drug use as a consequence of substance-induced alterations, or both.
METHODS: We used a functional magnetic resonance imaging monetary incentive delay task (MIDT) to investigate reward-loss neural response differences among 42

current cocaine users, 35 former cocaine users, and 47 healthy subjects who also completed psychological measures and tasks related to impulsivity and reward.
RESULTS: We found various reward processing-related group differences in several MIDT phases. Across task phases we found a control > current user > former user activation pattern, except for loss outcome, where former compared with current cocaine users activated ventral tegmental area more robustly. We also found regional prefrontal activation differences during loss anticipation between cocaine-using groups. Both groups of cocaine users scored higher than control subjects on impulsivity, compulsivity and reward-punishment sensitivity factors. In addition, impulsivity-related factors correlated positively with activation in amygdala and negatively with anterior cingulate activation during loss anticipation.
CONCLUSIONS: Compared with healthy subjects, both former and current users displayed abnormal brain activation patterns during MIDT performance. Both cocaine groups differed similarly from healthy subjects, but differences between former and current users were localized to the ventral tegmental area during loss outcome and to prefrontal regions during loss anticipation, suggesting that long-term cocaine abstinence does not normalize most reward circuit abnormalities. Elevated impulsivity-related factors that relate to loss processing in current and former users suggest that these tendencies and relationships may pre-exist cocaine addiction.

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147. Drug Alcohol Depend. 2013 Aug 1;131(3):222-9. doi:
10.1016/j.drugalcdep.2013.05.009. Epub 2013 Jun 12.

Morphometric abnormalities of the lateral ventricles in methamphetamine-dependent subjects.

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BACKGROUND: The presence of morphometric abnormalities of the lateral ventricles, which can reflect focal or diffuse atrophic changes of nearby brain structures, is not well characterized in methamphetamine dependence. The current study was aimed to examine the size and shape alterations of the lateral ventricles in methamphetamine-dependent subjects.
METHODS: High-resolution brain structural images were obtained from 37 methamphetamine-dependent subjects and 25 demographically matched healthy individuals. Using a combined volumetric and surface-based morphometric approach, the structural variability of the lateral ventricles, with respect to extent and location, was examined.
RESULTS: Methamphetamine-dependent subjects had an enlarged right lateral ventricle compared with healthy individuals. Morphometric analysis revealed a

region-specific pattern of lateral ventricular expansion associated with methamphetamine dependence, which was mainly distributed in the areas adjacent to the ventral striatum, medial prefrontal cortex, and thalamus.
CONCLUSIONS: Patterns of shape decomposition in the lateral ventricles may have relevance to the structural vulnerability of the prefrontal-ventral striatal-thalamic circuit to methamphetamine-induced neurotoxicity.

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148. Drug Alcohol Depend. 2013 Nov 1;133(1):235-41. doi: 10.1016/j.drugalcdep.2013.04.029. Epub 2013 Jun 2.

Hyperactivation of the cognitive control network in cocaine use disorders during a multisensory Stroop task.

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BACKGROUND: It has been suggested that individuals with cocaine use disorders (chronic cocaine abusers, CCA) have impairments in cognitive control, which likely contribute to impairments in decision making around drug use and relapse. However, deficits in cognitive control have currently only been studied under conditions of unisensory stimulation, which may not be reflective of more realistic multisensory drug cues.
METHODS: The current study employed functional magnetic resonance imaging (fMRI) to measure neuronal activity during a multisensory numeric Stroop task.
RESULTS: Despite few differences in reaction time, recently abstinent CCA (N=14) exhibited increased activation in prefrontal cortex, striatum and thalamus during cognitive control relative to a group of carefully matched controls (N=16). Importantly, these neuronal differences were relatively robust in classifying patients from controls (approximately 90% accuracy) and evident during conditions of both low (slow stimulus presentation rate) and relatively high (faster stimulus presentation rate) cognitive demand. In addition, CCA also failed to deactivate the default-mode network during high frequency visual trials.
CONCLUSIONS: In summary, current results indicate compensatory activation within the cognitive control network in recently abstinent CCA to achieve similar levels of behavioral performance.

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149. Am J Psychiatry. 2013 Nov;170(11):1326-34. doi: 10.1176/appi.ajp.2013.12070978.

Methamphetamine-induced disruption of frontostriatal reward learning signals: relation to psychotic symptoms.

Bernacer J, Corlett PR, Ramachandra P, McFarlane B, Turner DC, Clark L, Robbins TW, Fletcher PC, Murray GK.

OBJECTIVE: Frontostriatal circuitry is critical to learning processes, and its disruption may underlie maladaptive decision making and the generation of psychotic symptoms in schizophrenia. However, there is a paucity of evidence directly examining the role of modulatory neurotransmitters on frontostriatal function in humans. In order to probe the effects of modulation on frontostriatal circuitry during learning and to test whether disruptions in learning processes may be related to the pathogenesis of psychosis, the authors explored the brain representations of reward prediction error and incentive value, two key reinforcement learning parameters, before and after methamphetamine challenge.
METHOD: Healthy volunteers (N=18) underwent functional MRI (fMRI) scanning while performing a reward learning task on three occasions: after placebo, after methamphetamine infusion (0.3 mg/kg body weight), and after pretreatment with 400 mg of amisulpride and then methamphetamine infusion. Brain fMRI representations of learning signals, calculated using a reinforcement Q-learning algorithm, were compared across drug conditions.
RESULTS: In the placebo condition, reward prediction error was coded in the ventral striatum bilaterally and incentive value in the ventromedial prefrontal

cortex bilaterally. Reward prediction error and incentive value signals were disrupted by methamphetamine in the left nucleus accumbens and left ventromedial prefrontal cortex, respectively. Psychotic symptoms were significantly correlated with incentive value disruption in the ventromedial prefrontal and posterior cingulate cortex. Amisulpride pretreatment did not significantly alter methamphetamine-induced effects.
CONCLUSIONS: The results demonstrate that methamphetamine impairs brain representations of computational parameters that underpin learning. They also demonstrate a significant link between psychosis and abnormal monoamine-regulated learning signals in the prefrontal and cingulate cortices.

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PMID: 23732871 [Indexed for MEDLINE]

150. Eur Neuropsychopharmacol. 2013 Dec;23(12):1698-707. doi: 10.1016/j.euroneuro.2013.04.012. Epub 2013 May 25.

Cocaine users with comorbid Cluster B personality disorders show dysfunctional brain activation and connectivity in the emotional regulation networks during negative emotion maintenance and reappraisal.

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Cocaine dependence often co-occurs with Cluster B personality disorders. Since both disorders are characterized by emotion regulation deficits, we predicted that cocaine comorbid patients would exhibit dysfunctional patterns of brain activation and connectivity during reappraisal of negative emotions. We recruited 18 cocaine users with comorbid Cluster B personality disorders, 17 cocaine users without comorbidities and 21 controls to be scanned using functional magnetic resonance imaging (fMRI) during performance on a reappraisal task in which they had to maintain or suppress the emotions induced by negative affective stimuli. We followed region of interest (ROI) and whole-brain approaches to investigate brain activations and connectivity associated with negative emotion experience and reappraisal. Results showed that cocaine users with comorbid personality disorders had reduced activation of the subgenual anterior cingulate cortex during negative emotion maintenance and increased activation of the lateral orbitofrontal cortex and the amygdala during reappraisal. Amygdala activation correlated with impulsivity and antisocial beliefs in the comorbid group. Connectivity analyses showed that in the cocaine comorbid group the subgenual cingulate was less efficiently connected with the amygdala and the fusiform gyri and more efficiently connected with the anterior insula during maintenance, whereas during reappraisal the left orbitofrontal cortex was more efficiently connected with the amygdala and the right orbitofrontal cortex was less efficiently connected with the dorsal striatum. We conclude that cocaine users with comorbid Cluster B personality disorders have distinctive patterns of brain activation and connectivity during maintenance and reappraisal of negative emotions, which correlate with impulsivity and dysfunctional beliefs.

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151. Neurosci Lett. 2013 Aug 26;548:110-4. doi: 10.1016/j.neulet.2013.05.029. Epub 2013 May 22.

Cocaine addiction related reproducible brain regions of abnormal default-mode network functional connectivity: a group ICA study with different model orders.

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Model order selection in group independent component analysis (ICA) has a significant effect on the obtained components. This study investigated the reproducible brain regions of abnormal default-mode network (DMN) functional connectivity related with cocaine addiction through different model order settings in group ICA. Resting-state fMRI data from 24 cocaine addicts and 24 healthy controls were temporally concatenated and processed by group ICA using model orders of 10, 20, 30, 40, and 50, respectively. For each model order, the group ICA approach was repeated 100 times using the ICASSO toolbox and after clustering the obtained components, centrotype-based anterior and posterior DMN components were selected for further analysis. Individual DMN components were

obtained through back-reconstruction and converted to z-score maps. A whole brain mixed effects factorial ANOVA was performed to explore the differences in resting-state DMN functional connectivity between cocaine addicts and healthy controls. The hippocampus, which showed decreased functional connectivity in cocaine addicts for all the tested model orders, might be considered as a reproducible abnormal region in DMN associated with cocaine addiction. This finding suggests that using group ICA to examine the functional connectivity of the hippocampus in the resting-state DMN may provide an additional insight potentially relevant for cocaine-related diagnoses and treatments.

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152. Psychiatry Res. 2013 Jul 30;213(1):47-55. doi: 10.1016/j.pscychresns.2012.12.005. Epub 2013 May 18.

Prenatal cocaine exposure alters functional activation in the ventral prefrontal cortex and its structural connectivity with the amygdala.

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Prenatal cocaine exposure (PCE) is associated with arousal dysregulation, and alterations of amygdala activity in response to emotional arousal have previously been reported. However, voluntary regulation of emotional affect, enabling appropriate neural response to different streams of stimuli, must also engage prefrontal regions, yet the impact of PCE on these prefrontal mechanisms has not been investigated. Recent neuroimaging studies have shown the involvement of ventral prefrontal cortex (vPFC) in the modulation of amygdala reactivity and the mediation of effective emotional regulation. Based on these findings, using functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), the present study compared functional activations of the vPFC as well as its structural connectivity with the amygdala between groups of PCE and control adolescents. In a working memory task with emotional distracters, the PCE adolescents exhibited less capability of increasing their vPFC activation in response to increased memory load, which corresponded with their less suppressed amygdala activation. Reduced structural connectivity between the vPFC and the amygdala was also observed from DTI measurement in the PCE group. In addition, correlations between amygdala activation and (i) vPFC activation, as well as (ii) amygdala-vPFC structural connectivity, were observed in the control but not in the PCE group. These data complement previous findings of the impact of PCE on the activity of the amygdala and extend our understanding of the neurobiological mechanisms underlying the effect of PCE on arousal dysregulation reported in human and animal studies.

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153. Psychiatry Res. 2013 Jul 30;213(1):39-46. doi: 10.1016/j.pscychresns.2013.02.007. Epub 2013 May 17.

Altered functional connectivity of the insular cortex across prefrontal networks in cocaine addiction.

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Interoception is theorized to be an important process mediating substance use disorders, and the insular cortex is recognized as a core neural region supporting interoception. The purpose of this study was to compare the integration of the insular cortex into prefrontal-related resting-state networks between individuals with cocaine dependence and healthy controls. Participants comprised 41 patients with cocaine dependence and 19 controls who underwent a resting-state 3-T functional magnetic resonance imaging scan. Individuals with cocaine dependence demonstrated altered functional connectivity of the insular cortex, predominantly the right insular cortex, with all eight prefrontal-related resting-state networks identified through Independent Component Analysis (ICA). A

conjunction analysis demonstrated that the right insular cortex was the neural region with the highest number of common group differences across the networks. There was no evidence that insular cortex connectivity commonly differed between groups for non-prefrontal-related networks. Further, seed-based functional connectivity analyses extended the network analyses and indicated that cocaine dependence was associated with greater connectivity of the right insula with the dorsomedial prefrontal cortex, inferior frontal gyrus, and bilateral dorsolateral prefrontal cortex. These data support the hypothesis that cocaine dependence is related to altered functional interactions of the insular cortex with prefrontal networks. The results suggest possible neural mechanisms by which the insular cortex and interoceptive information influence cognitive control and decision-making processes presumably mediated by prefrontal networks in the cocaine dependence process.

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154. Neuroimage. 2013 Nov 1;81:213-21. doi: 10.1016/j.neuroimage.2013.05.016. Epub 2013 May 16.

Distributed effects of methylphenidate on the network structure of the resting brain: a connectomic pattern classification analysis.

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Methylphenidate is a psychostimulant medication that produces improvements in functions associated with multiple neurocognitive systems. To investigate the potentially distributed effects of methylphenidate on the brain's intrinsic network architecture, we coupled resting state imaging with multivariate pattern classification. In a within-subject, double-blind, placebo-controlled, randomized, counterbalanced, cross-over design, 32 healthy human volunteers received either methylphenidate or placebo prior to two fMRI resting state scans separated by approximately one week. Resting state connectomes were generated by placing regions of interest at regular intervals throughout the brain, and these connectomes were submitted for support vector machine analysis. We found that methylphenidate produces a distributed, reliably detected, multivariate neural signature. Methylphenidate effects were evident across multiple resting state networks, especially visual, somatomotor, and default networks. Methylphenidate reduced coupling within visual and somatomotor networks. In addition, default network exhibited decoupling with several task positive networks, consistent with methylphenidate modulation of the competitive relationship between these networks. These results suggest that connectivity changes within and between large-scale networks are potentially involved in the mechanisms by which methylphenidate improves attention functioning.

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155. Drug Alcohol Depend. 2013 Jul 1;131(1-2):56-65. doi:
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Resting state synchrony in long-term abstinent alcoholics with versus without comorbid drug dependence.

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BACKGROUND: We previously reported that when long-term abstinent alcoholics (LTAA; with no drug comorbidity) are compared to controls, they show increased resting state synchrony (RSS) in the executive control network and reduced RSS in the appetitive drive network suggestive of compensatory mechanisms that may facilitate abstinence. The aim of the present study was to investigate whether long-term abstinent alcoholics with comorbid stimulants dependence (LTAAS) show similar RSS mechanisms.
METHODS: Resting-state functional MRI data were collected on 36 LTAAS (20 females, age: 47.85±7.30), 23 LTAA (8 females, age: M=47.91±6.76), and 23

non-substance abusing controls (NSAC; 8 females, age: M=47.99±6.70). Using seed-based measures, we examined RSS with the nucleus accumbens (NAcc) and the subgenual anterior cingulate cortex (sgACC).

RESULTS: Results showed commonalities in LTAA and LTAAS RSS (similar enhanced executive control RSS and left insula RSS) as well as differences (no attenuation of appetitive drive RSS in LTAAS and no enhancement of RSS in right insula in LTAA).

CONCLUSIONS: We believe these differences are adaptive mechanisms that support abstinence. These findings suggest common as well as specific targets for treatment in chronic alcoholics with vs without comorbid stimulant dependence.

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156. Psychopharmacology (Berl). 2013 Sep;229(2):219-26. doi: 10.1007/s00213-013-3105-x. Epub 2013 Apr 19.

Methylphenidate reduces functional connectivity of nucleus accumbens in brain reward circuit.

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Release of dopamine in the nucleus accumbens (NAcc) is essential for acute drug reward. The present study was designed to trace the reinforcing effect of dopamine release by measuring the functional connectivity (FC) between the NAcc and brain regions involved in a limbic cortical-subcortical circuit during a dopaminergic challenge. Twenty healthy volunteers received single doses of methylphenidate (40 mg) and placebo on separate test days according to a double-blind, cross-over study design. Resting state functional magnetic resonance imaging (fMRI) was measured between 1.5 and 2 h postdosing. FC between regions of interest (ROI) in the NAcc, the medial dorsal nucleus (MDN) of the thalamus and remote areas within the limbic circuit was explored. Methylphenidate significantly reduced FC between the NAcc and the basal ganglia (i.e., subthalamic nucleus and ventral pallidum (VP)), relative to placebo. Methylphenidate also decreased FC between the NAcc and the medial prefrontal cortex (mPFC) as well as the temporal cortex. Methylphenidate did not affect FC between MDN and the limbic circuit. It is concluded that methylphenidate directly affects the limbic reward circuit. Drug-induced changes in FC of the NAcc may serve as a useful marker of drug activity in in the brain reward circuit.

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157. Neuropharmacology. 2014 Jul;82:143-50. doi: 10.1016/j.neuropharm.2013.02.018.

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Intact inhibitory control processes in abstinent drug abusers (I): a functional neuroimaging study in former cocaine addicts.

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Neuroimaging studies in current cocaine dependent (CD) individuals consistently reveal cortical hypoactivity across regions of the response inhibition circuit (RIC). Dysregulation of this critical executive network is hypothesized to account for the lack of inhibitory control that is a hallmark of the addictive

phenotype, and chronic abuse is believed to compound the issue. A crucial question is whether deficits in this circuit persist after drug cessation, and whether recovery of this system will be seen after extended periods of abstinence, a question with implications for treatment course and outcome. Utilizing functional magnetic resonance imaging (fMRI), we examined activation in nodes of the RIC in abstinent CD individuals (n = 27) and non-using controls (n = 45) while they performed a motor response inhibition task. In contrast to current users, these abstinent individuals, despite extended histories of chronic cocaine-abuse (average duration of use = 8.2 years), performed the task just as efficiently as non-users. In line with these behavioral findings, no evidence for between-group differences in activation of the RIC was found and instead, robust activations were apparent in both groups within the well-characterized nodes of the RIC. Similarly, our complementary Electroencephalography (EEG) investigation also showed an absence of behavioral and electrophysiological deficits in abstinent drug abusers. These results are consistent with an amelioration of neurobiological deficits in inhibitory circuitry following drug cessation, and could help explain how long-term abstinence is maintained. Finally, regression analyses revealed a significant association between level of activation in the right insula with inhibition success and increased abstinence duration in the CD cohort suggesting that this region may be integral to successful recovery from cocaine addiction.

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Functional and structural neural network characterization of serotonin transporter knockout rats.

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Brain serotonin homeostasis is crucially maintained by the serotonin transporter (5-HTT), and its down-regulation has been linked to increased vulnerability for anxiety- and depression-related behavior. Studies in 5-HTT knockout (5-HTT(-/-)) rodents have associated inherited reduced functional expression of 5-HTT with increased sensitivity to adverse as well as rewarding environmental stimuli, and in particular cocaine hyperresponsivity. 5-HTT down-regulation may affect normal neuronal wiring of implicated corticolimbic cerebral structures. To further our understanding of its contribution to potential alterations in basal functional and structural properties of neural network configurations, we applied resting-state functional MRI (fMRI), pharmacological MRI of cocaine-induced activation, and diffusion tensor imaging (DTI) in 5-HTT(-/-) rats and wild-type controls (5-HTT(+/+)). We found that baseline functional connectivity values and cocaine-induced neural activity within the corticolimbic network was not significantly altered in 5-HTT(-/-) versus 5-HTT(+/+) rats. Similarly, DTI

revealed mostly intact white matter structural integrity, except for a reduced fractional anisotropy in the genu of the corpus callosum of 5-HTT(-/-) rats. At the macroscopic level, analyses of complex graphs constructed from either functional connectivity values or structural DTI-based tractography results revealed that key properties of brain network organization were essentially similar between 5-HTT(+/+) and 5-HTT(-/-) rats. The individual tests for differences between 5-HTT(+/+) and 5-HTT(-/-) rats were capable of detecting significant effects ranging from 5.8% (fractional anisotropy) to 26.1% (pharmacological MRI) and 29.3% (functional connectivity). Tentatively, lower fractional anisotropy in the genu of the corpus callosum could indicate a reduced capacity for information integration across hemispheres in 5-HTT(-/-) rats. Overall, the comparison of 5-HTT(-/-) and wild-type rats suggests mostly limited effects of 5-HTT genotype on MRI-based measures of brain morphology and function.

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159. Proc Natl Acad Sci U S A. 2013 Mar 5;110(10):4093-8. doi: 10.1073/pnas.1207531110. Epub 2013 Feb 19.

Dorsolateral caudate nucleus differentiates cocaine from natural reward-associated contextual cues.

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Chronic drug administration induces neuroplastic changes within brain circuits regulating cognitive control and/or emotions. Following repeated pairings between drug intake and environmental cues, increased sensitivity to or salience of these contextual cues provoke conscious or unconscious craving and enhance susceptibility to relapse. To explore brain circuits participating in such experience-induced plasticity, we combined functional MRI with a preclinical drug vs. food self-administration (SA) withdrawal model. Specifically, two groups of rats were trained to associate odor cues with the availability of i.v. cocaine or oral sucrose, respectively. After 20 d of cocaine or sucrose SA followed by prolonged (30 d) forced abstinence, animals were presented with odor cues previously associated with or without (S+/S-) reinforcer (cocaine/sucrose) availability while undergoing functional MRI scans. ANOVA results demonstrate that a learning effect distinguishing S+ from S- was seen in the insula and nucleus accumbens, with the insula response reflecting the individual history of cocaine SA intake. A main effect of group, distinguishing cocaine from sucrose, was seen in the medial prefrontal cortex (infralimbic, prelimbic, and cingulate cortex) and dorsolateral striatum. Critically, only the dorsomedial striatum demonstrated a double dissociation between the two SA groups and learning (S+ vs. S-). These findings demonstrate altered cortico-limbic-striatal reward-related processing to learned, environment reward-associated contextual odor cues, which may serve as potential biomarkers for therapeutic interventions.

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Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects.

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CONTEXT Functional magnetic resonance imaging studies in attention-deficit/hyperactivity disorder (ADHD) revealed fronto-striato-parietal dysfunctions during tasks of inhibition and attention. However, it is unclear whether task-dissociated dysfunctions exist and to what extent they may be influenced by age and by long-term stimulant medication use. OBJECTIVE To conduct a meta-analysis of functional magnetic resonance imaging studies in ADHD during inhibition and attention tasks, exploring age and long-term stimulant medication use effects. DATA SOURCES PubMed, ScienceDirect, Web of Knowledge, Google Scholar, and Scopus databases were searched up to May 2012 for meta-analyses. Meta-regression methods explored age and long-term stimulant medication use

effects. STUDY SELECTION Twenty-one data sets were included for inhibition (287 patients with ADHD and 320 control subjects), and 13 data sets were included for attention (171 patients with ADHD and 178 control subjects). DATA EXTRACTION Peak coordinates of clusters of significant group differences, as well as demographic, clinical, and methodological variables, were extracted for each study or were obtained from the authors. DATA SYNTHESIS Patients with ADHD relative to controls showed reduced activation for inhibition in the right inferior frontal cortex, supplementary motor area, and anterior cingulate cortex, as well as striato-thalamic areas, and showed reduced activation for attention in the right dorsolateral prefrontal cortex, posterior basal ganglia, and thalamic and parietal regions. Furthermore, the meta-regression analysis for the attention domain showed that long-term stimulant medication use was associated with more similar right caudate activation relative to controls. Age effects could be analyzed only for the inhibition meta-analysis, showing that the supplementary motor area and basal ganglia were underactivated solely in children with ADHD relative to controls, while the inferior frontal cortex and thalamus were underactivated solely in adults with ADHD relative to controls. CONCLUSIONS Patients with ADHD have consistent functional abnormalities in 2 distinct domain-dissociated right hemispheric fronto-basal ganglia networks, including the inferior frontal cortex, supplementary motor area, and anterior cingulate cortex for inhibition and dorsolateral prefrontal cortex, parietal, and cerebellar areas for attention. Furthermore, preliminary evidence suggests that long-term stimulant medication use may be associated with more normal activation in right caudate during the attention domain.

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Neural network activation during a stop-signal task discriminates cocaine-dependent from non-drug-abusing men.

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Cocaine dependence is defined by a loss of inhibitory control over drug-use behaviors, mirrored by measurable impairments in laboratory tasks of inhibitory control. The current study tested the hypothesis that deficits in multiple subprocesses of behavioral control are associated with reliable neural-processing alterations that define cocaine addiction. While undergoing functional magnetic resonance imaging (fMRI), 38 cocaine-dependent men and 27 healthy control men performed a stop-signal task of motor inhibition. An independent component analysis on fMRI time courses identified task-related neural networks attributed to motor, visual, cognitive and affective processes. The statistical associations of these components with five different stop-signal task conditions were selected for use in a linear discriminant analysis to define a classifier for cocaine addiction from a subsample of 26 cocaine-dependent men and 18 controls. Leave-one-out cross-validation accurately classified 89.5% (39/44; chance accuracy = 26/44 = 59.1%) of subjects with 84.6% (22/26) sensitivity and 94.4%

(17/18) specificity. The remaining 12 cocaine-dependent and 9 control men formed an independent test sample, for which accuracy of the classifier was 81.9% (17/21; chance accuracy = 12/21 = 57.1%) with 75% (9/12) sensitivity and 88.9% (8/9) specificity. The cocaine addiction classification score was significantly correlated with a measure of impulsiveness as well as the duration of cocaine use for cocaine-dependent men. The results of this study support the ability of a pattern of multiple neural network alterations associated with inhibitory motor control to define a binary classifier for cocaine addiction.

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162. J Addict Med. 2013 Jan-Feb;7(1):8-16. doi: 10.1097/ADM.0b013e318273863a.

Reward-related brain response and craving correlates of marijuana cue exposure: a preliminary study in treatment-seeking marijuana-dependent subjects.

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OBJECTIVE: : Determining the brain substrates underlying the motivation to abuse addictive drugs is critical for understanding and treating addictive disorders. Laboratory neuroimaging studies have demonstrated differential activation of limbic and motivational circuitry (eg, amygdala, hippocampus, ventral striatum, insula, and orbitofrontal cortex) triggered by cocaine, heroin, nicotine, and alcohol cues. The literature on neural responses to marijuana cues is sparse. Thus, the goals of this study were to characterize the brain's response to marijuana cues, a major motivator underlying drug use and relapse, and determine whether these responses are linked to self-reported craving in a clinically relevant population of treatment-seeking marijuana-dependent subjects.
METHODS: : Marijuana craving was assessed in 12 marijuana-dependent subjects using the Marijuana Craving Questionnaire-Short Form. Subsequently, blood oxygen level dependent functional magnetic resonance imaging data were acquired during exposure to alternating 20-second blocks of marijuana-related versus matched nondrug visual cues.
RESULTS: : Brain activation during marijuana cue exposure was significantly greater in the bilateral amygdala and the hippocampus. Significant positive correlations between craving scores and brain activation were found in the ventral striatum and the medial and lateral orbitofrontal cortex ($P < 0.0001$).
CONCLUSIONS: : This study presents direct evidence for a link between reward-relevant brain responses to marijuana cues and craving and extends the current literature on marijuana cue reactivity. Furthermore, the correlative relationship between craving and brain activity in reward-related regions was observed in a clinically relevant sample (treatment-seeking marijuana-dependent subjects). Results are consistent with prior findings in cocaine, heroin, nicotine, and alcohol cue studies, indicating that the brain substrates of

cue-triggered drug motivation are shared across abused substances.

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Stimulant drugs trigger transient volumetric changes in the human ventral striatum.

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The ventral striatum (VStr) integrates mesolimbic dopaminergic and corticolimbic glutamatergic afferents and forms an essential component of the neural circuitry regulating impulsive behaviour. This structure represents a primary target of psychostimulant medication, the first-choice treatment for attention-deficit/hyperactivity disorder (ADHD), and is biochemically modified by

these drugs in animals. However, the effects of stimulants on the human VStr remain to be determined. We acquired anatomical brain MRI scans from 23 never-medicated adult patients with ADHD, 31 adult patients with a history of stimulant treatment and 32 control subjects, and VStr volumes were determined using individual rater-blinded region of interest delineation on high-resolution neuroanatomical scans. Furthermore, we also extracted VStr volumes before and after methylphenidate treatment in a subsample of the medication-naïve adult patients as well as in 20 never-medicated children with ADHD. We observed smaller VStr volumes in adult patients with a history of stimulant treatment in comparison to never-medicated patients. Moreover, our longitudinal analyses uncovered a reduction of grey matter volume in the bilateral VStr in adult patients after exposure to methylphenidate, which was followed by volumetric recovery to control level. In children, the same pattern of VStr volume changes was observed after treatment with methylphenidate. These findings suggest that the altered VStr volumes previously observed in patients with ADHD may represent a transitory effect of stimulant exposure rather than an intrinsic feature of the disorder. More generally, these data show that stimulant drugs can render plastic volume changes in human VStr neuroanatomy.

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164. Eur Neuropsychopharmacol. 2013 Oct;23(10):1151-64. doi: 10.1016/j.euroneuro.2012.10.014. Epub 2012 Nov 17.

MR imaging of the effects of methylphenidate on brain structure and function in

attention-deficit/hyperactivity disorder.

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Methylphenidate is the first-choice pharmacological intervention for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). The pharmacological and behavioral effects of methylphenidate are well described, but less is known about neurochemical brain changes induced by methylphenidate. This level of analysis may be informative on how the behavioral effects of methylphenidate are established. This paper reviews structural and functional MRI studies that have investigated effects of methylphenidate in children with ADHD. Structural MRI studies provide evidence that long-term stimulant treatment may normalize structural brain changes found in the white matter, the anterior cingulate cortex, the thalamus, and the cerebellum in ADHD. Moreover, preliminary evidence suggests that methylphenidate treatment may normalize the trajectory of cortical development in ADHD. Functional MRI has provided evidence that methylphenidate administration has acute effects on brain functioning, and even suggests that methylphenidate may normalize brain activation patterns as well as functional connectivity in children with ADHD during cognitive control, attention, and during rest. The effects of methylphenidate on the developing brain appear highly specific and dependent on numerous factors, including biological factors such as genetic predispositions, subject-related factors such as age and symptom

severity, and task-related factors such as task difficulty. Future studies on structural and functional brain changes in ADHD may benefit from inclusion strategies guided by current medication status and medication history. Further studies on the effects of methylphenidate treatment on structural and functional MRI parameters are needed to address unresolved issues of the long-term effects of treatment, as well as the mechanism through which medication-induced brain changes bring about clinical improvement.

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Insula and orbitofrontal cortical morphology in substance dependence is modulated by sex.

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BACKGROUND AND PURPOSE: Frontolimbic circuits are involved in learning and decision-making processes thought to be affected in substance-dependent individuals. We investigated frontolimbic cortical morphometry in substance-dependent men and women and determined whether morphometric measurements correlated with decision-making performance.

MATERIALS AND METHODS: Twenty-eight abstinent SDI (17 men/11 women) were compared with 28 controls (13 men/15 women). Cortical thicknesses and volumes were computed by using FreeSurfer. After controlling for age and intracranial volume, group and sex effects were analyzed in 3 a priori regions of interest: the insula, orbitofrontal cortex, and anterior cingulate cortex by using analysis of covariance. A secondary whole-brain analysis was conducted to verify region-of-interest results and to explore potential differences in other brain regions.

RESULTS: Region-of-interest analyses revealed a main effect of group on the left insula cortex, which was thinner in SDI compared with controls (P = .02). There was a group by sex interaction on bilateral insula volume (left, P = .02; right, P = .001) and right insula cortical thickness (P = .007). Compared with same-sex controls, female SDI had smaller insulae, whereas male SDI had larger insulae. Neither ACC nor OFC significantly differed across group. Performance on a decision-making task was better in controls than SDI and correlated with OFC measurements in the controls.

CONCLUSIONS: SDI and controls differed in insula morphology, and those differences were modulated by sex. No group differences in OFC were observed, but OFC measurements correlated with negative-reinforcement learning in controls. These preliminary results are consistent with a hypothesis that frontolimbic pathways may be involved in behaviors related to substance dependence.

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166. Hum Brain Mapp. 2014 Mar;35(3):760-78. doi: 10.1002/hbm.22212. Epub 2012 Nov 14.

Stochastic dynamic causal modeling of working memory connections in cocaine dependence.

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Although reduced working memory brain activation has been reported in several brain regions of cocaine-dependent subjects compared with controls, very little is known about whether there is altered connectivity of working memory pathways in cocaine dependence. This study addresses this issue by using functional magnetic resonance imaging-based stochastic dynamic causal modeling (DCM) analysis to study the effective connectivity of 19 cocaine-dependent subjects and 14 healthy controls while performing a working memory task. Stochastic DCM is an advanced method that has recently been implemented in SPM8 that can obtain improved estimates, relative to deterministic DCM, of hidden neuronal causes before convolution with the hemodynamic response. Thus, stochastic DCM may be less influenced by the confounding effects of variations in blood oxygen

level-dependent response caused by disease or drugs. Based on the significant regional activation common to both groups and consistent with previous working memory activation studies, seven regions of interest were chosen as nodes for DCM analyses. Bayesian family level inference, Bayesian model selection analyses, and Bayesian model averaging (BMA) were conducted. BMA showed that the cocaine-dependent subjects had large differences compared with the control subjects in the strengths of prefrontal-striatal modulatory (B matrix) DCM parameters. These findings are consistent with altered cortical-striatal networks that may be related to reduced dopamine function in cocaine dependence. As far as we are aware, this is the first between-group DCM study using stochastic methodology.

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167. J Nippon Med Sch. 2012;79(5):318-9.

Caffeine's effects on attentional networks in healthy subjects: a pharmacological functional magnetic resonance imaging study.

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PMID: 23123386 [Indexed for MEDLINE]

168. Hum Brain Mapp. 2014 Feb;35(2):414-28. doi: 10.1002/hbm.22184. Epub 2012 Sep 27.

Reduced fMRI activity predicts relapse in patients recovering from stimulant dependence.

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Relapse presents a significant problem for patients recovering from stimulant dependence. Here we examined the hypothesis that patterns of brain function obtained at an early stage of abstinence differentiates patients who later relapse versus those who remain abstinent. Forty-five recently abstinent stimulant-dependent patients were tested using a randomized event-related functional MRI (ER-fMRI) design that was developed in order to replicate a

previous ERP study of relapse using a selective attention task, and were then monitored until 6 months of verified abstinence or stimulant use occurred. SPM revealed smaller absolute blood oxygen level-dependent (BOLD) response amplitude in bilateral ventral posterior cingulate and right insular cortex in 23 patients positive for relapse to stimulant use compared with 22 who remained abstinent. ER-fMRI, psychiatric, neuropsychological, demographic, personal and family history of drug use were compared in order to form predictive models. ER-fMRI was found to predict abstinence with higher accuracy than any other single measure obtained in this study. Logistic regression using fMRI amplitude in right posterior cingulate and insular cortex predicted abstinence with 77.8% accuracy, which increased to 89.9% accuracy when history of mania was included. Using 10-fold cross-validation, Bayesian logistic regression and multilayer perceptron algorithms provided the highest accuracy of 84.4%. These results, combined with previous studies, suggest that the functional organization of paralimbic brain regions including ventral anterior and posterior cingulate and right insula are related to patients' ability to maintain abstinence. Novel therapies designed to target these paralimbic regions identified using ER-fMRI may improve treatment outcome.

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169. Dev Neurosci. 2012;34(4):310-7. doi: 10.1159/000337724. Epub 2012 Sep 13.

Abnormal striatal circuitry and intensified novelty seeking among adolescents who abuse methamphetamine and cannabis.

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It has been hypothesized that changes in striatal-mediated dopamine modulation during adolescence may increase the risk for initiating substance abuse as a result of its fundamental role in arbitrating reward sensitivity and motivation during learning and decision making. However, substance abuse during adolescence may also significantly modify striatal structure and function and concomitantly alter reward sensitivity and action control while this brain region is undergoing remodeling. In the present investigation, to assess the relationship of methamphetamine (Meth) or Meth and cannabis (CA) abuse to regional striatal morphology, we acquired structural magnetic resonance images, using a 3T Siemens Trio scanner, from three groups of adolescents composed of healthy controls (n = 10), Meth abusers (n = 9) and combined Meth and CA abusers (Meth+CA, n = 8). We also assessed novelty seeking using the novelty seeking subscale of Cloninger's Tridimensional Character Inventory. The results indicate that adolescent Meth+CA abusers have increased regional striatal volume and show intensified novelty seeking in contrast to the controls. The degree of Meth exposure was also positively correlated with regional striatal volume and novelty seeking in both the Meth and Meth+CA users. These preliminary findings support theories that

propose a role for the striatum in adolescent substance abuse and further indicate that novelty seeking may be related to the initiation of, or sustained, drug use.

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170. Drug Alcohol Depend. 2013 Feb 1;128(1-2):140-7. doi: 10.1016/j.drugalcdep.2012.08.018. Epub 2012 Sep 12.

Wavelet-transformed temporal cerebral blood flow signals during attempted inhibition of cue-induced cocaine craving distinguish prognostic phenotypes.

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BACKGROUND: Cocaine addicted patients with positive cocaine urine status at treatment entry are far less likely to have a successful treatment outcome. This work aims to identify brain substrates that can distinguish this group of patients from their cocaine-negative counterparts in order to better understand

this clinical phenotype. Going a step beyond conventional functional connectivity, we used wavelet transform coherence (WTC) to determine in which ways the temporal pattern of fMRI cerebral blood flow (CBF) signals during attempted inhibition of cue-induced cocaine craving may differ between these two groups.

METHODS: Using a critical node in motivational circuitry, amygdala, as a seed, whole brain correlations for the entire sample revealed a functional connection with the dorsal cingulate. Next, WTC maps of CBF were constructed for each individual, characterizing the temporal patterns between these two regions during craving inhibition.

RESULTS: As revealed by WTC, during attempted craving inhibition, the cocaine-negative subjects had significantly stronger and longer negative coherence between the amygdala and the dorsal cingulate, as compared to the cocaine-positive subjects. This relationship was neither evident in the resting state nor between two regions unrelated to inhibition processes.

CONCLUSIONS: The duration and strength of negative coherence calculated from wavelet-transformed CBF provide an objective and well-defined way to characterize brain responses during attempted inhibition of cue-induced craving, at the level of the individual. The stronger and sustained negative coherence in CBF between motivational (amygdala) and modulatory (dorsal cingulate) regions in cocaine-negative subjects may be a critical brain strength that fosters improved craving inhibition and thus, better clinical outcome.

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171. Addict Biol. 2014 May;19(3):415-26. doi: 10.1111/j.1369-1600.2012.00497.x. Epub 2012 Sep 14.

Re-appraisal of negative emotions in cocaine dependence: dysfunctional corticolimbic activation and connectivity.

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Cocaine dependence is associated with pronounced elevations of negative affect and deficient regulation of negative emotions. We aimed to investigate the neural substrates of negative emotion regulation in cocaine-dependent individuals (CDI), as compared to non-drug-using controls, using functional magnetic resonance imaging (fMRI) during a re-appraisal task. Seventeen CDI abstinent for at least 15 days and without other psychiatric co-morbidities and 18 intelligence quotient-matched non-drug-using controls participated in the study. Participants performed the re-appraisal task during fMRI scanning: they were exposed to 24 blocks of negative affective or neutral pictures that they should Observe (neutral pictures), Maintain (sustain the emotion elicited by negative pictures) or Suppress (regulate the emotion elicited by negative pictures through previously trained re-appraisal techniques). Task-related activations during two

conditions of interest (Maintain>Observe and Suppress>Maintain) were analyzed using the general linear model in SPM8 software. We also performed psychophysiological interaction (PPI) seed-based analyses based on one region from each condition: the dorsolateral prefrontal cortex (dlPFC-Maintain>Observe) and the inferior frontal gyrus (IFG-Suppress>Maintain). Results showed that cocaine users had increased right dlPFC and bilateral temporoparietal junction activations during Maintain>Observe, whereas they showed decreased right IFG, posterior cingulate cortex, insula and fusiform gyrus activations during Suppress>Maintain. PPI analyses showed that cocaine users had increased functional coupling between the dlPFC and emotion-related regions during Maintain>Observe, whereas they showed decreased functional coupling between the right IFG and the amygdala during Suppress>Maintain. These findings indicate that CDI have dysfunctional corticolimbic activation and connectivity during negative emotion experience and re-appraisal.

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172. Biol Psychiatry. 2013 Feb 1;73(3):211-8. doi: 10.1016/j.biopsych.2012.06.032. Epub 2012 Aug 1.

Effects of modafinil on neural correlates of response inhibition in alcohol-dependent patients.

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Comment in

Biol Psychiatry. 2013 Feb 1;73(3):207-8.

BACKGROUND: Impaired response inhibition is a key feature of patients with alcohol dependence. Improving impulse control is a promising target for the treatment of alcohol dependence. The pharmacologic agent modafinil enhances cognitive control functions in both healthy subjects and in patients with various psychiatric disorders. However, very little is known about the underlying neural correlates of improvements in response inhibition following modafinil.

METHODS: We conducted a randomized, double-blind, placebo-controlled, crossover study using functional magnetic resonance imaging with a stop signal task to examine effects of a single dose of modafinil (200 mg) on response inhibition and underlying neural correlates in abstinent alcohol-dependent patients (AD) (n = 16) and healthy control subjects (n = 16).

RESULTS: Within the AD group modafinil administration improved response inhibition (reflected by the stop signal reaction time [SSRT]) in subjects with initial poor response inhibition, whereas response inhibition was diminished in better performing subjects. In AD patients with initial poor response inhibition, modafinil-induced SSRT improvement was accompanied by greater activation in the thalamus and supplementary motor area (SMA) and reduced connectivity between the

thalamus and the primary motor cortex. In addition, the relationship between baseline response inhibition and modafinil-induced SSRT improvement was mediated by these changes in thalamus and SMA activation.
CONCLUSIONS: These findings indicate that modafinil can improve response inhibition in alcohol-dependent patients through its effect on thalamus and SMA function but only in subjects with poor baseline response inhibition. Therefore, baseline levels of response inhibition should be taken into account when considering treatment with modafinil in AD.

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173. Addict Biol. 2014 Mar;19(2):272-81. doi: 10.1111/j.1369-1600.2012.00472.x. Epub 2012 Jul 11.

Functional alteration in frontolimbic systems relevant to moral judgment in cocaine-dependent subjects.

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Cocaine addiction is characterized by persistent decision-making deficits, which are linked to structural and functional abnormalities in frontolimbic systems. Moral judgment is as a special instance of decision making, in which both cognitive and emotional signals must be adequately integrated to decide how to resolve moral dilemmas. Here, we employed a moral dilemmas functional magnetic resonance imaging (fMRI) task to explore possible alterations of frontolimbic systems in cocaine-dependent subjects. We also explored if these alterations relate to more basic deficits in functional connectivity within these systems during spontaneous resting-state activation. Ten cocaine-dependent subjects and 14 non-drug-using controls participated in the study. Cocaine-dependent subjects were carefully selected to discard potentially confounding co-morbidities, and they underwent a uniform supervised abstinence period of 10 days. Both groups were scanned, and fMRI maps were generated to identify (1) brain response to moral dilemmas; and (2) the strength of functional connectivity within frontolimbic systems during resting-state. During the moral dilemmas task, cocaine-dependent subjects showed reduced activation involving frontolimbic structures as the anterior cingulate cortex (ACC), left insula and brain stem. Connectivity analyses showed that cocaine users had less resting-state functional connectivity between ACC, thalamus, insula and brain stem. These results demonstrate that cocaine-dependent subjects have functional alterations in the frontolimbic systems that support moral judgment and social decision making.

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174. Psychol Addict Behav. 2013 Jun;27(2):477-88. doi: 10.1037/a0029092. Epub 2012 Jul 9.

Functional brain networks associated with cognitive control, cocaine dependence, and treatment outcome.

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Individuals with cocaine dependence often evidence poor cognitive control. The purpose of this exploratory study was to investigate networks of functional connectivity underlying cognitive control in cocaine dependence and examine the relationship of the networks to the disorder and its treatment. Independent component analysis (ICA) was applied to fMRI data to investigate if regional activations underlying cognitive control processes operate in functional networks, and whether these networks relate to performance and treatment outcome measures in cocaine dependence. Twenty patients completed a Stroop task during fMRI prior to entering outpatient treatment and were compared to 20 control

participants. ICA identified five distinct functional networks related to cognitive control interference events. Cocaine-dependent patients displayed differences in performance-related recruitment of three networks. Reduced involvement of a "top-down" fronto-cingular network contributing to conflict monitoring correlated with better treatment retention. Greater engagement of two "bottom-up" subcortical and ventral prefrontal networks related to cue-elicited motivational processing correlated with abstinence during treatment. The identification of subcortical networks linked to cocaine abstinence and cortical networks to treatment retention suggests that specific circuits may represent important, complementary targets in treatment development for cocaine dependence.

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175. Neuroimage. 2012 Oct 15;63(1):356-64. doi: 10.1016/j.neuroimage.2012.06.035. Epub 2012 Jun 26.

Anti-correlated networks, global signal regression, and the effects of caffeine in resting-state functional MRI.

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Resting-state functional connectivity magnetic resonance imaging is proving to be an essential tool for the characterization of functional networks in the brain. Two of the major networks that have been identified are the default mode network (DMN) and the task positive network (TPN). Although prior work indicates that these two networks are anti-correlated, the findings are controversial because the anti-correlations are often found only after the application of a pre-processing step, known as global signal regression, that can produce artifactual anti-correlations. In this paper, we show that, for subjects studied in an eyes-closed rest state, caffeine can significantly enhance the detection of anti-correlations between the DMN and TPN without the need for global signal regression. In line with these findings, we find that caffeine also leads to widespread decreases in connectivity and global signal amplitude. Using a recently introduced geometric model of global signal effects, we demonstrate that these decreases are consistent with the removal of an additive global signal confound. In contrast to the effects observed in the eyes-closed rest state, caffeine did not lead to significant changes in global functional connectivity in the eyes-open rest state.

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176. Neuropharmacology. 2013 Jan;64:160-7. doi: 10.1016/j.neuropharm.2012.06.026. Epub 2012 Jun 21.

The effect of caffeine on working memory load-related brain activation in middle-aged males.

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Caffeine is commonly consumed in an effort to enhance cognitive performance. However, little is known about the usefulness of caffeine with regard to memory enhancement, with previous studies showing inconsistent effects on memory performance. We aimed to determine the effect of caffeine on working memory (WM) load-related activation during encoding, maintenance and retrieval phases of a WM maintenance task using functional magnetic resonance imaging (fMRI). 20 healthy, male, habitual caffeine consumers aged 40-61 years were administered 100 mg of caffeine in a double-blind placebo-controlled crossover design. Participants were scanned in a non-withdrawn state following a workday during which caffeinated products were consumed according to individual normal use (range = 145-595 mg). Acute caffeine administration was associated with increased load-related activation compared to placebo in the left and right dorsolateral prefrontal cortex during WM encoding, but decreased load-related activation in the left

thalamus during WM maintenance. These findings are indicative of an effect of caffeine on the fronto-parietal network involved in the top-down cognitive control of WM processes during encoding and an effect on the prefrontal cortico-thalamic loop involved in the interaction between arousal and the top-down control of attention during maintenance. Therefore, the effects of caffeine on WM may be attributed to both a direct effect of caffeine on WM processes, as well as an indirect effect on WM via arousal modulation. Behavioural and fMRI results were more consistent with a detrimental effect of caffeine on WM at higher levels of WM load, than caffeine-related WM enhancement. This article is part of a Special Issue entitled 'Cognitive Enhancers'.

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177. J Atten Disord. 2014 Aug;18(6):511-20. doi: 10.1177/1087054712443158. Epub 2012 May 31.

Volumetric MRI differences in treatment naïve and chronically treated adolescents with ADHD-combined type.

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OBJECTIVE: The purpose of this study was to determine whether there are differences in the volume of specific brain regions using magnetic resonance imaging (MRI) between children and adolescents with ADHD and controls and whether such differences are related to the participants' history of stimulant treatment.
METHOD: A total of 16 healthy controls, 16 children, and adolescents with ADHD-combined (ADHD-C) type with a history of stimulant treatment, and 13 children and adolescents with ADHD-C type treatment naïve participated.
RESULTS: Total frontal, prefrontal, and caudate volumes were larger for children and adolescents with ADHD compared with controls with no differences based on medication history with larger right gray and white matter prefrontal volumes in the ADHD groups. A medication difference was found with the right anterior cingulate cortex smaller in children and adolescents without a treatment history.
CONCLUSION: These findings suggest that aberrant prefrontal and caudate volumes in ADHD-C may compromise functioning of the frontostriatal circuitry.

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178. Psychiatry Res. 2012 Apr 30;202(1):46-52. doi: 10.1016/j.pscychresns.2012.03.006. Epub 2012 May 17.

Functional interactions of HIV-infection and methamphetamine dependence during motor programming.

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Methamphetamine (METH) dependence is frequently comorbid with HIV infection and both have been linked to alterations of brain structure and function. In a previous study, we showed that the brain volume loss characteristic of HIV infection contrasts with METH-related volume increases in striatum and parietal cortex, suggesting distinct neurobiological responses to HIV and METH (Jernigan et al., 2005). Functional magnetic resonance imaging (fMRI) has the potential to reveal functional interactions between the effects of HIV and METH. In the present study, 50 participants were studied in four groups: an HIV+ group, a recently METH-dependent group, a dually affected group, and a group of unaffected community comparison subjects. An fMRI paradigm consisting of motor sequencing tasks of varying levels of complexity was administered to examine blood oxygenation level dependent (BOLD) changes. Within all groups, activity increased significantly with increasing task complexity in large clusters within sensorimotor and parietal cortex, basal ganglia, cerebellum, and cingulate. The task complexity effect was regressed on HIV status, METH status, and the HIV×METH interaction term in a simultaneous multiple regression. HIV was associated with less complexity-related activation in striatum, whereas METH was associated with

less complexity-related activation in parietal regions. Significant interaction effects were observed in both cortical and subcortical regions; and, contrary to expectations, the complexity-related activation was less aberrant in dually affected than in single risk participants, in spite of comparable levels of neurocognitive impairment among the clinical groups. Thus, HIV and METH dependence, perhaps through their effects on dopaminergic systems, may have opposing functional effects on neural circuits involved in motor programming.

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179. Addict Behav. 2013 Feb;38(2):1509-17. doi: 10.1016/j.addbeh.2012.04.006. Epub 2012 Apr 24.

Neurophysiological effects of modafinil on cue-exposure in cocaine dependence: a randomized placebo-controlled cross-over study using pharmacological fMRI.

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OBJECTIVE: Enhanced reactivity to substance related cues is a central characteristic of addiction and has been associated with increased activity in motivation, attention, and memory related brain circuits and with a higher probability of relapse. Modafinil was promising in the first clinical trials in cocaine dependence, and was able to reduce craving in addictive disorders. However, its mechanism of action remains to be elucidated. In this functional magnetic resonance imaging (fMRI) study therefore, cue reactivity in cocaine dependent patients was compared to cue reactivity in healthy controls (HCs) under modafinil and placebo conditions.

METHODS: An fMRI cue reactivity study, with a double-blind, placebo-controlled cross-over challenge with a single dose of modafinil (200mg) was employed in 13 treatment seeking cocaine dependent patients and 16 HCs.

RESULTS: In the placebo condition, watching cocaine-related pictures (versus neutral pictures) resulted in higher brain activation in the medial frontal cortex, anterior cingulate cortex, angular gyrus, left orbitofrontal cortex, and ventral tegmental area (VTA) in the cocaine dependent group compared to HCs. However, in the modafinil condition, no differences in brain activation patterns were found between cocaine dependent patients and HCs. Group interactions revealed decreased activity in the VTA and increased activity in the right ACC and putamen in the modafinil condition relative to the placebo condition in cocaine dependent patients, whereas such changes were not present in healthy controls. Decreases in self-reported craving when watching cocaine-related cues after modafinil administration compared to the placebo condition were associated with modafinil-induced increases in ACC and putamen activation.

CONCLUSIONS: Enhanced cue reactivity in the cocaine dependent group compared to healthy controls was found in brain circuitries related to reward, motivation,

and autobiographical memory processes. In cocaine dependent patients, these enhanced brain responses were attenuated by modafinil, mainly due to decreases in cue- reactivity in reward-related brain areas (VTA) and increases in cue reactivity in cognitive control areas (ACC). These modafinil-induced changes in brain activation in response to cocaine-related visual stimuli were associated with diminished self-reported craving. These findings imply that in cocaine dependent patients, modafinil, although mainly known as a cognitive enhancer, acts on both the motivational and the cognitive brain circuitry.

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180. Dev Neurosci. 2012;34(1):43-57. doi: 10.1159/000336242. Epub 2012 Mar 29.

Frontostriatal connectivity in children during working memory and the effects of prenatal methamphetamine, alcohol, and polydrug exposure.

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Various abnormalities in frontal and striatal regions have been reported in children with prenatal alcohol and/or methamphetamine exposure. In a recent fMRI study, we observed a correlation between accuracy on a working-memory task and functional activation in the putamen in children with prenatal methamphetamine and polydrug exposure. Because the putamen is part of the corticostriatal motor loop whereas the caudate is involved in the executive loop, we hypothesized that a loss of segregation between distinct corticostriatal networks may occur in these participants. The current study was designed to test this hypothesis using functional connectivity MRI. We examined 50 children ranging in age from 7 to 15, including 19 with prenatal methamphetamine exposure (15 of whom had concomitant prenatal alcohol exposure), 13 with prenatal exposure to alcohol but not methamphetamine, and 18 unexposed controls. We measured the coupling between blood oxygenation level dependent (BOLD) fluctuations during a working-memory task in four striatal seed regions and those in the rest of the brain. We found that the putamen seeds showed increased connectivity with frontal brain regions involved in executive functions while the caudate seeds showed decreased connectivity with some of these regions in both groups of exposed subjects compared to controls. These findings suggest that localized brain abnormalities resulting from prenatal exposure to alcohol and/or methamphetamine lead to a partial rewiring of corticostriatal networks. These results represent important progress in the field, and could have substantial clinical significance in helping devise more targeted treatments and remediation strategies designed to better serve the needs of this population.

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Connectomics signatures of prenatal cocaine exposure affected adolescent brains.

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Recent in vivo neuroimaging studies revealed that several brain networks are altered in prenatal cocaine exposure (PCE) affected adolescent brains. However, due to a lack of dense and corresponding cortical landmarks across individuals, the systematical alterations of functional connectivities in large-scale brain networks and the alteration of structural brain architecture in PCE affected brain are largely unknown. In this article, we adopted a newly developed data-driven strategy to build a large set of cortical landmarks that are consistent and corresponding across PCE adolescents and their matched controls. Based on these landmarks, we constructed large-scale functional connectomes and applied the well-established approaches of deriving genomics signatures in genome-wide gene expression studies to discover functional connectomics

signatures for the characterization of PCE adolescent brains. Results derived from experimental data demonstrated that 10 structurally disrupted landmarks were identified in PCE, and more importantly, the discovered informative functional connectomics signatures among consistent landmarks distinctively differentiate PCE brains from their matched controls.

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Neural correlates of the formation and retention of cocaine-induced stimulus-reward associations.

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BACKGROUND: Cocaine can elicit drug-seeking behavior for drug-predicting stimuli,

even after a single stimulus-cocaine pairing. Although orbitofrontal cortex is thought to be important during encoding and maintenance of stimulus-reward value, we still lack a comprehensive model of the neural circuitry underlying this cognitive process.

METHODS: We studied the conditioned effects of cocaine with monkey functional magnetic resonance imaging and classical conditioning by pairing a visual shape (conditioning stimulus [CS+]) with a noncontingent cocaine infusion; a control stimulus was never paired. We correlated the behavioral preference of the monkey for the CS+, as measured offline, with the activity induced by the CS+ relative to the control stimulus as function of time.

RESULTS: We observed that during formation of stimulus-cocaine associations strong CS+-induced functional magnetic resonance imaging activations emerged in frontal cortex that correlated significantly with behavioral CS+ preference. Afterward, CS+ preference correlated only with activity in early visual cortex. Control experiments suggest that these findings cannot be explained by increased familiarity for the CS+.

CONCLUSIONS: Our findings suggest a complex interaction between frontal and occipital cortex during cocaine conditioning. Frontal cortex is important for establishing novel representations of stimulus valence when cocaine is used as reinforcer, whereas early visual cortex is involved in retaining these cocaine-stimulus associations.

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183. Neuroimage. 2012 Apr 2;60(2):1015-24. doi: 10.1016/j.neuroimage.2012.01.058. Epub 2012 Jan 14.

Dissociable effects of methylphenidate, atomoxetine and placebo on regional cerebral blood flow in healthy volunteers at rest: a multi-class pattern recognition approach.

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The stimulant drug methylphenidate (MPH) and the non-stimulant drug atomoxetine (ATX) are both widely used for the treatment of attention deficit/hyperactivity disorder (ADHD), but their differential effects on human brain function are poorly understood. PET and blood oxygen level dependent (BOLD) fMRI have been used to study the effects of MPH and BOLD fMRI is beginning to be used to delineate the effects of MPH and ATX in the context of cognitive tasks. The BOLD signal is a proxy for neuronal activity and is dependent on three physiological parameters: regional cerebral blood flow (rCBF), cerebral metabolic rate of oxygen and cerebral blood volume. To identify areas sensitive to MPH and ATX and assist interpretation of BOLD studies in healthy volunteers and ADHD patients, it is therefore of interest to characterize the effects of these drugs on rCBF. In

this study, we used arterial spin labeling (ASL) MRI to measure rCBF non-invasively in healthy volunteers after administration of MPH, ATX or placebo. We employed multi-class pattern recognition (PR) to discriminate the neuronal effects of the drugs, which accurately discriminated all drug conditions from one another and provided activity patterns that precisely localized discriminating brain regions. We showed common and differential effects in cortical and subcortical brain regions. The clearest differential effects were observed in four regions: (i) in the caudate body where MPH but not ATX increased rCBF, (ii) in the midbrain/substantia nigra and (iii) thalamus where MPH increased and ATX decreased rCBF plus (iv) a large region of cerebellar cortex where ATX increased rCBF relative to MPH. Our results demonstrate that combining ASL and PR yields a sensitive method for detecting the effects of these drugs and provides insights into the regional distribution of brain networks potentially modulated by these compounds.

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184. Epilepsia. 2012 Feb;53(2):325-33. doi: 10.1111/j.1528-1167.2011.03377.x. Epub 2012 Jan 13.

Attention-deficit/hyperactivity disorder in childhood epilepsy: a neuropsychological and functional imaging study.

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PURPOSE: Children with epilepsy have a significant risk for attention-deficit/hyperactivity disorder (ADHD), which is often accompanied by deficits in working memory performance. However, it is not yet clear whether there are specific differences in the underlying mechanisms of working memory capability between children with epilepsy-related ADHD and those with developmental ADHD. There is evidence that methylphenidate can improve the behavioral difficulties in children with developmental ADHD. Whether this medication has the same effect on ADHD symptoms in patients with epilepsy is not yet well understood. The aim of the present study is, therefore, to evaluate whether boys with epilepsy-related ADHD and developmental ADHD share a common behavioral, pharmacoresponsive, and neurofunctional pathophysiology.
METHODS: Seventeen boys with diagnosed combined epilepsy/ADHD, 15 boys with developmental ADHD, and 15 healthy controls (aged 8-14 years) performed on working memory tasks (N-back) while brain activation was recorded using functional magnetic resonance imaging. Each patient was tested twice: once after the intake of methylphenidate and once without in a counterbalanced order.
KEY FINDINGS: On a behavioral level, we show that boys with epilepsy-related ADHD as well as those with developmental ADHD performed similarly poorly on tasks with high cognitive load when compared to healthy controls, and that intake of

methylphenidate improved performance almost to normal levels in both ADHD groups. On the functional level, both patient groups showed similar reductions of activation in all relevant parts of the functional network of working memory when compared to controls. Of interest, intake of methylphenidate did not significantly alter this activity pattern.
SIGNIFICANCE: Our data show strong similarities between epilepsy-related and developmental ADHD on the behavioral, pharmacoresponsive, and neural level, favoring the view that ADHD with and without epilepsy shares a common underlying neurobehavioral pathophysiology.

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185. Biol Psychiatry. 2012 Mar 1;71(5):458-66. doi: 10.1016/j.biopsych.2011.11.011. Epub 2011 Dec 29.

The effects of stimulant medication on working memory functional connectivity in attention-deficit/hyperactivity disorder.

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BACKGROUND: Working memory impairments are commonly found in attention-deficit/hyperactivity disorder (ADHD) and often improve with psychostimulant treatment. Little is known about how these medications affect the function of frontoparietal brain regions engaged for working memory. This study used functional magnetic resonance imaging (fMRI) to examine medication-related changes in brain activation and functional connectivity in ADHD.

METHODS: Eighteen ADHD-combined subtype youths (ages 11-17) twice completed a Sternberg working memory fMRI task in a randomized, double-blind, placebo-controlled design. Medications were individualized as patients' standard, clinically effective psychostimulant (e.g., methylphenidate or dextroamphetamine/amphetamine combination) dose. Brain activity and functional connectivity were characterized using group independent component analysis. SPM5 repeated-measures t tests compared ADHD patients' network engagement and regional functional connectivity on and off medication.

RESULTS: Independent component analysis identified six frontoparietal networks/components with hemodynamic responses to encoding/maintenance or retrieval phases of the Sternberg fMRI task. On medication, three of these networks significantly increased activation. Functional connectivity analyses found medication led to recruitment of additional brain regions that were not engaged into the networks when participants were on placebo. Also, medication strengthened connectivity of some frontoparietal regions. Many connectivity changes were directly related to improved working memory reaction time. Overall, there was strong evidence for regional functional connectivity changes following medication in structures previously implicated as abnormal in ADHD, such as anterior cingulate, ventrolateral prefrontal cortex, and precuneus.

CONCLUSIONS: Stimulant medication has widespread effects on the functional

connectivity of frontoparietal brain networks, which might be a mechanism that underlies their beneficial effects on working memory performance.

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186. Psychopharmacology (Berl). 2012 Jul;222(1):47-57. doi: 10.1007/s00213-011-2622-8. Epub 2011 Dec 28.

Methylphenidate modulates sustained attention and cortical activation in survivors of traumatic brain injury: a perfusion fMRI study.

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RATIONALE: Methylphenidate (MPH), the most widely prescribed psychostimulant to treat many neuropsychiatric conditions, is reported to improve attention and speed of processing in survivors of traumatic brain injury (TBI). The neural correlate of this efficacy, however, remains unclear.

OBJECTIVE: Using perfusion functional magnetic resonance imaging (fMRI) as a biomarker of regional neural activity, the current study aimed to examine the neural correlates of single-dose (0.3 mg/kg) MPH administration in a randomized

double-blind placebo-controlled crossover study design.

METHODS: Twenty-three individuals with moderate to severe TBI were tested on two occasions approximately 1 week apart. Perfusion fMRI scanning was carried out at rest and while participants performed cognitive tasks requiring sustained attention and working memory.

RESULTS: Behaviorally, MPH significantly improved both accuracy and reaction time (RT) in the sustained attention task but only RT in the working memory task. A trend of global reduction of cerebral blood flow by MPH was observed in all task conditions including resting. Voxel-wise whole-brain analysis revealed an interaction effect of drug by condition (MPH-placebo X task-rest) for the sustained attention task in the left posterior superior parietal cortex and parieto-occipital junction (BA 7/19). The magnitude of drug-related deactivation of this area during task performance was correlated with improvement in RT.

CONCLUSION: Suppression of activity in this area during task performance may reflect a compensatory mechanism by which MPH ameliorates attention impairments in TBI.

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187. Hum Brain Mapp. 2013 Mar;34(3):566-74. doi: 10.1002/hbm.21459. Epub 2011 Nov 18.

Broadband neurophysiological abnormalities in the medial prefrontal region of the default-mode network in adults with ADHD.

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Previous investigations of the default-mode network (DMN) in persons with attention-deficit/hyperactivity disorder (ADHD) have shown reduced functional connectivity between the anterior and posterior aspects. This finding was originally demonstrated in adults with ADHD, then in youth with ADHD, and has been tentatively linked to ultra low frequency oscillations within the DMN. The current study evaluates the specificity of DMN abnormalities to neuronal oscillations in the ultra low frequency range, and examines the regional specificity of these DMN aberrations in medicated and unmedicated adults with, and those without ADHD. An individually matched sample of adults with and without ADHD completed 6-minute sessions of resting-state magnetoencephalography (MEG). Participants with ADHD were known responders to stimulant medications and completed two sessions (predrug/postdrug). MEG data were coregistered to the participant's MRI, corrected for head motion, fitted to a regional-level source model, and subjected to spectral analyses to extract neuronal population activity in regions of the DMN. The unmedicated adults with ADHD exhibited broadband deficits in medial prefrontal cortices (MPFC), but not other DMN regions compared to adults without ADHD. Unmedicated patients also showed abnormal cross-frequency coupling in the gamma range between the MPFC and posterior cingulate areas, and disturbed balance within the DMN as activity in posterior regions was stronger than frontal regions at beta and lower frequencies, which dissipated at higher γ-frequencies. Administration of pharmacotherapy significantly increased

prefrontal alpha activity (8-14 Hz) in adults with ADHD, and decreased the cross-frequency gamma coupling. These results indicate that neurophysiological aberrations in the DMN of patients with ADHD are not limited to ultra slow oscillations, and that they may be primarily attributable to abnormal broadband activity in the MPFC.

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188. PLoS Biol. 2011 Nov;9(11):e1001194. doi: 10.1371/journal.pbio.1001194. Epub 2011 Nov 8.

Elimination of the vesicular acetylcholine transporter in the striatum reveals regulation of behaviour by cholinergic-glutamatergic co-transmission.

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Comment in

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Cholinergic neurons in the striatum are thought to play major regulatory functions in motor behaviour and reward. These neurons express two vesicular transporters that can load either acetylcholine or glutamate into synaptic vesicles. Consequently cholinergic neurons can release both neurotransmitters, making it difficult to discern their individual contributions for the regulation of striatal functions. Here we have dissected the specific roles of acetylcholine release for striatal-dependent behaviour in mice by selective elimination of the vesicular acetylcholine transporter (VAChT) from striatal cholinergic neurons. Analysis of several behavioural parameters indicates that elimination of VAChT had only marginal consequences in striatum-related tasks and did not affect spontaneous locomotion, cocaine-induced hyperactivity, or its reward properties. However, dopaminergic sensitivity of medium spiny neurons (MSN) and the behavioural outputs in response to direct dopaminergic agonists were enhanced, likely due to increased expression/function of dopamine receptors in the striatum. These observations indicate that previous functions attributed to striatal cholinergic neurons in spontaneous locomotor activity and in the rewarding responses to cocaine are mediated by glutamate and not by acetylcholine release. Our experiments demonstrate how one population of neurons can use two distinct neurotransmitters to differentially regulate a given circuitry. The data also raise the possibility of using VAChT as a target to boost dopaminergic function and decrease high striatal cholinergic activity, common neurochemical alterations in individuals affected with Parkinson's disease.

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Conflict of interest statement: The authors have declared that no competing interests exist.

189. Neurocase. 2012;18(6):441-9. doi: 10.1080/13554794.2011.627341. Epub 2011 Nov 14.

Functional connectivity during language processing in acute cocaine withdrawal: a pilot study.

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Recent research revealed decreased access to semantic and associative networks in acute cocaine withdrawal. In autism, such behavioral outcomes are associated with decreased functional connectivity using functional magnetic resonance imaging. Therefore, we wished to determine whether connectivity is also decreased in acute cocaine withdrawal. Eight subjects in acute cocaine withdrawal were compared to controls for connectivity in language areas while performing a task involving categorization of words according to semantic and phonological relatedness. Acute withdrawal subjects had significantly less overall connectivity during semantic relatedness, and a trend towards less connectivity during phonological relatedness. Of potential future interest is whether this might serve as an

imaging marker for treatment in patients.

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190. J Neurosci Methods. 2012 Feb 15;204(1):9-18. doi: 10.1016/j.jneumeth.2011.10.020. Epub 2011 Oct 28.

A robust experimental protocol for pharmacological fMRI in rats and mice.

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Pharmacological Magnetic Resonance Imaging (phMRI) methods have significantly expanded the stimulation repertoire available to preclinical fMRI research, by allowing to selectively probe the activity of specific brain circuitries and neurotransmitter systems. However, the application of phMRI to animal models is constrained by a number of experimental factors. Firstly, in order to prevent motion artefacts and reduce restraint-induced stress, phMRI studies are typically performed under anaesthesia. Moreover, several psychoactive drugs produce blood pressure changes and alterations in respiratory frequency that may perturb central haemodynamic readouts of brain function. Hence, the quality and outcome of phMRI studies is critically dependent on the ability to monitor and control

peripheral physiological parameters (i.e. blood pressure, arterial blood gases) that could alter phMRI readouts. Here we provide a thorough methodological description of a robust protocol to measure drug-induced cerebral blood volume changes in anaesthetised rats and mice. We show that the protocol ensures stable physiological parameters and robust phMRI response to the psychostimulant drug d-amphetamine in three different rat strains. We also document the successful application of the protocol to map the central effects produced by d-amphetamine in C57Bl/6J mice, a strain commonly used as background for the generation of transgenic lines, thus paving the way to the implementation of phMRI in genetically engineered animals.

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191. Neuropsychopharmacology. 2012 Feb;37(3):822-37. doi: 10.1038/npp.2011.260. Epub 2011 Nov 2.

Modulation of fronto-cortical activity by modafinil: a functional imaging and fos study in the rat.

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Modafinil (MOD) is a wake-promoting drug with pro-cognitive properties. Despite its increasing use, the neuronal substrates of MOD action remain elusive. In particular, animal studies have highlighted a putative role of diencephalic areas as primary neuronal substrate of MOD action, with inconsistent evidence of recruitment of fronto-cortical areas despite the established pro-cognitive effects of the drug. Moreover, most animal studies have employed doses of MOD of limited clinical relevance. We used pharmacological magnetic resonance imaging (phMRI) in the anesthetized rat to map the circuitry activated by a MOD dose producing clinically relevant plasma exposure, as here ascertained by pharmacokinetic measurements. We observed prominent and sustained activation of the prefrontal and cingulate cortex, together with weaker but significant activation of the somatosensory cortex, medial thalamic domains, hippocampus, ventral striatum and dorsal raphe. Correlation analysis of phMRI data highlighted enhanced connectivity within a neural network including dopamine projections from the ventral tegmental area to the nucleus accumbens. The pro-arousing effect of MOD was assessed using electroencephalographic recording under anesthetic conditions comparable to those used for phMRI, together with the corresponding Fos immunoreactivity distribution. MOD produced electroencephalogram desynchronization, resulting in reduced delta and increased theta frequency bands, and a pattern of Fos induction largely consistent with the phMRI study. Altogether, these findings show that clinically relevant MOD doses can robustly activate fronto-cortical areas involved in higher cognitive functions and a network of pro-arousing areas, which provide a plausible substrate for the wake-promoting and pro-cognitive effects of the drug.

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192. Neuroimage. 2012 Feb 1;59(3):2994-3002. doi: 10.1016/j.neuroimage.2011.10.001. Epub 2011 Oct 18.

Caffeine increases the temporal variability of resting-state BOLD connectivity in the motor cortex.

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Correlations between spontaneous fluctuations in the blood oxygenation level dependent (BOLD) signal measured with functional MRI are finding increasing use as measures of functional connectivity in the brain, where differences can potentially predict cognitive performance and diagnose disease. Caffeine, which is a widely consumed neural stimulant and vasoactive agent, has been found to decrease the amplitude and correlation of resting-state BOLD fluctuations, and hence is an important factor to consider in functional connectivity studies. However, because the BOLD signal is sensitive to neural and vascular factors, the

physiological mechanisms by which caffeine alters spontaneous BOLD fluctuations remain unclear. Resting-state functional connectivity has traditionally been assessed using stationary measures, such as the correlation coefficient between BOLD signals measured across the length of a scan. However, recent work has shown that the correlation of resting-state networks can vary considerably over time, with periods as short as 10 s. In this study, we used a sliding window correlation analysis to assess temporal variations in resting-state functional connectivity of the motor cortex before and after caffeine ingestion. We found that the temporal variability of BOLD correlation was significantly higher following a caffeine dose, with transient periods of strong correlation alternating with periods of low or negative correlation. This phenomenon was primarily due to increased variability in the phase difference between BOLD time courses in the left and right motor cortices. These results indicate that caffeine may cause underlying spontaneous neural fluctuations to go in and out of coherence more frequently, and emphasizes the need to consider non-stationary measures when studying changes in functional connectivity.

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193. Biol Psychiatry. 2011 Oct 15;70(8):754-62. doi: 10.1016/j.biopsych.2011.06.033.

Response perseveration in stimulant dependence is associated with striatal

dysfunction and can be ameliorated by a D(2/3) receptor agonist.

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BACKGROUND: Compulsivity is a hallmark of drug addiction and in animal models is measured by consecutive incorrect responses to a previously rewarded stimulus during reversal learning. The aim of this study was to measure behavioral and neural markers of compulsivity in stimulant-dependent individuals and to test whether these markers could be modulated by treatment with drugs targeting the dopamine system.

METHODS: In a randomized, double-blind, placebo-controlled, crossover design, stimulant-dependent individuals (SDIs; n = 18) and healthy volunteers (n = 18) received single doses of dopamine D(2/3) receptor antagonist (amisulpride, 400 mg) and agonist (pramipexole, 0.5 mg) drugs. To examine compulsivity and its dopaminergic modulation more generally, patients with obsessive-compulsive disorder (OCD; n = 18) were also included in the study.

RESULTS: SDIs made significantly more perseverative responses to the previously correct stimulus immediately following reversal, compared with both healthy volunteers and patients with OCD. Across all participants, the number of perseverative errors was negatively correlated with functional activation in right fronto-striato-parietal networks-in particular, the right caudate nucleus. In SDIs, perseveration-related caudate activation was abnormally reduced in the

placebo condition, but the dopamine D(2/3) agonist pramipexole normalized both perseverative responding and related activation of the right caudate.
CONCLUSIONS: Perseveration during reversal learning was associated specifically with stimulant dependence rather than with compulsive behaviors more generally. The beneficial effects of a dopamine agonist drug challenge on both behavior and associated brain activation in SDIs may indicate new avenues for pharmacologic treatment in stimulant dependence.

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194. Psychiatry Res. 2011 Nov 30;194(2):111-8. doi: 10.1016/j.pscychresns.2011.05.001. Epub 2011 Sep 29.

Lower activation in the right frontoparietal network during a counting Stroop task in a cocaine-dependent group.

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Dysregulation in cognitive control networks may mediate core characteristics of drug addiction. Cocaine dependence has been particularly associated with low activation in the frontoparietal regions during conditions requiring decision making and cognitive control. This functional magnetic resonance imaging (fMRI) study aimed to examine differential brain-related activation to cocaine addiction during an inhibitory control paradigm, the "Counting" Stroop task, given the uncertainties of previous studies using positron emission tomography. Sixteen comparison men and 16 cocaine-dependent men performed a cognitive "Counting" Stroop task in a 1.5T Siemens Avanto. The cocaine-dependent patient group and the control group were matched for age, level of education and general intellectual functioning. Groups did not differ in terms of the interference measures deriving from the counting Stroop task. Moreover, the cocaine-dependent group showed lower activation in the right inferior frontal gyrus, the right inferior parietal gyrus and the right superior temporal gyrus than the control group. Cocaine patients did not show any brain area with increased activation when compared with controls. In short, Stroop-interference was accompanied by lower activation in the right frontoparietal network in cocaine-dependent patients, even in the absence of inter-group behavioral differences. Our study is the first application of a counting Stroop task using fMRI to study cocaine dependence and yields results that corroborate the involvement of a frontoparietal network in the neural changes associated with attentional interference deficits in cocaine-dependent men.

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195. Eur J Neurosci. 2011 Sep;34(5):800-15. doi: 10.1111/j.1460-9568.2011.07806.x.

Cocaine self-administration leads to alterations in temporal responses to cocaine challenge in limbic and motor circuitry.

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Chronic use of cocaine is associated with lasting alterations in brain metabolism, circuitry, and receptor properties. We used neuroimaging with pharmacological magnetic resonance imaging to assess alterations in response to cocaine (0.5 mg/kg) in animals trained to self-administer cocaine on a fixed-ratio 5 schedule of reinforcement, as well as saline-yoked controls, after 28 days of cocaine abstinence. We fitted the cerebral blood volume (CBV) curves for full-width half-maximum (FWHM) as well as peak CBV response. There were significant increases in the FWHM of the response curves in the cocaine self-administering (SA) animals as compared with saline-yoked controls in the medial prefrontal cortex (mPFC) and the caudate/putamen (CPu), and increases in peak CBV in the M1 motor cortex, CPu, and pedunculopontine tegmental nucleus. Functional connectivity analysis showed increased correlations in the cocaine SA

rats upon acute cocaine challenge, especially in the S1, mPFC, and thalamus. As D3 receptor expression is postulated to increase following chronic cocaine administration, we also examined the response to 0.2 mg/kg of the D3-preferring agonist 7-hydroxy-N,N-di-n-propyl-2-aminotetralin (7-OHDPAT). Cocaine SA animals showed a decreased overall CBV response to this drug, except in the globus pallidus. The hypothalamus showed a negative CBV change in response to cocaine challenge, similar to that noted with the D3 agonist, and showed a smaller response in the cocaine SA animals than in the controls. Given the good coupling of cerebral hemodynamics with dopamine dynamics previously observed with pharmacological magnetic resonance imaging, these data suggest that increased persistence of dopamine in the prefrontal cortex may be responsible for some of the behavioral alterations observed subsequent to chronic cocaine use.

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196. Neuroimage. 2012 Jan 16;59(2):1461-8. doi: 10.1016/j.neuroimage.2011.08.003. Epub 2011 Aug 16.

Brain functional connectivity in stimulant drug dependence and obsessive-compulsive disorder.

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There are reasons for thinking that obsessive-compulsive disorder (OCD) and drug dependence, although conventionally distinct diagnostic categories, might share important cognitive and neurobiological substrates. We tested this hypothesis directly by comparing brain functional connectivity measures between patients with OCD, stimulant dependent individuals (SDIs; many of whom were non-dependent users of other recreational drugs) and healthy volunteers. We measured functional connectivity between each possible pair of 506 brain regional functional MRI time series representing low frequency (0.03-0.06 Hz) spontaneous brain hemodynamics in healthy volunteers (N=18), patients with OCD (N=18) and SDIs (N=18). We used permutation tests to identify i) brain regions where strength of connectivity was significantly different in both patient groups compared to healthy volunteers; and ii) brain regions and connections which had significantly different functional connectivity between patient groups. We found that functional connectivity of right inferior and superior orbitofrontal cortex (OFC) was abnormally reduced in both disorders. Whether diagnosed as OCD or SDI, patients with higher scores on measures of compulsive symptom severity showed greater reductions of right orbitofrontal connectivity. Functional connections specifically between OFC and dorsal medial pre-motor and cingulate cortex were attenuated in both patient groups. However, patients with OCD demonstrated more severe and extensive reductions of functional connectivity compared to SDIs. OCD

and stimulant dependence are not identical at the level of brain functional systems but they have some important abnormalities in common compared with healthy volunteers. Orbitofrontal connectivity may serve as a human brain systems biomarker for compulsivity across diagnostic categories.

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197. J Psychoactive Drugs. 2011 Apr-Jun;43(2):108-27.

Neurogenetics and clinical evidence for the putative activation of the brain reward circuitry by a neuroadaptagen: proposing an addiction candidate gene panel map.

Chen TJ(1), Blum K, Chen AL, Bowirrat A, Downs WB, Madigan MA, Waite RL, Bailey JA, Kerner M, Yeldandi S, Majmundar N, Giordano J, Morse S, Miller D, Fornari F, Braverman ER.

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This document presents evidence supporting the role of the KB220/KB220Z neuroadaptagens consisting of amino-acid neurotransmitter precursors and

enkephalinase-catecholamine-methyl-transferase (COMT) inhibition therapy called Neuroadaptagen Amino Acid Therapy (NAAT) in brain reward function. It is becoming increasingly clear that this novel formulation is the first neuroadaptagen known to activate the brain reward circuitry. Ongoing research repeatedly confirms the numerous clinical effects that ultimately result in significant benefits for victims having genetic antecedents for all addictive, compulsive and impulsive behaviors. These behaviors are correctly classified under the rubric of"Reward Deficiency Syndrome" (RDS). We are proposing a novel addiction candidate gene map. We present preliminary findings in the United States using qEGG and in China using Functional Magnetic Resonance Imaging (fMRI) regarding the effects of oral NAAT on the activation of brain reward circuitry in victims of SUD. In unpublished data utilizing an fMRI 2X2 design at resting state, NAAT in comparison to placebo shows activation of the caudate brain region and potentially a smoothing out of heroin-induced putamen (a site for emotionality) abnormal connectivity. Although awaiting final analysis, if confirmed by ongoing studies in China coupled with published qEEG results in America, showing an increase in alpha and low beta, NAAT may be shown to impact treatment outcomes.

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198. Front Psychiatry. 2011 Jul 12;2:43. doi: 10.3389/fpsyt.2011.00043. eCollection 2011.

Technical and conceptual considerations for performing and interpreting functional MRI studies in awake rats.

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Functional neuroimaging studies in rodents have the potential to provide insight into neurodevelopmental and psychiatric conditions. The strength of the technique lies in its non-invasive nature that can permit longitudinal functional studies in the same animal over its adult life. The relatively good spatial and temporal resolution and the ever-growing database on the biological and biophysical basis of the blood oxygen level dependent (BOLD) signal make it a unique technique in preclinical neuroscience research. Our laboratory has used imaging to investigate brain activation in awake rats following cocaine administration and during the presentation of lactation-associated sensory stimuli. Factors that deserve attention when planning functional magnetic resonance imaging studies in rats include technical issues, animal physiology and interpretability of the resulting data. The present review discusses the pros and cons of animal imaging with a particular focus on the technical aspects of studies with awake rats. Overall, the benefits of the technique outweigh its limitations and the rapidly evolving methods will open the way for more laboratories to employ the technique in neuroscience research.

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199. Drug Alcohol Depend. 2012 Jan 1;120(1-3):41-7. doi:
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MDMA (Ecstasy) association with impaired fMRI BOLD thalamic coherence and functional connectivity.

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BACKGROUND: MDMA exposure is associated with chronic serotonergic dysfunction in preclinical and clinical studies. A recent functional magnetic resonance imaging (fMRI) comparison of past MDMA users to non-MDMA-using controls revealed increased spatial extent and amplitude of activation in the supplementary motor area during motor tasks (Karageorgiou et al., 2009). Blood oxygenation level dependent (BOLD) data from that study were reanalyzed for intraregional coherence and for inter-regional temporal correlations between time series, as functional connectivity.
METHODS: Fourteen MDMA users and ten controls reporting similar non-MDMA abuse performed finger taps during fMRI. Fourteen motor pathway regions plus a pontine raphé region were examined. Coherence was expressed as percent of voxels positively correlated with an intraregional index voxel. Functional connectivity

was determined using wavelet correlations.

RESULTS: Intraregional thalamic coherence was significantly diminished at low frequencies in MDMA users compared to controls (p=0.009). Inter-regional functional connectivity was significantly weaker for right thalamo - left caudate (p=0.002), right thalamo - left thalamus (p=0.007), right caudate - right postcentral (p=0.007) and right supplementary motor area - right precentral gyrus (p=0.011) region pairs compared to controls. When stratified by lifetime exposure, significant negative associations were observed between cumulative MDMA use and functional connectivity in seven other region-pairs, while only one region-pair showed a positive association.

CONCLUSIONS: Reported prior MDMA use was associated with deficits in BOLD intraregional coherence and inter-regional functional connectivity, even among functionally robust pathways involving motor regions. This suggests that MDMA use is associated with long-lasting effects on brain neurophysiology beyond the cognitive domain.

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200. J Am Acad Child Adolesc Psychiatry. 2011 Aug;50(8):828-37.e3. doi: 10.1016/j.jaac.2011.05.010.

Abnormal amygdalar activation and connectivity in adolescents with

attention-deficit/hyperactivity disorder.

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OBJECTIVE: Emotional reactivity is one of the most disabling symptoms associated with attention-deficit/hyperactivity disorder (ADHD). We aimed to identify neural substrates associated with emotional reactivity and to assess the effects of stimulants on those substrates.

METHOD: We used functional magnetic resonance imaging (fMRI) to assess neural activity in adolescents with (n = 15) and without (n = 15) ADHD while they performed a task involving the subliminal presentation of fearful faces. Using dynamic causal modeling, we also examined the effective connectivity of two regions associated with emotional reactivity, i.e., the amygdala and the lateral prefrontal cortex (LPFC). The participants with ADHD underwent scanning both on and off stimulant medication in a counterbalanced fashion.

RESULTS: During the task, we found that activity in the right amygdala was greater in adolescents with ADHD than in control subjects. In addition, in adolescents with ADHD, greater connectivity was detected between the amygdala and LPFC. Stimulants had a normalizing effect on both the activity in the right amygdala and the connectivity between the amygdala and LPFC.

CONCLUSIONS: Our findings demonstrate that in adolescents with ADHD, a neural substrate of fear processing is atypical, as is the connectivity between the amygdala and LPFC. These findings suggest possible neural substrates for the

emotional reactivity that is often present in youths with ADHD, and provide putative neural targets for the development of novel therapeutic interventions for this condition.

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201. Neuropsychopharmacology. 2011 Nov;36(12):2431-40. doi: 10.1038/npp.2011.129. Epub 2011 Jul 20.

Neuroimaging evidence of altered fronto-cortical and striatal function after prolonged cocaine self-administration in the rat.

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Cocaine addiction is often modeled in experimental paradigms where rodents learn to self-administer (SA) the drug. However, the extent to which these models

replicate the functional alterations observed in clinical neuroimaging studies of cocaine addiction remains unknown. We used magnetic resonance imaging (MRI) to assess basal and evoked brain function in rats subjected to a prolonged, extended-access cocaine SA scheme. Specifically, we measured basal cerebral blood volume (bCBV), an established correlate of basal metabolism, and assessed the reactivity of the dopaminergic system by mapping the pharmacological MRI (phMRI) response evoked by the dopamine-releaser amphetamine. Cocaine-exposed subjects exhibited reduced bCBV in fronto-cortical areas, nucleus accumbens, ventral hippocampus, and thalamus. The cocaine group also showed an attenuated functional response to amphetamine in ventrostriatal areas, an effect that was significantly correlated with total cocaine intake. An inverse relationship between bCBV in the reticular thalamus and the frontal response elicited by amphetamine was found in control subjects but not in the cocaine group, suggesting that the inhibitory interplay within this attentional circuit may be compromised by the drug. Importantly, histopathological analysis did not reveal significant alterations of the microvascular bed in the brain of cocaine-exposed subjects, suggesting that the imaging findings cannot be merely ascribed to cocaine-induced vascular damage. These results document that chronic, extended-access cocaine SA in the rat produces focal fronto-cortical and striatal alterations that serve as plausible neurobiological substrate for the behavioral expression of compulsive drug intake in laboratory animals.

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PMCID: PMC3194070

PMID: 21775976 [Indexed for MEDLINE]

202. Biol Psychiatry. 2011 Sep 15;70(6):553-60. doi: 10.1016/j.biopsych.2011.05.008. Epub 2011 Jun 24.

An initial study of neural responses to monetary incentives as related to treatment outcome in cocaine dependence.

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BACKGROUND: Although cocaine dependence (CD) involves abnormalities in drug-related, reward-based decision making, it is not well understood whether these abnormalities generalize to nondrug-related cues and rewards and how neural functions underlying reward processing in cocaine abusers relate to treatment outcome.
METHODS: Twenty CD patients before treatment and 20 matched healthy control (HC) subjects participated in functional magnetic resonance imaging while performing a monetary incentive delay task. Outcomes through 8 weeks were assessed via percent cocaine-negative urine toxicology, self-reported cocaine abstinence, and treatment retention.
RESULTS: Among the whole sample, anticipation of working for monetary reward (i.e., reward anticipation) was associated with activation in the ventral striatum (VS), medial frontal gyrus, thalamus, right subcallosal gyrus, right insula, and left amygdala. Cocaine dependence compared with HC participants

exhibited greater activation during notification of rewarding outcome (i.e., reward receipt) in left and right VS, right caudate, and right insula. In CD participants during reward anticipation, activation in left and right thalamus and right caudate correlated negatively with percent cocaine-negative urine toxicology, activation in thalamus bilaterally correlated negatively with self-reported abstinence measures, and activation in left amygdala and parahippocampal gyrus correlated negatively with treatment retention. During reward notification, activation in right thalamus, right VS, and left culmen correlated negatively with abstinence and with urine toxicology.
CONCLUSIONS: These findings suggest that in treatment-seeking CD participants, corticolimbic reward circuitry is relatively overactivated during monetary incentive delay task performance and specific regional activations related to reward processing may predict aspects of treatment outcome and represent important targets for treatment development in CD.

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203. Drug Alcohol Depend. 2011 Dec 15;119(3):e51-7. doi: 10.1016/j.drugalcdep.2011.05.026. Epub 2011 Jun 23.

Deficits in default mode network activity preceding error in cocaine dependent

individuals.

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BACKGROUND: Cocaine dependence is associated with cognitive deficits and altered task-related cerebral activation in cognitive performance (see Li and Sinha, 2008, for a review). Relatively little is known whether these individuals are also impaired in regional brain activation of the default mode network (DMN). We demonstrated previously that greater activation of the default brain regions precedes errors in a stop signal task performed by healthy controls (SST, Li et al., 2007). We seek to determine whether individuals with cocaine dependence are impaired in DMN activity, specifically activity preceding error, as compared to the healthy people. We also examine the relation to years of cocaine use.
METHODS: Individuals with cocaine dependence (CD, n=23) and demographics-matched healthy controls (HC, n=27) performed a SST that employed a tracking procedure to adjust the difficulty of stop trials and elicit errors approximately half of the time. Blood oxygenation level dependent (BOLD) signals of go trials preceding stop error as compared to those preceding stop success trials were extracted with generalized linear models using statistical parametric mapping.
RESULTS: HC showed activation of bilateral precuneus and posterior cingulate cortices and ventromedial prefrontal cortex (vmPFC) preceding errors during the SST. In contrast, despite indistinguishable stop signal performance, CD did not show these error predicting activations. Furthermore, the effect size of error-preceding vmPFC activation was inversely correlated with years of cocaine

use.

CONCLUSIONS: These findings indicate DMN deficits and could potentially add to our understanding of the effects of chronic cocaine use on cerebral functions in cocaine dependence. Work to further clarify potential changes in functional connectivity and gray matter volume is warranted to understand the relevance of DMN to the pathology of cocaine misuse.

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204. Radiology. 2011 Aug;260(2):531-40. doi: 10.1148/radiol.11101918. Epub 2011 Jun 1.

Potential long-term effects of MDMA on the basal ganglia-thalamocortical circuit: a proton MR spectroscopy and diffusion-tensor imaging study.

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PURPOSE: To investigate the effects of 3,4-methylenedioxymethamphetamine (MDMA,

commonly known as "ecstasy") on the alterations of brain metabolites and anatomic tissue integrity related to the function of the basal ganglia-thalamocortical circuit by using proton magnetic resonance (MR) spectroscopy and diffusion-tensor MR imaging.

MATERIALS AND METHODS: This study was approved by a local institutional review board, and written informed consent was obtained from all subjects. Thirty-one long-term (>1 year) MDMA users and 33 healthy subjects were enrolled. Proton MR spectroscopy from the middle frontal cortex and bilateral basal ganglia and whole-brain diffusion-tensor MR imaging were performed with a 3.0-T system. Absolute concentrations of metabolites were computed, and diffusion-tensor data were registered to the International Consortium for Brain Mapping template to facilitate voxel-based group comparison.

RESULTS: The mean myo-inositol level in the basal ganglia of MDMA users (left: 4.55 mmol/L ± 2.01 [standard deviation], right: 4.48 mmol/L ± 1.33) was significantly higher than that in control subjects (left: 3.25 mmol/L ± 1.30, right: 3.31 mmol/L ± 1.19) ($P < .001$). Cumulative lifetime MDMA dose showed a positive correlation with the levels of choline-containing compounds (Cho) in the right basal ganglia ($r = 0.47$, $P = .02$). MDMA users also showed a significant increase in fractional anisotropy (FA) in the bilateral thalami and significant changes in water diffusion in several regions related to the basal ganglia-thalamocortical circuit as compared with control subjects ($P < .05$; cluster size, >50 voxels).

CONCLUSION: Increased myo-inositol and Cho concentrations in the basal ganglia of MDMA users are suggestive of glial response to degenerating serotonergic functions. The abnormal metabolic changes in the basal ganglia may consequently affect the inhibitory effect of the basal ganglia to the thalamus, as suggested by the increased FA in the thalamus and abnormal changes in water diffusion in

the corresponding basal ganglia-thalamocortical circuit.

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205. Psychiatry Res. 2011 Jun 30;192(3):167-75. doi:

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fMRI brain activation during a delay discounting task in HIV-positive adults with and without cocaine dependence.

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Cocaine use is associated with poorer HIV clinical outcomes and may contribute to neurobiological impairments associated with impulsive decision making. This study examined the effect of cocaine dependence on brain activation during a delay discounting task involving choices between smaller immediate rewards and larger delayed ones. Participants were 39 HIV-positive adults on antiretroviral therapy who had current cocaine dependence ("active," n=15), past cocaine dependence ("recovered," n=13), or no lifetime substance dependence ("naïve," n=11). Based

on responses on a traditional delay discounting task, three types of choices were individualized for presentation during functional magnetic resonance imaging: hard (similarly valued), easy (disparately valued), and no (single option). Active participants had significantly smaller increases in activation than naïve participants during hard versus easy choices bilaterally in the precentral gyrus and anterior cingulate cortex and in the right frontal pole (including dorsolateral, ventrolateral, and orbitofrontal cortex). During hard and easy choices relative to no choices, active participants had smaller increases in activation compared to naïve participants in frontoparietal cortical regions. These deficits in the executive network during delay discounting choices may contribute to impulsive decision making among HIV-positive cocaine users, with implications for risk behaviors associated with disease transmission and progression.

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PMID: 21546221 [Indexed for MEDLINE]

206. NMR Biomed. 2011 Dec;24(10):1392-400. doi: 10.1002/nbm.1702. Epub 2011 Apr 7.

The differences in neural network activity between methamphetamine abusers and healthy subjects performing an emotion-matching task: functional MRI study.

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Methamphetamine (MA) abusers commonly exhibit socially problematic behaviors, such as diminished empathy, decreased emotional regulation and interpersonal violence, which may be attributable to alterations in emotional experience. However, few studies have used functional MRI to examine directly the emotional experience of threatening or fearful non-face images in MA abusers. In this study, we investigated possible differences in neural correlates of negative emotional experiences between abstinent MA abusers and healthy subjects using complex visual scenes depicting fear or threat derived from the International Affective Picture System. In within-group analyses, healthy subjects and MA abusers activated a similarly distributed cortical network, prominently including the amygdala, fusiform gyrus, parahippocampal gyrus, ventrolateral prefrontal cortex and inferior frontal cortex. In between-group analyses, however, MA abusers showed a reduced activation in the bilateral dorsolateral prefrontal cortex and insula, and increased activation in the fusiform gyrus, hippocampus, parahippocampal gyrus and posterior cingulate cortex, relative to healthy subjects. Hypoactivation of the insula in MA abusers relative to healthy subjects suggests that the ability to have an emotional response to threatening scenes and empathy for another's pain could be compromised in MA abusers. Hyperactivity in the fusiform gyrus, parahippocampal gyrus and posterior cingulate cortex in MA abusers relative to healthy subjects indicates that threatening and fearful images from the International Affective Picture System may remind MA abusers of

episodic memory related to similar experiences. Therefore, functional impairment of these neural networks in MA abusers may contribute to altered emotional experience in social interactions, which could lead to increased negative mood and stress in interpersonal communication.

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207. Drug Alcohol Depend. 2011 May 1;115(1-2):137-44. doi: 10.1016/j.drugalcdep.2011.01.009. Epub 2011 Apr 3.

Enhanced cue reactivity and fronto-striatal functional connectivity in cocaine use disorders.

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Chronic cocaine use is associated with enhanced cue reactivity to drug stimuli. However, it may also alter functional connectivity (fcMRI) in regions involved in processing drug stimuli. Our aims were to evaluate the neural regions involved in subjective craving and how fcMRI may be altered in chronic cocaine users.

Fourteen patients with a confirmed diagnosis of cocaine abuse or dependence (CCA) and 16 gender, age, and education-matched healthy controls (HC) completed a cue reactivity task and a resting state scan while undergoing functional magnetic resonance imaging. CCA showed increased activation compared to HC in left dorsolateral prefrontal and bilateral occipital cortex in response to cocaine cues but not to appetitive control stimuli. Moreover, CCA also showed increased activation within the orbital frontal cortex (OFC) for cocaine cues relative to the appetitive stimuli during a hierarchical regression analysis. A negative association between subjective craving and activity in medial posterior cingulate gyrus (PCC) was also observed for CCA. CCA exhibited increased resting state correlation (positive) between cue-processing seed regions (OFC and ventral striatum), and negative connectivity between cue-processing regions and PCC/precuneus. These alterations in fcMRI may partially explain the neural basis of increased drug cue salience in CCA.

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PMID: 21466926 [Indexed for MEDLINE]

208. J Child Psychol Psychiatry. 2011 Jul;52(7):772-3. doi: 10.1111/j.1469-7610.2011.02401.x. Epub 2011 Mar 25.

Commentary: the only way is down. Augmented deactivation of the default mode network by increased catecholamine transmission--a general mechanism? Reflections

on Liddle et al. (2011).

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Comment on

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209. Biol Psychiatry. 2011 Jun 1;69(11):1117-23. doi: 10.1016/j.biopsych.2011.01.008. Epub 2011 Mar 2.

Frontal hyperconnectivity related to discounting and reversal learning in cocaine subjects.

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BACKGROUND: Functional neuroimaging studies suggest that chronic cocaine use is associated with frontal lobe abnormalities. Functional connectivity (FC) alterations of cocaine-dependent individuals (CD), however, are not yet clear. This is the first study to our knowledge that examines resting FC of anterior cingulate cortex (ACC) in CD. Because ACC is known to integrate inputs from different brain regions to regulate behavior, we hypothesized that CD will have connectivity abnormalities in ACC networks. In addition, we hypothesized that abnormalities would be associated with poor performance in delayed discounting and reversal learning tasks.

METHODS: Resting functional magnetic resonance imaging data were collected to look for FC differences between 27 CD (5 women, age: M = 39.73, SD = 6.14 years) and 24 control subjects (5 women, age: M = 39.76, SD = 7.09 years). Participants were assessed with delayed discounting and reversal learning tasks. With seed-based FC measures, we examined FC in CD and control subjects within five ACC connectivity networks with seeds in subgenual, caudal, dorsal, rostral, and perigenual ACC.

RESULTS: The CD showed increased FC within the perigenual ACC network in left middle frontal gyrus, ACC, and middle temporal gyrus when compared with control subjects. The FC abnormalities were significantly positively correlated with task performance in delayed discounting and reversal learning tasks in CD.

CONCLUSIONS: The present study shows that participants with chronic cocaine-dependency have hyperconnectivity within an ACC network known to be involved in social processing and "mentalizing." In addition, FC abnormalities found in CD were associated with difficulties with delay rewards and slower adaptive learning.

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210. Neuropsychopharmacology. 2011 May;36(6):1237-47. doi: 10.1038/npp.2011.9. Epub 2011 Feb 23.

Pattern classification of working memory networks reveals differential effects of methylphenidate, atomoxetine, and placebo in healthy volunteers.

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Stimulant and non-stimulant drugs can reduce symptoms of attention deficit/hyperactivity disorder (ADHD). The stimulant drug methylphenidate (MPH) and the non-stimulant drug atomoxetine (ATX) are both widely used for ADHD treatment, but their differential effects on human brain function remain unclear. We combined event-related fMRI with multivariate pattern recognition to characterize the effects of MPH and ATX in healthy volunteers performing a rewarded working memory (WM) task. The effects of MPH and ATX on WM were strongly dependent on their behavioral context. During non-rewarded trials, only MPH could

be discriminated from placebo (PLC), with MPH producing a similar activation pattern to reward. During rewarded trials both drugs produced the opposite effect to reward, that is, attenuating WM networks and enhancing task-related deactivations (TRDs) in regions consistent with the default mode network (DMN). The drugs could be directly discriminated during the delay component of rewarded trials: MPH produced greater activity in WM networks and ATX produced greater activity in the DMN. Our data provide evidence that: (1) MPH and ATX have prominent effects during rewarded WM in task-activated and -deactivated networks; (2) during the delay component of rewarded trials, MPH and ATX have opposing effects on activated and deactivated networks: MPH enhances TRDs more than ATX, whereas ATX attenuates WM networks more than MPH; and (3) MPH mimics reward during encoding. Thus, interactions between drug effects and motivational state are crucial in defining the effects of MPH and ATX.

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PMCID: PMC3079849
PMID: 21346736 [Indexed for MEDLINE]

211. J Pharmacol Exp Ther. 2011 May;337(2):324-34. doi: 10.1124/jpet.108.136689. Epub 2011 Feb 11.

Nonhuman primate positron emission tomography neuroimaging in drug abuse research.

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Positron emission tomography (PET) neuroimaging in nonhuman primates has led to significant advances in our current understanding of the neurobiology and treatment of stimulant addiction in humans. PET neuroimaging has defined the in vivo biodistribution and pharmacokinetics of abused drugs and related these findings to the time course of behavioral effects associated with their addictive properties. With novel radiotracers and enhanced resolution, PET neuroimaging techniques have also characterized in vivo drug interactions with specific protein targets in the brain, including neurotransmitter receptors and transporters. In vivo determinations of cerebral blood flow and metabolism have localized brain circuits implicated in the effects of abused drugs and drug-associated stimuli. Moreover, determinations of the predisposing factors to chronic drug use and long-term neurobiological consequences of chronic drug use, such as potential neurotoxicity, have led to novel insights regarding the pathology and treatment of drug addiction. However, similar approaches clearly need to be extended to drug classes other than stimulants. Although dopaminergic systems have been extensively studied, other neurotransmitter systems known to play a critical role in the pharmacological effects of abused drugs have been largely ignored in nonhuman primate PET neuroimaging. Finally, the study of brain activation with PET neuroimaging has been replaced in humans mostly by functional magnetic resonance imaging (fMRI). There has been some success in implementing pharmacological fMRI in awake nonhuman primates. Nevertheless, the unique versatility of PET imaging will continue to complement the systems-level strengths of fMRI, especially in the context of nonhuman primate drug abuse

research.

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PMCID: PMC3083112

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212. Biol Psychiatry. 2011 Apr 1;69(7):684-92. doi: 10.1016/j.biopsych.2010.11.022. Epub 2011 Jan 20.

Reduced interhemispheric resting state functional connectivity in cocaine addiction.

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BACKGROUND: Models of cocaine addiction emphasize the role of disrupted frontal circuitry supporting cognitive control processes. However, addiction-related alterations in functional interactions among brain regions, especially between the cerebral hemispheres, are rarely examined directly. Resting-state functional magnetic resonance imaging (fMRI) approaches, which reveal patterns of coherent spontaneous fluctuations in the fMRI signal, offer a means to quantify directly

functional interactions between the hemispheres. We examined interhemispheric resting-state functional connectivity (RSFC) in cocaine dependence using a recently validated approach, voxel-mirrored homotopic connectivity.

METHODS: We compared interhemispheric RSFC between 25 adults (aged 35.0 ± 8.8) meeting DSM-IV criteria for cocaine dependence within the past 12 months but currently abstaining (>2 weeks) from cocaine and 24 healthy comparisons (35.1 ± 7.5), group-matched on age, sex, education, and employment status.

RESULTS: We observed reduced prefrontal interhemispheric RSFC in cocaine-dependent participants relative to control subjects. Further analyses demonstrated a striking cocaine-dependence-related reduction in interhemispheric RSFC among nodes of the dorsal attention network, comprising bilateral lateral frontal, medial premotor, and posterior parietal areas. Further, within the cocaine-dependent group, RSFC within the dorsal attention network was associated with self-reported attentional lapses.

CONCLUSIONS: Our findings provide further evidence of an association between chronic exposure to cocaine and disruptions within large-scale brain circuitry supporting cognitive control. We did not detect group differences in diffusion tensor imaging measures, suggesting that alterations in the brain's functional architecture associated with cocaine exposure can be observed in the absence of detectable abnormalities in the white matter microstructure supporting that architecture.

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213. Drug Alcohol Depend. 2011 Jun 1;115(3):240-3. doi:
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The association between frontal-striatal connectivity and sensorimotor control in cocaine users.

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BACKGROUND: In addition to cognitive and emotional processing dysfunction, chronic cocaine users are also impaired at simple sensorimotor tasks. Many diseases characterized by compulsive movements, repetitive actions, impaired attention and planning are associated with dysfunction in frontal-striatal circuits. The aim of this study was to determine whether cocaine users had impaired frontal-striatal connectivity during a simple movement task and whether this was associated with sensorimotor impairment.
METHODS: Functional MRI data were collected from 14 non-treatment seeking cocaine users and 15 healthy controls as they performed a finger-tapping task. Functional coupling was quantified by correlating the timecourses of each pair of anatomically connected regions of interest. Behavioral performance was correlated with all functional coupling coefficients.

RESULTS: In controls there was a significant relationship between the primary motor cortex and the supplementary motor area (SMA), as well as the SMA and the dorsal striatum during ongoing movement. Cocaine users exhibited weaker fronto-striatal coupling than controls, while the cortical-cortical coupling was intact. Coupling strength between the SMA and the caudate was negatively correlated with reaction time in the users.
CONCLUSIONS: The observation that cocaine users have impaired cortical-striatal connectivity during simple motor performance, suggests that these individuals may have a fundamental deficit in information processing that influences more complex cognitive processes.

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214. Neuroimage. 2011 Mar 15;55(2):622-8. doi: 10.1016/j.neuroimage.2010.12.048. Epub 2010 Dec 23.

Quantitative pharmacologic MRI: mapping the cerebral blood volume response to cocaine in dopamine transporter knockout mice.

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The use of pharmacologic MRI (phMRI) in mouse models of brain disorders allows noninvasive in vivo assessment of drug-modulated local cerebral blood volume changes (ΔCBV) as one correlate of neuronal and neurovascular activities. In this report, we employed CBV-weighted phMRI to compare cocaine-modulated neuronal activity in dopamine transporter (DAT) knockout (KO) and wild-type mice. Cocaine acts to block the dopamine, norepinephrine, and serotonin transporters (DAT, NET, and SERT) that clear their respective neurotransmitters from the synapses, helping to terminate cognate neurotransmission. Cocaine consistently reduced CBV, with a similar pattern of regional ΔCBV in brain structures involved in mediating reward in both DAT genotypes. The largest effects (-20% to -30% ΔCBV) were seen in the nucleus accumbens and several cortical regions. Decreasing response amplitudes to cocaine were noted in more posterior components of the cortico-mesolimbic circuit. DAT KO mice had significantly attenuated ΔCBV amplitudes, shortened times to peak response, and reduced response duration in most regions. This study demonstrates that DAT knockout does not abolish the phMRI responses to cocaine, suggesting that adaptations to loss of DAT and/or retained cocaine activity in other monoamine neurotransmitter systems underlie these responses in DAT KO mice.

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215. Brain Res. 2011 Feb 23;1375:111-9. doi: 10.1016/j.brainres.2010.12.042. Epub 2010 Dec 21.

Right parietal hypoactivation in a cocaine-dependent group during a verbal working memory task.

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It has been suggested that cocaine addiction affects the engagement of the frontoparietal networks in executive functions, such as attention and working memory. Thus, our objective was to investigate brain differences between cocaine-dependent subjects and healthy controls during the performance of a verbal working memory task. Nineteen comparison men and nineteen cocaine-dependent men performed a 2-back task. Data were acquired on a 1.5-T Siemens Avanto. Image processing and statistical analyses were carried out using SPM5; Biological Parametric Mapping (BPM) was used for further morphometric and correlation analyses. No performance differences were found between groups. However, the dorsal part of the right inferior parietal cortex (BA 40) was less activated in the cocaine-dependent group. Cocaine patients did not overactive any

brain area when compared with controls. Our results show reduced activation in the brain areas related to the attention system in cocaine-dependent men while performing a verbal working memory task. Chronic cocaine use may affect the attentional system in the right parietal lobe, making patients more prone to attentional deficits.

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Recursive cluster elimination based support vector machine for disease state prediction using resting state functional and effective brain connectivity.

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BACKGROUND: Brain state classification has been accomplished using features such as voxel intensities, derived from functional magnetic resonance imaging (fMRI) data, as inputs to efficient classifiers such as support vector machines (SVM) and is based on the spatial localization model of brain function. With the advent

of the connectionist model of brain function, features from brain networks may provide increased discriminatory power for brain state classification.
METHODOLOGY/PRINCIPAL FINDINGS: In this study, we introduce a novel framework where in both functional connectivity (FC) based on instantaneous temporal correlation and effective connectivity (EC) based on causal influence in brain networks are used as features in an SVM classifier. In order to derive those features, we adopt a novel approach recently introduced by us called correlation-purged Granger causality (CPGC) in order to obtain both FC and EC from fMRI data simultaneously without the instantaneous correlation contaminating Granger causality. In addition, statistical learning is accelerated and performance accuracy is enhanced by combining recursive cluster elimination (RCE) algorithm with the SVM classifier. We demonstrate the efficacy of the CPGC-based RCE-SVM approach using a specific instance of brain state classification exemplified by disease state prediction. Accordingly, we show that this approach is capable of predicting with 90.3% accuracy whether any given human subject was prenatally exposed to cocaine or not, even when no significant behavioral differences were found between exposed and healthy subjects.
CONCLUSIONS/SIGNIFICANCE: The framework adopted in this work is quite general in nature with prenatal cocaine exposure being only an illustrative example of the power of this approach. In any brain state classification approach using neuroimaging data, including the directional connectivity information may prove to be a performance enhancer. When brain state classification is used for disease state prediction, our approach may aid the clinicians in performing more accurate diagnosis of diseases in situations where in non-neuroimaging biomarkers may be unable to perform differential diagnosis with certainty.

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217. J Child Psychol Psychiatry. 2011 Jul;52(7):761-71. doi: 10.1111/j.1469-7610.2010.02333.x. Epub 2010 Nov 12.

Task-related default mode network modulation and inhibitory control in ADHD: effects of motivation and methylphenidate.

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Comment in

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BACKGROUND: Deficits characteristic of attention deficit/hyperactivity disorder (ADHD), including poor attention and inhibitory control, are at least partially alleviated by factors that increase engagement of attention, suggesting a hypodopaminergic reward deficit. Lapses of attention are associated with attenuated deactivation of the default mode network (DMN), a distributed brain system normally deactivated during tasks requiring attention to the external world. Task-related DMN deactivation has been shown to be attenuated in ADHD relative to controls. We hypothesised that motivational incentives to balance

speed against restraint would increase task engagement during an inhibitory control task, enhancing DMN deactivation in ADHD. We also hypothesised that methylphenidate, an indirect dopamine agonist, would tend to normalise abnormal patterns of DMN deactivation.

METHOD: We obtained functional magnetic resonance images from 18 methylphenidate-responsive children with ADHD (DSM-IV combined subtype) and 18 pairwise-matched typically developing children aged 9-15 years while they performed a paced Go/No-go task. We manipulated motivational incentive to balance response speed against inhibitory control, and tested children with ADHD both on and off methylphenidate.

RESULTS: When children with ADHD were off-methylphenidate and task incentive was low, event-related DMN deactivation was significantly attenuated compared to controls, but the two groups did not differ under high motivational incentives. The modulation of DMN deactivation by incentive in the children with ADHD, off-methylphenidate, was statistically significant, and significantly greater than in typically developing children. When children with ADHD were on-methylphenidate, motivational modulation of event-related DMN deactivation was abolished, and no attenuation relative to their typically developing peers was apparent in either motivational condition.

CONCLUSIONS: During an inhibitory control task, children with ADHD exhibit a raised motivational threshold at which task-relevant stimuli become sufficiently salient to deactivate the DMN. Treatment with methylphenidate normalises this threshold, rendering their pattern of task-related DMN deactivation indistinguishable from that of typically developing children.

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218. Neuroimage. 2011 Feb 14;54(4):3067-75. doi: 10.1016/j.neuroimage.2010.10.072. Epub 2010 Oct 30.

Abnormal brain activation during working memory in children with prenatal exposure to drugs of abuse: the effects of methamphetamine, alcohol, and polydrug exposure.

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Structural and metabolic abnormalities in fronto-striatal structures have been reported in children with prenatal methamphetamine (MA) exposure. The current study was designed to quantify functional alterations to the fronto-striatal circuit in children with prenatal MA exposure using functional magnetic resonance imaging (fMRI). Because many women who use MA during pregnancy also use alcohol, a known teratogen, we examined 50 children (age range 7-15), 19 with prenatal MA exposure, 15 of whom had concomitant prenatal alcohol exposure (the MAA group),

13 with heavy prenatal alcohol but no MA exposure (ALC group), and 18 unexposed controls (CON group). We hypothesized that MA exposed children would demonstrate abnormal brain activation during a visuospatial working memory (WM) "N-Back" task. As predicted, the MAA group showed less activation than the CON group in many brain areas, including the striatum and frontal lobe in the left hemisphere. The ALC group showed less activation than the MAA group in several regions, including the right striatum. We found an inverse correlation between performance and activity in the striatum in both the CON and MAA groups. However, this relationship was significant in the caudate of the CON group but not the MAA group, and in the putamen of the MAA group but not the CON group. These findings suggest that structural damage in the fronto-striatal circuit after prenatal MA exposure leads to decreased recruitment of this circuit during a WM challenge, and raise the possibility that a rewiring of cortico-striatal networks may occur in children with prenatal MA exposure.

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219. Neuroimage. 2011 Feb 14;54(4):3101-10. doi: 10.1016/j.neuroimage.2010.10.060. Epub 2010 Oct 26.

Methylphenidate enhances brain activation and deactivation responses to visual attention and working memory tasks in healthy controls.

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Methylphenidate (MPH) is a stimulant drug that amplifies dopamineric and noradrenergic signaling in the brain, which is believed to underlie its cognition enhancing effects. However, the neurobiological effects by which MPH improves cognition are still poorly understood. Here, functional magnetic resonance imaging (fMRI) was used together with working memory (WM) and visual attention (VA) tasks to test the hypothesis that 20mg oral MPH would increase activation in the dorsal attention network (DAN) and deactivation in the default mode network (DMN) as well as improve performance during cognitive tasks in healthy men. The group of subjects that received MPH (MPH group; N=16) had higher activation than the group of subjects who received no medication (control group: N=16) in DAN regions (parietal and prefrontal cortex, regions increasingly activated with increased cognitive load) and had increased deactivation in the insula and posterior cingulate cortex (regions increasingly deactivated with increased cognitive load) and these effects did not differ for the VA and the WM tasks. These findings provide the first evidence that MPH enhances activation of the DAN whereas it alters DMN deactivation. This suggests that MPH (presumably by amplifying dopamine and noradrenergic signaling) modulates cognition in part through its effects on DAN and DMN.

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220. Neuroimage. 2011 Jan 15;54(2):1130-9. doi: 10.1016/j.neuroimage.2010.08.045. Epub 2010 Sep 8.

Imaging separation of neuronal from vascular effects of cocaine on rat cortical brain in vivo.

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MRI techniques to study brain function assume coupling between neuronal activity, metabolism and flow. However, recent evidence of physiological uncoupling between neuronal and cerebrovascular events highlights the need for methods to simultaneously measure these three properties. We report a multimodality optical approach that integrates dual-wavelength laser speckle imaging (measures changes in blood flow, blood volume and hemoglobin oxygenation), digital-frequency-ramping optical coherence tomography (images quantitative 3D vascular network) and Rhod(2) fluorescence (images intracellular calcium for

measure of neuronal activity) at high spatiotemporal resolutions (30 µm, 10 Hz) and over a large field of view (3×5 mm(2)). We apply it to assess cocaine's effects in rat cortical brain and show an immediate decrease (3.5±0.9 min, phase 1) in the oxygen content of hemoglobin and the cerebral blood flow followed by an overshoot (7.1±0.2 min, phase 2) lasting over 20 min whereas Ca(2+) increased immediately (peaked at t=4.1±0.4 min) and remained elevated. This enabled us to identify a delay (2.9±0.5 min) between peak neuronal and vascular responses in phase 2. The ability of this multimodality optical approach for simultaneous imaging at high spatiotemporal resolutions permits us to distinguish the vascular versus cellular changes of the brain, thus complimenting other neuroimaging modalities for brain functional studies (e. g., PET, fMRI).

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221. Hum Brain Mapp. 2011 May;32(5):759-70. doi: 10.1002/hbm.21059.

Increased "default mode" activity in adolescents prenatally exposed to cocaine.

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Prenatal cocaine exposure (PCE) is associated with attention/arousal dysregulation and possible inefficiencies in some cognitive functions. However, the neurobiological bases of these teratogenic effects have not been well characterized. Because activities in the default mode network (DMN) reflect intrinsic brain functions that are closely associated with arousal regulation and cognition, alterations in the DMN could underlie cognitive effects related to PCE. With resting-state and task activation functional magnetic resonance imaging (fMRI), this study investigated the possible PCE related changes in functional brain connectivity and brain activation in the DMN. In the resting state, the PCE group was found to have stronger functional connectivity in the DMN, as compared to the nonexposed controls. During a working memory task with emotional distracters, the PCE group exhibited less deactivation in the DMN and their fMRI signal was more increased by emotional arousal. These data revealed additional neural effects related to PCE, and consistent with previous findings, indicate that PCE may affect behavior and functioning by increasing baseline arousal and altering the excitatory/inhibitory balancing mechanisms involved in cognitive resource allocation.

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222. Neuroimage. 2010 Nov 1;53(2):593-601. doi: 10.1016/j.neuroimage.2010.06.066. Epub 2010 Jul 11.

Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity.

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Preclinical models have consistently demonstrated the importance of the mesocorticolimbic (MCL) brain reward system in drug dependence, with critical molecular and cellular neuroadaptations identified within these structures following chronic cocaine administration. Cocaine dependent individuals manifest alterations in reward functioning that may relate to changes induced by cocaine or to pre-existing differences related to vulnerability to addiction. The circuit level manifestations of these drug-induced plastic changes and predispositions to drug dependence are poorly understood in preclinical models and virtually unknown in human drug dependence. Using whole-brain resting-state fMRI connectivity analysis with 'seed voxels' placed within individual nodes of the MCL system, we report network-specific functional connectivity strength decreases in cocaine users within distinct circuits of the system, including between ventral tegmental area (VTA) and a region encompassing thalamus/lentiform nucleus/nucleus accumbens, between amygdala and medial prefrontal cortex (mPFC), and between hippocampus and dorsal mPFC. Further, regression analysis on regions showing

significant functional connectivity decrease in chronic cocaine users revealed that the circuit strength between VTA and thalamus/lentiform nucleus/nucleus accumbens was negatively correlated with years of cocaine use. This is the first evidence of circuit-related changes in human cocaine dependence and is consistent with the range of cognitive and behavioral disruptions seen in cocaine dependence. As potential circuit level biomarkers of cocaine dependence, these circuit alterations may be usefully applied in treatment development and monitoring treatment outcome.

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223. Am J Psychiatry. 2010 Aug;167(8):977-86. doi: 10.1176/appi.ajp.2010.09091259. Epub 2010 Jul 1.

Basal ganglia surface morphology and the effects of stimulant medications in youth with attention deficit hyperactivity disorder.

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OBJECTIVE: Disturbances in the basal ganglia portions of cortico-striato-thalamo-cortical circuits likely contribute to the symptoms of attention deficit hyperactivity disorder (ADHD). The authors examined the morphologic features of the basal ganglia nuclei (caudate, putamen, and globus pallidus) in children with ADHD.

METHOD: A total of 104 individuals (combined-type ADHD patients: N=47; healthy comparison subjects: N=57), aged 7 to 18 years, were examined in a cross-sectional case-control study using anatomical magnetic resonance imaging. Conventional volumes and the surface morphology for the basal ganglia were measured.

RESULTS: Overall volumes were significantly smaller only in the putamen. Analysis of the morphological surfaces revealed significant inward deformations in each of the three nuclei, localized primarily in portions of these nuclei that are components of limbic, associative, and sensorimotor pathways in the cortico-striato-thalamo-cortical circuits in which these nuclei reside. The more prominent these inward deformations were in the patient group, the more severe the ADHD symptoms. Surface analyses also demonstrated significant outward deformations of all basal ganglia nuclei in the ADHD children treated with stimulants compared with those ADHD youth who were untreated. These stimulant-associated enlargements were in locations similar to the reduced volumes detected in the ADHD group relative to the comparison group. The outward deformations associated with stimulant medications attenuated the statistical effects of the primary group comparisons.

CONCLUSIONS: These findings potentially represent evidence of anatomical

dysregulation in the circuitry of the basal ganglia in children with ADHD and suggest that stimulants may normalize morphological features of the basal ganglia in children with the disorder.

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224. Addict Biol. 2010 Oct;15(4):504-16. doi: 10.1111/j.1369-1600.2010.00230.x.

Altered neural response of the appetitive emotional system in cocaine addiction: an fMRI Study.

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Research on addiction suggests that emotional alterations play an essential role in the development, maintenance, relapse and treatment outcome of substance abuse disorders. Although many neuroimaging studies focussed on the neural response to conditioned stimuli, much less is known about the neural response to natural affective stimuli in this pathological population. Previous research has demonstrated an altered emotional experience and autonomic response to emotional

stimuli using the International Affective Picture System (IAPS) in drug abusers. Here we aimed, using functional magnetic resonance imaging (fMRI), to study the alterations in the neural responsitivity to pleasant (erotic), unpleasant and neutral IAPS stimuli in cocaine addiction. Thirty-two cocaine-dependent subjects and 26 matched controls completed an fMRI session during the presentation of a set of IAPS pictures as background, while performing a letter discrimination task. Consistent with previous studies, emotional pictures activated an emotional network including amygdala, medial prefrontal cortex, orbitofrontal cortex and occipito-temporal areas in both groups. However, compared with controls, the cocaine group showed a significant hypoactivation of the dorsal and ventral striatum (including the nucleus accumbens), thalamus, parietal cortex and dorso-medial prefrontal cortex (dmPFC) when processing pleasant pictures. The analysis of pleasant versus unpleasant stimuli suggested that between-group differences in the dmPFC and striatal activation may be attributed to arousal processing rather than valence. These results could reflect the neural basis for the reduced ability of cocaine-dependent subjects to experience pleasure by daily natural reinforcers, suggesting that these alterations in the emotion processing may play an important role in drug dependence, treatment and relapse.

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225. J Atten Disord. 2010 Jul;14(1):69-78. doi: 10.1177/1087054709347444.

Stimulant medication and prefrontal functional connectivity during working memory in ADHD: a preliminary report.

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OBJECTIVE: Recent theoretical and empirical work suggests that while unmedicated, children with ADHD have a deficit in subcortical processing that leads to greater and more varied prefrontal cortical (PFC) activation, compared to (a) age-matched control participants and (b) their own brain activity while on stimulant medication. This pattern has been described elsewhere as inefficient.

METHOD: Functional magnetic resonance imaging (fMRI) and functional connectivity analyses were used during a working memory task for five female adolescents with ADHD, aged 11 to 17 years, both on and off their usual dose of stimulant medication.

RESULTS: On medication, adolescents with ADHD demonstrated less PFC activation and less functional connectivity between frontal and subcortical regions compared to off medication.

CONCLUSIONS: Because of the small sample size, results are presented as preliminary findings which await replication in a larger sample. However, these findings lend support to the idea that remediation of inefficiencies in PFC function for individuals with ADHD by stimulant medication may be related, in part, to frontal-subcortical connectivity.

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226. Dev Neurosci. 2010 Jul;32(2):125-38. doi: 10.1159/000286215. Epub 2010 Jun 3.

Pharmacologic neuroimaging of the ontogeny of dopamine receptor function.

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Characterization of the ontogeny of the cerebral dopaminergic system is crucial for gaining a greater understanding of normal brain development and its alterations in response to drugs of abuse or conditions such as attention-deficit hyperactivity disorder. Pharmacological MRI (phMRI) was used to determine the response to dopamine transporter (DAT) blockers cocaine and methylphenidate (MPH), the dopamine releaser D-amphetamine (AMPH), the selective D1 agonist dihydrexidine, and the D2/D3 agonist quinpirole in young (<30 days old) and adult (>60 days old) rats. In adult rats, cocaine (0.5 mg/kg i.v.) or MPH (2 mg/kg) induced primarily positive cerebral blood volume (rCBV) changes in the dopaminergic circuitry, but negative rCBV changes in the young animals. Microdialysis measurements in the striatum showed that young rats have a smaller

increase in extracellular dopamine in response to cocaine than adults. The young rats showed little rCBV response to the selective D1 agonist dihydrexidine in contrast to robust rCBV increases observed in the adults, whereas there was a similar negative rCBV response in the young and adult rats to the D2 agonist quinpirole. We also performed a meta-analysis of literature data on the development of D1 and D2 receptors and the DAT. These data suggest a predominance of D2-like over D1-like function between 20 and 30 days of age. These combined results suggested that the dopamine D1 receptor is functionally inhibited at young age.

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227. PLoS One. 2010 May 25;5(5):e10815. doi: 10.1371/journal.pone.0010815.

Disrupted functional connectivity with dopaminergic midbrain in cocaine abusers.

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BACKGROUND: Chronic cocaine use is associated with disrupted dopaminergic neurotransmission but how this disruption affects overall brain function (other than reward/motivation) is yet to be fully investigated. Here we test the hypothesis that cocaine addicted subjects will have disrupted functional connectivity between the midbrain (where dopamine neurons are located) and cortical and subcortical brain regions during the performance of a sustained attention task.
METHODOLOGY/PRINCIPAL FINDINGS: We measured brain activation and functional connectivity with fMRI in 20 cocaine abusers and 20 matched controls. When compared to controls, cocaine abusers had lower positive functional connectivity of midbrain with thalamus, cerebellum, and rostral cingulate, and this was associated with decreased activation in thalamus and cerebellum and enhanced deactivation in rostral cingulate.
CONCLUSIONS/SIGNIFICANCE: These findings suggest that decreased functional connectivity of the midbrain interferes with the activation and deactivation signals associated with sustained attention in cocaine addicts.

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228. Neuroimage. 2010 Aug 15;52(2):429-35. doi: 10.1016/j.neuroimage.2010.04.192. Epub 2010 Apr 24.

Evidence of increased activation underlying cognitive control in ecstasy and

cannabis users.

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Evidence suggests that users of ecstasy (3,4-methylenedioxymethamphetamine) have behavioural and cognitive deficits and show increased impulsivity. Impulse control impairments have been shown to be common to a number of addictive behaviours and may constitute a risk factor for drug abuse and dependence. The aim of this study was to investigate brain activation during response inhibition and performance monitoring in current recreational drug users who predominantly used ecstasy. Twenty drug users (ten female) and twenty healthy controls were scanned during performance of a response-inhibition GO/NOGO task using functional magnetic resonance imaging. No performance deficits were evident. However, the drug user group revealed elevated frontal and parietal BOLD response during successful inhibitions, and temporal, frontal, and cingulate hyperactivity during commission errors. In addition, the users showed reduced deactivation in the default-mode network during task performance. Whether contributing to or arising from drug use, these results reveal dysregulation in brain regions subserving cognitive control and default-mode processes in current recreational drug users mirroring effects previously observed for "harder" drugs of abuse.

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229. Mol Psychiatry. 2010 Nov;15(11):1053-66. doi: 10.1038/mp.2010.6. Epub 2010 Feb 16.

A common variant of the latrophilin 3 gene, LPHN3, confers susceptibility to ADHD and predicts effectiveness of stimulant medication.

Arcos-Burgos M(1), Jain M, Acosta MT, Shively S, Stanescu H, Wallis D, Domené S, Vélez JI, Karkera JD, Balog J, Berg K, Kleta R, Gahl WA, Roessler E, Long R, Lie J, Pineda D, Londoño AC, Palacio JD, Arbelaez A, Lopera F, Elia J, Hakonarson H, Johansson S, Knappskog PM, Haavik J, Ribases M, Cormand B, Bayes M, Casas M, Ramos-Quiroga JA, Hervas A, Maher BS, Faraone SV, Seitz C, Freitag CM, Palmason H, Meyer J, Romanos M, Walitza S, Hemminger U, Warnke A, Romanos J, Renner T, Jacob C, Lesch KP, Swanson J, Vortmeyer A, Bailey-Wilson JE, Castellanos FX, Muenke M.

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Attention-Deficit/Hyperactivity Disorder (ADHD) has a very high heritability (0.8), suggesting that about 80% of phenotypic variance is due to genetic factors. We used the integration of statistical and functional approaches to discover a novel gene that contributes to ADHD. For our statistical approach, we

started with a linkage study based on large multigenerational families in a population isolate, followed by fine mapping of targeted regions using a family-based design. Family- and population-based association studies in five samples from disparate regions of the world were used for replication. Brain imaging studies were performed to evaluate gene function. The linkage study discovered a genome region harbored in the Latrophilin 3 gene (LPHN3). In the world-wide samples (total n=6360, with 2627 ADHD cases and 2531 controls) statistical association of LPHN3 and ADHD was confirmed. Functional studies revealed that LPHN3 variants are expressed in key brain regions related to attention and activity, affect metabolism in neural circuits implicated in ADHD, and are associated with response to stimulant medication. Linkage and replicated association of ADHD with a novel non-candidate gene (LPHN3) provide new insights into the genetics, neurobiology, and treatment of ADHD.

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230. Psychiatry Res. 2010 Mar 30;181(3):174-82. doi: 10.1016/j.pscychresns.2009.11.003. Epub 2010 Feb 12.

Working memory fMRI activation in cocaine-dependent subjects: association with treatment response.

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Functional magnetic resonance imaging (fMRI) studies of early abstinence cocaine users offer information about the state of the brain when most cocaine users seek treatment. This study examined the relationship between pretreatment brain function and subsequent treatment response in 19 treatment-seeking early abstinence cocaine-dependent (CD) subjects. These subjects and 14 non-drug-using control subjects underwent fMRI while performing a working memory task with three levels of difficulty. CD subjects were then randomized to treatment studies. Results showed CD subjects had significantly lower (random effects, corrected for multiple comparisons) brain activation in caudate, putamen, cingulate gyrus, middle and superior frontal gyri, inferior frontal gyrus pars triangularis and pars opercularis, precentral gyrus, and thalamus compared with non-drug-using controls. Within CD subjects, thalamic activation significantly correlated with treatment response. This study shows CD subjects in early abstinence have alterations of brain function in frontal, striatal, and thalamic brain regions known to be part of a circuit associated with motor control, reward, and cognition. Subjects with pretreatment thalamic deactivation showed the poorest treatment response, possibly related to thalamic involvement in mesocortical and mesolimbic dopamine projections.

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231. Neuroreport. 2010 Feb 17;21(3):157-62. doi: 10.1097/WNR.0b013e328330eb9e.

Longitudinal monitoring of motor neuron circuitry in FALS rats using in-vivo phMRI.

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Amyotrophic lateral sclerosis (ALS) presents challenges for diagnosis and objective monitoring of disease progression. We show, using pharmacologic MRI, that alterations in motor circuitry can be characterized using a passive stimulus in a rat model of familial ALS as a function of symptom progression. Presymptomatic familial ALS rats had a pattern of activation to amphetamine that was statistically indistinguishable from the wild-type controls. In contrast, symptomatic rats showed significantly decreased response in sensorimotor cortex and increased response in M2 motor cortex, caudate/putamen, and thalamus. These results are similar to findings in humans of altered response to motor tasks in ALS. It may be plausible to use a passive amphetamine challenge as a biomarker to assess progression of the disease and efficacy of potential treatments.

DOI: 10.1097/WNR.0b013e328330eb9e

PMCID: PMC2848450

PMID: 20118741 [Indexed for MEDLINE]

232. Hum Psychopharmacol. 2010 Jan;25(1):63-70. doi: 10.1002/hup.1083.

Alterations in cortical activity of male methamphetamine abusers performing an empathy task: fMRI study.

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OBJECTIVES: We investigate possible differences in neural correlates of empathy processing between abstinent methamphetamine (MA) abusers and healthy subjects using functional magnetic resonance imaging (fMRI).

METHODS: Nineteen abstinent MA abusers (mean age of 36.06 years, range 31-52 years) and 19 healthy subjects (mean age of 37.05 years, range 33-42 years) participated in this study. A visual fMRI activation paradigm was used, comprising a series of cartoons, each depicting a short story. There were two categories of stories: empathy (Empathy) and Physical causality (Physical). fMRI images were acquired using a 3.0 T whole-body scanner. All fMRI data were analyzed using MATLAB v. 7.2 and SPM5.

RESULTS: Both MA subjects and controls exhibited activation in the dorsomedial prefrontal cortex. Despite this similarity in activation patterns, we found that the two groups differed in the activation of several cortical regions associated with the processing of empathy information. Hypoactivations of the orbitofrontal cortex, temporal poles, and hippocampus in MA abusers relative to healthy subjects suggests that the ability of empathic response could be compromised in abstinent MA abusers ($p < 0.05$, corrected for a small volume).
CONCLUSIONS: Functional impairments in the empathic neural network caused by MA may contribute to the misunderstanding of others and to the erosion of social interactions in MA abusers.

DOI: 10.1002/hup.1083
PMID: 20041477 [Indexed for MEDLINE]

233. Brain Res. 2010 Feb 8;1313:143-61. doi: 10.1016/j.brainres.2009.11.064. Epub 2009 Dec 2.

Dopamine-induced changes in neural network patterns supporting aversive conditioning.

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The aim of the present paper is to assess the effects of altered dopamine (DA) transmission on the functional connectivity among brain regions mediating aversive conditioning in humans. To this aim, we analyzed a previous published data set from a double-blind design combined with functional magnetic resonance imaging (fMRI) recordings in which healthy volunteers were randomly assigned to one of three drug groups: amphetamine (an indirect DA agonist), haloperidol (DA D2 receptor antagonist), and placebo. Participants were exposed to an aversive classical conditioning paradigm using cutaneous electrical stimulation as the unconditioned stimulus (US), and visual cues as the conditioned stimuli (CS) where one colour (CS+) was followed by the US in 33% of the trials and another colour (CS-) had no consequences. All participants reported awareness of stimulus contingencies. Group analysis of fMRI data revealed that the left ventral striatum (VS) and amygdala activated in response to the CS+ in all the three groups. Because of their activation patterns and documented involvement in aversive conditioning, both regions were used as seeds in the functional connectivity analysis. To constrain the functional networks obtained to relate to the conditioned response, we also correlated seed activity with the Galvanic Skin Response (GSR). In the placebo group, the right ventral tegmental area/substantia nigra (VTA/SN), bilateral caudate, right parahippocampal gyrus, left inferior parietal lobule (IPL), bilateral postcentral gyrus, bilateral middle frontal (BA 46), orbitofrontal, and ventromedial prefrontal cortices (PFC, BA 10/11) correlated with the VS and amygdala seeds in response to the CS+ compared to the CS-. Enhancing dopamine transmission via amphetamine was associated with reduced task differences and significant functional connectivity for both CS+ and CS- conditions between the left VS seed and regions modulated by DA, such as the left VTA/SN, right caudate, left amygdala, left middle frontal gyrus (BA 46), and bilateral ventromedial PFC (BA 10). Blocking dopamine transmission via

haloperidol was associated with significant functional connectivity across an alternate network of regions including the left amygdala seed and the right insula, the left ACC (BA 24/32), bilateral IPL (BA 40), precuneus (BA 7), post-central gyrus, middle frontal gyrus (BA 46), and supplementary motor area (SMA, BA 6) to the CS+ versus the CS-. These data provide insight into the distinct effects of DA agents on the functional connectivity between striatal, limbic, and prefrontal areas.

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PMID: 19961836 [Indexed for MEDLINE]

234. Psychiatry Res. 2010 Jan 30;181(1):15-23. doi: 10.1016/j.pscychresns.2009.07.009.

Loss of laterality in chronic cocaine users: an fMRI investigation of sensorimotor control.

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Movement disturbances are often overlooked consequences of chronic cocaine abuse.

The purpose of this study was to systematically investigate sensorimotor performance in chronic cocaine users and characterize changes in brain activity among movement-related regions of interest (ROIs) in these users. Functional magnetic resonance imaging data were collected from 14 chronic cocaine users and 15 age- and gender-matched controls. All participants performed a sequential finger-tapping task with their dominant, right hand interleaved with blocks of rest. For each participant, percent signal change from rest was calculated for seven movement-related ROIs in both the left and right hemisphere. Cocaine users had significantly longer reaction times and higher error rates than controls. Whereas the controls used a left-sided network of motor-related brain areas to perform the task, cocaine users activated a less lateralized pattern of brain activity. Users had significantly more activity in the ipsilateral (right) motor and premotor cortical areas, anterior cingulate cortex and the putamen than controls. These data demonstrate that, in addition to the cognitive and affective consequences of chronic cocaine abuse, there are also pronounced alterations in sensorimotor control in these individuals, which are associated with functional alterations throughout movement-related neural networks.

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PMCID: PMC2794910
PMID: 19959345 [Indexed for MEDLINE]

235. Psychiatry Res. 2010 Jan 30;181(1):57-63. doi: 10.1016/j.pscychresns.2009.07.004.

Cocaine addiction: diffusion tensor imaging study of the inferior frontal and anterior cingulate white matter.

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Inferior frontal and anterior cingulate white matter integrity in 32 cocaine-dependent subjects was compared with that in 33 age-matched healthy control subjects. Diffusion tensor imaging data were acquired with a 1.5-T magnetic resonance imaging system. Cocaine-dependent subjects presented significantly lower fractional anisotropy values in inferior frontal white matter at the anterior-posterior commissure plane and higher anterior cingulate white matter values than control subjects. White matter integrity was also associated with impulsivity and motivation to change (Readiness to Change Questionnaire). These findings support the hypothesis that cocaine dependence involves a disruption of orbitofrontal connectivity and suggest that the anterior cingulate brain area might play a role in the motivation to change.

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PMID: 19959341 [Indexed for MEDLINE]

236. Am J Psychiatry. 2009 Nov;166(11):1286-94. doi: 10.1176/appi.ajp.2009.08050724. Epub 2009 Sep 15.

An FMRI study of the effects of psychostimulants on default-mode processing

during Stroop task performance in youths with ADHD.

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OBJECTIVE: The authors examined the effect of psychostimulants on brain activity in children and adolescents with ADHD performing the Stroop Color and Word Test.

METHOD: The authors acquired 52 functional MRI scans in 16 youths with ADHD who were known responders to stimulant medication and 20 healthy comparison youths. Participants with ADHD were scanned on and off medication in a counterbalanced design, and comparison subjects were scanned once without medication.

RESULTS: Stimulant medication significantly improved suppression of default-mode activity in the ventral anterior cingulate cortex in the ADHD group. When off medication, youths with ADHD were unable to suppress default-mode activity to the same degree as comparison subjects, whereas when on medication, they suppressed this activity to comparison group levels. Greater activation of the lateral prefrontal cortex when off medication predicted a greater reduction in ADHD symptoms when on medication. Granger causality analyses demonstrated that activity in the lateral prefrontal and ventral anterior cingulate cortices mutually influenced one another but that the influence of the ventral anterior cingulate cortex on the lateral prefrontal cortex was significantly reduced in youths with ADHD off medication relative to comparison subjects and increased significantly to normal levels when ADHD youths were on medication.

CONCLUSIONS: Psychostimulants in youths with ADHD improved suppression of default-mode activity in the ventral anterior cingulate and posterior cingulate cortices, components of a circuit in which activity has been shown to correlate with the degree of mind-wandering during attentional tasks. Stimulants seem to improve symptoms in youths with ADHD by normalizing activity within this circuit and improving its functional interactions with the lateral prefrontal cortex.

DOI: 10.1176/appi.ajp.2009.08050724

PMCID: PMC3289412

PMID: 19755575 [Indexed for MEDLINE]

237. Neuropharmacology. 2009 Dec;57(7-8):640-52. doi: 10.1016/j.neuropharm.2009.08.013. Epub 2009 Aug 26.

Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naïve children with ADHD during a rewarded continuous performance task.

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BACKGROUND: Children with Attention Deficit Hyperactivity Disorder (ADHD) have deficits in motivation and attention that can be ameliorated with the indirect

dopamine agonist Methylphenidate (MPH). We used functional magnetic resonance imaging (fMRI) to investigate the effects of MPH in medication-naïve children with ADHD on the activation and functional connectivity of "cool" attentional as well as "hot" motivation networks.

METHODS: 13 medication-naïve children with ADHD were scanned twice, under either an acute clinical dose of MPH or Placebo, in a randomised, double-blind design, while they performed a rewarded continuous performance task that measured vigilant selective attention and the effects of reward. Brain activation and functional connectivity was compared to that of 13 healthy age-matched controls to test for normalisation effects of MPH.

RESULTS: MPH normalised performance deficits that were observed in children with ADHD compared to controls. Under placebo, children with ADHD showed reduced activation and functional inter-connectivity in bilateral fronto-striato-parieto-cerebellar networks during the attention condition, but enhanced activation in the orbitofrontal and superior temporal cortices for reward. MPH within children with ADHD enhanced the activation of fronto-striato-cerebellar and parieto-temporal regions. Compared to controls, MPH normalised differences during vigilant attention in parieto-temporal activation and fronto-striatal and fronto-cerebellar connectivity; MPH also normalised the enhanced orbitofrontal activation in children with ADHD in response to reward.

CONCLUSIONS: MPH normalised attention differences between children with ADHD and controls by both up-regulation of dysfunctional fronto-striato-thalamo-cerebellar and parieto-temporal attention networks and down-regulation of hyper-sensitive orbitofrontal activation for reward processing. MPH thus shows context-dependent dissociative modulation of both motivational and attentional neuro-functional networks in children with ADHD.

DOI: 10.1016/j.neuropharm.2009.08.013

PMID: 19715709 [Indexed for MEDLINE]

238. Neurosci Lett. 2009 Nov 20;465(3):267-71. doi: 10.1016/j.neulet.2009.07.065. Epub 2009 Jul 26.

Cocaine-induced metabolic activation in cortico-limbic circuitry is increased after exposure to the histone deacetylase inhibitor, sodium butyrate.

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Drug-induced inhibition of histone deacetylase (HDAC) results in the modification of many behavioral changes resulting from exposure to cocaine and other stimulant drugs-of-abuse, but a comprehensive map of the neuronal circuitries involved is lacking. The present study used blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD fMRI) in awake rats to determine the effects of the HDAC inhibitor, sodium butyrate (SBt) on brain metabolic activation patterns during the initial stage of repeated cocaine administration. Three groups of rats received cocaine during BOLD fMRI, (i) acutely for the first time, or pretreated for 2 days with either (ii) saline or (iii) SBt 30 min prior to cocaine. Acute but not repeated exposure to cocaine resulted in widespread BOLD activation in fore- and mid-brain. Pretreatment with SBt restored BOLD signals in the forebrain

after repeated cocaine exposure, including a pronounced activation in the anterior thalamus, the hippocampus/amygdala and various portions of limbic and sensory cortex. Mesocorticolimbic areas showed a similar trend, but did not reach statistical significance. These findings suggest that HDACi modulation after repeated stimulant exposure involves cortico-limbic circuitry regulating emotion, motivation and memory.

DOI: 10.1016/j.neulet.2009.07.065
PMCID: PMC2760625
PMID: 19638299 [Indexed for MEDLINE]

239. PLoS One. 2009 Jun 30;4(6):e6102. doi: 10.1371/journal.pone.0006102.

Dopamine transporters in striatum correlate with deactivation in the default mode network during visuospatial attention.

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BACKGROUND: Dopamine and dopamine transporters (DAT, which regulate extracellular dopamine in the brain) are implicated in the modulation of attention but their specific roles are not well understood. Here we hypothesized that dopamine modulates attention by facilitation of brain deactivation in the default mode

network (DMN). Thus, higher striatal DAT levels, which would result in an enhanced clearance of dopamine and hence weaker dopamine signals, would be associated to lower deactivation in the DMN during an attention task.
METHODOLOGY/PRINCIPAL FINDINGS: For this purpose we assessed the relationship between DAT in striatum (measured with positron emission tomography and [(11)C]cocaine used as DAT radiotracer) and brain activation and deactivation during a parametric visual attention task (measured with blood oxygenation level dependent functional magnetic resonance imaging) in healthy controls. We show that DAT availability in caudate and putamen had a negative correlation with deactivation in ventral parietal regions of the DMN (precuneus, BA 7) and a positive correlation with deactivation in a small region in the ventral anterior cingulate gyrus (BA 24/32). With increasing attentional load, DAT in caudate showed a negative correlation with load-related deactivation increases in precuneus.
CONCLUSIONS/SIGNIFICANCE: These findings provide evidence that dopamine transporters modulate neural activity in the DMN and anterior cingulate gyrus during visuospatial attention. Our findings suggest that dopamine modulates attention in part by regulating neuronal activity in posterior parietal cortex including precuneus (region involved in alertness) and cingulate gyrus (region deactivated in proportion to emotional interference). These findings suggest that the beneficial effects of stimulant medications (increase dopamine by blocking DAT) in inattention reflect in part their ability to facilitate the deactivation of the DMN.

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PMCID: PMC2699543
PMID: 19564918 [Indexed for MEDLINE]

240. J Dev Behav Pediatr. 2009 Jun;30(3):185-92. doi: 10.1097/DBP.0b013e3181a7ee6b.

Effects of prenatal methamphetamine exposure on verbal memory revealed with functional magnetic resonance imaging.

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OBJECTIVE: Efforts to understand specific effects of prenatal methamphetamine (MA) exposure on cognitive processing are hampered by high rates of concomitant alcohol use during pregnancy. We examined whether neurocognitive systems differed among children with differing prenatal teratogenic exposures when they engaged in a verbal memory task.
PATIENTS AND METHODS: Participants (7-15 years) engaged in a verbal paired associate learning task while undergoing functional magnetic resonance imaging. The MA group included 14 children with prenatal MA exposure, 12 of whom had concomitant alcohol exposure. They were compared with 9 children with prenatal alcohol but not MA exposure (alcohol-exposed only) and 20 unexposed controls. Groups did not differ in age, gender, or socioeconomic status. Participants' IQ and verbal learning performance were measured using standardized instruments.
RESULTS: The MA group activated more diffuse brain regions, including bilateral

medial temporal structures known to be important for memory, than both the alcohol-exposed only and the CON groups. These group differences remained after IQ was covaried. More activation in medial temporal structures by the MA group compared with the alcohol-exposed only group cannot be explained by performance differences because both groups performed at similar levels on the verbal memory task.

CONCLUSIONS: More diffuse activation in the MA group during verbal memory may reflect recruitment of compensatory systems to support a weak verbal memory network. Differences in activation patterns between the MA and alcohol-exposed only groups suggest that prenatal MA exposure influences the development of the verbal memory system above and beyond effects of prenatal alcohol exposure.

DOI: 10.1097/DBP.0b013e3181a7ee6b

PMCID: PMC2745202

PMID: 19525715 [Indexed for MEDLINE]

241. Biol Psychiatry. 2009 Oct 15;66(8):769-76. doi: 10.1016/j.biopsych.2009.04.026. Epub 2009 Jun 11.

Cocaine acute "binge" administration results in altered thalamocortical interactions in mice.

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BACKGROUND: Abnormalities in both thalamic and cortical areas have been reported in human cocaine addicts with noninvasive functional magnetic resonance imaging. Given the substantial involvement of the thalamocortical system in sensory processing and perception, we defined electrophysiology-based protocols to attempt a characterization of cocaine effects on thalamocortical circuits.
METHODS: Thalamocortical function was studied in vivo and in vitro in mice after cocaine "binge" administration. In vivo awake electroencephalography (EEG) was implemented in mice injected with saline, 1 hour or 24 hours after the last cocaine "binge" injection. In vitro current- and voltage-clamp whole-cell patch-clamp recordings were performed from slices including thalamic relay ventrobasal (VB) neurons.
RESULTS: In vivo EEG recordings after cocaine "binge" administration showed a significant increment, compared with saline, in low frequencies while observing no changes in high-frequency gamma activity. In vitro patch recordings from VB neurons after cocaine "binge" administration showed low threshold spikes activation at more negative membrane potentials and increments in both I(h) and low voltage activated T-type calcium currents. Also, a 10-mV negative shift on threshold activation level of T-type current and a remarkable increment in both frequency and amplitudes of gamma-aminobutyric acid-A-mediated minis were observed.
CONCLUSIONS: Our data indicate that thalamocortical dysfunctions observed in cocaine abusers might be due to two distinct but additive events: 1) increased low frequency oscillatory thalamocortical activity, and 2) overinhibition of VB neurons that can abnormally "lock" the whole thalamocortical system at low frequencies.

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PMID: 19520366 [Indexed for MEDLINE]

242. Neuroimage. 2009 May 15;46(1):56-63. doi: 10.1016/j.neuroimage.2009.02.001. Epub 2009 Feb 12.

Caffeine reduces resting-state BOLD functional connectivity in the motor cortex.

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In resting-state functional magnetic resonance imaging (fMRI), correlations between spontaneous low-frequency fluctuations in the blood oxygenation level dependent (BOLD) signal are used to assess functional connectivity between different brain regions. Changes in resting-state BOLD connectivity measures are typically interpreted as changes in coherent neural activity across spatially distinct brain regions. However, this interpretation can be complicated by the complex dependence of the BOLD signal on both neural and vascular factors. For example, prior studies have shown that vasoactive agents that alter baseline cerebral blood flow, such as caffeine and carbon dioxide, can significantly alter the amplitude and dynamics of the task-related BOLD response. In this study, we examined the effect of caffeine (200 mg dose) on resting-state BOLD connectivity

in the motor cortex across a sample of healthy young subjects (N=9). We found that caffeine significantly ($p<0.05$) reduced measures of resting-state BOLD connectivity in the motor cortex. Baseline cerebral blood flow and spectral energy in the low-frequency BOLD fluctuations were also significantly decreased by caffeine. These results suggest that caffeine usage should be carefully considered in the design and interpretation of resting-state BOLD fMRI studies.

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PMCID: PMC2686062
PMID: 19457356 [Indexed for MEDLINE]

243. Neuroimage. 2009 Aug 1;47(1):302-11. doi: 10.1016/j.neuroimage.2009.03.064. Epub 2009 Apr 2.

Community structure in networks of functional connectivity: resolving functional organization in the rat brain with pharmacological MRI.

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In the study of functional connectivity, fMRI data can be represented mathematically as a network of nodes and links, where image voxels represent the nodes and the connections between them reflect a degree of correlation or

similarity in their response. Here we show that, within this framework, functional imaging data can be partitioned into 'communities' of tightly interconnected voxels corresponding to maximum modularity within the overall network. We evaluated this approach systematically in application to networks constructed from pharmacological MRI (phMRI) of the rat brain in response to acute challenge with three different compounds with distinct mechanisms of action (d-amphetamine, fluoxetine, and nicotine) as well as vehicle (physiological saline). This approach resulted in bilaterally symmetric sub-networks corresponding to meaningful anatomical and functional connectivity pathways consistent with the purported mechanism of action of each drug. Interestingly, common features across all three networks revealed two groups of tightly coupled brain structures that responded as functional units independent of the specific neurotransmitter systems stimulated by the drug challenge, including a network involving the prefrontal cortex and sub-cortical regions extending from the striatum to the amygdala. This finding suggests that each of these networks includes general underlying features of the functional organization of the rat brain.

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PMID: 19345737 [Indexed for MEDLINE]

244. World J Biol Psychiatry. 2009;10(4 Pt 2):495-502. doi: 10.1080/15622970902789148.

Pathophysiology of NSS in ADHD.

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Attention deficit/hyperactivity disorder (ADHD) is the behavioural disorder most commonly diagnosed in childhood. In addition to the main symptoms of inattention, impulsiveness and hyperactivity, neurological soft signs (NSS) are often associated with ADHD. NSS are discrete motor and sensory disorders that cannot be linked to specific cerebral lesions. We review all the scientific contributions on NSS in ADHD. The conclusions support the presence of an alteration in the neural networks for motor control inhibition, at the base of the pathophysiology of NSS in children with ADHD, as well as a possible central role of dopamine in these neural circuits.

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PMID: 19337883 [Indexed for MEDLINE]

245. Neuroimage. 2009 Jul 1;46(3):817-26. doi: 10.1016/j.neuroimage.2009.02.029. Epub 2009 Mar 2.

Prior MDMA (Ecstasy) use is associated with increased basal ganglia-thalamocortical circuit activation during motor task performance in humans: an fMRI study.

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MDMA (3,4-methylenedioxymethamphetamine; Ecstasy) is a popular recreational drug that produces long-lasting serotonin (5-HT) neurotoxicity consisting of reductions in markers for 5-HT axons. 5-HT innervates cortical and subcortical brain regions mediating motor function, predicting that MDMA users will have altered motor system neurophysiology. We used functional magnetic resonance imaging (fMRI) to assay motor task performance-associated brain activation changes in MDMA and non-MDMA users. 24 subjects (14 MDMA users and 10 controls) performed an event-related motor tapping task (1, 2 or 4 taps) during fMRI at 3 T. Motor regions of interest were used to measure percent signal change (PSC) and percent activated voxels (PAV) in bilateral motor cortex, sensory cortex, supplementary motor area (SMA), caudate, putamen, pallidum and thalamus. We used SPM5 to measure brain activation via three methods: T-maps, PSC and PAV. There was no statistically significant difference in reaction time between the two groups. For the Tap 4 condition, MDMA users had more activation than controls in the right SMA for T-score (p=0.02), PSC (p=0.04) and PAV (p=0.03). Lifetime episodes of MDMA use were positively correlated with PSC for the Tap 4 condition on the right for putamen and pallidum; with PAV in the right motor and sensory cortex and bilateral thalamus. In conclusion, we found a group difference in the right SMA and positive dose-response association between lifetime exposure to MDMA and signal magnitude and extent in several brain regions. This evidence is consistent with MDMA-induced alterations in basal ganglia-thalamocortical circuit

neurophysiology and is potentially secondary to neurotoxic effects on 5-HT signaling. Further studies examining behavioral correlates and the specific neurophysiological basis of the observed findings are warranted.

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PMCID: PMC2805435

PMID: 19264142 [Indexed for MEDLINE]

246. Science. 2008 Dec 12;322(5908):1700-2. doi: 10.1126/science.1164908.

Modafinil shifts human locus coeruleus to low-tonic, high-phasic activity during functional MRI.

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Comment in

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Models of cognitive control posit a key modulatory role for the pontine locus coeruleus-norepinephrine (LC-NE) system. In nonhuman primates, phasic LC-NE activity confers adaptive adjustments in cortical gain in task-relevant brain networks, and in performance, on a trial-by-trial basis. This model has remained

untested in humans. We used the pharmacological agent modafinil to promote low-tonic/high-phasic LC-NE activity in healthy humans performing a cognitive control task during event-related functional magnetic resonance imaging (fMRI). Modafanil administration was associated with decreased task-independent, tonic LC activity, increased task-related LC and prefrontal cortex (PFC) activity, and enhanced LC-PFC functional connectivity. These results confirm in humans the role of the LC-NE system in PFC function and cognitive control and suggest a mechanism for therapeutic action of procognitive noradrenergic agents.

DOI: 10.1126/science.1164908
PMID: 19074351 [Indexed for MEDLINE]

247. Eur J Paediatr Neurol. 2009 Nov;13(6):516-23. doi: 10.1016/j.ejpn.2008.10.008. Epub 2008 Dec 3.

Effects of methylphenidate on working memory functioning in children with attention deficit/hyperactivity disorder.

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BACKGROUND AND AIMS: Children with attention deficit/hyperactivity disorder

(ADHD) often show deficits in working memory performance. Methylphenidate (MPH) is an effective medication to improve these cognitive difficulties. This study aimed to clarify which effect MPH induces on the underlying functional networks of working memory.

METHODS: Fourteen boys diagnosed with ADHD and 12 healthy controls were investigated using functional magnetic resonance imaging (fMRI). Each patient was tested twice, once with medication and once without. The fMRI experiments consisted of three verbal N-back tasks with increasing difficulty. Functional images were acquired on a 3 Tesla head scanner.

RESULTS: On the behavioral level, medicated patients performed similar to healthy controls and significantly better than without medication. On the functional level, patients showed the expected frontal and parietal activations, which were more pronounced in the 2- and 3-back tasks. Healthy controls showed significantly more activation in these regions and additional activation in the cerebellum. Interestingly, patients showed an additional effect of laterality. Left-sided frontal and parietal activation in patients was significantly less pronounced than in controls.

CONCLUSION: Functional data indicate different activation patterns in verbal working memory tasks between healthy controls and patients with ADHD irrespective of medication condition. Intake of MPH led to a clear improvement on a behavioral level. However, this effect was not reflected by changes in functional brain organization. MPH-induced changes leading to better performance in verbal working memory tasks might be very subtle and therefore not detectable by fMRI.

DOI: 10.1016/j.ejpn.2008.10.008

PMID: 19056305 [Indexed for MEDLINE]

248. Psychopharmacology (Berl). 2009 Mar;202(4):599-610. doi:
10.1007/s00213-008-1338-x. Epub 2008 Sep 26.

Brain activation by short-term nicotine exposure in anesthetized wild-type and beta2-nicotinic receptors knockout mice: a BOLD fMRI study.

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RATIONALE: The behavioral effects of nicotine and the role of the beta2-containing nicotinic receptors in these behaviors are well documented. However, the behaviors altered by nicotine rely on the functioning on multiple brain circuits where the high-affinity beta2-containing nicotinic receptors (beta2*nAChRs) are located.
OBJECTIVES: We intend to see which brain circuits are activated when nicotine is given in animals naïve for nicotine and whether the beta2*nAChRs are needed for its activation of the blood oxygen level dependent (BOLD) signal in all brain areas.
MATERIALS AND METHODS: We used functional magnetic resonance imaging (fMRI) to measure the brain activation evoked by nicotine (1 mg/kg delivered at a slow rate for 45 min) in anesthetized C57BL/6J mice and beta2 knockout (KO) mice.

RESULTS: Acute nicotine injection results in a significant increased activation in anterior frontal, motor, and somatosensory cortices and in the ventral tegmental area and the substantia nigra. Anesthetized mice receiving no nicotine injection exhibited a major decreased activation in all cortical and subcortical structures, likely due to prolonged anesthesia. At a global level, beta2 KO mice were not rescued from the globally declining BOLD signal. However, nicotine still activated regions of a meso-cortico-limbic circuit likely via alpha7 nicotinic receptors.
CONCLUSIONS: Acute nicotine exposure compensates for the drop in brain activation due to anesthesia through the meso-cortico-limbic network via the action of nicotine on beta2*nAChRs. The developed fMRI method is suitable for comparing responses in wild-type and mutant mice.

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PMID: 18818904 [Indexed for MEDLINE]

249. Biol Psychiatry. 2009 Jan 15;65(2):160-4. doi: 10.1016/j.biopsych.2008.07.030. Epub 2008 Sep 18.

Medial orbitofrontal cortex gray matter is reduced in abstinent substance-dependent individuals.

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BACKGROUND: Chronic exposure to drugs of addiction induces cellular adaptations in orbitofrontal cortex (OFC) and associated limbic-prefrontal pathways that might underlie abuse-related behavior. A propensity to make risky decisions in spite of substantial negative consequences might be mediated by medial OFC dysfunction in substance-dependent individuals (SDI). We tested the hypothesis that medial OFC gray matter (GM) volume would be lower in SDI compared with control subjects.

METHODS: Nineteen SDI and 20 control subjects participated. The SDI were dependent on two or more substances, most often cocaine, amphetamine, and alcohol, with mean duration of abstinence 4.7, 2.4, and 3.2 years, respectively. High-resolution T1-weighted images were acquired on a 3-T magnetic resonance system. Image processing and analyses were conducted with voxel-based morphometry (VBM) implemented in Statistical Parametric Mapping (SPM) 5. Differences in regional GM volume were tested with an analysis of covariance model, co-varying for global GM and age. Statistical maps were set at $p < .05$, corrected for multiple comparisons. Medial OFC GM volume was correlated with behavioral performance on a modified gambling task.

RESULTS: There was lower GM volume specifically in bilateral medial OFC in SDI compared with control subjects. There was a small but significant correlation between medial OFC GM and persistence of playing high-risk decks on a modified gambling task.

CONCLUSIONS: This is the first study to use VBM with whole brain correction for multiple comparisons in SDI after prolonged abstinence. Reduced medial OFC GM might reflect long-term adaptations within the reward-learning circuit underlying pathological decision-making in substance dependence.

DOI: 10.1016/j.biopsych.2008.07.030

PMCID: PMC2640220

PMID: 18801475 [Indexed for MEDLINE]

250. Neurosci Lett. 2008 Oct 24;444(2):117-21. doi: 10.1016/j.neulet.2008.08.033. Epub 2008 Aug 15.

Electrical stimulation modulates the amphetamine-induced hemodynamic changes: an fMRI study to compare the effect of stimulating locations and frequencies on rats.

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Our previous fMRI and microdialysis measurements showed that electroacupuncture (EA) at LI4 was effective in alleviating excessive cerebral dopamine release induced by d-amphetamine (AMPH) in rats. We now compare the effect of EA in adjusting excess dopamine release at two stimulating frequencies (2 Hz versus 100 Hz at LI4) and at two acupoints (forepaw (LI4) versus hindpaw (ST36), at 2 Hz). fMRI measurements of relative cerebral blood volume (rCBV) were used to monitor the brain activity of "rest", followed by AMPH challenge, 10 min "rest", and then

20 min of EA.RESULTS: EA at LI4 and ST36 significantly attenuated the AMPH-induced rCBV increases in the striatum, S1 cortex, and thalamus. Frequency: EA at 100 Hz induced greater attenuation of rCBV than EA at 2 Hz in the S1, insula, anterior cingulate cortices, dorsolateral striatum, and thalamus. Acupoints: EA at LI4 modulated a broader area in the medial anterior striatum while EA at ST36 modulated a more site-specific area in the dorsolateral striatum. In the thalamus, EA at LI4 showed greater attenuating effect than EA at ST36 did. However, in the insular cortex, EA at ST36 showed stronger attenuation. CONCLUSION: EA at both LI4 and ST36 was effective in restoring dopamine homeostasis from an excess state, with the most effective response at LI4 with 100 Hz, while the responses to 2Hz EA at LI4 and ST36 showed slightly different spatial distribution of MR signal. This therefore provided insight into the neurophysiological basis of electroacupuncture effects in cortical and subcortical circuits.

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PMCID: PMC2602879
PMID: 18722508 [Indexed for MEDLINE]

251. Drug Alcohol Depend. 2008 May 1;95(1-2):115-28. doi: 10.1016/j.drugalcdep.2007.12.014. Epub 2008 Mar 4.

Reduced posterior mesofrontal cortex activation by risky rewards in substance-dependent patients.

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Substance-dependent individuals show disadvantageous decision-making, as well as altered frontocortical recruitment when performing experimental tasks. We investigated whether substance-dependent patients (SDP) would show blunted recruitment of posterior mesofrontal cortex (PMC) by a conflict between concurrently increasing reward and risk of penalty in a monetary game of "chicken." SDP and controls performed: motor control (no reward) trials, guaranteed reward trials in which reward was not at risk, and risky trials where subjects were required to terminate their reward accrual before a secret varying time limit or else "bust" and forfeit that trial's winnings (low penalty) or the current trial's winnings plus an equal amount of previous winnings (high penalty). Reward accrual duration at risk of "busting" correlated negatively with trait neuroticism. The contrast between winning guaranteed reward versus non-reward activated the caudate head bilaterally in SDP but not controls. Accumulation of money at risk of low- or high-penalty (contrasted with accumulating guaranteed money) activated the PMC in both groups, but with a greater magnitude and more anterior extent in controls. Pre-decision signal increase in a PMC volume of interest negatively correlated with risk-taking in low-penalty trials, and was blunted in SDP relative to controls under both penalty conditions after controlling for individual differences in actual risk-taking and the higher neuroticism of SDP. These data suggest that SDP are characterized by a combination of: (a) striatal hypersensitivity to reward, and (b) under-recruitment of the specialized conflict-monitoring circuitry of the PMC

when reward entails potential penalties.

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PMCID: PMC2327254

PMID: 18295984 [Indexed for MEDLINE]

252. PLoS One. 2008 Jan 30;3(1):e1506. doi: 10.1371/journal.pone.0001506.

Prelude to passion: limbic activation by "unseen" drug and sexual cues.

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BACKGROUND: The human brain responds to recognizable signals for sex and for rewarding drugs of abuse by activation of limbic reward circuitry. Does the brain respond in similar way to such reward signals even when they are "unseen", i.e., presented in a way that prevents their conscious recognition? Can the brain response to "unseen" reward cues predict the future affective response to recognizable versions of such cues, revealing a link between affective/motivational processes inside and outside awareness?

METHODOLOGY/PRINCIPAL FINDINGS: We exploited the fast temporal resolution of event-related functional magnetic resonance imaging (fMRI) to test the brain

response to "unseen" (backward-masked) cocaine, sexual, aversive and neutral cues of 33 milliseconds duration in male cocaine patients (n = 22). Two days after scanning, the affective valence for visible versions of each cue type was determined using an affective bias (priming) task. We demonstrate, for the first time, limbic brain activation by "unseen" drug and sexual cues of only 33 msec duration. Importantly, increased activity in an large interconnected ventral pallidum/amygdala cluster to the "unseen" cocaine cues strongly predicted future positive affect to visible versions of the same cues in subsequent off-magnet testing, pointing both to the functional significance of the rapid brain response, and to shared brain substrates for appetitive motivation within and outside awareness.

CONCLUSIONS/SIGNIFICANCE: These findings represent the first evidence that brain reward circuitry responds to drug and sexual cues presented outside awareness. The results underscore the sensitivity of the brain to "unseen" reward signals and may represent the brain's primordial signature for desire. The limbic brain response to reward cues outside awareness may represent a potential vulnerability in disorders (e.g., the addictions) for whom poorly-controlled appetitive motivation is a central feature.

DOI: 10.1371/journal.pone.0001506
PMCID: PMC2204052
PMID: 18231593 [Indexed for MEDLINE]

253. Psychopharmacology (Berl). 2008 Mar;196(4):543-53. Epub 2007 Nov 14.

Neuronal dysfunction of a long projecting multisynaptic pathway in response to

methamphetamine using manganese-enhanced MRI.

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RATIONALE: Manganese (Mn2+)-enhanced magnetic resonance imaging (MEMRI) is an emerging in vivo MR approach for pharmacological research. One new application of MEMRI in this area is to characterize functional changes of a specific neural circuit that is essential to the central effects of a drug challenge.
OBJECTIVES: To develop and validate such use of MEMRI in neuropharmacology, the current study applied MEMRI to visualize functional changes within a multisynaptic pathway originating from fasciculus retroflexus (FR) that is central to a commonly abused psychostimulant, methamphetamine (MA).
METHODS: Twelve rats were injected intraperitoneally with MA (10 mg/kg) or saline every 2 h for a total of four injections. After 6 days, Mn2+ was injected into the habenular nucleus (FR origin) of all animals, and MEMRI was repeatedly performed at certain points in time over 48 h. The evolution of Mn2+-induced signal enhancement was assessed across the FR tract, the ventral tegmental area (VTA), the striatum, the nucleus accumbens, and the prefrontal cortex (PFC), in both MA-injected animals and controls.
RESULTS: MA treatment was found to affect the complexity and efficiency of Mn2+ uptake in the VTA, via the FR tract, with significantly increased Mn2+ accumulation in the VTA, the dorsomedial part of the striatum, and the PFC.
CONCLUSIONS: MEMRI successfully visualizes disruptions in the multisynaptic

pathway as the consequences of repeated MA exposure. MEMRI is potentially an important method in the future to investigate functional changes within a specific pathway under the influences of pharmacological agents, given its excellent functional, in vivo, spatial, and temporal properties.

DOI: 10.1007/s00213-007-0990-x
PMID: 18000655 [Indexed for MEDLINE]

254. Neuro Endocrinol Lett. 2007 Oct;28(5):604-9.

Asymmetry of basal ganglia in children with attention deficit hyperactivity disorder.

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Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatry disorder with several key symptoms, such as inattentiveness, impulsivity and hyperactivity. Neuropsychiatry studies have implicated the frontostriatal circuit in the pathological physiology of the disorder. Using magnetic resonance imaging (MRI), we examined the basal ganglia in 13 ADHD patients and eight unaffected comparison children. The volume of caudate, putamen and globus pallidus was measured. In the ADHD patients, we detected an increased left > right asymmetry

of the basal ganglia. This reversal of asymmetry in the globus pallidus and caudate nucleus were statistically significant. These finding provide further evidence of morphological brain abnormalities in ADHD.

PMID: 17994006 [Indexed for MEDLINE]

255. Drug Alcohol Depend. 2008 Jan 11;93(1-2):93-102. Epub 2007 Oct 26.

Differences in cortical activity between methamphetamine-dependent and healthy individuals performing a facial affect matching task.

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Erratum in
Drug Alcohol Depend. 2009 May 1;10(3):213-4.

As individuals who abuse methamphetamine (MA) often exhibit socially maladaptive behaviors such as violence and aggression, it is possible that they respond abnormally to social cues. To investigate this issue, we exposed 12 MA-dependent participants (abstinent 5-16 days) and 12 healthy comparison participants to fearful and angry faces while they performed an affect matching task during

functional magnetic resonance imaging (fMRI). Although the groups did not differ in task performance, the healthy participants showed more task-related activity than the MA-dependent participants in a set of cortical regions consisting of the ventrolateral prefrontal cortex (VLPFC), temporoparietal junction (TPJ), anterior and posterior temporal cortex, and fusiform gyrus in the right hemisphere, and the cuneus in the left hemisphere. In contrast, the MA-dependent participants showed more task-related activity than the healthy participants in the dorsal anterior cingulate cortex (dACC). As expected, the task elicited activation of the amygdala in both groups; however, contrary to expectation, we found no difference between groups in this activation. Dorsal ACC hyperactivity, along with high self-ratings of hostility and interpersonal sensitivity in the MA-dependent group, suggest a hyper-sensitivity to socially threatening cues in the MA-dependent participants, while lower VLPFC activation could point to a deficit in integrating socio-emotional information and/or regulating this limbic hyperactivity. Additional activation differences in neural circuitry related to social cognition (TPJ, anterior, and posterior temporal cortex) suggest further socio-emotional deficits. Together, the results point to cortical abnormalities that could underlie the socially inappropriate behaviors often shown by individuals who abuse MA.

DOI: 10.1016/j.drugalcdep.2007.09.009

PMCID: PMC2270785

PMID: 17964741 [Indexed for MEDLINE]

256. Curr Psychiatry Rep. 2007 Oct;9(5):401-7.

Recent advances in structural and functional brain imaging studies of attention-deficit/hyperactivity disorder.

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The field of neuroimaging of attention-deficit/hyperactivity disorder (ADHD) is now 30 years old. This brief selective review highlights the increasing sophistication of recent structural and functional neuroimaging studies of ADHD. In volumetric studies, investigators are examining extra-frontal, as well as frontal-striatal circuits and beginning to differentiate the potential effects of medication exposure. Functional MRI studies are focusing on familial/genetic influences and enrolling medication naïve, as well as medicated children with ADHD. A promising trend is the application of resting state approaches to mapping functional connectivity, which provides unexpectedly detailed information about interregional relationships while bypassing potentially confounding issues related to task performance. These developments allow us to conclude that neuroimaging studies of ADHD will increasingly inform our understanding of the neuronal substrates of ADHD.

PMID: 17915080 [Indexed for MEDLINE]

257. Brain Res. 2007 Sep 26;1171:83-92. Epub 2007 Aug 10.

Widespread disruption in brain activation patterns to a working memory task during cocaine abstinence.

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Cocaine abstinence is associated with impaired performance in cognitive functions including attention, vigilance and executive function. Here we test the hypothesis that cognitive dysfunction during cocaine abstinence reflects in part impairment of cortical and subcortical regions modulated by dopamine. We used functional magnetic resonance imaging (fMRI) to study brain activation to a verbal working memory task in cocaine abusers (n=16) and healthy controls (n=16). Compared to controls, cocaine abusers showed: (1) hypoactivation in the mesencephalon, where dopamine neurons are located, as well as the thalamus, a brain region involved in arousal; (2) larger deactivation in dopamine projection regions (putamen, anterior cingulate, parahippocampal gyrus, and amygdala); and (3) hyperactivation in cortical regions involved with attention (prefrontal and parietal cortices), which probably reflects increased attention and control processes as compensatory mechanisms. Furthermore, the working memory load activation was lower in the prefrontal and parietal cortices in cocaine abusers when compared with controls, which might reflect limited network capacity. These

abnormalities were accentuated in the cocaine abusers with positive urines for cocaine at time of study (as compared to cocaine abusers with negative urines) suggesting that the deficits may reflect in part early cocaine abstinence. These findings provide evidence of impaired function of regions involved with executive control, attention and vigilance in cocaine abusers. This widespread neurofunctional disruption is likely to underlie the cognitive deficits during early cocaine abstinence and to reflect involvement of dopamine as well as other neurotransmitters.

DOI: 10.1016/j.brainres.2007.06.102
PMCID: PMC2048813
PMID: 17765877 [Indexed for MEDLINE]

258. J Child Psychol Psychiatry. 2007 Sep;48(9):899-913.

ADHD- and medication-related brain activation effects in concordantly affected parent-child dyads with ADHD.

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BACKGROUND: Several studies have documented fronto-striatal dysfunction in

children and adolescents with attention deficit/hyperactivity disorder (ADHD) using response inhibition tasks. Our objective was to examine functional brain abnormalities among youths and adults with ADHD and to examine the relations between these neurobiological abnormalities and response to stimulant medication.
METHOD: A group of concordantly diagnosed ADHD parent-child dyads was compared to a matched sample of normal parent-child dyads. In addition, ADHD dyads were administered double-blind methylphenidate and placebo in a counterbalanced fashion over two consecutive days of testing. Frontostriatal function was measured using functional magnetic resonance imaging (fMRI) during performance of a go/no-go task.
RESULTS: Youths and adults with ADHD showed attenuated activity in fronto-striatal regions. In addition, adults with ADHD appeared to activate non-fronto-striatal regions more than normals. A stimulant medication trial showed that among youths, stimulant medication increased activation in fronto-striatal and cerebellar regions. In adults with ADHD, increases in activation were observed in the striatum and cerebellum, but not in prefrontal regions.
CONCLUSIONS: This study extends findings of fronto-striatal dysfunction to adults with ADHD and highlights the importance of frontostriatal and frontocerebellar circuitry in this disorder, providing evidence of an endophenotype for examining the genetics of ADHD.

DOI: 10.1111/j.1469-7610.2007.01761.x
PMID: 17714375 [Indexed for MEDLINE]

259. Biol Psychiatry. 2008 Jan 15;63(2):222-30. Epub 2007 Jul 17.

Expectation modulates human brain responses to acute cocaine: a functional magnetic resonance imaging study.

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BACKGROUND: Human expectation of psychoactive drugs significantly alters drug effects and behavioral responses. However, their neurophysiological mechanisms are not clear. This study investigates how cocaine expectation modulates human brain responses to acute cocaine administration.
METHODS: Twenty-six right-handed non-treatment-seeking regular cocaine abusers participated in this study. Changes in blood oxygenation level-dependent (BOLD) signals were measured, and online behavioral ratings during cocaine expectation and acute cocaine administration were recorded.
RESULTS: Distinct regional characteristics in BOLD responses to expected and unexpected cocaine infusions were observed in the medial orbitofrontal gyrus (Brodmann area [BA] 11), frontal pole (BA 10), and anterior cingulate gyrus regions. Active engagement in the amygdala and the lateral orbitofrontal cortex (OFC; BA 47) by unexpected but not expected cocaine infusion was discovered. Cocaine expectation did not change BOLD responses to acute cocaine administration in a set of subcortical substrates, the nucleus accumbens, ventral putamen, ventral tegmental area, and thalamus.

CONCLUSIONS: These results suggest that cocaine expectation modulates neural-sensitivity adaptation between the expected events and the actual outcomes but did not modulate the pharmacological characteristics of cocaine. In addition, the amygdala-lateral OFC circuitry plays an important role in mediating stimulus-outcome relations and contextual factors of drug abuse.

DOI: 10.1016/j.biopsych.2007.03.021
PMID: 17644071 [Indexed for MEDLINE]

260. Am J Addict. 2007 May-Jun;16(3):174-82.

An fMRI study of the interaction of stress and cocaine cues on cocaine craving in cocaine-dependent men.

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Acute stress is associated with relapse in cocaine addiction, possibly through the activation of craving-related neural circuitry. Neural responses to cocaine cues and acute stress were investigated in an fMRI study. Ten male participants mentally re-enacted personalized scripts about cocaine use and a neutral experience both with and without a stressor present (anticipation of electrical shock). Interaction analysis between script type and stress condition revealed

greater activation of the posterior cingulate cortex and of the parietal lobe during the cocaine script in the presence of the stressor. These data suggest that stress may precipitate relapse in cocaine addiction by activating brain areas that mediate reward processing and the attentional and mnemonic bias for drug use reminders.

DOI: 10.1080/10550490701375285
PMID: 17612820 [Indexed for MEDLINE]

261. Psychiatry Res. 2007 Aug 15;155(3):189-201. Epub 2007 Jun 19.

Thalamo-cortical dysfunction in cocaine abusers: implications in attention and perception.

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Cocaine affects sensory perception and attention, but little is known about the neural substrates underlying these effects in the human brain. We used functional magnetic resonance imaging (fMRI) and a sustained visuospatial attention task to assess if the visual attention network is dysfunctional in cocaine abusers (n=14) compared to age-, gender-, and education-matched controls (n=14). Compared with

controls, cocaine abusers showed (1) hypo-activation of the thalamus, which may reflect noradrenergic and/or dopaminergic deficits; (2) hyper-activation in occipital and prefrontal cortices, which may reflect increased visual cortical processing to compensate for inefficient visual thalamic processing; and (3) larger deactivation of parietal and frontal regions possibly to support the larger hemodynamic supply to the hyper-activated brain regions. These findings provide evidence of abnormalities in thalamo-cortical responses in cocaine abusers that are likely to contribute to the impairments in sensory processing and in attention. The development of therapies that diminish these thalamo-cortical deficits could improve the treatment of cocaine addiction.

DOI: 10.1016/j.pscychresns.2007.03.002
PMCID: PMC2265105
PMID: 17582746 [Indexed for MEDLINE]

262. Magn Reson Imaging. 2007 Jul;25(6):811-20. Epub 2007 Apr 18.

Pharmacological modulation of functional connectivity: the correlation structure underlying the phMRI response to d-amphetamine modified by selective dopamine D3 receptor antagonist SB277011A.

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Pharmacological MRI (phMRI) experiments utilise fMRI time series methods to map the central effect of pharmaceutical compounds. The typical univariate maps may, however, integrate the effects of several different neurotransmitter systems or underlying mechanisms. The results may thus be spatially and/or mechanistically nonspecific. Intersubject correlation analysis based on the phMRI response amplitude can more directly identify patterns of functional connectivity underlying the central effects of an acutely administered compound. In this article, we extend this approach to experiments where the effects of one compound in modulating the response to another are of interest. Specifically, we show a modulation of the correlation structure of a probe compound (d-amphetamine) by pretreatment with the selective dopamine D3 receptor antagonist SB277011A in the rat. The strongest modifications in the correlation patterns occurred in connection with the ventral tegmental area, the source of mesolimbic dopamine projections and a key substrate in the reward system.

DOI: 10.1016/j.mri.2007.02.017

PMID: 17442525 [Indexed for MEDLINE]

263. Magn Reson Med. 2007 Apr;57(4):704-13.

Functional connectivity in the pharmacologically activated brain: resolving networks of correlated responses to d-amphetamine.

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We investigated the functional connectivity structure underlying the widespread relative cerebral blood volume (rCBV) response to d-amphetamine in the rat brain by systematically analyzing the intersubject correlations between the response amplitudes in 48 atlas-defined brain structures. A cluster analysis resolved three distinct networks of brain regions that exhibited closely coupled responses: one corresponding to primary dopamine projections from the midbrain to the striatum, a second consisting predominantly of forebrain cortical and basal ganglia regions that share a widespread correlation pattern resembling the univariate group response, and a third including structures in the periventricular dopamine system. These results suggest that different functional networks underlie the brain's response to d-amphetamine. This approach may provide important new insights regarding the central systems that underlie pharmacological action.

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PMID: 17390353 [Indexed for MEDLINE]

264. J Child Psychol Psychiatry. 2007 Mar-Apr;48(3-4):262-87.

Brain basis of early parent-infant interactions: psychology, physiology, and in vivo functional neuroimaging studies.

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Parenting behavior critically shapes human infants' current and future behavior. The parent-infant relationship provides infants with their first social experiences, forming templates of what they can expect from others and how to best meet others' expectations. In this review, we focus on the neurobiology of parenting behavior, including our own functional magnetic resonance imaging (fMRI) brain imaging experiments of parents. We begin with a discussion of background, perspectives and caveats for considering the neurobiology of parent-infant relationships. Then, we discuss aspects of the psychology of parenting that are significantly motivating some of the more basic neuroscience research. Following that, we discuss some of the neurohormones that are important for the regulation of social bonding, and the dysregulation of parenting with cocaine abuse. Then, we review the brain circuitry underlying parenting, proceeding from relevant rodent and nonhuman primate research to human work. Finally, we focus on a study-by-study review of functional neuroimaging studies in humans. Taken together, this research suggests that networks of highly conserved hypothalamic-midbrain-limbic-paralimbic-cortical circuits act in concert to support aspects of parent response to infants, including the emotion, attention, motivation, empathy, decision-making and other thinking that are required to navigate the complexities of parenting. Specifically, infant stimuli activate basal forebrain regions, which regulate brain circuits that handle specific nurturing and caregiving responses and activate the brain's more general

circuitry for handling emotions, motivation, attention, and empathy--all of which are crucial for effective parenting. We argue that an integrated understanding of the brain basis of parenting has profound implications for mental health.

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PMCID: PMC4318551

PMID: 17355399 [Indexed for MEDLINE]

265. Biol Psychiatry. 2007 Oct 1;62(7):765-72. Epub 2007 Jan 16.

Temporal difference modeling of the blood-oxygen level dependent response during aversive conditioning in humans: effects of dopaminergic modulation.

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BACKGROUND: The prediction error (PE) hypothesized by the temporal difference model has been shown to correlate with the phasic activity of dopamine neurons during reward learning and the blood-oxygen level dependent (BOLD) response during reward and aversive conditioning tasks. We hypothesized that dopamine would modulate the PE related signal in aversive conditioning and that haloperidol would reduce PE related activity, while an acute dose of amphetamine would increase PE related activity in the ventral striatum.

METHODS: Healthy participants took an acute dose of amphetamine, haloperidol, or placebo. We used functional magnetic resonance imaging (fMRI) to measure the BOLD signal while they carried out an aversive conditioning task, using cutaneous electrical stimulation as the unconditioned stimulus (US) and yellow and blue circles as conditioned stimulus (CS+ and CS-, respectively).
RESULTS: Prediction error related BOLD activity was seen only in the ventral striatum in the placebo subjects. The subjects given amphetamine showed a wider network of PE related BOLD activity, including the ventral striatum, globus pallidus, putamen, insula, anterior cingulate, and substantia nigra/ventral tegmental area. Haloperidol subjects did not show PE related activity in any of these regions.
CONCLUSIONS: Our results provide the first demonstration that the modulation of dopamine transmission affects both the physiological correlates and PE related BOLD activity during aversive learning.

DOI: 10.1016/j.biopsych.2006.10.020
PMID: 17224134 [Indexed for MEDLINE]

266. Am J Psychiatry. 2007 Jan;164(1):43-51.

Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction?

Goldstein RZ(1), Alia-Klein N, Tomasi D, Zhang L, Cottone LA, Maloney T, Telang F, Caparelli EC, Chang L, Ernst T, Samaras D, Squires NK, Volkow ND.

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Comment in

Am J Psychiatry. 2007 Jan;164(1):4-6.

OBJECTIVE: This study attempted to examine the brain's sensitivity to monetary rewards of different magnitudes in cocaine abusers and to study its association with motivation and self-control.

METHOD: Sixteen cocaine abusers and 13 matched healthy comparison subjects performed a forced-choice task under three monetary value conditions while brain activation was measured with functional magnetic resonance imaging. Objective measures of state motivation were assessed by reaction time and accuracy, and subjective measures were assessed by self-reports of task engagement. Measures of trait motivation and self-control were assessed with the Multidimensional Personality Questionnaire.

RESULTS: The cocaine abusers demonstrated an overall reduced regional brain responsivity to differences between the monetary value conditions. Also, in comparison subjects but not in cocaine abusers, reward-induced improvements in performance were associated with self-reports of task engagement, and money-induced activations in the lateral prefrontal cortex were associated with parallel activations in the orbitofrontal cortex. For cocaine abusers, prefrontal cortex sensitivity to money was instead associated with motivation and self-control.

CONCLUSIONS: These findings suggest that in cocaine addiction 1) activation of the corticolimbic reward circuit to gradations of money is altered; 2) the lack

of a correlation between objective and subjective measures of state motivation may be indicative of disrupted perception of motivational drive, which could contribute to impairments in self-control; and 3) the lateral prefrontal cortex modulates trait motivation and deficits in self-control, and a possible underlying mechanism may encompass a breakdown in prefrontal-orbitofrontal cortical communication.

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PMID: 17202543 [Indexed for MEDLINE]

267. Neurotoxicol Teratol. 2007 Jan-Feb;29(1):116-25. Epub 2006 Dec 6.

1H MRS-detectable metabolic brain changes and reduced impulsive behavior in adult rats exposed to methylphenidate during adolescence.

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Administration of methylphenidate (MPH, Ritalin) to children affected by attention deficit hyperactivity disorder (ADHD) is an elective therapy, which however raises concerns for public health, due to possible persistent neuro-behavioral alterations. We investigated potential long-term consequences at

adulthood of MPH exposure during adolescence, by means of behavioral and brain MRS assessment in drug-free state. Wistar adolescent rats (30- to 44-day-old) were treated with MPH (0 or 2 mg/kg once/day for 14 days) and then left undisturbed until adulthood. Levels of impulsive behavior were assessed in the intolerance-to-delay task: Food-restricted rats were tested in operant chambers with two nose-poking holes, delivering one food pellet immediately, or five pellets after a delay whose length was increased over days. MPH-exposed animals showed a less marked shifting profile from the large/late to the small/soon reward, suggesting reduced basal levels of impulsivity, compared to controls. In vivo MRI-guided 1H MRS examinations at 4.7 T in anaesthetised animals revealed long-term biochemical changes in the dorsal striatum (STR), nucleus accumbens (NAcc), and prefrontal cortex (PFC) of MPH-exposed rats. Notably, total creatine and taurine, metabolites respectively involved in bioenergetics and synaptic efficiency, were up-regulated in the STR and conversely down-regulated in the NAcc of MPH-exposed rats. A strong correlation was evident between non-phosphorylated creatine in the STR and behavioral impulsivity. Moreover, unaltered total creatine and increased phospho-creatine/creatine ratio were detected in the PFC, suggesting improved cortical energetic performance. Because of this enduring rearrangement in the forebrain function, MPH-exposed animals may be more efficient when faced with delay of reinforcement. In summary, MPH exposure during adolescence produced enduring MRS-detectable biochemical modifications in brain reward-related circuits, which may account for increased self-control capacity of adult rats.

DOI: 10.1016/j.ntt.2006.11.010

PMID: 17196789 [Indexed for MEDLINE]

268. Neuroimage. 2007 Feb 15;34(4):1627-36. Epub 2006 Dec 26.

In vivo mapping of functional connectivity in neurotransmitter systems using pharmacological MRI.

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Pharmacological MRI (phMRI) methods map the hemodynamic response to drug challenge as a surrogate for changes in neuronal activity. However, the central effects of drugs can be complex and include activity at the primary site of action, downstream effects in other brain regions and direct effects on vasculature and neurovascular coupling. Univariate analysis, normally applied to phMRI data, does not discriminate between these effects, and can result in anatomically non-specific activation patterns. We analysed inter-subject correlations in the amplitude of the slow phMRI response to map functionally connected brain regions recruited in response to pharmacological challenge. Application of D-amphetamine and fluoxetine revealed well-defined functional structure underlying the widespread signal changes detected via standard methods. Correlated responses were found to delineate key neurotransmitter pathways selectively targeted by these drugs, corroborating a tight correspondence between the phMRI response and changes in neurotransmitter systems specific to the pharmacological action. In vivo mapping of correlated responses in this way

greatly extends the range of information available from phMRI studies and provides a new window into the function of neurotransmitter systems in the active state. This approach may provide new important insights regarding the central systems underlying pharmacological action.

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PMID: 17188903 [Indexed for MEDLINE]

269. Psychiatry Res. 2007 Jan 15;154(1):69-84. Epub 2006 Dec 20.

Low-resolution brain electromagnetic tomography (LORETA) identifies brain regions linked to psychometric performance under modafinil in narcolepsy.

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Low-resolution brain electromagnetic tomography (LORETA) showed a functional deterioration of the fronto-temporo-parietal network of the right hemispheric vigilance system in narcolepsy and a therapeutic effect of modafinil. The aim of this study was to determine the effects of modafinil on cognitive and thymopsychic variables in patients with narcolepsy and investigate whether neurophysiological vigilance changes correlate with cognitive and subjective vigilance alterations at the behavioral level. In a double-blind,

placebo-controlled crossover design, EEG-LORETA and psychometric data were obtained during midmorning hours in 15 narcoleptics before and after 3 weeks of placebo or 400 mg modafinil. Cognitive investigations included the Pauli Test and complex reaction time. Thymopsychic/psychophysiological evaluation comprised drive, mood, affectivity, wakefulness, depression, anxiety, the Symptom Checklist 90 and critical flicker frequency. The Multiple Sleep Latency Test (MSLT) and the Epworth Sleepiness Scale (ESS) were performed too. Cognitive performance (Pauli Test) was significantly better after modafinil than after placebo. Concerning reaction time and thymopsychic variables, no significant differences were observed. Correlation analyses revealed that a decrease in prefrontal delta, theta and alpha-1 power correlated with an improvement in cognitive performance. Moreover, drowsiness was positively correlated with theta power in parietal and medial prefrontal regions and beta-1 and beta-2 power in occipital regions. A less significant correlation was observed between midmorning EEG LORETA and the MSLT; between EEG LORETA and the ESS, the correlation was even weaker. In conclusion, modafinil did not influence thymopsychic variables in narcolepsy, but it significantly improved cognitive performance, which may be related to medial prefrontal activity processes identified by LORETA.

DOI: 10.1016/j.pscychresns.2006.04.005
PMID: 17187965 [Indexed for MEDLINE]

270. Sleep. 2006 Nov;29(11):1471-81.

Modafinil activates cortical and subcortical sites in the sleep-deprived state.

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SUBJECT OBJECTIVES: To assess the effect of the wake-promoting drug modafinil on working memory and brain activation in the executive network, following a single night of sleep deprivation.DESIGN: Randomized, placebo-controlled, 4-arm, double-blind evaluation of a single 200-mg dose of modafinil on working memory (1-, 2-, and 3-back)-related functional brain activation and performance following overnight sleep deprivation.

SETTING: General Clinical Research Center, Biomedical Imaging Center.

SUBJECTS: Eight medication-free men, aged 21 to 35 years.

INTERVENTIONS: Overnight sleep deprivation, single-dose 200-mg modafinil, functional magnetic resonance imaging

MEASUREMENTS AND RESULTS: Brain activation patterns and regional signal intensity based on the blood-oxygen level-dependent signal were assessed. The following reaction times were used as measures of performance: (1) attention in the scanner before functional scanning, (2) "back" responses during the active-task block, and (3) attention during the baseline task block. Contrast of activation maps among conditions revealed sleep-deprivation and drug effects, and their interactions. Performance in the deprived state was enhanced by modafinil only at an intermediate (2-back) level of task difficulty and was associated with the recruitment of increased cortical activation volumes. Strong and consistent individual differences in performance were noted on the working memory tasks.

CONCLUSIONS: Modafinil effectively counters the adverse effects of overnight

sleep deprivation on working memory but only when task difficulty is moderate, recruiting extensive areas in the executive network to do so. Interindividual differences in working-memory performance are stable trait characteristics.

PMID: 17162995 [Indexed for MEDLINE]

271. Neuropsychobiology. 2006;54(2):107-13. Epub 2006 Nov 13.

Diffusion tensor imaging of the corpus callosum in addiction.

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Diffusion tensor imaging, a novel technique with an increased capability of detecting abnormalities in the white matter, has increasingly been employed in the study of the biology of addictions. A comprehensive search from a range of databases was conducted and publications on this topic were selected. Nine reports, eight published and one unpublished, met criteria for inclusion, five on alcoholism, three on cannabis and one on cocaine use. Findings of this review suggest focal disruption of commissural connectivity in the corpus callosum. In alcoholism, the genu and splenium were particularly affected with a different pattern in men and women, and an association with age and duration of substance

use. In cocaine dependence, the genu and rostral body showed significant damage. Cannabis consumption may be associated with white matter disruption, but there is not sufficient evidence to support pathological changes in the corpus callosum. The improved detection of white matter pathology with diffusion tensor imaging supports the importance of future research in this field.

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PMID: 17108711 [Indexed for MEDLINE]

272. Ann N Y Acad Sci. 2006 Aug;1074:365-76.

Neural effects of MDMA as determined by functional magnetic resonance imaging and magnetic resonance spectroscopy in awake marmoset monkeys.

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We used functional magnetic resonance imaging (fMRI) to investigate the acute effects of a recreational dose (1 mg/kg p.o.) of 3,4-methylenedioxymethamphetamine (MDMA) on regional brain activity in awake, restrained marmoset monkeys. In a second study, magnetic resonance spectroscopy

(MRS) and postmortem measurements of serotonin transporter (SERT) binding and serotonin (5-HT) concentrations were used to determine the neurotoxic effects of low (4 x 1 mg/kg p.o.) and high (4 x 10 mg/kg i.m.) doses of MDMA. Several brain areas were significantly activated by the low oral dose of MDMA, including the midbrain raphe nuclei, hippocampus, hypothalamus, amygdala, and the corticostriatal circuit composed of the dorsal thalamus, sensory motor cortex, and basal ganglia. MDMA activated the primary visual cortex under baseline conditions and also enhanced the visual cortical response to photic stimulation. The onset of brain activation correlated well with the rise in plasma MDMA concentrations measured in separate monkeys given the same drug treatment. In the second study, the ratio of N-acetylaspartate (NAA; a putative neuronal marker) to creatine was significantly reduced in the hypothalamus following either MDMA treatment regimen, suggesting a particular vulnerability of this structure to MDMA-induced damage. Monkeys given the high-dose regimen also showed prolonged hyperthermia and reductions in 5-HT and SERT in a number of brain areas. These results are the first to identify the pattern of MDMA-induced brain activation in a nonhuman primate model, and they further suggest that even recreational doses of MDMA may have adverse consequences as indicated by the reduced hypothalamic NAA/creatine ratio.

DOI: 10.1196/annals.1369.036

PMID: 17105934 [Indexed for MEDLINE]

273. Neuroimage. 2006 Nov 15;33(3):913-22. Epub 2006 Sep 14.

Methylphenidate modulates cerebral post-stroke reorganization.

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OBJECTIVE: We hypothesized that a single dose of methylphenidate (MP) would modulate cerebral motor activation and behavior in patients having suffered a subcortical stroke.

METHODS: Eight men with a single stroke on the corticospinal tract resulting in a pure motor hemiparesia were included in a randomized, cross-over, double-blind, placebo-controlled study. Patients were first evaluated 17 days after stroke onset by validated neurological scales, motor tests and fMRI (flexion/extension of the digits) after 20 mg MP or placebo. Seven days later, the patients underwent the same protocol and received the drug they had not taken at the first evaluation. Each patient was his own control.

RESULTS: Placebo intake did not change performance. MP compared to placebo elicited a significant improvement in motor performance of the affected hand at the finger tapping test. MP induced: (1) a hyperactivation of the ipsilesional primary sensorimotor cortex including the motor hand and face areas and of the contralesional premotor cortex; (2) a hypoactivation of the ipsilesional anterior cingulum. Hyperactivation in the face motor area correlated positively with the improvement in performance.

CONCLUSION: We demonstrated that the reorganized network may efficiently be

targeted by the drug and that the effect of MP might partly rely on an improvement in attention/effort through cingulum modulation.

DOI: 10.1016/j.neuroimage.2006.07.014
PMID: 16978883 [Indexed for MEDLINE]

274. Alcohol Clin Exp Res. 2006 Aug;30(8):1349-54.

Blockade of cue-induced brain activation of abstinent alcoholics by a single administration of amisulpride as measured with fMRI.

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BACKGROUND: Once alcohol dependence is established, alcohol-associated cues may induce dopamine release in the reward system, which is accompanied by alcohol craving and may lead to relapse. In cocaine addicts, dopamine release in the thalamus was positively correlated with cocaine craving. We tested the effects of the atypical dopamine D(2/3) blocker amisulpride on cue-induced brain activation in a functional magnetic resonance imaging (fMRI) paradigm.
METHODS: Alcohol-associated and neutral pictures were presented in a block design to 10 male abstinent alcoholics (1-3 weeks after detoxification) and 10 healthy men during fMRI. The fMRI scans were acquired before and 2 hours after the oral

application of 400 mg amisulpride. Before and after each scan, alcohol craving was measured with visual analogue scales.
RESULTS: Before the application of amisulpride, alcohol versus control cues elicited a higher blood oxygen level-dependent (BOLD) signal in the left frontal and orbitofrontal lobe, left cingulate gyrus, bilateral parietal lobe, and bilateral hippocampus in alcoholics compared with healthy controls. After amisulpride, alcoholics showed a reduced activation in the right thalamus compared with the first scan. Alcoholics no longer showed significant differences in their cue-elicited BOLD response after amisulpride medication compared with medication-free controls. Self-reported craving was not affected by amisulpride medication.
CONCLUSIONS: Amisulpride medication was associated with reduced cue-induced activation of the thalamus, a brain region closely connected with frontostriatal circuits that regulate behavior and may influence relapse risk.

DOI: 10.1111/j.1530-0277.2006.00174.x
PMID: 16899037 [Indexed for MEDLINE]

275. Magn Reson Imaging. 2006 Jul;24(6):707-14. Epub 2006 May 26.

Imaging brain activity in conscious monkeys following oral MDMA ("ecstasy").

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Recreational use of 3,4-methylenedioxymethamphetamine (MDMA;"ecstasy") poses worldwide potential health problems. Clinical studies show that repeated exposure to low oral doses of MDMA has toxic effects on the brain, altering cognitive and psychosocial behavior. Functional magnetic resonance imaging in conscious marmoset monkeys was used to evaluate the sensitivity of the brain to an oral dose of MDMA (1 mg/kg). Following MDMA administration, the midbrain raphe nuclei and substantia nigra, major sources of serotonin and dopamine, were activated as were the hippocampus, hypothalamus and amygdala. The corticostriatal circuit of dorsal thalamus, sensorimotor cortex and basal ganglia showed a robust, coherent activation pattern. Two key reward areas, the nucleus accumbens and prefrontal cortex, and most other cortical regions showed little activation. The visual cortex, however, showed intense activation without applied visual stimuli. These data identify brain areas and functional circuits sensitive to a recreational dose of MDMA, some of which may be vulnerable to long-term intermittent exposure to this drug.

DOI: 10.1016/j.mri.2006.03.010
PMID: 16824965 [Indexed for MEDLINE]

276. Prog Neuropsychopharmacol Biol Psychiatry. 2006 Jul;30(5):887-98. Epub 2006 Mar 6.

Monoamine and motor responses to cocaine are co-deficient in the Fawn-Hooded depressed animal model.

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The Fawn-Hooded (FH) genetic animal model of depression continues to be of interest because the FH model has limited biochemical and immune function. The FH animal has an inherited trait, platelet storage pool deficiency (PSPD), an hemorrhagic disorder that is also a component of Chediak-Higashi syndrome (CHS). CHS is a pyrogenic infectious childhood disease; few patients live past the age of 20. Our hypothesis was that FH animals may exhibit different monoamine and motor responses to cocaine versus the Sprague-Dawley (SD) "normal" animal strain, which does not have the FH trait. Therefore, selective neuromolecular imaging (NMI) of the monoamines, dopamine (DA) and 5-HT within nucleus accumbens (NAcc) of behaving male FH versus SD rats was performed in vivo with BRODERICK PROBE sensors and a semiderivative voltammetric circuit. Each animal was placed in a faraday chamber and electrochemical signals were detected via a mercury commutator and flexible cable. Baseline values for neurotransmitters and behavior were derived during the last half-hour of habituation behavior. Release of DA and 5-HT was detected selectively, at separate oxidation potentials, within seconds, before and after intraperitoneal administration of the psychostimulant, cocaine (10 mg/kg). At the same time, frequencies of ambulations and central ambulations were separately monitored with infrared photobeams, which surrounded the faraday chamber. Data were compared by ANOVA analysis followed by Tukey's post hoc test. The data showed that (1) DA release in NAcc of behaving FH animals did not

respond to cocaine; neither first hour nor second hour values significantly differed from baseline (both hours, $p>0.05$), whereas SD animals exhibited a significant increase in cocaine-induced DA release in NAcc (both hours, $p<0.001$). The ability for acute cocaine to increase DA release in NAcc was significantly greater in SD than in FH animals ($p<0.001$). (2) 5-HT release in NAcc of behaving FH animals was not significantly increased by cocaine (both hours, $p>0.05$), whereas 5-HT release in NAcc of SD animals was significantly increased after cocaine (both hours, $p<0.001$). The ability for acute cocaine to increase 5-HT release was significantly greater in SD than in FH animals ($p<0.001$). (3) Ambulations in the FH strain were modestly, yet significantly, enhanced after cocaine during both hours of study ($p<0.05$, $p<0.001$, respectively) as were ambulations in the SD strain. Nonetheless, the ability for acute cocaine to increase ambulations was significantly greater in SD than in FH animals in the first hour ($p<0.001$). (4) Central ambulations in the FH strain was not affected by cocaine (both hours, $p>0.05$), whereas SD animals showed a significant increase in central ambulatory activity in both hours of the cocaine study ($p<0.001$). The ability for acute cocaine to increase central ambulations was significantly greater in SD than in FH animals ($p<0.001$). Thus, this is the first study to determine in vivo the neurochemical response to acute cocaine in the behaving FH animal. Moreover, this is the first study to determine in vivo and simultaneously the neurochemical and behavioral response to acute cocaine in the FH strain in comparison with SD animals, a "normal" strain. Remarkable deficiencies in the ability for acute cocaine to alter neurochemistry and behavior in animals with the FH trait are shown. These studies emphasize the need to look differentially at cocaine effects in biochemically and immune-compromised subjects versus "normal" subjects.

DOI: 10.1016/j.pnpbp.2006.01.012

PMID: 16626846 [Indexed for MEDLINE]

277. Drug Alcohol Depend. 2006 Jun 28;83(2):157-62. Epub 2006 Jan 6.

Thirsty heroin addicts show different fMRI activations when exposed to water-related and drug-related cues.

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Relapse to drug use is frequently preceded or caused by craving, an intense desire for drug. Advances in functional brain imaging techniques make it possible to directly investigate this special mental state in vivo and non-invasively. Extant imaging studies on craving have been mostly on cocaine which is the dominant drug abused in the U.S. Employing functional MRI, we examined substance specificity of the neural circuitry underlying craving for heroin. Heroin is the primary drug abused in south-east Asia and has, particularly, become a serious social problem for China in recent years. Following abstinence from water and drug, 14 active heroin addicts (all male, mean age 33.2 years, average drug use history 7.1 years) underwent scanning inside a 1.5T Philips MR scanner during exposure to water-related, drug-related, and neutral cues. Water-related cues

elicited anterior cingulate activation (Brodmann's area BA 32/24). Drug-related cues activated bilateral inferior frontal cortex (BA 44/45), confirming the critical role of prefrontal cortex in drug craving. Results suggest heroin craving may involve different neural substrates than do desire from basic physiological drives, such as thirst. As the first fMRI study of heroin craving, our study adds to the scant but much-needed brain imaging literature on heroin addiction.

DOI: 10.1016/j.drugalcdep.2005.11.012
PMID: 16406379 [Indexed for MEDLINE]

278. Magn Reson Med. 2006 Jan;55(1):9-15.

Assessment of dynamic susceptibility contrast cerebral blood flow response to amphetamine challenge: a human pharmacological magnetic resonance imaging study at 1.5 and 4 T.

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Pharmacological MRI (phMRI) techniques can be used to monitor the neurophysiological effects of central nervous system (CNS) active drugs. In this

study, we investigated whether dynamic susceptibility contrast (DSC) perfusion imaging employing the use of superparamagnetic iron oxide nanoparticles (Resovist) could be used to measure hemodynamic response to d-amphetamine challenge in human subjects at both 1.5 and 4 T. Significant changes in cerebral blood flow (CBF) were found in focal regions associated with the nigrostriatal circuit and mesolimbic and mesocortical dopaminergic pathways. More significant CBF responses were found at higher field strength, mainly within striatal structures. The results from this study indicate that DSC perfusion imaging using Resovist can be used to assess the efficacy of CNS-active drugs and may play a role in the development of novel psychiatric therapies at the preclinical level.

DOI: 10.1002/mrm.20749
PMID: 16342159 [Indexed for MEDLINE]

279. Br J Radiol. 2005 Nov;78(935):997-1004.

Chasing "chasing the dragon" with MRI: leukoencephalopathy in drug abuse.

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Spongiform leukoencephalopathy is a rare complication from inhalation of heated heroin vapour, a practice called "chasing the dragon". The MRI findings are

considered pathognomonic, making MRI important for diagnosis. This is especially true in busy urban emergency departments where a variety of patients may present obtunded, unable or unwilling to provide a useful history. Even though the MR pattern of "chasing" toxicity is considered pathognomonic, there are mimickers. We compare the MRI findings of two classic cases of chasing leukoencephalopathy with one case of mimickery from cocaine exposure only. All three cases had diffuse symmetrical white matter changes. MR spectroscopy (MRS) in chasing patients showed increased lactic acid and myo-inositol, decreased N-acetyl aspartate and creatine, normal to slightly decreased choline, and normal lipid peak. MRS in the cocaine exposure patient showed marked increase in lactic acid and lipids. MR perfusion in one chasing patient was normal.IN CONCLUSION: (1) All three cases have MR findings suggestive of spongiform leukoencephalopathy. MRS may help differentiate toxicity due to inhaled heroin from other non-heroin related toxicities. (2) Discordance between perfusion and spectroscopy in one chasing patient adds evidence that the disease is due to impaired energy metabolism at the cellular level. (3) MR findings of spongiform leukoencephalopathy secondary to chasing heroin can progress despite apparent abstinence of the drug and during clinical improvement, suggesting the MR changes may represent an evolving injury.

DOI: 10.1259/bjr/61535842

PMID: 16249600 [Indexed for MEDLINE]

280. Neuropsychopharmacology. 2006 Jun;31(6):1318-26.

Cerebellar vermis involvement in cocaine-related behaviors.

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Although the cerebellum is increasingly being viewed as a brain area involved in cognition, it typically is excluded from circuitry considered to mediate stimulant-associated behaviors since it is low in dopamine. Yet, the primate cerebellar vermis (lobules II-III and VIII-IX) has been reported to contain axonal dopamine transporter immunoreactivity (DAT-IR). We hypothesized that DAT-IR-containing vermis areas would be activated in cocaine abusers by cocaine-related cues and, in healthy humans, would accumulate DAT-selective ligands. We used BOLD fMRI to determine whether cocaine-related cues activated DAT-IR-enriched vermis regions in cocaine abusers and positron emission tomography imaging of healthy humans to determine whether the DAT-selective ligand [11C]altropane accumulated in those vermis regions. Cocaine-related cues selectively induced BOLD activation in lobules II-III and VIII-IX in cocaine users, and, at early time points after ligand administration, we found appreciable [11C]altropane accumulation in lobules VIII-IX, possibly indicating DAT presence in this region. These data suggest that parts of cerebellar vermis mediate cocaine's persisting and acute effects. In light of prior findings illustrating vermis connections to midbrain dopamine cell body regions, established roles for the vermis as a locus of sensorimotor integration and motor planning, and findings of increased vermis activation in substance abusers during

reward-related and other cognitive tasks, we propose that the vermis be considered one of the structures involved in cocaine- and other incentive-related behaviors.

DOI: 10.1038/sj.npp.1300937

PMID: 16237382 [Indexed for MEDLINE]

281. Exp Neurol. 2005 Dec;196(2):244-53. Epub 2005 Oct 19.

Long-term functional consequences of quinolinic acid striatal lesions and their alteration following an addition of a globus pallidus lesion assessed using pharmacological magnetic resonance imaging.

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Erratum in

Exp Neurol. 2006 Dec;202(2):522. Daphna, Joel [corrected to Joel, Daphna].

The present study tested the hypothesis that lesion to the rat globus pallidus (GP) can "normalize" the functioning of the basal ganglia-thalamocortical circuits in striatal-lesioned rats by assessing the functional connectivity of these regions using functional magnetic resonance imaging (fMRI). Changes in

brain activation following systemic administration of amphetamine were assessed in (1) rats sustaining a unilateral lesion to the striatum, (2) rats sustaining a combined striatal and pallidal lesion, and (3) control rats. Striatal-lesioned rats showed attenuated cortical activation following amphetamine administration and lower correlations between the responses to amphetamine in different brain regions compared to control rats. Although the addition of an excitotoxic GP lesion failed to prevent striatal lesion-induced attenuation of cortical activation by amphetamine, it was effective in "normalizing" the correlations between the responses to amphetamine in the different areas. These results suggest that, although the GP lesion is ineffective in correcting the global changes in activity caused by the striatal lesion, it may have the capacity to partially restore alterations in functional connectivity resulting from the striatal lesion. These results are further discussed in view of our previous demonstration that lesions to the GP can reverse several behavioral deficits produced by a striatal lesion.

DOI: 10.1016/j.expneurol.2005.07.023
PMID: 16236282 [Indexed for MEDLINE]

282. Psychopharmacology (Berl). 2005 Dec;183(2):171-80. Epub 2005 Nov 9.

Neural activity associated with stress-induced cocaine craving: a functional magnetic resonance imaging study.

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OBJECTIVE: Stress is known to increase cocaine craving and relapse risk in cocaine dependence. Identifying neural activity associated with stress and stress-induced cocaine craving is important in understanding the neurobiology of cocaine craving and relapse.

METHOD: Blood oxygenation level dependent (BOLD) signal changes were assessed in a functional magnetic resonance imaging (fMRI) session with healthy controls and treatment-engaged, abstinent, cocaine-dependent individuals (patients) as they participated in brief guided imagery and recall of three personal stress and three personal neutral situations.

RESULTS: During stress, patients showed significantly less BOLD activation than controls in specific frontal and para-limbic regions, such as the anterior cingulate (AC) region, left hippocampal/parahippocampal region, right fusiform gyrus, and the right postcentral gyrus. On the other hand, patients had increased activity in the caudate and dorsal striatum region during stress, activation that was significantly associated with stress-induced cocaine craving ratings.

CONCLUSIONS: Patients failed to activate AC and related circuits during stress, regions associated with control, and regulation of emotion and distress states. Instead, they exhibited greater craving-related activation in the dorsal striatum, a region related to reward pathways and part of the obsessive-compulsive circuitry. Such functional alterations in stress processing may underlie the stress-related vulnerability to cocaine relapse often observed in cocaine-dependent individuals in early recovery.

DOI: 10.1007/s00213-005-0147-8

PMID: 16163517 [Indexed for MEDLINE]

283. Am J Psychiatry. 2005 Sep;162(9):1605-13.

Altered neural substrates of cognitive control in childhood ADHD: evidence from functional magnetic resonance imaging.

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OBJECTIVE: The study compared the neural bases of two cognitive control operations, interference suppression and response inhibition, between children with and children without attention deficit hyperactivity disorder (ADHD).

METHOD: Ten children (7-11 years of age) with combined-type ADHD and 10 comparison subjects matched for age and gender underwent rapid event-related functional magnetic resonance imaging (fMRI) during performance of a modified flanker task. Functional maps were generated through group averaging and performance-based correlational analyses.

RESULTS: Interference suppression in ADHD subjects was characterized by reduced engagement of a frontal-striatal-temporal-parietal network that subserved healthy performance. In contrast, response inhibition performance relied upon different

regions in the two groups, frontal-striatal in comparison subjects but right superior temporal in ADHD children.
CONCLUSIONS: Alteration in the neural basis of two cognitive control operations in childhood ADHD was characterized by distinct, rather than unitary, patterns of functional abnormality. Greater between-group overlap in the neural network activated for interference suppression than in response inhibition suggests that components of cognitive control are differentially sensitive to ADHD. The ADHD children's inability to activate the caudate nucleus constitutes a core abnormality in ADHD. Observed functional abnormalities did not result from prolonged stimulant exposure, since most children were medication naive.

DOI: 10.1176/appi.ajp.162.9.1605
PMCID: PMC4535914
PMID: 16135618 [Indexed for MEDLINE]

284. Neurosci Lett. 2005 Dec 2;389(2):88-93.

Global and regional gray matter reductions in ADHD: a voxel-based morphometric study.

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Attention deficit hyperactivity disorder (ADHD) is a developmental disorder characterized by inattentiveness, motor hyperactivity and impulsivity. According to neuroimaging data, the neural substrate underlying ADHD seems to involve fronto-striatal circuits and the cerebellum. However, there are important discrepancies between various studies, probably due to the use of different techniques. The aim of this study is to examine cerebral gray (GM) and white (WM) matter abnormalities in a group of ADHD children using a voxel-based morphometry protocol. The sample consisted of 25 children/adolescents with DSM-IV TR diagnosis of ADHD (medicated, aged 6-16 years) who were compared with 25 healthy volunteer children/adolescents. ADHD brains on an average showed a global volume decrease of 5.4% as compared to controls. Additionally, there were regionally specific effects in the left fronto-parietal areas (left motor, premotor and somatosensory cortex), left cingulate cortex (anterior/middle/posterior cingulate), parietal lobe (precuneus bilaterally), temporal cortices (right middle temporal gyrus, left parahippocampal gyrus), and the cerebellum (bilateral posterior). There were no differences in WM volume between ADHD children and control subjects. The results are consistent with previous studies that used different techniques, and may represent a possible neural basis for some of the motor and attentional deficits commonly found in ADHD.

DOI: 10.1016/j.neulet.2005.07.020

PMID: 16129560 [Indexed for MEDLINE]

285. Neuroimage. 2005 Dec;28(4):904-14. Epub 2005 Aug 2.

Neural responses to acute cocaine administration in the human brain detected by fMRI.

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An improved functional MRI (fMRI) method for the reduction of susceptibility artifacts has been utilized to measure blood oxygen level-dependent (BOLD) responses to acute cocaine administration in the human brain of cocaine users. Intravenous administration of cocaine (20 mg/70 kg) activated mesolimbic and mesocortical dopaminergic projection regions and showed temporal positive or negative BOLD responses. These results obtained from human cocaine users supported the involvement of the dopaminergic pathway in cocaine addiction from animal models. In addition, the cocaine administration also induced activations in the hierarchical brain networks in the anterior prefrontal cortex (aPFC) of the Brodmann area 10 (BA10) and orbitofrontal cortex (OFC). It is suggested that the dopaminergic pathways and the hierarchical brain networks may participate in mediating cocaine reward processes, associative learning, motivation, and memory in cocaine addiction in the human brain.

DOI: 10.1016/j.neuroimage.2005.06.039
PMID: 16061398 [Indexed for MEDLINE]

286. Psychopharmacology (Berl). 2005 Aug;180(4):634-43. Epub 2005 Sep 14.

Processing efficiency of a verbal working memory system is modulated by amphetamine: an fMRI investigation.

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RATIONALE: Working memory performance may be improved or decreased by amphetamine, depending on baseline working memory capacity and amphetamine dosage. This variable effect suggests an optimal range of monaminergic activity for working memory, either below or above which it is compromised. We directly tested this possibility with human participants by varying amphetamine dosage and measuring the efficiency of cortical processing in brain regions associated with working memory.
OBJECTIVES: The modulation of cortical processing in a verbal working memory network by dextroamphetamine (D-amph) was examined using BOLD functional magnetic resonance imaging (fMRI) with healthy participants. The goal of the study was to test the hypothesis of an inverted U-shaped relationship between D-amph dose and processing efficiency of a verbal working memory system.
METHODS: D-amph dosage was increased cumulatively every 2 h across four scanning sessions collected in a single day. The primary measure used for analyses in this study was the extent of activation in brain regions empirically defined as a

working memory network.

RESULTS: An inverted U-shaped relationship was observed between the amount of D-amph administered and working memory processing efficiency. This relationship was specific to brain areas functionally defined as working memory regions and to the encoding/maintenance phase (as opposed to the response phase) of the task.

CONCLUSION: The results are consistent with the hypothesis that the neurochemical effects of amphetamine modulate the efficiency of a verbal working memory system. The effect of amphetamine on working memory in healthy individuals may provide insight regarding the working memory deficits seen in schizophrenia, given the overlap between neurochemical systems affected by amphetamine, and those disordered in schizophrenia.

DOI: 10.1007/s00213-005-0025-4

PMID: 15983790 [Indexed for MEDLINE]

287. No To Shinkei. 2005 Mar;57(3):227-31.

[Amnesia following left medial frontal subcortical hemorrhage: a case report].

[Article in Japanese]

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There has been a controversy as to the contribution of the frontal lobe to human memory function. We describe a 49-year-old right-handed patient with memory disturbance following a left medial frontal subcortical hematoma. Her amnesia was characterized by (1) predominant anterograde amnesia, (2) difficulty in both voluntary recall and recognition tasks, (3) a great number of false-alarm responses in a recognition task, and (4) no confabulation. An MRI demonstrated that her lesion was restricted to the left medial frontal area and anterior cingulate gyrus. This case represents a rare instance of amnesia following damage to the frontal lobe. We speculated that the unique feature of her memory impairment resulted from combined lesions in the medial frontal subcortical white matter and anterior cingulate gyrus. It seems that Papez's circuite participated in the development of these symptoms.

PMID: 15912758 [Indexed for MEDLINE]

288. Brain Dev. 2005 Dec;27(8):544-50.

Functional MRI in attention-deficit hyperactivity disorder: evidence for hypofrontality.

Zang YF(1), Jin Z, Weng XC, Zhang L, Zeng YW, Yang L, Wang YF, Seidman LJ, Faraone SV.

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Comment in

Brain Dev. 2005 Dec;27(8):541-3.

Using event-related functional magnetic resonance imaging to study the Stroop effect on both behavioral and brain activation of ADHD children off or on methylphenidate (MPH). Nine ADHD boys (aged 9.8-14.5 years) and 9 age-matched normal controls were included. A Stroop-like paradigm was used. AFNI (Analysis of Functional NeuroImaging) and its Deconvolution Analysis were used in a descriptive comparison between ADHD and control groups. (1) Both behavioral reaction time and brain activation showed Stroop effect in controls but neither was found in ADHD children off MPH. When MPH was administered, the Stroop effect tended to appear. (2) The activation volume (AV) of prefrontal cortex (PFC) in both the neutral (NC) and interference conditions (IC) in ADHD children off MPH was smaller than in controls. AV of anterior cingulate cortex in the IC in ADHD children off MPH was smaller than that in controls, but was similar in the NC to that in controls. AV of the basal ganglia, insula and cerebellum was also smaller in the IC, but was larger in the NC for ADHD children off MPH compared with controls. These findings are consistent with prior findings of hypofrontality in ADHD children and implicate a compensatory network including basal ganglia, insula and cerebellum for relative lower cognitive load tasks.

DOI: 10.1016/j.braindev.2004.11.009

PMID: 15876503 [Indexed for MEDLINE]

289. Neuropsychopharmacology. 2005 May;30(5):936-43.

The neural consequences of repeated cocaine exposure revealed by functional MRI in awake rats.

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The use of functional magnetic resonance imaging (fMRI) in animal models of cocaine addiction is an invaluable tool for investigating the neuroadaptations that lead to this psychiatric disorder. We used blood-oxygen-level-dependent (BOLD) MRI in awake rats to identify the neuronal circuits affected by repeated cocaine administration. Rats were given an injection of cocaine (15 mg/kg, i.p.) or its vehicle for 7 days, abstained from injections for 1 week, and challenged with an intracerebroventricular cocaine injection during functional imaging. Acute cocaine produced robust positive BOLD responses across well-known monoamine-enriched brain regions, such as the prefrontal cortex, nucleus accumbens, dorsal striatum, sensory cortex, hippocampus, thalamus, and midbrain areas. However, repeated cocaine administration resulted in lower BOLD responses in the prefrontal cortex, agranular insular cortex, nucleus accumbens, ventral pallidum, and dorsomedial thalamus, among other brain regions. Reductions in BOLD intensity were not associated with variations in cerebrovascular reactivity

between drug naive rats and those repeatedly exposed to cocaine. Therefore, the lower metabolic activation in response to cocaine could reflect a reduced neuronal and/or synaptic activity upon repeated administration.

DOI: 10.1038/sj.npp.1300653

PMCID: PMC2962946

PMID: 15637636 [Indexed for MEDLINE]

290. Am J Psychiatry. 2004 Nov;161(11):1990-7.

The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder.

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OBJECTIVE: Recent studies have suggested that attention deficit hyperactivity disorder (ADHD) is associated with abnormalities in basal ganglia and prefrontal cortical functioning. However, these studies have primarily relied upon cognitive tasks that reflect impulse control rather than attentional mechanisms.

METHOD: The authors used functional magnetic resonance imaging to investigate the neural correlates of selective and divided attention in a randomized, double-blind, placebo-controlled pharmacological challenge with methylphenidate

in 15 adolescents with ADHD (ages 14-17), eight adolescents with reading disorder (ages 12-17), and four adolescents with both reading disorder and ADHD (ages 14-18) who were scanned during both a methylphenidate and a placebo session. Fourteen healthy comparison subjects (ages 12-20) who were not given methylphenidate served as the primary comparison group.
RESULTS: During the divided attention task, unmedicated subjects with ADHD or reading disorder recruited the left ventral basal ganglia significantly less than the healthy comparison subjects. Methylphenidate led to an increase in activation in this region but had no effect on task performance. Subjects with ADHD also recruited the middle temporal gyrus significantly less than the comparison subjects, but methylphenidate did not have a direct effect on activation in this region.
CONCLUSIONS: These results suggest that ADHD is associated with abnormal processing in attentional networks, with specific dysfunction in striatal circuitry. Methylphenidate may act to normalize activity within this network.

DOI: 10.1176/appi.ajp.161.11.1990
PMID: 15514398 [Indexed for MEDLINE]

291. J Neurosci. 2004 Oct 27;24(43):9553-60.

Mapping dopamine function in primates using pharmacologic magnetic resonance imaging.

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Dopamine (DA) receptors play a central role in such diverse pathologies as Parkinson's disease, schizophrenia, and drug abuse. We used an amphetamine challenge combined with pharmacologic magnetic resonance imaging (phMRI) to map DA-associated circuitry in nonhuman primates with high sensitivity and spatial resolution. Seven control cynomolgous monkeys and 10 MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-treated parkinsonian primates were studied longitudinally using both positron emission tomography (PET) and phMRI. Amphetamine challenge (2.5 mg/kg, i.v.) in control monkeys increased relative cerebral blood volume (rCBV) in a number of brain regions not described previously, such as parafascicular thalamus, precentral gyrus, and dentate nucleus of the cerebellum. With the high spatial resolution, we were also able to readily identify changes in rCBV in the anterior cingulate, substantia nigra, ventral tegmental area, caudate (tail and head), putamen, and nucleus accumbens. Amphetamine induced decreases in rCBV in occipital and posterior parietal cortices. Parkinsonian primates had a prominent loss of response to amphetamine, with relative sparing of the nucleus accumbens and parafascicular thalamus. There was a significant correlation between rCBV loss in the substantia nigra and both PET imaging of dopamine transporters and behavioral measures. Monkeys with partial lesions as defined by 2beta-carbomethoxy-3beta-(4-fluorophenyl) tropane binding to dopamine transporters showed recruitment of premotor and motor cortex after amphetamine stimulus similar to what has been noted in Parkinson's patients during motor tasks. These data indicate that phMRI is a powerful tool for

assessment of dynamic changes associated with normal and dysfunctional DA brain circuitry in primates.

DOI: 10.1523/JNEUROSCI.1558-04.2004

PMCID: PMC2629666

PMID: 15509742 [Indexed for MEDLINE]

292. Eur Child Adolesc Psychiatry. 2004;13 Suppl 1:I71-9.

Neuronal network models of ADHD -- lateralization with respect to interhemispheric connectivity reconsidered.

Roessner V(1), Banaschewski T, Uebel H, Becker A, Rothenberger A.

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BACKGROUND: Recent research on structural and functional anatomy related to ADHD has concentrated on fronto-striatocerebellar circuits. These findings and resultant neurobiological models of ADHD may explain some of the disturbances. On the other hand, there is some evidence that the restricted look at anterior-posterior anomalies might neglect the important additional information of lateralization problems related to hemispheric connectivity.

OBJECTIVE: Hence, the role of lateralization in the pathophysiology of ADHD should be reconsidered.

METHOD: After a short review of imaging studies in ADHD the special role of the corpus callosum (including the influence of its anomalies on general brain development, lateralization and functioning) is outlined and the first case of total agenesis of corpus callosum in a child with ADHD is presented and discussed within this context.
CONCLUSIONS: In view of the remaining inconsistencies concerning structural and functional brain anomalies in ADHD, attention should be paid not only to anterior- posterior but also to left-right aspects of functional and structural brain anomalies. This should include disturbances probably related to anomalies of the corpus callosum, especially in regard to co-existing problems like dyslexia and developmental coordination disorder.

DOI: 10.1007/s00787-004-1007-5
PMID: 15322958 [Indexed for MEDLINE]

293. Neuropsychopharmacology. 2004 Sep;29(9):1715-22.

Methamphetamine activates reward circuitry in drug naïve human subjects.

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Amphetamines are highly addictive drugs that have pronounced effects on emotional and cognitive behavior in humans. These effects are mediated through their potent dopaminergic agonistic properties. Dopamine has also been implicated in the modulation of responses of the 'reward circuit' in animal and human studies. In this study we use functional magnetic resonance imaging (fMRI) to identify the brain circuitry involved in the psychostimulant effect of methamphetamine in psychostimulant-naïve human subjects. Seven healthy volunteers were scanned in a 3T MR imaging system. They received single-blind intravenous infusions of methamphetamine (0.15 mg/kg), and rated their experience of 'mind-racing' on a button press throughout the experiment. Data were analyzed with statistical parametric mapping methods. Amphetamine administration activated the medial orbitofrontal cortex, the rostral part of the anterior cingulate cortex, and the ventral striatum. Ratings of 'mind-racing' after methamphetamine infusion correlated with activations in the rostral part of the anterior cingulate cortex and in the ventral striatum. In addition, activations in the medial orbitofrontal cortex were independent of motor and related responses involved in making the ratings. These findings indicate that the first administration of a psychostimulant to human subjects activates classical reward circuitry. Our data also support recent hypotheses suggesting a central role for the orbitofrontal cortex in drug reinforcement and the development of addiction.

DOI: 10.1038/sj.npp.1300481

PMID: 15138439 [Indexed for MEDLINE]

294. Psychopharmacology (Berl). 2004 May;173(3-4):383-90. Epub 2003 Nov 28.

Preliminary evidence of hippocampal dysfunction in adolescent MDMA ("ecstasy") users: possible relationship to neurotoxic effects.

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RATIONALE: 3,4-Methylenedioxymethamphetamine (MDMA or ecstasy) is a potent and selective serotonin neurotoxin whose use is growing among adolescents. Although cognitive deficits among adult MDMA users are well documented, little is known of the cognitive and brain functional sequelae of MDMA use during adolescence.
OBJECTIVE: We tested for evidence of cognitive deficits and changes in brain function in a pilot sample of adolescent MDMA users, who were compared with adolescent non-users of MDMA.
METHODS: Selective and divided attention and verbal working memory were examined in six adolescent MDMA users and six non-users of MDMA who were similar in age, gender, IQ, and other substance use. Brain function was assessed during performance of the working memory task using functional magnetic resonance imaging (fMRI).
RESULTS: MDMA users had significantly prolonged reaction times during tests of selective and divided attention, and failed to deactivate the left hippocampus normally during high verbal working memory load.
CONCLUSIONS: MDMA use in adolescence may be associated with cognitive impairments and dysfunction of inhibitory circuits within the hippocampus. Further work is urgently needed to delineate the developmental impact and long-term functional

and clinical significance of MDMA use during adolescence.

DOI: 10.1007/s00213-003-1679-4

PMID: 14647960 [Indexed for MEDLINE]

295. Ment Retard Dev Disabil Res Rev. 2003;9(3):184-95.

A review of the biological bases of ADHD: what have we learned from imaging studies?

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Attention Deficit Hyperactivity Disorder (ADHD) is a common and impairing neuropsychiatric disorder with onset at preschool age. Although a significant amount of progress has been made investigating the neurobiology of this disorder, its precise etiology still remains unclear. Converging evidence from studies of the neuropharmacology, genetics, neuropsychology, and neuroimaging of ADHD imply the involvement of fronto-striatal circuitry in ADHD. However, while it does appear that poor inhibitory control and the deficits in fronto-striatal circuitry associated with it are central, there is evidence to suggest that more posterior cerebral areas are also implicated in this disorder. Anatomical studies suggest widespread reductions in volume throughout the cerebrum and cerebellum, while

functional imaging studies suggest that affected individuals activate more diffuse areas than controls during the performance of cognitive tasks. The future impact of new MR imaging methodologies on the field is discussed.

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PMID: 12953298 [Indexed for MEDLINE]

296. Mult Scler. 2003 Jun;9(3):219-27.

Fatigue associated with multiple sclerosis: diagnosis, impact and management.

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In patients with multiple sclerosis (MS) fatigue is the most common symptom and one of the most disabling features. As many as 40% have described it as the single most disabling symptom--a higher percentage than weakness, spasticity, motor problems, or bowel or bladder problems. The etiology and pathophysiology of MS-related fatigue remain unknown. Studies have failed to demonstrate an association between MS-related fatigue and the level of disability, clinical

disease subtype, or gender, although recent data show an association between MS-related fatigue and depression and quality of life. Imaging studies using positron emission tomography suggest that fatigue in MS is related to hypometabolism of specific brain areas, including the frontal and subcortical circuits. The impact of fatigue on patient functioning and quality of life clearly warrants intervention. In addition to nonpharmacologic measures, such as exercise and energy conservation strategies, several pharmacologic agents have been evaluated for their ability to reduce MS-related fatigue, including amantadine, central nervous system stimulants (pemoline), and the novel wake-promoting agent modafinil.

DOI: 10.1191/1352458503ms904oa
PMID: 12814166 [Indexed for MEDLINE]

297. Restor Neurol Neurosci. 1998 Jun;12(2-3):185-93.

Mitochondrial activity in the mapping of functional brain changes in schizophrenia.

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The main contributors to the search for functional brain changes in schizophrenia in the past years have employed imaging techniques such as positron emission

tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI). Our laboratory has applied a novel strategy involving the post-mortem measurement of the mitochondrial respiratory chain enzyme cytochrome-c-oxidase (COX) to address the question of regional metabolic changes in schizophrenia. This approach is based upon a strong body of evidence which indicates that neuronal COX is highly regulated by the energy demands of the cell and as such represents an endogenous marker of cellular energy metabolism over time. Our original findings indicated that COX activity may be reduced in the striatum and frontal cortex consistent with the concept that a state reduced activity in cortico-striatal circuits may underlie schizophrenia. Subsequent studies from our laboratory on the effects of neuroleptics, PCP, and methamphetamine on animals, have provided additional evidence that a state of dopaminergic overactivity or glutamatergic underactivity produces a hypometabolic state similar to that which is evident in the brains of schizophrenics.

PMID: 12671314

298. Psychiatry Clin Neurosci. 2003 Feb;57(1):9-15.

Pathogenesis of schizophrenia: Part II. Temporo-frontal two-step hypothesis.

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The objective of the present study was to provide a pathophysiological model of the development of schizophrenia. The method used was the selective review of recent findings, including those of animal models from our own department, to clarify the relationship between morphological brain changes and dopamine metabolism, and the pathophysiology of schizophrenia. The results showed that entorhinal cortex-lesioned animals had increased concentrations of dopamine in the amygdala, and methamphetamine-induced dopamine release in the amygdala of lesioned rats was significantly enhanced compared with sham-operated rats. These results and the morphological findings in schizotypal disorder patients support the view that temporal lobe changes may underlie a vulnerability to schizophrenia. Latent dysfunction in these regions may become clinically apparent as positive psychotic symptoms due to additional frontal lobe changes in schizophrenia. For the emergence of positive Schneiderian symptoms, aberrant activity of sociality-related circuits, including the amygdala was postulated. In conclusion, a temporo-frontal two-step hypothesis for the development of schizophrenia was suggested.

DOI: 10.1046/j.1440-1819.2003.01073.x
PMID: 12519449 [Indexed for MEDLINE]

299. Psychopharmacology (Berl). 2002 Oct;163(3-4):352-61. Epub 2002 Aug 29.

Functional imaging and neurochemical correlates of stimulant self-administration in primates.

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RATIONALE: Recent advances in neuroimaging and in vivo neurochemistry have documented drug-induced functional changes in brain activity under physiologically relevant conditions. These approaches have significant strengths and important limitations that should be considered.

OBJECTIVES: The present review describes current in vivo approaches to characterize drug effects as they relate to behavior, and highlights key contributions derived from each approach in the context of stimulant self-administration in primates.

METHODS: Techniques relating in vitro neurochemistry to behavioral pharmacology are compared to several in vivo approaches, including microdialysis, positron emission tomography (PET) neuroimaging and functional magnetic resonance imaging (fMRI).

RESULTS: In vitro neurochemical correlates of behavioral pharmacology established a significant relationship between dopamine and the reinforcing effects of abused stimulants. Subsequent in vivo microdialysis studies in behaving animals supported a critical role for nucleus accumbens dopamine in the reinforcing effects of stimulants. PET neuroimaging in monkeys and humans documented a close relationship between dopamine transporter (DAT) occupancy in vivo and the reinforcing effects of stimulants. The effectiveness of selective DAT inhibitors to reduce cocaine self-administration also was linked to DAT occupancy in vivo.

Lastly, the measurement of cerebral blood flow and metabolism with PET and fMRI has begun to define the neuronal circuitry influenced by acute and chronic stimulant exposure.
CONCLUSIONS: Collectively, in vivo neurochemistry and functional imaging have complemented in vitro approaches and have enhanced our current understanding of the neurobiology of abused stimulants.

DOI: 10.1007/s00213-002-1207-y
PMID: 12373436 [Indexed for MEDLINE]

300. Biol Psychiatry. 2002 Jun 1;51(11):890-5.

Reduced frontal white matter integrity in cocaine dependence: a controlled diffusion tensor imaging study.

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BACKGROUND: In vivo magnetic resonance studies have found that cocaine dependence is associated with T2 signal hyperintensities and metabolite abnormalities in cerebral white matter (WM). Functional neuroimaging studies have suggested that chronic cocaine use is primarily associated with frontal lobe deficits in regional cerebral blood flow and brain glucose metabolism levels; however, the effects of cocaine dependence, if any, on frontal WM microstructure are unknown.

Thus, we sought to examine the effects of cocaine dependence on frontal WM integrity.

METHODS: Diffusion tensor imaging was employed to examine the WM integrity of frontal regions at four levels: 10 mm above, 5 mm above, 0 mm above, and 5 mm below the anterior commissure-posterior commissure (AC-PC) plane. The fractional anisotropy (FA) of 12 cocaine-dependent patients and 13 age-similar control subjects was compared.

RESULTS: The cocaine-dependent patients had significantly reduced FA in the frontal WM at the AC-PC plane and a trend toward reduced FA at 5 mm below the AC-PC plane, suggestive of reduced WM integrity in these regions.

CONCLUSIONS: These findings were consistent with the hypothesis that cocaine dependence involves alterations in orbitofrontal connectivity, which may be involved in the decision-making deficits seen in this disorder.

PMID: 12022962 [Indexed for MEDLINE]

301. Proc Natl Acad Sci U S A. 2002 Feb 19;99(4):2344-9. Epub 2002 Jan 8.

Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model.

Bjorklund LM(1), Sánchez-Pernaute R, Chung S, Andersson T, Chen IY, McNaught KS, Brownell AL, Jenkins BG, Wahlestedt C, Kim KS, Isacson O.

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Comment in

Proc Natl Acad Sci U S A. 2002 Feb 19;99(4):1755-7.

Although implantation of fetal dopamine (DA) neurons can reduce parkinsonism in patients, current methods are rudimentary, and a reliable donor cell source is lacking. We show that transplanting low doses of undifferentiated mouse embryonic stem (ES) cells into the rat striatum results in a proliferation of ES cells into fully differentiated DA neurons. ES cell-derived DA neurons caused gradual and sustained behavioral restoration of DA-mediated motor asymmetry. Behavioral recovery paralleled in vivo positron emission tomography and functional magnetic resonance imaging data demonstrating DA-mediated hemodynamic changes in the striatum and associated brain circuitry. These results demonstrate that transplanted ES cells can develop spontaneously into DA neurons. Such DA neurons can restore cerebral function and behavior in an animal model of Parkinson's disease.

DOI: 10.1073/pnas.022438099

PMCID: PMC122367

PMID: 11782534 [Indexed for MEDLINE]

302. Neuroimage. 2001 Nov;14(5):1159-67.

Pharmacological MRI mapping of age-associated changes in basal ganglia circuitry of awake rhesus monkeys.

Zhang Z(1), Andersen A, Grondin R, Barber T, Avison R, Gerhardt G, Gash D.

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While the pathophysiological changes induced by the loss of dopamine innervation in the basal ganglia by Parkinson's disease (PD) are well studied, little is known about functional changes in the neural circuitry of this area during normal aging. Here we report the first survey of age-associated changes in the basal ganglia of behaviorally characterized, awake rhesus monkeys, using pharmacological MRI to map responses to dopaminergic stimulation. Apomorphine, a mixed D(1)/D(2) dopamine receptor agonist, evoked little change in the substantia nigra (SN) of aged animals while significantly reducing activation in young adult monkeys. Compared to young animals, both apomorphine and d-amphetamine (which increases synaptic dopamine levels) significantly increased activation of the aged rhesus globus pallidus externa (GPe). In addition, the aged animals showed decreased activity in the putamen in response to d-amphetamine administration. Although the responses in the SN and putamen of the aged monkeys differed from those in animal models of PD, the apomorphine-evoked activation of their GPe corresponded with apomorphine-induced increases in neuronal activity seen in Parkinson's patients and animal models. Given the major role of the GPe in regulating motor behavior, the altered responses in the aged GPe may contribute significantly to the motor slowing and movement dysfunctions characterizing

advanced age.

Copyright 2001 Academic Press.

DOI: 10.1006/nimg.2001.0902

PMID: 11697947 [Indexed for MEDLINE]

303. Magn Reson Med. 2001 Sep;46(3):628-9.

fcMRI--mapping functional connectivity or correlating cardiac-induced noise?

Lund TE.

PMID: 11550260 [Indexed for MEDLINE]

304. Rinsho Shinkeigaku. 2001 Feb-Mar;41(2-3):126-31.

[Paradoxical embolism with Chiari network, subsequently being accompanied by probable incomplete infarction: a case report].

[Article in Japanese]

Kasuya J(1), Tanaka C, Nakagawara J, Nakamura H, Suzuki Y.

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We presented a patient of paradoxical embolism with Chiari network, subsequently being accompanied by probable incomplete infarction. This 21-year-old man suffered from consciousness disorder, aphasia and right hemiparesis, and hospitalized in November 6, 1999. Magnetic resonance imaging showed mixed intensity on T1 and T2-weighted images in part of the areas of the left anterior and middle cerebral arteries. Cerebral angiography revealed the early venous fillings and the capillary blushs. These findings implicated stroke in young adult. Still more transcranial color-flow imaging showed high intensity transient signals with "Chirp" sounds on the left middle cerebral artery. Transesophageal echocardiography detected Chiari network. Chiari network was thought the course of cerebral infarction. Over again 123I-IMP single-photon emission CT findings revealed the marked reduction of his cerebral blood flow comprehensively in the left hemispherium. It was suggested that the recanalization after the paradoxical cerebral embolism had caused incomplete infarction.

PMID: 11481855 [Indexed for MEDLINE]

305. Am J Psychiatry. 2000 Nov;157(11):1789-98.

Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli.

Garavan H(1), Pankiewicz J, Bloom A, Cho JK, Sperry L, Ross TJ, Salmeron BJ, Risinger R, Kelley D, Stein EA.

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OBJECTIVE: Cocaine-related cues have been hypothesized to perpetuate drug abuse by inducing a craving response that prompts drug-seeking behavior. However, the mechanisms, underlying neuroanatomy, and specificity of this neuroanatomy are not yet fully understood.
METHOD: To address these issues, experienced cocaine users (N=17) and comparison subjects (N=14) underwent functional magnetic resonance imaging while viewing three separate films that portrayed 1) individuals smoking crack cocaine, 2) outdoor nature scenes, and 3) explicit sexual content. Candidate craving sites were identified as those that showed significant activation in the cocaine users when viewing the cocaine film. These sites were then required to show significantly greater activation when contrasted with comparison subjects viewing the cocaine film (population specificity) and cocaine users viewing the nature film (content specificity).
RESULTS: Brain regions that satisfied these criteria were largely left lateralized and included the frontal lobe (medial and middle frontal gyri, bilateral inferior frontal gyrus), parietal lobe (bilateral inferior parietal lobule), insula, and limbic lobe (anterior and posterior cingulate gyrus). Of the 13 regions identified as putative craving sites, just three (anterior cingulate, right inferior parietal lobule, and the caudate/lateral dorsal nucleus) showed significantly greater activation during the cocaine film than during the sex film

in the cocaine users, which suggests that cocaine cues activated similar neuroanatomical substrates as naturally evocative stimuli in the cocaine users. Finally, contrary to the effects of the cocaine film, cocaine users showed a smaller response than the comparison subjects to the sex film.
CONCLUSIONS: These data suggest that cocaine craving is not associated with a dedicated and unique neuroanatomical circuitry; instead, unique to the cocaine user is the ability of learned, drug-related cues to produce brain activation comparable to that seen with nondrug evocative stimuli in healthy comparison subjects.

DOI: 10.1176/appi.ajp.157.11.1789
PMID: 11058476 [Indexed for MEDLINE]

306. Eur J Nucl Med. 2000 Sep;27(9):1410-4.

Impaired dopaminergic neurotransmission in patients with traumatic brain injury: a SPECT study using 123I-beta-CIT and 123I-IBZM.

Donnemiller E(1), Brenneis C, Wissel J, Scherfler C, Poewe W, Riccabona G, Wenning GK.

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Structural imaging suggests that traumatic brain injury (TBI) may be associated with disruption of neuronal networks, including the nigrostriatal dopaminergic

pathway. However, to date deficits in pre- and/or postsynaptic dopaminergic neurotransmission have not been demonstrated in TBI using functional imaging. We therefore assessed dopaminergic function in ten TBI patients using [123I]2-beta-carbomethoxy-3-beta-(4-iodophenyl)tropane (beta-CIT) and [123I]iodobenzamide (IBZM) single-photon emission tomography (SPET). Average Glasgow Coma Scale score (+/-SD) at the time of head trauma was 5.8+/-4.2. SPET was performed on average 141 days (SD +/-92) after TBI. The SPET images were compared with structural images using cranial computerised tomography (CCT) and magnetic resonance imaging (MRI). SPET was performed with an ADAC Vertex dual-head camera. The activity ratios of striatal to cerebellar uptake were used as a semiquantitative parameter of striatal dopamine transporter (DAT) and D2 receptor (D2R) binding. Compared with age-matched controls, patients with TBI had significantly lower striatal/cerebellar beta-CIT and IBZM binding ratios (P< or =0.01). Overall, the DAT deficit was more marked than the D2R loss. CCT and MRI studies revealed varying cortical and subcortical lesions, with the frontal lobe being most frequently affected whereas the striatum appeared structurally normal in all but one patient. Our findings suggest that nigrostriatal dysfunction may be detected using SPET following TBI despite relative structural preservation of the striatum. Further investigations of possible clinical correlates and efficacy of dopaminergic therapy in patients with TBI seem justified.

PMID: 11007526 [Indexed for MEDLINE]

307. Nat Med. 2000 Apr;6(4):470-3.

Functional deficits in basal ganglia of children with attention-deficit/hyperactivity disorder shown with functional magnetic resonance imaging relaxometry.

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Attention-deficit/hyperactivity disorder is a highly heritable and prevalent neuropsychiatric disorder estimated to affect 6% of school-age children. Its clinical hallmarks are inattention, hyperactivity and impulsivity, which often respond substantially to treatment with methylphenidate or dextroamphetamine. Etiological theories suggest a deficit in corticostriatal circuits, particularly those components modulated by dopamine. We developed a new functional magnetic resonance imaging procedure (T2 relaxometry) to indirectly assess blood volume in the striatum (caudate and putamen) of boys 6-12 years of age in steady-state conditions. Boys with attention-deficit/hyperactivity disorder had higher T2 relaxation time measures in the putamen bilaterally than healthy control subjects. Relaxation times strongly correlated with the child's capacity to sit still and his accuracy in accomplishing a computerized attention task. Daily treatment with methylphenidate significantly changed the T2 relaxation times in the putamen of children with attention-deficit/hyperactivity disorder, although the magnitude and direction of the effect was strongly dependent on the child's unmedicated activity state. There was a similar but nonsignificant trend in the right caudate. T2 relaxation time measures in thalamus did not differ

significantly between groups, and were not affected by methylphenidate. Attention-deficit/hyperactivity disorder symptoms may be closely tied to functional abnormalities in the putamen, which is mainly involved in the regulation of motor behavior.

DOI: 10.1038/74737

PMID: 10742158 [Indexed for MEDLINE]

308. Synapse. 2000 Apr;36(1):57-65.

Detection of the effects of dopamine receptor supersensitivity using pharmacological MRI and correlations with PET.

Nguyen TV(1), Brownell AL, Iris Chen YC, Livni E, Coyle JT, Rosen BR, Cavagna F, Jenkins BG.

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Receptor supersensitivity is an important concept for understanding neurotransmitter and receptor dynamics. Traditionally, detection of receptor supersensitivity has been performed using autoradiography or positron emission tomography (PET). We show that use of magnetic resonance imaging (MRI) not only enables one to detect dopaminergic supersensitivity, but that the hemodynamic time course reflective of this fact is different in different brain regions. In

rats unilaterally lesioned with intranigral 6-hydroxydopamine, apomorphine injections lead to a large increase in hemodynamic response (cerebral blood volume, CBV) in the striato-thalamo-cortico circuit on the lesioned side but had little effect on the intact side. Amphetamine injections lead to increases in hemodynamic responses on the intact side and little on the lesioned side in the same animals. The time course for the increase in CBV after either amphetamine or apomorphine administration was longer in striatum and thalamus than in frontal cortex. (11)C-PET studies of ligands which bind to the dopamine transporter (2-beta-carbomethoxy-3-beta-(4-fluorophenyl)tropane 1, 5-naphthalnendisulfonate, WIN 35, 428 or CFT) and D2 receptors (raclopride) confirm that there is a loss of presynaptic dopamine terminals as well as upregulation of D2 receptors in striatum in these same animals. Pharmacologic MRI should become a sensitive tool to measure functional supersensitivity in humans, providing a complementary picture to that generated using PET studies of direct receptor binding.

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PMID: 10700026 [Indexed for MEDLINE]

309. Magn Reson Med. 2000 Jan;43(1):45-51.

Cocaine administration decreases functional connectivity in human primary visual and motor cortex as detected by functional MRI.

Li SJ(1), Biswal B, Li Z, Risinger R, Rainey C, Cho JK, Salmeron BJ, Stein EA.

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Functional magnetic resonance imaging (fMRI) was conducted to observe the effects of cocaine administration on the physiological fluctuations of fMRI signal in two brain regions. Seven long-term cocaine users with an average age of 32 years and 8 years of cocaine use history were recruited for the study. A T2*-weighted fast echo-planar imaging (EPI) pulse sequence was employed at 1.5 T to acquire three sets of brain images for each subject under three conditions (at rest, after saline injection, and after cocaine injection [0.57 mg/kg]). Cross-correlation maps were constructed using the synchronous, low frequency signal from voxel time courses after filtering respiratory, cardiac, and other physiological noise. A quantitative evaluation of the changes in functional connectivity was made using spatial correlation coefficient (SCC) analysis. A marked 50% reduction in SCC values in the region of primary visual cortex and 43% reduction in SCC values in the region of primary motor cortex were observed after cocaine administration. This significant reduction in SCC values in these cortical regions is a reflection of changes in neuronal activity. It is suggested that the observed changes in low frequency components after acute cocaine administration during a resting, no-task situation may be used as a baseline reference source when assessing the effects of cocaine on task-driven activation or on mesolimbic dopamine pathways.

PMID: 10642730 [Indexed for MEDLINE]

310. Ann N Y Acad Sci. 1999 Jun 29;877:523-47.

Functional magnetic resonance imaging of brain reward circuitry in the human.

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To produce behavior, motivational states necessitate at least three fundamental operations, including (1) selection of objectives focused on goal-objects, (2) compilation of goal-object information, and (3) determination of physical plans for securing goal-objects. The second of these general operations has been theorized to involve three subprocesses: (a) feature detection and other perceptual processing of putative goal-object "rewards," (b) valuation of goal-object worth in the context of potential hedonic deficit states, and (c) extraction of incidence and temporal data regarding the goal-object. A number of subcortical brain regions appear to be involved in these three informational subprocesses, in particular, the amygdala, sublenticular extended amygdala (SLEA) of the basal forebrain, and nucleus accumbens/subcallosal cortex (NAc/SCC). Components of the amygdala, SLEA, and NAc/SCC together constitute the larger anatomic structure of the extended amygdala. Functional magnetic resonance imaging (fMRI) studies of humans have recently begun to localize these subcortical regions within the extended amygdala during specific experimental

conditions. In this manuscript, two human cocaine- infusion studies and one cognitive psychology experiment are reviewed in relation to their pattern of fMRI activation within regions of the extended amygdala. Activation in the NAc/SCC, in particular, is evaluated in relation to a hypothesis that one function of the NAc/SCC and associated brain regions is the evaluation of goal-object incidence data for the computation of conditional probabilities regarding goal-object availability. Further work is warranted to test hypothesized functions for all regions within the extended amygdala and integrate them toward an understanding of motivated behavior.

PMID: 10415669 [Indexed for MEDLINE]

311. Brain. 1997 Dec;120 (Pt 12):2207-17.

Cognitive deficits in Huntington's disease are predicted by dopaminergic PET markers and brain volumes.

Bäckman L(1), Robins-Wahlin TB, Lundin A, Ginovart N, Farde L.

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The main aim of this study was to investigate the relationship between dopaminergic markers and brain volumes for striatal and cortical structures, and cognitive performance in patients with Huntington's disease and control subjects.

We used PET and MRI data as predictors of performance in tasks assessing executive function, visuospatial ability, episodic memory, verbal fluency, perceptual speed and reasoning. The dopamine neurotransmission parameters (D1 and D2 receptor density and dopamine transporter density) and the volumetric measurements for caudate and putamen accounted for substantial portions of the variance across the majority of cognitive tasks. In addition, frontal volume showed a strong relationship with all cognitive tasks. D1 binding and volume measurements for the temporal cortex and thalamic volume showed associations with a select number of cognitive tasks. The overall data pattern is consistent with the view that Huntington's disease may be characterized as a frontostriatal dementia, in which cognitive deficits may result from pathological changes at multiple sites in the frontostriatal circuitry.

PMID: 9448576 [Indexed for MEDLINE]

312. Neuron. 1997 Sep;19(3):591-611.

Acute effects of cocaine on human brain activity and emotion.

Breiter HC(1), Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JP, Mathew RT, Rosen BR, Hyman SE.

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We investigated brain circuitry mediating cocaine-induced euphoria and craving using functional MRI (fMRI). During double-blind cocaine (0.6 mg/kg) and saline infusions in cocaine-dependent subjects, the entire brain was imaged for 5 min before and 13 min after infusion while subjects rated scales for rush, high, low, and craving. Cocaine induced focal signal increases in nucleus accumbens/subcallosal cortex (NAc/SCC), caudate, putamen, basal forebrain, thalamus, insula, hippocampus, parahippocampal gyrus, cingulate, lateral prefrontal and temporal cortices, parietal cortex, striate/extrastriate cortices, ventral tegmentum, and pons and produced signal decreases in amygdala, temporal pole, and medial frontal cortex. Saline produced few positive or negative activations, which were localized to lateral prefrontal cortex and temporo-occipital cortex. Subjects who underwent repeat studies showed good replication of the regional fMRI activation pattern following cocaine and saline infusions, with activations on saline retest that might reflect expectancy. Brain regions that exhibited early and short duration signal maxima showed a higher correlation with rush ratings. These included the ventral tegmentum, pons, basal forebrain, caudate, cingulate, and most regions of lateral prefrontal cortex. In contrast, regions that demonstrated early but sustained signal maxima were more correlated with craving than with rush ratings; such regions included the NAc/SCC, right parahippocampal gyrus, and some regions of lateral prefrontal cortex. Sustained negative signal change was noted in the amygdala, which correlated with craving ratings. Our data demonstrate the ability of fMRI to map dynamic patterns of brain activation following cocaine infusion in cocaine-dependent subjects and provide evidence of dynamically changing brain networks associated with cocaine-induced euphoria and cocaine-induced craving.

PMID: 9331351 [Indexed for MEDLINE]

313. Clin Pediatr (Phila). 1997 Jul;36(7):381-93.

Toward a pathophysiology of attention-deficit/hyperactivity disorder.

Castellanos FX(1).

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(1)Child Psychiatry Branch, National Institute of Mental Health (NIMH), Bethesda, MD, USA.

Converging insights into attention-deficit/hyperactivity disorder (ADHD) support the notion that ADHD is best characterized behaviorally as a disorder of self-regulation or executive functioning. Anatomic neuroimaging studies suggest that the relevant regulatory circuits include the prefrontal cortex and the basal ganglia, which are modulated by dopaminergic innervation from the midbrain and by stimulant medications. The emerging model proposed in this review encompasses a developmental perspective into this common condition.

DOI: 10.1177/000992289703600702
PMID: 9241475 [Indexed for MEDLINE]

314. Rinsho Shinkeigaku. 1991 Aug;31(8):842-6.

[A case of posttraumatic parkinsonism].

[Article in Japanese]

Takeda M(1), Okuda B, Tomino Y, Tachibana H, Sugita M.

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We report a case of a 52-year-old man with posttraumatic parkinsonism. He was admitted to our department because of right-sided hand tremor and gait disturbance. He had suffered from a severe head injury incurred in a traffic accident with brief unconsciousness 6 months before admission. Three weeks after his injury, tremor and rigidity in the right upper limb developed, and he walked dragging his right leg. Five months after his injury, he received 1-dopa therapy, exhibiting a moderate improvement in parkinsonian symptoms. On admission, he was demented to a mild degree with masked face and monotonous speech. He presented with resting-postural-kinetic tremor and muscle rigidity on the right side. Cranial CT and MRI showed no abnormality. Inter-peak latencies of waves III to V of BAEP were significantly longer in this patient than in normal subjects. This BAEP findings suggested an upper brainstem lesion. 123I-IMP SPECT disclosed decreased cerebral blood flow in the left thalamus, bilateral frontal and parietal cortices. We diagnosed this case as having posttraumatic parkinsonism. Parkinsonism in the present case may be due to the involvement of multiple neuronal circuits of the extrapyramidal system at the level of the midbrain to the thalamus.

PMID: 1764860 [Indexed for MEDLINE]

Appendix S

Chapter 2 – Bias Detection 1

Study	**Intervention**	**Co-morbidity**	**Power <20: Low >30: High**	**Nicotine use recorded**	**STROBE rating**	**Comments**
Adinoff_Basal_2015	In-patient	-	High	Yes	56	Cravings assessed several days before MRI
Berlingeri_Resting_2017	-	-	Low	Yes	50	
Camchong_Changes_2014	In-patient	-	Low	-	56	
Camchong_Frontal_2011	-	8 CUD MDD	Standard	-	56	
Cisler_Altered_2013	-	-	High	-	52	
Contreras-Rodriguez_Cocaine_2015	Out-patient	-	Standard	-	58	
Ding_Cocaine_2013	-	-	Standard	-	40	
Geng_Salience_2017	In-patient	-	High	Yes	56	IQ below 60 for both groups
Gu_Mesocorticolimbic_2010	-	-	High	Yes	54	IQ below 60 for both groups
Ipser_Distinct_2018	Out-patient/ NTS	-	Standard	Yes	56	
Kelly_Reduced_2011	-	4 CUD MDD, 1 PTSD	Standard	Yes	56	
Kohno_Midbrain_2016	-	-	High	Yes	56	
Kohno_Relationship_2018	Out-patient/ NTS	-	High	Yes	56	Time between MRI and blood draws could be better controlled for
Kohno_Risky_2014	Some out- some in-patient	-	Standard	Yes	54	
Konova_Effects_2015	NTS	CUD 1 heroin dpd, 2 cannabis abuse, 2 alcohol abuse	Low	Yes	50	
Liang_Interactions_2015	NTS	-	High	-	52	IQ below 60 for both groups
Mansoory_Analysis_2017	-	-	Low	Yes	46	

McHugh_Cortico_2014	In-patient	-	High	Yes	55	
McHugh_Executive_2017	In-patient	-	High	Yes	55	
McHugh_Striatal_2013	In-patient	-	High	Yes	55	
Meunier_Brain_2012	Out-patient/ NTS	CUD 2 cannabis dpd, 5 alcohol abuse	Low	Yes	56	
Moeller_Abnormal_2016	-	-	Standard	Yes	56	Included participants with incomplete data sets
Ray_Altered_2015	-	-	Standard	Yes	56	Not corrected for multiple comparisons due to sample size
Ray_Effective_2016	-	-	Standard	Yes	56	
Ray_Modeling_2017	-	-	Standard	Yes	26	Amygdala removed
Regner_Topdown_2016	In-patient	-	High	Yes	54	Controversy about Granger Causality and polysubstance users
Rish_Evaluating_2016	NTS	CUD 1 heroin dpd, 2 cannabis abuse, 2 alcohol abuse	Low	Yes	31	Limitations of filter-based approach
VerdejoGarcia_Functional_2014	In-patient		Low	-	58	
Wang_HyperConnected_2015	In-patient	CUD 6 alcohol dpd, 2 alcohol abuse, 1 cannabis dpd, 2 cannabis abuse	Standard	Yes	56	
Wilcox_Enhanced_2011	-	CUD 3 on benzodiazepines, 2 on anti-psychotics, 1 CNS depressant, 5 SSRI's, 7% cannabis dpd, 7% cannabis abuse, 43% alcohol dpd	Low	Yes	54	IQ below 60 for CUD
Wisner_Intrinsic_2013	-	-	High	-	58	

MDD = major depressive disorder **NTS** = not treatment seeking

Appendix T

Chapter 2 – Other Substances Used

	Cigarettes		Alcohol		Cannabis		Other	
	SUD	**HC**	**SUD**	**HC**	**SUD**	**HC**	**SUD**	**HC**
Adinoff_Basal_2015	68% 1,0±0,9 packs/day Relapse 67% 0,9±0,9 packs/day remission	5% 0,05±0,2 packs/day	8 relapse 7 remission	0	3 relapse 3 remission	0	1 MA 3 Opioids	-
Berlingeri_Resting_2017	4	<15/day	8	-	-	-	-	-
Camchong_Changes_2014	-	-	-	-	-	-	-	-
Camchong_Frontal_2011	-	-	<14 drinks/week, men & <10/week women	-	-	-	-	-
Cisler_Altered_2013	85,4% 10,33±6,51 /day 23,94±8,97 YoU	5,26% 0,79±3,44 /day 1,05±4,59 YoU	-	-	10%	-	-	-
Contreras-Rodriguez_Cocaine_2015	670,0±435,3 /month Relapse 398,3±354,5 / month remission	102,4±125,0 /month	7,7±9,9 /month Relapse 8,0±21,1 remission	58,1±51,3 /month	-	-	-	-
Ding_Cocaine_2013	13 smokers	3 smokers	12	0	11	0	-	-
Geng_Salience_2017	16 non 35 low 13 high relapse 12,0±10,6 remission	41 non 10 low 16 high	10 abuse 51 recreation	3 depend 17 abuse 40 rec	7 SUD abuse 22 rec, 5 HC depend 16 abuse 31 rec	-	1 MA rec 3 Opioid rec	1 MA dpd 2 MA rec 1 Opioid dpd 2 Opioid abuse 6 Opioid rec 1 hallucinogenic abuse

								2 PCP abuse 1 qualude dpd
Gu_Mesocorticolimbic_2010	15 depnd 2 abuse 14 rec	9 depend 5 rec	2 abuse 31 rec	1 HC abuse 24 rec	5 abuse 15 rec	-	-	1 Opioid rec
Ipser_Distinct_2018	81,50%	50%	66,70%	69,20%	51,20%	69,20%	-	-
Kelly_Reduced_2011	9 non, 10 smokers, 7 heavy, 5 unknown	3 smokers, 8 unknown	-	-	-	-	-	-
Kohno_Midbrain_2016	Study 1 - 19/19, Study 2 - 18/20	Study 1 - 0/26, Study 2 - 5/18	Study 1 - 5,37±7,88 days used in past 30, Study 2 - 3,45±6,89 d/used	study 1 - 5,39±6,70 d/u, Study 2 - 3,50±6,89	Study 1 - 10,11±13 d/u, Study 2 - 2,70±7,26 d/u	Study 1 - 0,08±0,27 d/u, Study 2 - 0,11±0,47	-	-
Kohno_Relationship_2018	24/30	2/30	3,43±12,48 drinks/day	1,99±2,44 drinks/day	-	-	-	-
Kohno_Risky_2014	20/25	16/27	4,68±1,64 days used in last 30	4,36±1,15 d/u	1,68±0,70 d/u in 30	0,08±0,08	-	-
Konova_Effects_2015	12	-	1	-	2	-	-	-
Liang_Interactions_2015	14 non, 22 light, 11 heavy	18 non, 17, light, 12 heavy	-	-	3 +ve urine test	-	-	-
Mansoory_Analysis_2017	12/17	-	12/17	-	12/17 hashish	-	4/17 cocaine 8/17 Heroin 9/17 Cyst heroin	-
McHugh_Cortico_2014	19/24, 16,00±8,52 /day, 24,32±9,32 years Relapse 16/21, 12,94±2,63/day, 17,88±9,07 years remission	1/22	2,50±2,30 drinks/week Relapse 2,76±2,28 drinks/week remission	2,06±2,09 drinks/week	3 relapsed, 3 remission	-	2 relapse Opioids 1 remission Opioids 1 remission other drug use	-
McHugh_Executive_2017	19/24, 16,00±8,52 /day, 24,32±9,32 years Relapse	1/22	2,50±2,30 drinks/week Relapse 2,76±2,28	2,06±2,09 drinks/week	3 relapsed, 3 remission	-	2 relapse Opioids 1 remission Opioids	-

	16/21, 12,94±2,63/day, 17,88±9,07 years remission		drinks/week remission				1 remission other drug use	
McHugh_Striatal_2013	19/24, 16,00±8,52 /day, 24,32±9,32 years Relapse 16/21, 12,94±2,63/day, 17,88±9,07 years remission	1/22	2,50±2,30 drinks/week Relapse 2,76±2,28 drinks/week remission	2,06±2,09 drinks/week	3 relapsed, 3 remission	-	2 relapse Opioids 1 remission Opioids 1 remission other drug use	-
Meunier_Brain_2012	-	-	-	-	-	-	8/18 MA 10/18 Cocaine	-
Moeller_Abnormal_2016	16current/ past, 12 current 8,8±3,9 p/day	2 current/ past	1/22 past 10/22	-	1/22 past 6/22	-	1/22 Opioids	-
Ray_Altered_2015	13/20 smokers, 5,1±2,3 - 1-7 days/week, 6,3±3,0 - 1,5-13 cigarettes/day	6/17 smokers, 5,7±2,3 3-7 days/week, 2,8±0,29 2,5-3 cigarettes/day	13/20 drinkers, 1,9±0,55, 1-25 days/month, 2,1±0,92 - 1-3,5 drinks/occ	6/17 drinkers, 4,0±1,4 - 2,5-6,5 day/month, 1,7±0,42 - 1-2 drinks/occ	-	-	-	-
Ray_Effective_2016	13/20 smokers, 5,1±2,3 - 1-7 days/week, 6,3±3,0 - 1,5-13 cigarettes/day	6/17 smokers, 5,7±2,3 3-7 days/week, 2,8±0,29 2,5-3 cigarettes/day	13/20 drinkers, 1,9±0,55, 1-25 days/month, 2,1±0,92 - 1-3,5 drinks/occ	6/17 drinkers, 4,0±1,4 - 2,5-6,5 day/month, 1,7±0,42 - 1-2 drinks/occ	-	-	-	-
Ray_Modeling_2017	13/20 smokers, 5,1±2,3 - 1-7 days/week, 6,3±3,0 - 1,5-13 cigarettes/day	6/17 smokers, 5,7±2,3 3-7 days/week, 2,8±0,29 2,5-3 cigarettes/day	13/20 drinkers, 1,9±0,55, 1-25 days/month, 2,1±0,92 - 1-3,5 drinks/occ	6/17 drinkers, 4,0±1,4 - 2,5-6,5 day/month, 1,7±0,42 - 1-2 drinks/occ	-	-	-	-
Regner_Topdown_2016	35/50	8/50	35/50	-	20/50	-	16/50 Opioids 9/50 Other	-
Rish_Evaluating_2016	14/18	-	1	-	2	-	-	-
VerdejoGarcia_Functional_2014	-	-	-	-	-	-	-	-

Wang_HyperConnected_2015	7,67±6,0 cigarettes/day, duration 15,61±12,1 years	-	6/20 dependence 2/20 with abuse	-	1/20 dependence, 2/20 abuse	-	-	-
Wilcox_Enhanced_2011	2,63±2,07 fagerstrom	1,71±2,22 fagerstrom	-	-	-	-	-	-
Wisner_Intrinsic_2013	-	-	-	-	-	-	-	-