Intrinsic Functional Brain Connectivity in South African Methamphetamine Users Undergoing Inpatient Treatment, With or Without Additional Cognitive Training

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Abstract

Background: Methamphetamine (MA) abuse is a global crisis that exacerbates socio-politico-economic burdens in South Africa. MA use is associated with a myriad of neural abnormalities of structure and function, with associated neurocognitive deficits, particularly executive function (EF). Working memory (WM) training has been identified as a potential adjunct to treatment of substance use disorder (SUD) to improve EF in the hope of reducing relapse rates. Neuroimaging suggests MA alters intrinsic resting state functional connectivity (rsFC), and this may contribute to neuropsychological deficits observed in methamphetamine use disorder (MUD).

Methods: This nested study analysed data described in Brooks et al. (2016), in which WM training was used as an adjunct to inpatient treatment of MUD. Healthy controls (HC, N = 25) were compared to two MUD groups, one receiving treatment as usual (TAU, N = 17), and one receiving additional cognitive training (CT, N = 24) in the form of a modified version of the 'N-back' task (C-Ya). This task was also used to assess WMA in the neural scanner, using conditions of 0-back and 1-back across groups. The current research explored these data in a novel manner through examining rsFC.

Hypotheses: It was predicted that: 1) HC and MUD participants would differ on measures of WMA, but WMA would improve in MA groups at follow-up compared to baseline and this would be augmented in the CT group; 2) rsFC networks of neural regions supporting WM would be predictive of ability to perform well and improve on WM tasks; and 3) MA groups would display heightened rsFC activity within and between resting state neural networks of the default mode network (DMN) and canonical cognitive control networks (CCNs).

Results: Significant differences were observed between HC and MA groups in race and level of education, but not on WMA as tested in the scanner. The CT group, who completed WMA 3-back conditions, demonstrated significant improvement on this task post-

intervention. Exploratory regression models showed the WM rsFC network did not demonstrate significant relationships with any clinical, demographic, or WM variables when controlling for multiple comparisons. Heightened connectivity within and between the DMN and CCNs was observed in the MUD compared to the HC group, which provided support for hypothesis 3. Exploratory multivariate regression models demonstrated race, age, education, duration of drug use, and an interaction of group and abstinence may impact rsFC in these networks. Post-hoc analyses identified pairwise network combinations affected by these variables.

Conclusions: Despite limitations of this small study, it offers tentative preliminary insights into the largely unexplored field of rsFC in MA populations. This study supports limited research demonstrating hyperconnectivity within and between CCNs and DMN of MA users. This study also offers support for recent research suggesting that easier conditions of the N-back task may not reliably test all aspects of WM function. Exploratory analyses of covariates potentially affecting rsFC provide a platform for directions of future research.

Keywords: Methamphetamine, resting state FMRI, resting state functional connectivity, working memory, working memory training, default mode network, cognitive control networks

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Background and Rationale

Despite being a relative newcomer to the illicit substance market, methamphetamine (MA) use has exploded since its first appearance in the 1970s, and is now regarded as the most popular psychostimulant worldwide (Chomchai & Chomchai, 2015; United Nations Office on Drugs and Crime [UNODC], 2016). Referred to colloquially as 'speed,' 'meth,' 'ice,' 'crystal,' 'crank,' 'yaba,' 'shabu,' and 'tik,' (amongst other names), MA abuse has resulted in a worldwide pandemic (Barr et al., 2006; Chomchai & Chomchai, 2015; Courtney & Ray, 2014). In fact, marijuana is the only drug that outranks MA in terms of use on a global scale (UNODC, 2014, 2016). As a 'designer drug' that does not rely on plant extractions for active elements, the manufacturing process of MA into its various forms (base, powder, pill, and crystal) is not geographically restricted. When considering factors of influence in MA production, there exists a combination of: 1) a lack of constraints related to fauna and climate (UNODC, 2016), 2) the relatively simple manufacturing process of synthesising MA from various primary ingredients readily available in fertiliser, matches, and non-prescription pharmaceuticals such as decongestants (Barr et al., 2006; Stoneberg, Shukla, & Magness, 2018), and 3) a wealth of information outlining clear instructions for concocting MA available on the Internet (Barr et al., 2016). Cumulatively, this creates an environment conducive to ease of manufacture in almost any country, thus contributing to the current global nature of the MA crisis (Stoneberg et al., 2018; UNODC, 2016).

Although first created in Japan in 1919, the surge of methamphetamine use can be traced back to the introduction of the Drug Abuse Prevention and Control Act of 1970, which mandated restricted scheduling of amphetamine-type stimulants (ATS) in the United States of America (U.S.A) (Gonzales, Mooney, & Rawson, 2010). Originally used to suppress the

appetites and stifle fatigue of American soldiers in World War II, the 1950s and 1960s saw widespread civilian usage of ATS, as they were readily prescribed to treat depression and obesity (Courtney & Ray, 2014). As a result of a rapid decline in ATS availability following the mandated narrowing of acceptable medical usage, illegal production of MA using phenyl-2-propanone (P2P), ephedrine, and pseudoephrine began in the U.S.A. The chemical components of choice for MA synthesis fluctuated according to availability and legal restriction throughout the 1980s, but resulted in an overall increase in use, with a marked upswing in the 1990s. The 2005 Combat Methamphetamine Epidemic Act constrained access to pseudoephrine-based products and resulted in a marginal decline of use in the 2000s, but this was countered by production using P2P regaining popularity (Courtney & Ray, 2014; Maxwell & Brecht, 2011). The increasing ease of manufacturing MA of higher purity rates at lower costs lends to the recent rapid proliferation of demand for MA, as evidenced by the startling increase from 2010 to 2011 of reported MA laboratories in the U.S. (2 754 to 11 116) and tonnes of MA seized by government forces (15 to 23) (UNODC, 2013). However, although MA abuse largely originated in the United States, the present-day burden of methamphetamine on public health is certainly not circumscribed to this region.

While the characteristics of MA pertaining to purity, preferred form, favoured method of administration (ingestion, snorting, smoking, or injection), user demographics, and core ingredients for production vary across regions, the overarching emergency of MA abuse has extended its reach across the globe. Worldwide formulation and trafficking of MA remain on a steady climb. Despite numerous legislative efforts to combat MA supply, little reductive effect is realised as alternative methods of production are devised (Stoneberg et al., 2018). Overwhelmingly, recent research clearly establishes that all regions around the world are engaged in the manufacturing, trafficking, and consumption of MA (for in-depth reviews, see

Chomchai & Chomchai, 2015; Courtney & Ray, 2014; Stoneberg et al., 2018; Vearrier, Greenberg, Miller, Okanekua, & Haggerty, 2012) - and South Africa is no exception.

Methamphetamine Use in the South African Context

Socio-political restructure in the wake of apartheid's dismantlement allowed for South Africa's (SA) reintroduction to trading in the global industry. This included illegitimate markets, and as a result, MA emerged in SA in the 1990s, with significant use becoming apparent in 2004 (Peltzer et al., 2010; UNODC, 2012). Colloquially known as 'tik' (after the sound emitted by MA in its powder or crystalline form when heated), South African users mostly consume MA through a glass pipe or lightbulb by smoking it. This method of administering the drug is associated with more rapid acute effects, as well as more hazardous health outcomes, than alternative methods such as ingestion or snorting (Chomchai & Chomchai, 2015; Plüddemann, Myers, & Parry, 2008). The use of MA in SA and, most notably, the Western Cape, has since proliferated at an unprecedented rate: trends demonstrate the swiftest upsurge in use and treatment admissions for a specific recreational substance ever recorded in the country. In recent years, nearly 50% of admissions to drug treatment centres in the Western Cape have been related to MA use (Meade et al., 2015; Plüddemann et al., 2008; South African Community Epidemiology Network on Drug Use [SACENDU], 2014). Outranking both alcohol and cannabis, Western Cape treatment centres describe MA as the most frequently reported primary drug of choice in both adolescent and adult groups (SACENDU, 2019). Cape Town has been described as the epicentre of SA's MA predicament, aided by heavy gang presence in the province and the city's busy trading ports proving to be convenient for illegal drug trafficking (Carney, Myers, Louw, Lombard, & Flisher, 2013; Parry et al., 2008). Of noteworthy concern is not only the rise in MA use in SA (mimetic of the global increase), but also the escalation of adolescents abusing the drug and presenting for treatment, which is dissimilar to worldwide trends (Plüddemann et al.,

2008). Additionally, unique context-specific factors in SA interact with various aspects of the MA epidemic to present a distinct expression of the MA abuse phenomenon.

Although MA abuse is recognised as a global problem, it exacerbates SA's public health crises in light of the country's socioeconomic climate (Mushanyu, Nyabadza, & Stewart, 2015; Plüddemann et al., 2008; Watt et al, 2014; Weybright, Caldwell, Wegner, Smith, & Jacobs, 2016). MA has been found to acutely increase libido, sexual endurance, aggression, impulsivity, hypervigilance, restlessness, physical activity, and wakefulness, while simultaneously reducing inhibitions and pain thresholds (Chomchai & Chomchai, 2015; Dawe, Davis, Lapworth, & McKetin, 2009; Panenka et al., 2013; Watt et al., 2014). This pattern is acutely detrimental in the South African context, as these MA-related responses contribute to increased violence and risky behaviour. This has drastic implications for SA's elevated incidence of socio-political-economic afflictions, which include HIV/AIDS and other sexually transmitted infections; domestic, intimate partner, and community violence of a physical and sexual nature; unemployment; childhood neglect; risky substance abuse practices (e.g. needle-sharing); unwanted pregnancy; hazardous transactional sex practices; crime rates; as well as mental health problems such as anxiety, depression, and psychosis (Chomchai & Chomchai, 2015; Henry, Minassian, & Perry, 2010; Plüddemann et al., 2008; Plüddemann, Flisher, McKetin, Parry, & Lombard, 2010; Watt et al., 2014; Weybright et al., 2016).

As a result, MA use in SA exerts a heavy societal and economic toll. SA's annual expenditure on substance abuse interventions is estimated to amount to over R20 billion – of which a considerable portion can be attributed to MA use (Mushanyu et al., 2015; Watt et al., 2014). Indirect costs to the country are incurred through educational drop-out, incarceration, corruption, law enforcement burden, prevention initiatives, and productivity decline associated with MA abuse. Due to the sheer number of people meeting the criteria for

substance use disorder (SUD) with MA as a primary drug of choice, one might assume direct costs of physical and mental healthcare and rehabilitation associated with people dependent on MA are exorbitant. While these direct costs do place a significant financial burden on the state, the reality is far more complex than simply a large number of people presenting for treatment – paradoxically, only a small proportion of MA users are able to access treatment services (Meade et al., 2015). However, the expense of treatment is exacerbated by extremely high readmission rates associated with MA users (Meade et al., 2015). Research demonstrates a harrowing picture following treatment for MA dependence: with a lack of approved pharmacological treatments to support MA abstinence (Elkashef et al., 2008; Karila et al., 2010), one-year relapse rates of 61% and five-year relapse rates nearing 80% in MA users (Brecht & Herbeck, 2014; Choi, Lim, Chen, & Jenkins, 2018), it is evident that issues facing people dependent on MA are unlikely to be absolved simply by completing inpatient treatment. In the event that users have the means to gain access to treatment, the threat of statistically likely relapse associated with MA is compounded by the well-documented 'revolving door' phenomenon demonstrated across abuse of various substances in South Africa's mental healthcare system (for a review, see Petersen & Lund, 2011). SACENDU (2019) trends depict a relatively stable percentage of first-time admissions to treatment attributable to MA. This demonstrates that the MA crisis continues to extend its reach to new users across the Western Cape, in addition to MA having one of the highest readmission rates of substances and underscoring the ineffectual treatment of methamphetamine use disorder (MUD).

The economic, social, and interpersonal liabilities on both macro- and micro-levels associated with MA use and addiction underscore the urgency for providing more effective treatment for MUD in South Africa. However, successful rehabilitation hinges upon the foundation of a thorough understanding of the physiological sequelae of MA consumption,

addiction, and withdrawal. In order to determine how to treat MA patients in the most effective manner, it is imperative that attempts are made to unravel the neural mechanisms, structural effects, functional processes, and cognitive consequences associated with MA use and dependence as a first step towards tackling SA's MA affliction.

Understanding Neural Effects of Methamphetamine: Psychopharmacological Processes

MA is a potent psychostimulant that affects the central nervous system through a number of molecular processes to produce a variety of pharmacological effects. Primarily, this sympathomimetic substance works to release monoamine neurotransmitters, such as serotonin, epinephrine, norepinephrine, and especially dopamine (Barr et al., 2006; Chomchai & Chomchai, 2015; Moszczynska, 2016). As MA has high lipid solubility and a similar molecular structure to monoamines, it readily crosses the blood-brain barrier and is taken into neurons and nerve terminals by monoamine receptors. MA also rapidly redistributes monoamines through a process of passive diffusion, crossing neuronal membranes and releasing them from nerve terminals, as well as increasing activity of tyrosine hydroxylase, a dopamine-synthesizing enzyme (Barr et al., 2006; Moszczynska, 2016). In addition to these elevation processes, MA also inhibits monoamine reuptake transporter activity (notably, dopamine transporters at the cell surface to inhibit dopamine reuptake) and monoamine metabolism by inhibiting monoamine oxidase, resulting in increased monoamine levels within the neuronal cytosol (intracellular fluid) and synaptic cleft (Barr et al., 2006; Homer et al., 2008; Moszczynska, 2016). Cumulatively, these processes result in excessive levels of the aforementioned monoamines (with a distinct emphasis on the dopaminergic system), which leads to overstimulation of these neurotransmitter pathways. This has the potential to increase glutamate production, ultimately resulting in excitotoxicity and neuronal death (Barr et al., 2006; Halpin, Collins, & Yamamoto, 2014; Moszczynska, 2016).

Psychological and Physiological Effects of Methamphetamine. Upon ingestion of MA, near-immediate psychological and widespread physiological effects can be observed as a result of alterations in neurotransmitter activity. Volkow et al. (2010) demonstrated that after consumption, MA is disseminated throughout almost all organs in the body, with the highest concentrations in the brain, lungs, and liver. The brain, liver, and stomach also retained traces of MA for the longest period of time relative to other organs (Volkow et al. 2010). Acute behavioural effects of MA include heightened mood or euphoria; alertness and energy; attention and speed of processing; curiosity, risky decision-making; arousal, sexuality, and sexual endurance; psychomotor activity and dexterity; aggression; and productivity (Fernández-Serrano, Pérez-García, & Verdejo-García, 2011; Homer et al., 2008; Jan, Kydd, & Russell, 2012; Watt et al., 2014). During the acute intoxication phase, it has also been found to reduce fatigue, appetite, anxiety, and paranoia (Fernández-Serrano et al., 2011; Homer et al., 2008; Jan et al., 2012; Watt et al., 2014). MA also stimulates the release of epinephrine and norepinephrine, triggering sympathetic responses that may include vasoconstriction and related systolic and diastolic blood pressure elevation, tachycardia, cardiac arrhythmia and ischemia, diaphoresis, tremors, hyperreflexia, hyperpyrexia, peripheral hyperthermia, mydriasis, intracranial haemorrhage, seizures, stomach cramps, and agitation, as well as delirium and psychosis (Barr et al., 2006; Chomchai & Chomchai, 2015; Meredith, Jaffe, Ang-Lee, & Saxon, 2005; Panenka et al., 2013; Vearrier et al., 2012). Acute responses to MA may last for a surprisingly lengthy period of time (between 8-13 hours, as compared to the effects of cocaine lasting 1-3 hours) as a result of MA's extended elimination half-life and high ratio of central to peripheral nervous system action (Barr et al., 2006; Vearrier et al., 2012). Once MA's effects begin to wear off, users experience a 'crash', or severe withdrawal, in which a constellation of depression-like consequences often arise. These may include dysphoria, melancholy, anhedonia, social difficulties, irritability, fatigue

and anergia, hypersomnia, suicidality, aggression, paranoia, and extreme cravings for MA (Barr et al., 2006; Chomchai & Chomchai, 2015; Homer et al., 2008; Meredith et al., 2005). The intensity of both the positive experiences while MA acts upon the body and the physical and mental collapse once the drug has worn off contributes to the extremely addictive nature of the drug and its high relapse rate following treatment (Halpin et al., 2014; SACENDU, 2018).

Neurological Effects of Sustained Methamphetamine Use. In addition to the positive reinforcement associated with MA intoxication and the traumatic repercussions of comedown and withdrawal, the neurological repercussions observed in repeated MA use also contribute to sustained use, addiction, and MA-associated relapse. The repeated overstimulation of neurotransmitter release associated with chronic MA use has been found to affect several monoamine pathways, but deterioration of the dopaminergic systems (as indicated by diminished dopamine levels and receptor depletion) is most prevalent, especially in the striatum. This is evidenced by post-mortem investigations of MA-affected brains exhibiting an up to 60% depletion in striatal dopamine levels, with the caudate showing dopamine reductions as severe as in patients with Parkinson's disease (Barr et al., 2006; Panenka et al., 2013; Scott et al., 2007), as well as in vivo studies demonstrating reduced dopamine transporter levels in the orbitofrontal cortex, dorsolateral prefrontal cortex (DLPFC), striatum, nucleus accumbens, and amygdala (Barr et al., 2006). Indeed, the literature firmly supports the preferential degradation of dopamine systems as a result of impaired dopamine reserves and nerve terminals, and to a lesser (but still significant) extent, the breakdown of serotonergic systems associated with damage to serotonin nerve terminals and reduced serotonin transporter levels in orbitofrontal, temporal, and anterior cingulate regions observed in chronic MA use (Barr et al., 2006; Halpin et al., 2013; Homer et al., 2008; Meredith et al., 2005; Panenka et al., 2013; Rusyniak, 2013; Scott et al., 2007; Thanos

et al., 2017). In addition to MA's effects on neurotransmitter systems on a molecular level, structural and functional brain abnormalities associated with chronic MA use have become an increasingly popular area of research.

Methamphetamine and Neuroimaging: A Relatively New Journey

The development and refinement of neuroimaging techniques in recent decades has allowed for exciting new investigations into the structural, functional, and metabolic neural abnormalities proposed to arise from sustained MA use. This research plays a crucial role in the elucidation of how repeated exposure to MA alters the brain on a physiological level, and the manner in which these neural adjustments may affect cognitive and behavioural processes.

Positron Emission Tomography. Reviews of research involving positron emission tomography (PET) neuroimaging data collected from MA samples (Hart, Marvin, Silver, & Smith, 2012; Jan et al., 2012; Salo & Fassbender, 2011) provide insight into the neurochemical metabolism of neurons in the MA-affected brain. Although there are a number of conflicting results in terms of regional metabolic activity, there is repeated evidence in the literature indicating that dopamine (specifically, D2 and D2-like D3) receptors in abstinent MA-specific abusers have significantly reduced availability in striatal regions. Interestingly, and in opposition to the hypometabolism of the brain associated with alcohol and cocaine abuse, MA abusers demonstrate global cortical glucose hypermetabolism. During short-term abstinence, once controlling for the global increase in metabolic activity in MA groups, reduced metabolisation has been observed in the striatum, anterior cingulate cortex, insula, and thalamus. Although longitudinal data is extremely limited on account of the majority of subjects not meeting the criteria for MA abstinence at follow-up, reviews of observed samples (with follow-up periods spanning from three months to 18 years) indicate that thalamic metabolisation normalises, while metabolism of the

striatum does not. Dopaminergic integrity, as measured by dopamine transporter binding and receptor density, is repeatedly found to be unaffected by the length of time users remained abstinent. This inability of the striatum to recover may be a result of permanent dopaminergic system dysfunction due to damaged striatal dopamine axons and terminals, or grey matter excitotoxicity resulting in diminished cortical input to the region (Hart, Marvin, Silver, & Smith, 2012; Jan et al., 2012; Salo & Fassbender, 2011).

Magnetic Resonance Imaging. Of note, magnetic resonance imaging (MRI) studies have observed that repeated MA exposure is associated with a variety of structural alterations in the brain. Although more research in human subjects of varying degrees of MA use and abstinence is required, evidence thus far consistently correlates MA use with loss of cortical grey matter in adults (with the exception of Jernigan et al. [2005], with findings of increased parietal grey matter volume in people with MUD, although this should not be conflated with greater neuronal density [Scott et al., 2007]). Despite no significant differences in total grey matter volume between MA and healthy groups, diminished cortical volume has been demonstrated in the cingulate, limbic, paralimbic, hippocampal, and frontal regions through MRI scans and voxel-based morphometry (VBM) analyses (Barr et al., 2006; Berman et al., 2008; Daumann et al., 2011; Salo & Fassbender, 2011; Sabrini, Wang, Lin, Ian, Curley, 2019; Scott et al., 2007; Thompson et al., 2004). Additionally, reduced cortical thickness has also been observed in six year-old children exposed to MA in utero when compared to matched controls, although the extent and regions affected were found to be influenced by gender (Roos, Jones, Howells, Stein, & Donald, 2014). Conversely, enlargement of subcortical structures has been correlated with MA use in prenatally-exposed infants, with specific reference to the striatum, nucleus accumbens, and globus pallidus of the basal ganglia (Barr et al., 2006; Chang et al., 2005; Jan et al., 2012; Panenka et al., 2013; Roos, et al., 2014; Scott et al., 2007). These engorged volumes are particularly interesting when

considering the aforementioned PET evidence for reduced metabolic activity in striatal structures, and may be indicative of an inflammatory response, compensatory neural strategies or growth, or increased glial activity (Scott et al., 2007).

It should be noted that MA's structural effects are by no means constrained to grey matter. As well as alterations in cerebrovasculature (Barr et al., 2006; Panenka et al., 2013), significant white matter anomalies have been consistently reported within the context of MA use, as evidenced by both standard and diffusion-weighted MRI procedures. These are typically described by investigators as hypertrophic (i.e., denser), but ineffective, white matter pathways, especially related to temporal, occipital, and cingulate areas (Barr et al., 2006; Hart et al., 2012; Panenka et al., 2013; Scott et al., 2007; Salo & Fassbender, 2011), which are thought to be related to cerebral perfusion deficits associated with MA abuse (Bae et al., 2006). These macroscopic alterations are coupled with reduced white matter integrity in frontal and anterior cingulate cortices. This is denoted by the microscopic variations in white matter of MA abusers, observable through diffusion-tensor imaging (DTI) techniques revealing lower fractional anisotropy (i.e., the probability of diffusion of water molecules across the membrane of a structure is increased as a result of diminished coherent directionality of fibres) in MA users than non-using controls (Jan et al., 2012; Salo & Fassbender, 2011; Sabrini et al., 2019). Although MA users do not demonstrate overall loss of volume in the corpus callosum, certain abnormalities have been reported: specifically, the genu (anterior region) appears to have increased curvature, while the isthmus and posterior midbody are smaller in width compared to healthy controls (Oh et al., 2005). While structural research into MA-affected populations, especially non-abstinent users, must continue to be gathered to build a larger base of support in the literature, the existing studies provide a foundation to explore new avenues beyond that of gross structural alterations due to

MA. Consequently, recent research has begun to delve into the investigation of functional neural abnormalities associated with MA use and dependence.

Functional Effects of Methamphetamine. Technological advancements since the 1990s have led to the development of functional magnetic resonance imaging (FMRI), which has provided an invaluable platform to explore neural correlates that may underscore particular cognitive functions. A simplistic manner of understanding this non-invasive neuroimaging technique is that FMRI makes use of a method involving the flow, volume, and oxygen levels of cerebral blood, known as the blood-oxygen level dependent (BOLD) signal. As oxyhaemoglobin and glucose, and therefore blood flow, are required by particular neural regions for the energy-demanding activity of neuronal firing to carry out cognitive processes, the ratio of oxygenated arterial blood to deoxygenated venous blood increases locally, and this creates the MRI contrast signal in comparison to surrounding tissues (Salo & Fassbender, 2011; Soares et al., 2016). FMRI has been praised as a robust and easily reproducible neuroimaging technique with high spatial resolution and reliable signal measures for event-related processes. Although the temporal resolution of haemodynamic responses does limit precisely delineating psychological processes, FMRI has been described as an ideal and safe method for long-term and repeated data collection owing to its non-invasive nature (Jan et al., 2012; Salo & Fassbender, 2011; Soares et al., 2016). The use of FMRI research investigating the MA population is still comparatively new, with the first study being conducted in 2002. Since then, task-based FMRI in MA populations has been inclined towards investigating tasks relying on emotional regulation, social cognition, reward processing, and particularly, tasks requiring the recruitment of executive function (EF).

Executive Function (EF) and Methamphetamine Use. EF is a broad term referring to the higher-order processes of cognition that enable individuals to direct, control, manage, and guide their behaviour. These abilities include initiation and inhibition, planning and

sequencing procedures, generativity, creation and maintenance of goals (incorporating the monitoring and adaptation of behaviour to align with said goals), cognitive flexibility, impulse control, set-shifting, judgement, and decision-making (Banich & Compton, 2011; Zillmer, Spiers, & Culbertson, 2008). The deterioration of EF has repeatedly been implicated in SUD, and particularly MUD (for reviews, see Dean, Groman, Morales, & London, 2013; Jan et al., 2012; Sabrini et al., 2019). Currently, the available literature indicates that people who are dependent on MA experience reduced or inefficient activity in frontal (particularly, the dorsolateral prefrontal cortex [DLPFC] and orbitofrontal cortex [OFC]), parietal, insula, and cingulate cortices, as well as frontostriatal and frontoparietal hypo-connectivity when carrying out tasks that require EF processes, especially those involving impulse control, decision-making, and working memory (see, for example, Fassbender, Lesh, Ursu, & Salo, 2015; Goldstein & Volkow, 2011; Hoffman et al., 2008; Homer et al., 2008; Monterosso et al., 2007; Nestor, Ghahremani, Monterosso, & London, 2011; Paulus, Tapert, & Schuckit, 2005; Salo, Fassbender, Buonocore, & Ursu, 2012; Salo et al., 2009; Weafer, Van Hedger, Keedy, Nwaokolo, & Wit, 2018; Zhong et al., 2016). Lower levels of activation in prefrontal, insular, and posterior parietal cortices during decision-making tasks successfully predicted relapse rates of a sample of abstinent MA users (Paulus et al., 2005). Cumulatively, the abovementioned literature suggests that a number of neurocognitive factors associated with MA may contribute to poor decision-making processes and thus, relapse. These include: 1) a lack of assessment processes involving selective and switching attention, and salience attribution (associated with inferior parietal and anterior insular activation); 2) ineffective integration of cognitive and emotional information from previous success rates in order to evaluate possible future outcomes (associated with activity of the insula); and 3) diminished activity in prefrontal regions impeding rational judgement and decision-making.

Conversely, heightened neural activity has been found to be elicited in striatal regions in MA users during prediction and delay discounting tasks, in which a preference for an immediate small reward is favoured over waiting to receive a larger reward at a later time (Bischoff-Grethe et al., 2017; Paulus et al., 2005). This increased activation in the ventral striatum has been linked to reward expectation, and the simultaneous upregulation in this area and downregulation of the executive prefrontal cortex has been linked to risky, rather than considered, decision-making processes in MA users (Kohno, Morales, Ghahremani, Hellemann, & London, 2014; Sabrini et al., 2019). Thus, the brains of MA users are characterised by the dual-systems model of ineffective top-down cognitive control systems and sensitised bottom-up reward systems often described in addiction (McClure & Bickel, 2014). Additionally, exposure to MA-related cues has been found to elicit heightened neural activity in ventral striatal and medial frontal regions in individuals with MUD relative to healthy controls, with significant correlations being observed between the number of days since last administration of MA and ventral striatum activation (Malcolm et al., 2016). These patterns of neuronal firing during event-related FMRI highlight the functional neural abnormalities associated with MA abuse and provide crucial insight into the manner in which the MA-affected brain approaches tasks.

Nevertheless, a limitation of task-based FMRI is that study findings may be biased by idiosyncratic characteristics of the specific tasks employed, which may distort the emerging picture of the functional effects of MA exposure (Sutherland, McHugh, Parivadath, & Stein, 2012). For this reason, a valuable direction in MA research should involve reducing possible confounds through the use of an even newer neuroimaging technique – that of resting state functional connectivity (rsFC) analysis.

Resting State Functional Magnetic Resonance Imaging. As with task-based FMRI, resting state FMRI (rsFMRI) measures the BOLD data that signifies neural activation.

However, instead of examining the brain while subjects participate in a task, rsFC seeks to identify intrinsic functional connectivity (i.e., temporal co-activation of anatomically and spatially distinct neural regions) systems while the individual is 'at rest' – that is, not engaging in any directed tasks or cognitive exercises (Van den Heuval & Hulshoff Pol, 2010). This approach offers a mechanism for exploring the 'bigger picture' of neuronal communication and organisation and how this may translate to everyday functional abilities, as the magnitude of within- and between-network correlations holds behavioural significance (Guerra-Carillo, Mackey, & Bunge, 2014; Van den Heuval & Hulshoff Pol, 2010). As well as providing insight into individual and group differences between subjects of interest, the utilisation of rsFMRI in long-term, repeated measures studies is able to yield data on the plasticity of neural networks within individuals (Guerra-Carillo et al., 2014).

The rsFMRI literature surrounding addiction points to inefficient but hyper-connected neural networks in users, and is observed across a variety of primary drugs of choice (Krmpotich et al., 2013; Ma et al., 2010). However, it is impossible to accurately transpose investigations of a number of substances that differ vastly in terms of molecular structure, physiological effects, and neural reactivity, and assume it is applicable to the unique workings of MA. At present, there is a dearth of literature investigating rsFC in MA users. Of note, the cognitive control networks (CCNs) – a series of functionally connected neural networks pertaining to executive function and attentional control, including the salience attribution network, frontoparietal brain network, cingulo-opercular network, and the ventral and dorsal attention networks (Cole et al., 2013) have been of specific interest in SUDs. The limited MUD-related research indicates abnormalities of these networks, involving a number of structures in the frontal (particularly, prefrontal) and parietal cortices, such as the anterior cingulate cortex, DLPFC, dorsal premotor cortex, anterior insular cortex, inferior frontal junction, and the posterior parietal cortex (Allen et al., 2011; Cole & Schneider, 2007; Cole et

al., 2013; Ipser et al., 2016). Additionally, elevated rsFC in the mesocorticolimbic system (comprising the ventral tegmental area, ventral striatum, amygdala, hippocampus, and medial prefrontal cortex regions), implicated in pathological drug-seeking and risky decision-making has been observed in people with MUD, coupled with reduced frontal activation (Kohno et al., 2014; Kohno et al., 2016). It is believed that these frontostriatal abnormalities may be associated with the reward-processing irregularities of heightened responses to drugs and drug cues, as well as ineffectual cognitive control recruitment strategies (Kohno et al., 2014; Kohno et al., 2016; Weafer et al., 2019).

Furthermore, as well as CCN alterations, Ipser et al. (2016) found evidence of abnormal inter-network connectivity in chronic MA users, specifically in the interactions between the CCNs and default mode network (DMN), which involves the precuneus, cingulate cortex, angular gyrus, and inferior and medial frontal gyri (Allen et al., 2011). The DMN is implicated in self-referential activities (such as theory of mind and processing social information in relation to oneself), evaluative thoughts, unconscious processing, supporting emotional processing, stimulus-independent thoughts or 'mind-wandering' (Mars et al. 2012; Raichle, 2015, Fox et al., 2005). This is thought to be a task-negative system that is anticorrelated with task-positive networks, such that activity in the DMN decreases as cognitive demand of tasks increases, and has greater levels of activity when an individual is at rest (versus engaging in goal-oriented processes) (Fox, Zhang, Snyder, & Raichle, 2009). A recent study (Li et al., 2020) investigating cerebellar-cerebral functional connectivity in long-term (six months) MA-abstinent participants demonstrated significantly elevated rsFC in pairwise combinations of the cerebellum and DMN, as well as the cerebellum and affective-limbic networks (including the amygdala, thalamus, and cingulate gyrus) when compared to healthy controls.

In terms of the limited research regarding intra-network interactions between the anterior and posterior DMN, hyper-connectivity suggestive of inefficient processing and increased glucose metabolisation has been observed by Ipser et al. (2016). This heightened functional connectivity was moderated by lengthier periods since last use of MA, which was interpreted by researchers as indicating a degree of neural recovery in MA abusers with abstinence. These findings are consistent with data highlighting structural and functional abnormalities in prefrontal regions and corticostriatal dopaminergic transmission, which support the cognitive changes observed in MA users, especially the impaired executive function and particularly working memory deficits evidenced in people dependent on MA (Howells et al., 2014; Ipser et al., 2016; Jan et al., 2012; Kohno et al., 2014; Kohno et al., 2016; Kohno et al., 2018; London, Kohno, Morales, & Ballard, 2015).

Working Memory Deficits: A Key Element of the Neuropsychological Picture of Methamphetamine Dependence

Behavioural measures of EF further support the neuroimaging evidence indicating inefficient functioning of cognitive control networks. Throughout the literature, the MUD population demonstrates a reduced capacity for impulse control, delay discounting, and, of particular interest in this study, working memory (WM). The domain of WM simultaneously encapsulates and subserves processes associated with EF, as it recruits attentional and mnemonic mechanisms to selectively allow for information to be actively held in mind for future use, but with the cognitive flexibility to update, prioritise, and allocate salience to aspects of this information without succumbing to temporal or distractional interference (Bickel, Moody, & Quisenberry, 2014; Bledowski, Kaiser, & Rahm, 2010). In terms of self-regulation and goal-directed behaviour, WM abilities allow individuals to formulate and mentally represent objectives, and exert attentional control to monitor and evaluate steps towards this goal while diverting attention away from desires or cravings (Hoffman et al.,

2012). A recent meta-analysis of 44 studies investigating cognitive deficits observed in MUD (Potvin et al., 2018) outlines the neuropsychological picture of MUD as one with large deficits in impulse control, reward-related, and decision-making domains, which are implicitly tied with working memory processes (Bechara & Martin, 2004; Brooks, Funk, Young, & Schiöth, 2017). People presenting with MUD consistently demonstrate impaired emotional decision-making, difficulties adjusting short-term to long-term reward achievement strategies, shortfalls in motor response inhibition, reduced sensitivity to loss and incorporating negative experiences into future choices, and heightened impulsivity and delay discounting (Gonzalez et al., 2007; Monterosso et al., 2007; Potvin et al., 2018). Monterosso et al. (2007) found that when control participants were presented with an 'easy-choice' condition of a decision-making task, neural signal change was much smaller than that observed in response to a 'hard-choice' condition, but MA participants did not exhibit the same discrepancy. This elevated recruitment of neural resources across easy and difficult conditions points to inefficient functional connectivity, and indicates that it may be more difficult for MA users to make decisions (Monterosso et al., 2007).

These studies exemplify a pattern repeatedly demonstrated in people who abuse MA - a shortfall of appropriate working memory processes, associated sensation-seeking, and impulsive actions without full consideration of consequences. However, as impulsivity traits have been found to predict substance abuse and dependence in populations who use substances, it is unclear whether these characteristics are a result of MA dependence, or whether they precipitate it (Ersche et al., 2013; Potvin et al., 2018). Regardless, it is evident that these elements of WM dysfunction impair the everyday abilities of people with MUD (Henry et al., 2010) and that disinhibition, delay discounting, and impulsivity significantly threaten the likelihood of remaining in treatment, behaving in contravention of treatment facility rules, and abstinence (Bickel et al., 2014; Stevens et al., 2014). As a result, these

diminished cognitive capabilities should be targeted in treatment of SUD, particularly MUD, to facilitate cognitive remediation and support abstinence through maximising treatment efficacy, as emerging evidence suggests that a measure of working memory recovery is possible in abstinent users (Rubenis, Fitzpatrick, Lubman, & Verdjo-Garcia, 2017; Vocci, 2008; Zhong et al., 2016).

Cognitive Training

Considering the brain's remarkable plasticity, it seems reasonable to posit that targeting of dysfunctional neurobehavioural systems in respective neurocompromised conditions using the sophisticated technology of the modern era should produce significant cognitive improvements (Vinogradov, Flisher, & de Villers-Sidani, 2012). The application of cognitive training is still relatively new, but has begun to be investigated in populations with schizophrenia, attention-deficit hyperactivity disorder (ADHD), mood and anxiety disorders, autism spectrum disorders, traumatic brain injury survivors, the elderly, and SUDs (Keshavan, Vinogradov, Rumsey, Sherrill, & Wagner, 2014). This has primarily taken the form of four types of cognitive training: cognitive bias modification, response inhibition training, goal-management training, and working memory training (Verdejo-Garcia, 2016).

Given the urgency of the global MUD burden and the nonexistence of approved pharmacological treatments to support therapeutic interventions, exploration of these cognitive training approaches should be a priority in MA-related research. Cognitive bias modification (CBM) and response inhibition training have almost exclusively been applied to alcohol use disorders. The evidence indicates that neural mechanisms relating to impulsivity and approach actions, rather than cognitive control, may be affected in these treatments, although this is modulated by the effects of age and previous detoxification attempts (Verdejo-Garcia, 2016). These forms of cognitive training have shown potential for the treatment of alcohol use disorders and should be further investigated across treatment for

other SUDs. However, the dissimilarities of the neural effects of alcohol and MA, coupled with the lack of available evidence for executive recovery in these treatments, suggest that these may not be the most appropriate forms of cognitive training for MUD patients.

A limited number of studies suggest that goal-management training, when paired with mindfulness meditation, may improve some behavioural measures of working memory in polysubstance or alcohol users (Alfonso, Caracuel, Delgado-Pastor, & Verdejo-Garcia, 2011; Gonçalves et al., 2014; Valls-Serrano, Caracuel, & Verdejo-Garcia, 2016). However, a combination of factors collectively negates the impetus to consider this as a supplementary treatment method of choice for MUD in the South African context. Firstly, there exists a lack of available evidence with regard to neuroimaging data and demonstrable improvements in widespread executive functions for this time-, resource- and monetarily-demanding treatment (seven to eight two-hour therapist-facilitated sessions to stretch attentional and executive capacities). Additionally, a noteworthy consideration is that MA was not represented as a drug of choice (or, in fact, even use), in any of these samples. It is possible that this form of training may be found in future research to be effective across populations, but further preliminary research is crucial. In light of the resource-intensive nature of this method, it may not be a viable option for the majority of individuals with MUD in this country.

Working Memory Training. Finally, research of late has begun to investigate working memory training (WMT) as a topic of interest in various populations. Recent discussions around WM have begun to move away from the rigid conceptualisation of WM as being able to retain seven, plus or minus two, items in mind, arguing instead for WM as the capacity to harness greater cognitive control over impulse processes (Constantinidis & Klingberg, 2016; Olesen, Westerberg, & Klingberg, 2003). These reviewers recognise improvements reported in verbal and visuospatial WM following WMT. Yet questions regarding the efficacy of WMT remain, in light of a lack of evidence across studies and

populations demonstrating far-transfer effects to 'important real-world cognitive skills,' (Melby-Lervåg et al., 2016, p. 523) such as verbal and nonverbal abilities, word decoding, reading comprehension, and mathematics (Shipstead, Redick, & Engle, 2012; Melby-Lervåg, Redick, & Hulme, 2016). Indeed, WMT findings have been mixed in terms of behavioural efficacy as measured by generalisability and sustainability in healthy populations. However, it should be noted that demonstration of significant improvements in individuals possessing efficient EF may be less marked or consistent than in populations with executive dysfunction (Bickel et al., 2014). The emerging picture of WMT in substance abuse groups, and in stimulant users in particular, is encouraging, especially when considering that recent research presents preliminary evidence to suggest that WMT may be a valuable component of SUD treatment, as it could enhance cognitive strategies that promote abstinence.

In the first study of its kind, Bickel, Yi, Landes, Hill, & Baxter (2011) determined that computerised WMT as an adjunct to inpatient treatment for stimulant abuse significantly correlated with diminished delay discounting. Active and control training groups experienced identical treatment conditions, with one exception. While the active training group was required to engage in WM processes to progress through the active training programme, the computerised control training programme identified answers for the control group, meaning WM resources did not need to be recruited. With this study design, results cannot be attributable to other factors, such as additional attention given to the active training group. Notable research in this vein has demonstrated that the largest effects of WMT are observed in patients who demonstrate the highest degree of delay discounting at commencement of treatment (Bickel et al., 2014); and self-report impulsivity and self-regulation measures of MA abusers improve with WMT (Brooks et al., 2017). Interestingly, a voxel-based morphometry (VBM) study examining volumetric alterations in MA patients in treatment found the WMT group to be associated with increased trends towards

normalisation of bilateral basal ganglia regions relative to control participants, and that elevated WM accuracy correlated with increases in right middle frontal and orbitofrontal cortical regions (Brooks et al., 2016). These results, coupled with the relative ease of administration of training (i.e., half an hour of computerised or smartphone-based WMT, in contrast to the resource demands of CBM) suggest that this may be a promising supplement to rehabilitation of people battling MUD in South Africa and necessitates further research in this field.

The correlational patterns of decreased delay discounting and WMT may speak to a neural overlap between working memory mechanisms and delay discounting (i.e., future valuation), which may account for this particular amelioration of dysfunction in the absence of other executive improvements (Bickel et al., 2014). It has been postulated that hyperactivity in the bottom-up impulsive neural system in SUD begins to override the reflective prefrontal neural system, and this hijacking of neural resources from the top-down system results in dysfunctional executive processes as saliency of drug-related cues, craving, and motivation-related reward is up-regulated; while inhibitory control decreases, leading to failure to consider long-term consequences of taking drugs, and increased delay discounting (Bechara, 2005; Bickel et al., 2014, Ma et al., 2010, Goldstein & Volkow, 2002). Neuroimaging data suggests that repetitive WMT may recruit and strengthen neuroplasticity in major neural regions associated with WM processes, such as the DLPFC, medial prefrontal cortex, parietal cortex, insula, and striatum (Verdejo-Garcia, 2016; Wesley & Bickel, 2014). This is evidenced by training-associated neural activity increases in prefrontal and parietal cortical regions in healthy controls following WMT; as well as in populations with a high propensity for deficits associated with impulsivity, self-regulation, and attention (such as children with learning difficulties and attention deficit hyperactive disorder) (Olesen et al.,

2003). Further research is necessary to evaluate whether these findings translate to MUD populations.

Novelty: Resting State FMRI and Working Memory Training in the Methamphetamine-Dependent Population

As this review demonstrates, we are only beginning to scratch the surface of the neural processes affected by chronic MA use. In light of the valuable contributions further research could provide in terms of understanding the neurobiology of MA addiction and clinical applications of this data for effective treatment and rehabilitation of MA users, it is imperative that this field is further explored. The proposed study aims to address the gaps outlined in the literature, as described above. This study will build on the emerging research that suggests WMT may be a worthwhile adjunct to substance abuse treatment. Positive outcomes associated with EF, impulse control, and neural structure and function are observed in preliminary studies with patients involved in treatment for substance abuse (Bickel et al., 2014; Bickel et al., 2011; Brooks et al., 2016; Brooks et al., 2017; Constantinidis & Klingberg, 2016; Olesen et al., 2003; Verdejo-Garcia, 2016; Wesley & Bickel, 2014). In light of these results, the proposed research seeks to incorporate this by examining differences between rsFC data of healthy controls (HC) and people in inpatient treatment for MUD, of which a subset of MA participants engage in working memory training. Furthermore, this research will examine potentially impactful variables associated with rsFC of a 'working memory network' mask (see Table 1 and Figure 1 in Methods) derived from NeuroSynth, a platform that synthesizes brain-mapping results from neuroimaging studies across the globe (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). In order to allow for greater interpretability of study findings, WM function of the study sample will also be examined in relation to the canonical CCNs – the bilateral frontoparietal networks, the salience network, and the dorsal attention network – as well as the DMN.

This research will build on results from a parent study (Brooks et al, 2016; 2017), which demonstrates that at baseline, MA users produce significantly poorer results than HC in terms of EF, depression, self-regulation, perceived self-control, and impulsivity. Post-intervention, participants in the treatment as usual (TAU) group demonstrated significantly poorer results than HC on measures of impulsivity and self-regulation, while those in the cognitive training group (CT) did not differ from HC on any questionnaire measures besides longer response time in the Trail Making Test (TMT) and several items on the Self-Regulation Questionnaire (though not on overall self-regulation). VBM analyses in the parent study demonstrated significant main and interaction effects of group type and WM accuracy on the size of a number of neural regions, including bilateral putamen, cerebellum, basal ganglia, right middle frontal cortex, and orbitofrontal cortex, which support executive and working memory functions (Brooks, 2016). In this study, the primary research question will be to determine whether baseline measures of WM network rsFC predict performance on tasks of WMA in MA users. Additionally, the identification of potential demographic and clinical variables that may impact differences in connectivity across CCN, DMN, and WM resting state networks in healthy controls and drug-using participants will be explored.

Aims and Hypotheses

This study aims to investigate neural connectivity characteristics of MA users undergoing inpatient treatment for SUD through an analysis of resting state functional connectivity (rsFC) data of its parent study (Brooks et al., 2016). The primary focus of this study will be examining changes in WMA, how rsFC may be predictive of WMA performance, and variables that may be predictive indicators of connectivity in WM neural networks affected by MA abuse. Through these analyses, this investigation aims to expand on the limited research of the impact of MA on intrinsic functional neural connectivity.

Aim 1

The investigation of WMA performance in MA users receiving treatment as usual (TAU), or with additional cognitive training (CT), and a group of HC participants. Between-groups analyses will compare WMA across all three groups at baseline, across patient groups at follow-up, and within patient groups pre- and post-intervention. In order to provide context for interpreting the results of these analyses, demographic and clinical characteristics across groups will be examined.

Hypothesis 1. It is expected that the HC group and entire MA group (i.e., TAU and CT groups combined) will show significant differences on WMA measures at baseline, but no such difference will be evident between the MA groups. There will be statistically significant differences in WMA performance in both MA groups at follow-up compared to baseline. It is predicted that these differences will be particularly apparent in CT patients, who have received additional WM training every weekday for the duration of the intervention. WMA performance in the CT group at follow-up will more closely resemble that observed for the HC group than for the TAU group. These findings would support the argument that CT ameliorates abnormalities in WM performance associated with MA use.

It is predicted that there will be no significant differences between HC, TAU, and CT groups in terms of demographic variables, with the possible exception of level of education, as drug-using and healthy populations have been found to differ in this regard (Herman-Stahl, Krebs, Kroutil, & Heller, 2007; Ramlagan, Peltzer, & Matseke, 2010).

Aim 2

To investigate whether baseline rsFC of WM neural networks in MA users is predictive of the ability to perform well and improve on WMT training tasks. Exploratory analyses will investigate potential impacts of demographic and clinical variables on connectivity in these regions. As there is no established canonical 'working memory network', this analysis will be based on a NeuroSynth-derived WM network (Yarkoni et al., 2011).

Hypothesis 2. Baseline rsFC of the NeuroSynth-derived WM network will be predictive of performance and improvement on WM tasks in MA users.

Aim 3

To identify canonical resting state networks that may be important in supporting WM functions, by examining the association between baseline rsFC and WM measures in HC, as well as comparing group differences in these networks. This aims to provide greater interpretability of the study findings in light of other research in this field. Additionally, exploratory multiple regression models will attempt to identify clinical and demographic variables that may affect connectivity in regions identified as supporting WM function.

Hypothesis 3. WM performance will be predicted within the HC group by connectivity within and/or between three canonical CCNs (the bilateral frontoparietal networks, the salience network, and the dorsal attention network), as well as the DMN. It is predicted that the MA group will demonstrate elevated rsFC in within and between networks implicated in HCs as subserving WM.

Methods

Study design

The proposed research is a nested analysis using data from a previously completed study (HREC 554/2012). The design outlined here will therefore describe elements of the original study relevant to this secondary analysis. This research will be based on data from a pilot study (Brooks et al., 2016) that investigated neuroimaging, cognitive neuropsychological, and self-report affective measures of MA patients in treatment for SUD, with half of the participants receiving WMT as an adjunct to treatment. The investigation of differences in functional connectivity will therefore follow this quasi-experimental study design, using both repeated measures and between-group comparisons to explore WM performance and rsFC. Repeated measures comparisons will be run on all MA users, examining pre- and post-treatment WMA. Exploratory analyses will investigate whether rsFC of the NeuroSynth WM network is predictive of WMA performance and improvement. Between-groups comparisons will include: 1) WMA of HC versus both groups of MA patients at baseline and follow-up, to ascertain whether normalisation towards healthy WM performance is demonstrated after treatment and if this effect is augmented by WMT; 2) rsFC of the DMN and CCNs in HC versus both MA patient groups at baseline to establish existing differences in functional connectivity; and 3) variables that may impact rsFC in these groups.

Characteristics of parent study sample

Participants (n=66) were recruited in the area of Cape Town, South Africa, and were all males between the ages of 18-50. The following groups comprise the participants:

Group 1: Treatment as usual (TAU): 17 inpatients with a history of MA addiction receiving inpatient treatment for MUD. Patients participated in baseline and follow-up testing.

Group 2: Cognitive training (CT): 24 inpatients with a history of MA addiction who would receive TAU, as well as additional cognitive exercises in the form of computer-based WMT. Patients participated in baseline and follow-up testing.

Group 3: Healthy controls (HC): 25 members of the general public, who were matched on the basis of age and gender to MA inpatients, served as a control group and were only assessed at a baseline condition.

Recruitment Procedure

Participants from MA groups were recruited from Maitland Treatment Centre in Cape Town, South Africa between January 2013 and September 2014. After being identified as eligible for the study by clinicians (see below
for inclusion and exclusion criteria) in their first week of admission, participants were invited by clinicians to take part in the study. If potential subjects expressed interest in participating, they were introduced to the researchers at the end of their second week of treatment (the end of the programme's Orientation phase – see Appendix B). Researchers worked through the appropriate informed consent forms (see Appendix C) and established that each participant understood their potential involvement in the study. If the participant demonstrated understanding and a desire to take part, they signed the appropriate consent forms and were assigned to either CT or TAU group on an alternating basis as they entered the programme (as participation was staggered, based on admission of eligible patients to the clinic). This approach was taken in order to prevent any potential systematic bias in group allocation.

Participants for the HC group were recruited publicly and matched by age and gender to participants from MA groups. Upon providing informed consent, these participants

underwent only a single MRI scan and in-scanner WMA assessment, as well as completing the questionnaire booklet.

Participants were educated about informed consent, the right to withdraw at any time, issues of confidentiality, possible risks and benefits, and the right to request further information or publications of the study.

Inclusion and exclusion criteria

All participants involved were required to be fluent in English, right-handed, and have a negative HIV status. The HC group were required to have no history of SUD (including alcohol), no Axis 1 DSM-IV psychiatric diagnosis (current or previous), and no pre-existing neurological conditions. In order to be eligible for the MA group, inpatients were required to use MA as their primary substance, have no history of alcohol dependence (although, as determined by clinical screening, participants were allowed to have infrequent alcohol use and/or concurrently use cannabis or methaquolone), no previous or existing history of psychosis (as determined by clinicians upon admission), and not be taking prescription medication for the duration of the study.

Participants were intentionally excluded (total $N = 24$) for a number of reasons, such as inclusion and exclusion criteria, emotional distress in the clinic leading clinicians to recommend withdrawal from the study, issues with neural scans (such as poor quality scans being produced, equipment failure, and a lack of output log files); as well as participant dropout at follow-up ($N = 6$) (for a detailed CONSORT diagram outlining excluded participants, please see Appendix A).

Further, according to this study's protocol, participants were to be excluded on the basis of poor quality scans, as defined by increased framewise displacement values, and minimal (less than four minutes) acceptable rsFMRI data able to be used from the scans.

Research Procedures and Data Collection Methods

Overview of Procedure: Main Study. A visual depiction of the study design in the form of a CONSORT diagram can be found in Appendix A. In light of the potentially turbulent and stressful experience for patients being admitted to Maitland Treatment Centre, and possibly experiencing extreme withdrawal symptoms, researchers only made contact with patients after their two-week orientation phase at the clinic was complete (see Appendix B). This two-week phase of no contact with researchers guaranteed two weeks of abstinence from MA due to the rigorous supervision at the clinic, and allowed patients a safe environment for processing the physical, emotional, and cognitive discomfort associated with withdrawal and entering a rehabilitation facility, without the added burden of being asked to join a study.

During the Orientation phase, clinicians identified patients who may be appropriate for the study (in terms of meeting the appropriate study criteria, as well as personal ability to cope with participation) and enquired whether they would be open to meeting with the researchers to further discuss the study. Researchers met with patients who expressed interest in participating, and detailed the purposes of the study, as well as the patients' right to informed consent, and what this meant in the context of this study by working through the informed consent forms with each participant. This included their right to withdraw at any time without repercussions or consequences for their treatment; possible risks and benefits associated with the study, issues of confidentiality, and the right to contact researchers for further information and request publications from this data.

After two weeks of guaranteed abstinence in the clinic during the orientation phase, all inpatient participants completed a baseline MRI scan, a WMA assessment inside the scanner, and a booklet of questionnaires (which included measures of impulsivity [Barratt Impulsivity Scale], self-regulation [Self-Regulation Questionnaire], anxiety/depression

[Hospital Anxiety and Depression Scale], EF [Trail Making Task], and general demographics). Participants would then complete four weeks of either treatment as usual, or treatment with additional cognitive training. The testing process was repeated at the culmination of the intervention for the follow-up condition.

Participants assigned to the TAU condition followed the programme outlined in Appendix B. Those assigned to the CT condition were required to complete five half-hour sessions per week of WMT on a daily (weekday) basis for four weeks (a level of repetition advised by Vinogradov et al. [2012]), as well as engaging in treatment as usual. Cognitive training occurred in the form of daily engagement with a computer-based WM task called 'Curb Your Addiction (C-Ya). C-Ya is a variation of the N-Back (Kirchner, 1958) task, modified with a distracting background mosaic designed to mimic real-world peripheral distractions and was developed by the authors of the main study (Brooks et al., 2016) in collaboration with Fontera Digital Works. Participants were initially guided through the task by a researcher. In this study, levels 0-3 (known as 0-back, 1-back, 2-back, and 3-back) were used, with each numeric level indicating an increase in difficulty, requiring increasing prefrontal cortex resources. Participants engaged in the 0-back condition until they fully understood the task and false positives and negatives were extinguished. Once obtaining 80% accuracy, participants were permitted to move to the next level of difficulty on the following day, as previous work investigating the effects of WMT saw 80% accuracy being the highest level of accuracy obtained (Olesen & Westerberg, 2003). During the 0-back level, participants are required to press the laptop's space bar when a 'target letter' ('X') appears on the screen, recruiting attentional processes. In the ensuing conditions of increasing difficulty (1-, 2-, and 3-back), participants must recruit WM processes in order to recall the letters shown 1 before, 2 before, or 3 before (respective to the condition names) the letter on screen, and press the space bar when the letter on screen matches the target letter. A

maximum of 20 sessions were completed during the four-week period. Response times and errors were recorded by the programme and output in the form of a text document, to allow for the calculation of working memory accuracy. Errors were identified on the basis of commission: pressing the space bar when the letter did not match the target letter (i.e., a false positive response); and omission: not pressing the space bar when the letter did match the target letter (i.e., a false negative).

All patients, prior to four weeks of active treatment, as well as HC, underwent a baseline neuroimaging scan at Cape University Brain Imaging Centre (CUBIC) at Tygerberg Hospital in Cape Town, South Africa, as well as completing a number of neuropsychological measures and a booklet of self-report questionnaires. Participants then completed four weeks of treatment, with the TAU group engaging in the standard programme of the clinic (see Appendix B), and the CT group engaging in the programme with additional cognitive exercises in the form of WMT. This WMT involved completing half an hour of the Curb Your Addiction (C-Ya) programme on a laptop per day on weekdays, as previously outlined.

Following the four-week period of active participation in the rehabilitation programme with or without additional cognitive training, all MA participants underwent a second session of neuroimaging and questionnaire/neuropsychological task completion. Although participants remained in the treatment centre for two weeks following their four-week study enrolment (i.e., spending a total of eight weeks in treatment), researchers were not in contact with patients during the final two weeks of the programme, as they began working through sensitive adjustments necessary for returning to their environment outside of the centre. At the end of their participation, all participants at baseline received R150 (South African currency, approximately equivalent to $10) in food vouchers. Once the MA group (both TAU and CT participants) completed the follow-up measures after the study's 4-week period, they received an additional R150 food voucher. Appropriate ethical procedures as per

guidelines set out in the Declaration of Helsinki and approved locally by the University of Cape Town Human Research Ethics Committee (Ref: 554/2012) were adhered to throughout the duration of the main study. All participants were debriefed and compensated (as described above). TAU participants were assured that the cognitive training task would be made available to them after the study's conclusion.

Measures. A brief description of the WM instrument utilized in the study for which data was analysed for this thesis are listed below, as well as demographic and clinical variable of interest.

Working memory accuracy (WMA). The C-Ya computerised task, as described above, was used to gauge WMA in each participant. Testing within the scanner followed the format of the C-Ya task used for the CT group, but for the fact that the testing condition was limited to a total of 12 minutes of the test version, instead of the weekday training of half an hour. To measure WMA, participants alternated between the 0-back and 1-back levels for six minutes each to gather data on commission errors (responding to a non-target letter) and omission errors (not responding to a target letter). These were recorded to a log file in order to calculate a measure of working memory accuracy by using the following algorithm:

$[1 - ((\text{number of commissions} + \text{number of omissions})/ \text{total possible correct})] \times 100$

as per Miller et al., 2009.

NeuroSynth WM network mask. Table 1 details neural regions identified by NeuroSynth as supporting WM function and comprising the WM network. Figure 1 shows a visual representation of the clusters in this network and was created using the Mango (Multi-image Analysis GUI, [Research Imaging Institute, UTHSCSA - http://rii.uthscsa.edu/mango/index.html]) MRI viewer. The first sagittal image was taken from slice 50, with every fifth subsequent image captured.

Table 1

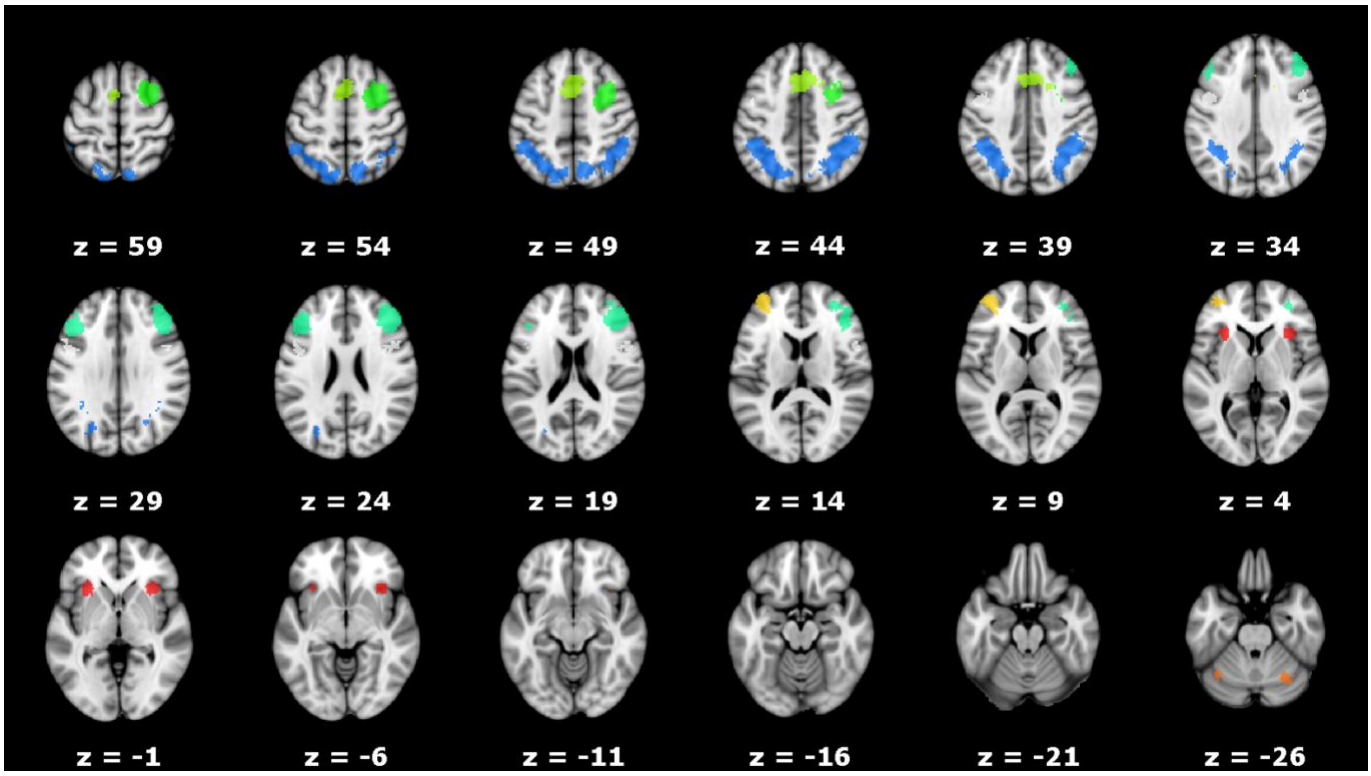
Regions of interest identified in the NeuroSynth WM network

Abbreviation	Cluster Name (Colour in Figure 1)	Notes	Size (Voxels)
Parietal	Parietal cortex (blue)	Bilateral inferior and superior parietal cortex. Right hemisphere also includes angular and supramarginal gyrus.	3885
DLPFC	Dorsolateral prefrontal cortex (turquoise)	Bilateral. DLPFC and inferior frontal cortex.	1802
Front.R	Right frontal gyri (bright green)	Right middle frontal, superior frontal, and precentral gyrus.	1085
dACC	Dorsal anterior cingulate cortex (red)	Bilateral.	944
Front.L	Left frontal gyri (yellow)	Predominantly left middle frontal gyrus, some overlap with DLPFC.	288
Cerebellum	Cerebellum (orange)	Bilateral.	390
Ant.In	Anterior insula (grey)	Bilateral.	395
Precentral	Precentral gyrus (lime green)	Bilateral, slightly larger right hemisphere cluster.	544

Note. Voxel size is 3x3x3mm. The colour indicating each cluster in Figure 1 is included in brackets.

Figure 1

Clusters included in the NeuroSynth WM mask



Data acquisition & Data Analysis

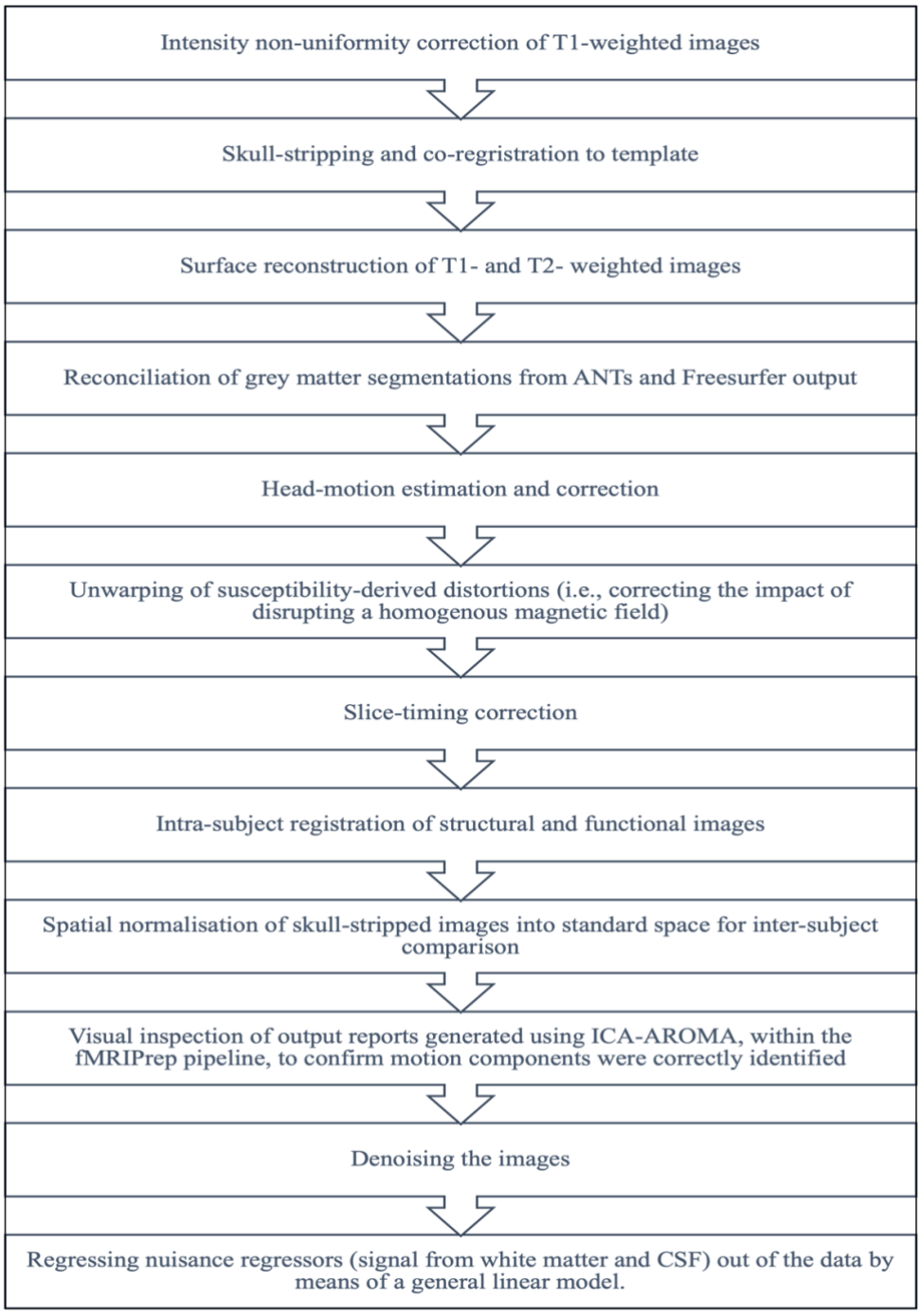
FMRI was acquired at Cape University Brain Imaging Centre (CUBIC) at Tygerberg Hospital, Cape Town, South Africa. The resting-state echo-planar images (EPIs) were acquired using a 3T Siemens Magnetom Allegra Syngo MR 2004A scanner with a 4-channel head coil using a T2* gradient echo sequence (TR=3s; TE=25ms; FA=90°; Voxel size=3x3x3mm). A total of 36 transverse slices with a thickness of 3mm and a total of 278 EPIs were acquired. Structural images were recorded for normalization and co-registration purposes using a T1 sequence (TR=2.5s; FoV=256mm; Voxel size=1x1x1mm) acquiring 160 slices per full brain image with a thickness of 1mm (Brooks et al., 2016).

In order to analyse the brain scans, pre-processing procedures were employed by use of an open-source neuroimaging pipeline known as fMRIPrep (Esteban et al., 2017), followed by further processing using the Analysis of Functional NeuroImages (AFNI)

neuroimaging software suite (https://afni.nimh.nih.gov). After converting the raw .DICOM images for the respective anatomical and functional sequences to the .NifTI format, each participant's data underwent a series of pre-processing steps (see Figure 2) in order to obtain the usable resting state data for analysis.

Figure 2

Pre-processing procedures of neural scans as per fMRIPREP and AFNI



Note. Software tools employed in this pipeline included Freesurfer, FSL ANTs, Nipype, and ICA-AROMA.

Independent Components Analysis (ICA). Following the pre-processing steps to obtain 'clean' data – i.e., data that has had all unnecessary noise removed and appropriate corrections performed – a probabilistic ICA, as implemented in FSL's MELODIC tool (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL; Jenkinson, et al., 2012) was executed on the resting-state fMRI images for the HC group only, to identify candidate WM networks. These include the CCNs (the bilateral frontoparietal networks, the salience network, and the dorsal attention network), and the DMN. Subject-specific versions of CCNs used for within-network analyses were identified by means of the dual regression procedure, as implemented within MELODIC. These were used to corroborate the validity of the NeuroSynth (Yarkoni et al., 2011) mask, generated by meta-analyses of activation coordinates of 1091 WM studies to produce a WM network. Time-series data for the individualised networks were subsequently extracted for the use of generation of connectivity matrices.

Extraction of connectivity coefficients for statistical analyses. Masks of individual clusters in the identified networks were used as seeds for whole-brain connectivity analysis. Using these seeds as markers across the entire dataset, AFNI's '3DNetCorr' command generated correlation matrices containing Pearson's correlation coefficients between each pair of seeds in each network, as well as corresponding Fisher Z-transformed connectivity matrices. Specifically, multivariate linear regression models were produced using the 3dMVM tool (Chen, Saad, Britton, Pine, & Cox, 2013). This suite of functions examines a number of neural regions of interest through treating multiple pairwise network connections as within-subject repeated-measure factors, while concurrently correcting the effect of continuous covariates in order to produce relevant WM network models. AFNI's 'fat_mvm' component of the FATCAT toolbox (Taylor & Saad, 2013; Taylor, Chen, Cox, & Saad, 2016) was employed to test group differences in within- and between-network connectivity of the relevant seeds.

Statistical analyses. RStudio for Mac (version 3.5.3) (RStudio Team, 2020) and AFNI's FATCAT (Taylor & Saad, 2013) toolbox were used to analyse the data, to investigate the following aforementioned between-group differences:

***Hypothesis 1*.** As determined by Shapiro-Wilk tests of normality (Shapiro & Wilk, 1965), WMA in-scanner performance was not normally distributed. As a result, non-parametric equivalents were employed for this variable, using the Kruskal-Wallis test (Kruskal & Wallis, 1952) for analyses between all three groups, and Wilcoxon signed rank tests with continuity connection (Wilcoxon, 1945) for repeated-measures and between-patient groups. One-way ANOVA and Chi-squared analyses were conducted at baseline to detect any existing group differences in clinical and demographic characteristics between HC, TAU, and CT groups. As standard ANOVA assumptions were upheld for these continuous variables, as determined by visually inspecting plots of data, the Shapiro-Wilk test of normality, and Levene's test of homogeneity of variance (Levene, 1961), non-parametric equivalents were not necessary.

Hypothesis 2. As significant differences were not observed in the repeated measures tests of WMA in hypothesis 1, the assumption that rsFC could predict change in WMA at 0- and 1-back was rendered irrelevant. As such, exploratory analyses were undertaken in an attempt to identify potential covariates associated with what may be a more accurate representation of WM function – the 3-back condition (see discussion for details). However, data for this condition was only available for CT patients, and as a result, all analyses pertained to this singlular group. Using FATCAT, network connectivity was modelled as a dependent variable and terms representing interactions between WM accuracy (3-back), demographic information, clinical variables were included in a multivariate model of CT participant data. When statistically significant effects were found in the overall model, post-hoc analyses were assessed to identify specific networks for which connectivity differs by

covariate. These covariates were tested in separate multivariate regression models, in order to maximise the power of the analyses to detect effects, an important consideration given the small sample size.

Hypothesis 3. Multivariate linear models modelled connectivity coefficients as the dependent variable within the canonical CCNs and DMN networks identified by ICA. Similarly, correlation matrices generated from binarised whole-network seeds were employed to assess the relationship between WM performance and between-network connectivity. In instances in which WM significantly predicts connectivity within the omnibus model (at alpha < 0.05), post-hoc multiple regression analyses for all pairwise comparisons of clusters (within-network analysis) and networks (between-network analysis) will be inspected. This will seek to identify where connectivity differs, as well as the direction of the difference. Covariates of interest as described in hypothesis 2 were again included in exploratory models. All models of network connectivity were conducted using the FATCAT interface to AFNI's 3dMVM utility as described above.

To control for the risk of false positive findings given the number of comparisons in the small sample, the false discovery rate [FDR] correction RStudio (2020) was used to calculate adjusted p-values for hypotheses 2 and 3.

Ethics

This research can be classified as a minimal risk study. The study is a nested analysis of its parent study and therefore presented no risk to participants. As this research is analysis-centred, the only conceivable risks could have been of privacy and confidentiality breaches. When giving consent to take part in the parent study, participants agreed that their data could be used for future analysis. Details of participant names were stored in one file location and given a Unique Identification Code to relate to all other information stored about the participant (locked in filing cabinet and password protected electronically). This ensured

that personal information about each subject was not easy to locate or access, and thus remained anonymous. For the current study, only these Unique Identification Codes were used – i.e., the identity of the participants remained anonymous, even to the researchers. All data has been, and will continue to be stored in locked cabinets and password-protected server locations.

Participants did not directly benefit from the proposed study, but potential advantages to furthering knowledge in this area include a broader impact in clinical, social, and academic spheres. As research into rsfMRI is limited, especially with regard to WMT and its potential clinical impacts (another relatively novel field), this study will contribute to the development of exploration into functional connectivity systems in MA users. This research has the potential to stimulate further investigation of clinical implementation of WMT as an adjunct to inpatient treatment and a prevention strategy in populations identified as being at risk for MA addiction. As a simple, cost-effective adjunct to inpatient treatment, this may help to reduce the societal burden of MA use by reducing readmission rates and expenses, and potentially preventing MA addiction. This may positively impact economic spheres through reducing the burden of MA on the state and individuals, and social spheres through decreasing behavioural ills associated with MA use.

End of Study

All participants in the parent study (from all groups) were provided with the opportunity to make use of the cognitive training game following their intervention, and were told that this may assist with cultivating self-control. Participants were provided with a summary of findings from the parent study, and those who wished to receive further information were flagged as future recipients of findings from further studies using this data. For the current study, the research exists to fulfil dissertation requirements in completion of a Master of Science (Medicine, Neuroscience) Degree at the University of Cape Town. It is

likely that this data will be used to present at conferences and the findings submitted to peer-reviewed journals.

Ethical and Regulatory Compliance

The study fully complied with the latest version of the Declaration of Helsinki (2008) and the Department of Health: Ethics in Health Research: Principles, Structures and Processes (2004) at the time. It also utilized the Guidelines for Good Clinical Practice in the Conduct of Clinical Trials in Human Participants in South Africa (2006).

Results

Hypothesis 1: Differences in WMA and establishing baseline characteristics across groups

As determined by Shapiro-Wilk tests of normality, all WMA scores were not normally distributed, and given the small sample size, the Wilcoxon signed rank tests with continuity connection (Wilcoxon, 1945) were used as a nonparametric alternative to removing outliers and conducting t-tests. Paired-sample Wilcoxon tests of WMA (0- and 1-back conditions) in the scanner indicated that neither the CT ($V = 52.5$, $p = 0.305$) nor the TAU ($V = 39.5$, $p = 0.239$) group improved significantly at follow-up compared to baseline. Independent sample Wilcoxon tests between CT and TAU groups using the delta scores of in-scanner WMA were also nonsignificant ($W = 104$, $p = 0.982$). Descriptive statistics and results of statistical analyses across all participant groups are presented in Table 2.

Table 2

Descriptive statistics: HC, CT, and TAU participants at baseline

Variable	HC (N = 25)	CT (N = 25)	TAU (N = 17)	Inferential statistics: Between-Group Differences
Age (years)	28.08 (5.85)	28.16 (9.63)	28.29 (6.21)	F (2, 64) = 0.004 p = 0.996
Duration of MA use (years)	N/A	9.00 (3.47)	10.24 (3.97)	t (31.32) = 1.042 p = 0.305
Abstinence period (weeks)	N/A	8.92 (3.31)	9.53 (0.96)	t (28.21) = -1.157 p = 0.257
Working Memory Accuracy	91.43 (8.91)	79.13 (24.33)	82.75 (19.98)	H (2) = 4.41 p = 0.111
Education	No Matric: 1 Matric: 1 Bachelor's Degree: 14 Honours: 6 PhD: 3	No Matric: 15 Matric: 7 No Data: 3	No Matric: 10 Matric: 7	X^2 (8) = 56.61 p < 0.001*
Race	White: 15 Coloured: 3 Black: 7	Coloured: 23 Other: 2	Coloured: 15 Black: 2	X^2 (6) = 52.78 p < 0.001*

Note. Standard statistical assumptions for ANOVA were upheld for all variables but WMA. As a result, the nonparametric Kruskal-Wallis test was used for WMA. Significant results are marked with an asterisk (*). It should be noted that while discourse in Americentrism often frames 'coloured' as a derogatory term for people of colour, this is not the case in South Africa. In the South African context, 'coloured' is another term for 'mixed race' and, as well as being a subset of racial classification, holds various cultural connotations (Gradin, 2013).

All continuous descriptive data are presented as means with standard deviations in parentheses. Abstinence period is measured in weeks and pertains to the number of weeks without using MA prior to commencement of the study. Working Memory Accuracy is measured as a percentage of correct responses obtained on the N-Back-based task test completed in the scanner as per the formula described in the Methods section. No significant between-groups differences were observed for age or WMA at baseline, although nonsignificant tendencies indicated patient groups performed more poorly than controls.

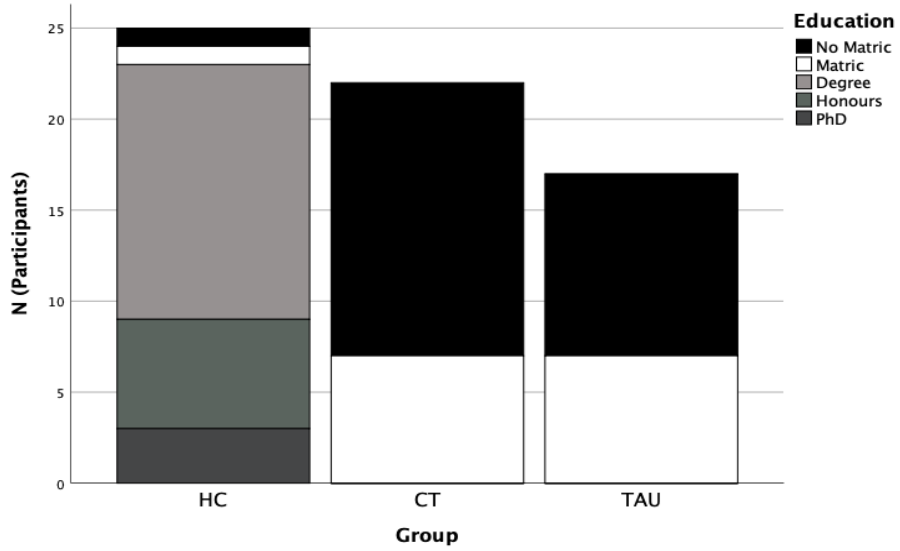
Independent sample Wilcoxon tests demonstrated that no significant differences were found between the two patient groups in terms of duration of MA use (W = 177.5, p =0.372) or duration of abstinence prior to the study (W = 158.5, p = 0.230).

Categorical variables of education and race are presented as number of participants and were analysed using chi-squared. Education refers to highest level of formal education obtained. Gender was not included as a variable as all participants were male. At baseline, the three groups were found to be significantly different in terms of level of education and race.

As illustrated in Figure 3, while the HC group was almost exclusively comprised of participants with a minimum of tertiary-level education, no participants in the patient groups obtained education further than a matric certificate. It should also be noted that the majority of the patient groups were comprised of participants who had not acquired a matric level of education, while this was the case for only one participant in the HC group. As a result of these significant differences, education was recoded as a binarised variable of 'matric plus' versus 'no matric' for exploratory analyses.

Figure 3

Stacked bar chart: Representation of level of education across groups

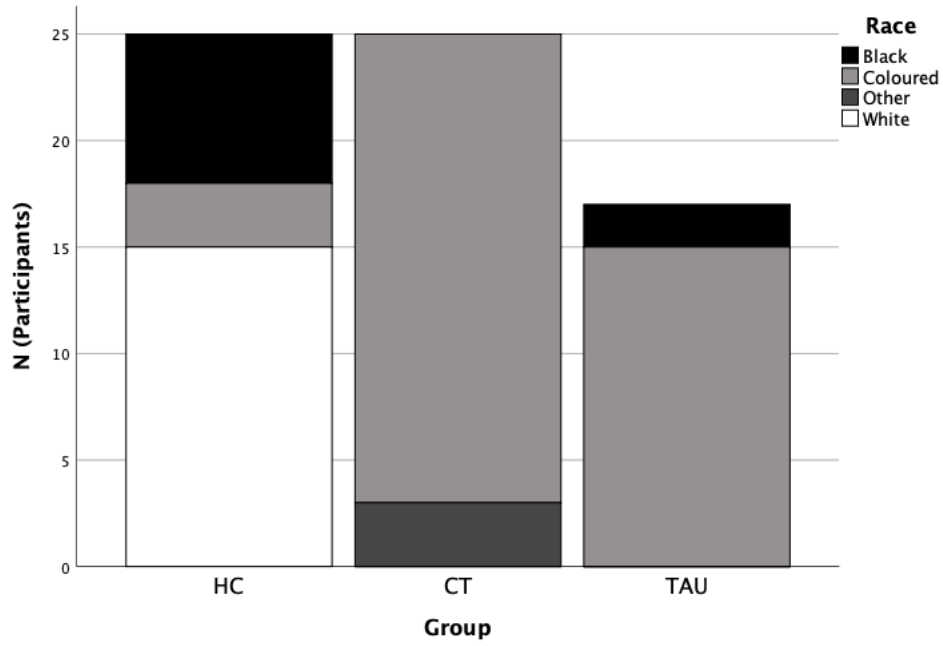


Note. This chart excludes data for three CT participants, as it was not recorded in the original data for the parent study.

As evident in Figure 4, while the HC group was predominantly made up of white participants, the CT and TAU groups included no white participants. The CT group was the only group including participants choosing 'other' in terms of racial identity, as well as being the only group that did not feature black participants.

Figure 4

Stacked bar chart: Representation of race across groups



As significant between-groups differences were observed in terms of race, it would not be appropriate to include this in a multivariate model investigating covariates and their association with average connectivity across groups for hypothesis 3. As such, race was investigated across pairwise networks in the HC group as an exploratory analysis. As the original classification system of the factor included multiple levels, the race variable was recoded to a binary of 'white' versus 'non-white', to help increase the power of these tests.

Hypothesis 2: Relating covariates to rsFC within the WM network in CT participants

The lack of change in in-scanner WMA rendered the intended hypothesis of using rsFC of a WM network as a predictor of change of WMA (0-1 and 1- back) null and void. For this reason, exploratory analyses using data from the 3-back condition of the WMA task (completed pre- and post-intervention, outside of the scanner) were undertaken. It should be

noted that this data was only available for CT participants (N = 17, due to participant drop-out and missing data). A significant difference was observed between 3-back WMA pre- and post-intervention in CT participants (V = 132, p = 0.001). Further exploratory analyses, as per Table 3, were conducted to further investigate associations between rsFC of the WM network, the 3-back measure of WMA, and clinical and demographic variables.

Table 3

CT participants: Results of exploratory multivariate linear models of the NeuroSynth WM network

Variable	X^2	p	*FDR-adjusted p*
Abstinence	0.36	0.55	0.55
Age	2.68	0.10	0.20
Drug Duration	0.71	0.40	0.55
Education	0.52	0.47	0.55
WMA Baseline (3-back)	4.79	0.029*	0.17
WMA Delta Score (3-back)	3.37	0.067	0.20

Note: WMA was calculated using the CT group's performance on the WM task at the 3-back level, completed out of the scanner. WMA delta score is calculated as the change in WMA from baseline to follow-up. Significant results are marked with an asterisk (*).

In light of the small sample size (N = 17), each variable in the table above was added individually to a model with WM network connectivity covariates as the dependent variable. Average motion was included as a covariate in all models to control for potential noise effects. To control for the risk of false positive findings given the number of comparisons in the small sample, RStudio was used to calculate adjusted p-values (false discovery rate [FDR] correction) for all omnibus model results provided by FATCAT. Prior to FDR corrections, baseline WMA was the only significant variable associated with rsFC of the WM network. Given that this potential relationship was consistent with initial hypothesis predictions, despite the lack of significant results when adjusting for multiple comparisons, preliminary post-hoc analyses were explored (see Table 4). However, it should be noted that

these analyses should be treated with a measure of caution. These are reported to serve only as prefatory indications of regions that may be of interest in future studies of a larger sample size in the event of baseline WMA demonstrating a significant association with rsFC in the NeuroSynth-derived WM network.

Table 4

Post-hoc analyses: WMA (3-back) at baseline WM network connections in CT group

Pairwise Clusters	*t*	*p*	*FDR-adjusted p*
Parietal – Precentral	2.22	0.043*	0.06†
DLPFC – Precentral	2.39	0.032*	0.06†
Front.R – Cerebellum	-1.83	0.088	1.00
dACC – Front.L	1.79	0.095	1.00
dACC – Ant.In	2.87	0.012*	0.06†
dACC – Precentral	2.32	0.036*	0.06†
Cerebellum – Ant.In	2.50	0.026*	0.06†

Note. Pairwise connections trending towards significance and those of significance before correcting for multiple comparisons are reported. Results of significance ($p < 0.05$) are marked with an asterisk (*). Results trending towards significance are marked with a dagger (†). FDR-adjusted p-values are presented. Results for all pairwise combinations included in the model are listed in Appendix D.

Results of significance between rsFC and baseline WMA were observed in five of the 28 pairwise cluster connections within the WM network before correcting for multiple comparisons. Of these five results, three included the precentral gyrus cluster, two included the dorsal anterior cingulate cortex, and two included the anterior insula. While FDR adjusted p-values were not significant, the pattern of these results trending towards significance may suggest that motor network connectivity may be a component influencing baseline WMA (3-back), considering the regions involved.

Hypothesis 3: Comparison of rsFC across groups and exploratory analyses of covariates

Table 5 presents a summary of the DMN components and CCNs included in analyses. Full names, neural regions included, and abbreviations are included.

Table 5

Abbreviations and regions included in resting state networks

Abbreviation	Network Name	Neural Regions Included in Network
DMN.Ant	Anterior default mode network	Medial prefrontal cortex, anterior cingulate cortex, inferior parietal lobule (Raichle, 2015)
DMN.Prec	Precuneal default mode network	Precuneus, lateral parietal cortex, angular gyrus, posterior cingulate cortex (Raichle, 2015)
DMN.Pcc	Posterior cingulate cortex default mode network	Posterior cingulate cortex, precuneus, angular gyrus, hippocampus, parahippocampal gyrus, occipital cortex (Raichle, 2015)
Dan	Dorsal attention network	Orbitofrontal cortex, inferior parietal sulcus (Corbetta & Shulman, 2002).
Sal	Salience network	Dorsal anterior cingulate cortex, orbital anterior insula (Seeley et al., 2007).
Fpr.Left	Left frontoparietal network	Left: anterior prefrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, anterior inferior parietal lobule, anterior insular cortex (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008)
Fpr.Right	Right frontoparietal network	Right: anterior prefrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, anterior inferior parietal lobule, anterior insular cortex (Vincent et al., 2008)

Table 6 presents the significant between-groups differences in average connectivity at baseline found in various pairwise neural networks after between-groups differences proved

to be significant, F (2, 63) = 24.54, $p < 0.001$. Results trending towards significance showed the HC group demonstrated lower average connectivity overall than both the CT ($t = 1.84$; $p = 0.070$) and TAU ($t = 1.80$; $p = 0.077$) groups.

Table 6

Pairwise comparisons of average connectivity between groups at baseline

	Average Connectivity: Correlation Coefficients			Between-Group Differences: ANOVA (df = 2, 63)		
Paired Networks	HC (n=25)	CT (n=24)	NT (n=17)	+CT – HC	+TAU – HC	+TAU – CT
Dan – DMN.Prec	0.44 (0.24)	0.52 (0.20)	0.43 (0.29)	0.69 (0.609)	0.28 (0.862)	-0.34 (0.873)
Dan – DMN.Pcc	0.15 (0.26)	0.13 (0.28)	0.21 (0.34)	-0.51 (0.712)	0.81 (0.513)	1.28 (0.634)
Dan – DMN.Ant	-0.22 (0.26)	-0.22 (0.27)	-0.11 (0.43)	-0.24 (0.864)	1.10 (0.362)	1.31 (0.634)
Dan – Fpr.Left	0.33 (0.16)	0.33 (0.26)	0.29 (0.32)	-0.08 (0.936)	-0.15 (0.883)	-0.07 (0.981)
Dan – Fpr.Right	0.28 (0.26)	0.44 (0.21)	0.41 (0.27)	1.84 (0.147)	1.80 (0.147)	0.12 (0.981)
Dan – Sal	0.27 (0.15)	0.27 (0.30)	0.35 (0.33)	1.11 (0.382)	2.12 (0.082)†	1.12 (0.635)
DMN.Prec – DMN.Pcc	0.42 (0.19)	0.62 (0.20)	0.73 (0.12)	3.72 (0.007)*	5.75 (0.007)*	2.35 (0.231)
DMN.Prec – Fpr.Right	0.24 (0.29)	0.40 (0.22)	0.45 (0.25)	1.69 (0.181)	2.65 (0.029)*	1.11 (0.635)
DMN.Prec – Sal	0.18 (0.30)	0.17 (0.25)	0.28 (0.28)	-0.22 (0.864)	1.34 (0.299)	1.54 (0.635)
DMN.Pcc – Sal	0.20 (0.24)	0.27 (0.26)	0.19 (0.37)	0.82 (0.544)	0.16 (0.883)	-0.59 (0.873)
DMN.Ant – DMN.Prec	0.16 (0.30)	0.31 (0.27)	0.54 (0.17)	1.92 (0.147)	4.65 (0.007)*	2.90 (0.105)
DMN.Ant – DMN.Pcc	0.29 (0.25)	0.59 (0.16)	0.64 (0.13)	5.20 (0.007)*	5.61 (0.007)*	0.88 (0.798)
DMN.Ant. – Fpr.Left	0.19 (0.35)	0.42 (0.28)	0.46 (0.29)	2.19 (0.112)	2.61 (0.028)*	0.63 (0.874)
DMN.Ant – Fpr.Right	0.13 (0.23)	0.28 (0.24)	0.36 (0.24)	2.00 (0.147)	3.00 (0.016)*	1.17 (0.634)
DMN.Ant – Sal	0.16 (0.28)	0.29 (0.30)	0.24 (0.38)	1.34 (0.278)	0.72 (0.551)	-0.50 (0.873)
Fpr.Left – DMN.Prec	0.34 (0.25)	0.46 (0.26)	0.49 (0.19)	1.89 (0.147)	2.10 (0.082)†	0.38 (0.873)
Fpr.Left – DMN.Pcc	0.24 (0.26)	0.47 (0.17)	0.33 (0.27)	3.10 (0.016)*	1.20 (0.353)	-1.62 (0.634)
Fpr.Left – Fpr.Right	0.29 (0.26)	0.53 (0.21)	0.54 (0.22)	3.39 (0.007)*	3.11 (0.015)*	0.02 (0.981)
Fpr.Left – Sal	0.28 (0.23)	0.47 (0.21)	0.49 (0.29)	2.34 (0.092)†	2.66 (0.029)*	0.53 (0.873)
Fpr.Right – DMN.Pcc	0.30 (0.24)	0.41 (0.23)	0.42 (0.24)	1.42 (0.161)	1.65 (0.193)	0.36 (0.873)
Fpr.Right – Sal	0.36 (0.24)	0.48 (0.23)	0.43 (0.29)	1.56 (0.123)	1.10 (0.362)	-0.32 (0.873)

Note: The table presents group differences at baseline in correlation coefficients after adjusting for subject motion. All average connectivity correlation coefficients are presented as means with standard deviations in parentheses. All between-group differences are presented as t-values with FDR-adjusted p values in parentheses. ANOVA results of significance ($p < 0.05$) are marked with an asterisk (*). ANOVA results trending towards significance are marked with a dagger (†). Unadjusted p values and their corresponding FDR-adjusted p values are presented in Appendix E.

Of the 21 pairwise network combinations, the TAU group displayed significantly greater connectivity than HC in eight of these (DMN.Prec – DMN.Pcc; DMN.Ant – DMN.Pcc; DMN.Ant – Fpr.Left; DMN.Ant – Fpr.Right; Fpr.Left – Fpr.Right; Fpr.Left – Sal; DMN.Prec – Fpr.Right; DMN.Ant – DMN.Prec). This included four of the six combinations

examining the anterior DMN network, as well as four of the six combinations including the left frontoparietal network, and four of the six combinations including the precuneal DMN network. Additionally, two pairwise combinations were observed to be trending towards significance (Dan – Sal; Left.Fpr – DMN.Prec).

Prior to adjusting for multiple comparisons (for a full depiction of unadjusted p-values and their corresponding FDR-adjusted values, please see Appendix E), the CT group produced significantly larger connectivity values than HC in seven pairwise combinations (DMN.Prec – DMN.Pcc; DMN.Ant – DMN.Pcc; DMN.Ant – Fpr.Left; DMN.Ant – Fpr.Right; Fpr.Left – Fpr.Right; Fpr.Left – Sal; Fpr.Left – DMN.Pcc). Many of these network combinations were the same as those that were significant in the TAU group, also including four combinations including the anterior DMN, as well as four including the left frontoparietal network. However, after correcting for multiple comparisons, only four networks were still found to be significant (DMN.Prec – DMN.Pcc; DMN.Ant – DMN.Pcc; Fpr.Left – DMN.Pcc; Fpr.Left – Fpr.Right), with one trending towards significance (Fpr.Left – Sal).

Of the patient groups, the TAU group uniquely demonstrated larger connectivity values than HC in three pairwise combinations of networks (Dan – Sal; DMN.Prec – Fpr.Right; DMN.Ant – DMN.Prec). The only pair of networks where the CT group uniquely yielded significantly greater connectivity coefficients than the HC group was that of the Fpr.Left – DMN.Pcc combination. There was no evidence of greater connectivity values in any pairwise combination of networks for the HC group over the MA groups, and no significant differences were found between the two MA patient groups for any pairwise combination of networks.

Race (as a binarised variable) was found to be statistically significant when included as a covariate while modelling connectivity in HC ($X^2 = 6.37$, $p = 0.011$). Being non-white

was associated with significantly higher average connectivity in the paired network of DMN.Ant – DMN.Prec (t = 3.27; p = 0.003), and, although not significant, a similar trend towards significance was observed in the Dan – Sal paired network (t = 2.06 ; p = 0.051).

Exploratory linear regression models were constructed to investigate potential effects of covariates on average connectivity across all groups (Table 7). Connectivity coefficients were modelled as the dependent variable, with each covariate added separately while controlling for average motion. This approach of modelling individual independent variables was employed to avoid type 1 errors that may arise from including too many variables for the small sample size.

Table 7

Exploratory multivariate models of network connectivity: Covariates of interest across all groups

Variable	X^2	p
Age	10.81	0.001*
Education	32.30	<0.001*
Drug Duration	5.94	0.02*
Interaction: Group X Abstinence	27.51	<0.001*
Use of other drugs	0.72	0.40

Note. Significant results are marked with an asterisk(*). Unadjusted p values are presented..

Significant between-groups differences were observed for multivariate models when including covariates of age, level of education (recoded as a binary variable, as previously outlined), and duration of drug use. A significant interaction effect between group and duration of abstinence prior to admission was observed in the model.

Post-hoc tests were performed to determine which specific pairwise combinations of networks were implicated in all of these results (see Table 8). No significant results were obtained when modelling multivariate analyses including covariates of WMA and use of other drugs.

Table 8

Post-hoc analyses of covariates included in multivariate linear models

Paired Networks	Age	Education (+No Matric – Matric)	Drug Duration	Interaction: Group X Abstinence (+CT – TAU)
Dan – DMN.Prec				
Dan – DMN.Pcc				-2.04 (0.048)*
Dan – DMN.Ant				
Dan – Fpr.Left				
Dan – Fpr.Right				
Dan – Sal	2.85 (0.006)*	-1.68 (0.098)		
DMN.Prec – DMN.Pcc				-1.98 (0.055)
DMN.Prec – Fpr.Right				-1.86 (0.070)
DMN.Prec – Sal	1.96 (0.054)			
DMN.Pcc – Sal			-2.16 (0.037)*	
DMN.Ant – DMN.Prec	2.10 (0.039)*			-2.49 (0.005)*
DMN.Ant – DMN.Pcc	-1.83 (0.072)		-1.88 (0.068)	
DMN.Ant – Fpr.Left		3.40 (0.001)*	-3.15 (0.003)*	
DMN.Ant – Fpr.Right		2.72 (0.009)*	-2.15 (0.038)*	
DMN.Ant – Sal		2.80 (0.006)*	-2.67 (0.013)*	
Fpr.Left – DMN.Prec				-3.00 (0.005)*
Fpr.Left – DMN.Pcc		2.33 (0.023)*	-2.59 (0.014)*	
Fpr.Left – Fpr.Right		2.13 (0.037)*		
Fpr.Left – Sal				2.14 (0.039)*
Fpr.Right – DMN.Pcc				
Fpr.Right – Sal				1.91 (0.063)

Note: t values are reported with unadjusted *p* values in parentheses. Significant results are marked with an asterisk (*), and results trending towards significance ($p < 0.1$) are reported. Results for age and education include data from all three groups, while drug-related variables (i.e., duration of drug use and length of abstinence) refer only to the two patient groups. Signs (positive and negative) indicate the directionality of the relationship, whereby a negative value for a main effect indicates decreasing connectivity with increasing value of the variable, and positive values indicate positive associations of variable and connectivity values.

Post-hoc analyses of the multivariate linear models demonstrated which pairwise combinations were significantly influenced by covariates. A positive relationship between age and connectivity was observed between the Dan - Sal networks, as well as between the DMN.Ant – DMN.Prec.

With education as a binarised variable, completing formal secondary schooling, (versus not obtaining a matric certificate) was associated with significantly lower average connectivity value in five pairwise combinations of networks. This negative relationship was found in the DMN.Ant – Fpr.Left, DMN.Ant – Fpr.Right, DMN.Ant – Sal, Fpr.Left – DMN.Pcc, and Fpr.Left – Fpr.Right pairwise networks.

When drug duration was factored into the model of MA groups, greater drug duration was associated with significantly lower connectivity in the following five paired networks: DMN.Pcc – Sal, DMN.Ant – Fpr.Left, DMN.Ant – Fpr.Right, DMN.Ant – Sal, and DMN.Pcc – Fpr.Left. Given the literature and other results in this sample suggesting that adverse conditions are often associated with heightened connectivity, this negative relationship was an unexpected result. In an attempt to understand this, drug duration (previously entered as a continuous variable measured in years), was dichotomised at the median (9.5 years) into a binary variable. Participants across both MA groups with duration of drug use below this were coded into a ‘low’ group (i.e., shorter duration of drug use), while subjects above the median were allocated to the ‘high’ group (i.e., longer duration of drug use). Descriptive statistics for the five pairwise combinations of interest are presented in Table 9. Across all combinations of networks, the group with longer duration of drug use demonstrated lower average connectivity means, but higher standard deviations and larger ranges in connectivity values. Visual inspection of these box plots confirmed that positive correlations coefficients were attenuated amongst those with longer duration of use for all network combinations.

Table 9

Descriptive statistics: average connectivity values of low and high duration of drug use

Paired Networks	Low (N = 22)			High (N = 20)		
	Mean (SD)	Range	Median	Mean (SD)	Range	Median
DMN.Pcc – Sal	0.32 (0.28)	1.01	0.24	0.15 (0.32)	1.28	0.52
DMN.Pcc – Fpr.Left	0.46 (0.21)	0.70	0.50	0.36 (0.23)	0.96	0.43
DMN.Ant – Fpr.Left	0.54 (0.19)	0.65	0.51	0.33 (0.32)	1.22	0.28
DMN.Ant – FPR.Right	0.39 (0.21)	0.80	0.35	0.23 (0.25)	0.98	0.21
DMN.Ant – Sal	0.38 (0.27)	1.01	0.36	0.14 (0.35)	1.08	0.18

Note. Descriptive statistics of average connectivity are presented as means with standard deviations in parentheses, as well as the range within the groups of low and high duration of use.

A significant interaction effect was found between MA groups and duration of abstinence, with four pairs of networks implicated in the post-hoc model: DMN.Pcc – Dan, DMN.Ant – DMN.Pcc, DMN.Prec – Fpr.Left, and Left.Fpr – Sal. As presented in Table 10, post-hoc analyses of linear regression models were run using connectivity coefficients for each of the 4 network combinations as the respective dependent variable, with abstinence as a predictor variable and controlling for average subject motion.

Table 10

Post-hoc analysis of interaction effects of 'group' and 'abstinence' between CT and TAU participants

Paired Networks	*F (df)*		*Adjusted R^2(p)*		*Pearson correlation (p)*		
	CT	TAU	CT	TAU	CT (outliers removed)	CT (outliers present)	TAU
DMN.Ant – DMN.Prec	1.29 (2, 18)	0.56 (2, 14)	0.03 (0.30)	-0.06 (0.58)	0.11 (0.62)	-0.50 (0.01)*	0.21 (0.42)
Dan – DMN.Pcc	5.28 (2, 18)	0.68 (2, 14)	0.30 (0.02)*	-0.04 (0.52)	-0.04 (0.87)	-0.45 (0.03)*	0.24 (0.36)
Left.Fpr – DMN.Prec	1.63 (2, 18)	2.01 (2, 14)	0.06 (0.22)	0.11 (0.17)	-0.15 (0.51)	-0.60 (0.002)*	0.40 (0.11)
Left.Fpr – Sal	1.86 (2, 18)	0.06 (2, 14)	0.08 (0.18)	-0.13 (0.94)	0.01 (1.0)	0.46 (0.02)*	0.03 (0.91)

Note: Significant results are marked with an asterisk (*). Pearson correlations are reported twice for the CT group, with one column presenting results with three participants identified by Cook's distance test as outliers removed, and one column presenting results including all CT participants previously included in the model.

Only one linear model was found to be significant (the DMN.Prec – Dan pairwise combination in the CT group). Pearson correlations were conducted using residualised Fisher-Z transformed connectivity values (i.e., regressing average motion of each participant from their connectivity coefficients to account for average motion) and abstinence in each pairwise combination in each group. Significant correlations were observed in all four pairwise network combinations in the CT group when including all available participant data. However, Cook's distance tests demonstrated that three CT participants were significant outliers, and were therefore removed from the models. These subsequent analyses demonstrated no significant correlations between connectivity and abstinence in any pairwise combination of networks in either group. This suggests that FATCAT's linear model may not be robust to violations of normality, and is discussed further in the limitations section. The sensitivity to the interaction effect of group and abstinence to the exclusion of outliers may reflect the tendency of interaction terms in regression models to lack statistical power. Nevertheless, it should be noted that the main effects found in the model may still reflect important impacts, and should not be discounted.

When observing the results reported, the statistical power of a study with such a small sample size should be noted. A post-hoc power analysis using RStudio (2020) determined that the current study could detect large effect sizes ($f = 0.4$) with a power of 0.70, and moderate effect sizes ($f = 0.25$) with a power of 0.32.

Discussion

This study aimed to analyse previously collected data (Brooks et al., 2016) in a novel manner. This involved investigating rsFMRI in people receiving treatment for MA abuse to identify variables that may be associated with rsFC in regions associated with WM, how these neural networks may differ between HC and those affected by MA abuse, and preliminary evaluations of WM tasks and potential associations with rsFC. Taken together, this research has provided an interesting set of results with regard to its parent study, resting state functional connectivity in MA users and potential covariates thereof, and the efficacy of measures of WMA.

Parent Study: Demographic and Clinical Differences Between Groups

As illustrated in Table 2, the prediction that HC and patient groups would not significantly differ in demographic variables, except possibly for education level, was only partially supported. Groups were equivalent with respect to age, as to be expected, given that HC were matched to patient participants on this basis. It was hypothesised that groups may differ in terms of highest level of education obtained, and this proved to be a statistically significant difference, X^2 (8, 64) = 56.61, $p < 0.001$. Figure 3 clearly illustrates this discrepancy, with the majority of participants in both patient groups (CT N = 15; TAU N = 10) not completing formal secondary schooling, as compared to one participant in the healthy control group not obtaining a matric certificate. Matric was the highest level of education demonstrated in the patient groups (N = 7 for each group). Conversely, the large majority of HC participants (N = 23) had a minimum of an undergraduate tertiary education qualification, with a large proportion of those (N = 9) possessing postgraduate qualifications, and a single participant having only a matric certificate. These results are consistent with the literature, as lower levels of education have been associated with a greater likelihood of abusing substances in general, and MA specifically (Herman-Stahl et al., 2007; Ramlagan,

Peltzer, & Matseke, 2010), although the causative directionality of MA abuse and lower levels of education cannot be definitively concluded.

In contrast to preliminary hypotheses, chi-squared analyses demonstrated significant between-groups differences in race, X^2 (6, 64) = 52.78, $p < 0.001$. While the HC group had a majority of white participants (N = 15), with only three coloured and seven black subjects, neither patient group had any white participants. Instead, both patient groups mostly comprised of coloured subjects (CT N = 23; TAU N = 15). The large proportion of coloured patient participants in the study does reflect the consistent trend of this being the largest racially represented group in people admitted for MA use in the Western Cape (SACENDU, 2019). However, the lack of similarity between groups leaves race as a potential confounding factor in this study, as discussed further in the limitations section.

The two MA groups did not significantly differ on clinical variables of duration of drug use and length of abstinence prior to admission. This is reasonable and supports the validity of the sampling methods employed in the parent study, as these groups should not have had cause to differ on these measures.

Differences in WMA: 0-Back Condition

Contrary to original hypotheses, no significant differences in WMA (0-back) at baseline were observed between the three groups. As there were no significant differences found between the groups on the basis of WMA at baseline, the expected trend of CT participants normalising towards HC performance could not be observed. The MA groups were not expected to differ between one another, and had a (nonsignificant) tendency to perform more poorly than HC. Nevertheless, this element of the study did not support the emerging literature suggesting that WMT may improve EF functions such as WM (Bickel et al., 2014; Bickel et al., 2011; Brooks et al., 2016; Brooks et al., 2017; Constantinidis & Klingberg, 2016; Olesen et al., 2003; Verdejo-Garcia, 2016; Wesley & Bickel, 2014).

Given the small sample size, it is possible that the lack of quantitative differences between HC and patients is a result of inadequate power to detect an effect in this study. It has been widely demonstrated that populations abusing MA yield poorer performance on tasks of WM than HC (for a meta-analysis, see Potvin et al., 2018). A plausible contributory factor to the lack of differences observed between groups on the measure regarded as WMA may lie in the fact that only 0-back and 1-back conditions of the N-back task were assessed and compared between groups. These levels have been described as tasks requiring WM maintenance – protecting necessary information from being replaced by impertinent material – as opposed to levels 2-back and higher, which necessitate the additional recruitment of WM manipulation – updating, controlling, and altering essential information held in mind (Rac-Lubashevsky & Kessler, 2016). Beatty et al. (2015) found evidence indicating that although performance on relatively easier levels (2-back conditions) of the N-back task is likely to improve with repeated engagement, only improvement on more challenging levels (3-back and above) was predictive of improved performance on other tasks measuring WM. Collectively, this may suggest that the 0-back and 1-back conditions used as an indication of WMA in the parent study may not have been cognitively demanding enough to provide a valid representation of WM manipulation, and may have instead reflected WM maintenance and/or attentional factors, and this may be a reason for the lack of differentiation between HC and MA groups. In future, pains should be taken in designing fMRI-compatible tasks to accurately test the recruitment of WM processes. This would help to avoid the potential for non-discrimination between-groups on the basis of lack of cognitive demand.

Resting State Functional Connectivity: WM Network and WMA (3-back) in CT Participants

The lack of significant differences between 1) in-scanner WMA at pre- and post-intervention in the respective CT and TAU groups, and 2) delta scores of in-scanner WMA

between the two patient groups, resulted in the proposed hypothesis of investigating WM network rsFC as a predictor of this data obsolete. It is possible that the lack of improvement in the CT group could be attributed to the use of the WM task conditions as described above. For this reason, exploratory analyses using the 3-back condition of the WMA task were investigated, in line with its potential to more accurately reflect WM functions. It should be noted that this data was only collected for CT participants, and thus, only this group can be discussed here.

Using FATCAT, regression models aimed to assess potential associations of clinical, demographic, and WMA (3-back) variables with rsFC activation in MA users receiving additional WMT during inpatient treatment. A WM network mask (see Table 1 and Figure 1 for a detailed description) obtained from NeuroSynth (Yarkoni et al., 2011) was utilised to identify individual clusters within this network to be used for whole-brain connectivity analyses in CT participants using baseline neuroimaging data. Average motion was included in all models to control for individual subject motion and reduce noise effects, but all other variables were individually modelled with rsFC data. Analyses were executed in this manner to avoid over-fitting too many variables in a single model in light of the small sample size (N = 17, as preparatory steps for FATCAT implementation yielded error messages regarding unsatisfactory data for eight participants and necessitated the removal of these subjects). Although baseline WMA (3-back) initially appeared to demonstrate a significant effect on rsFC in the overall model, this was no longer significant when applying the FDR correction to control for multiple comparisons. However, prefatory post-hoc analyses were conducted, given that this result was consistent with hypotheses that connectivity of the WM network would predict WM measures. Although these should be treated with caution, given the non-significant overall effect using FDR-adjusted p-values, baseline WMA (3-back) was positively associated with increased rsFC in five pairwise components of the WM network

(Parietal – Precentral; DLPFC – Precentral; dACC – Ant.In; dACC – Precentral; and Cerebellum – Ant.In). The inclusion of clusters involving the precentral and parietal gyri, as well as the cerebellum, all of which are known to be involved in motor coordination (Martin, 2012) suggests that there may be a degree of motor network involvement predicting performance on WMA (3-back).

Results indicate that in this sample of CT participants, variance of rsFC in the WM network could not be predicted by age, level of education, length of abstinence, or drug duration, and that this functional connectivity could not predict WMA (3-back) delta scores (i.e., capability of improvement on task performance). With regard to aging effects, healthy older adults have been found to demonstrate alterations in resting state networks (including the DMN and dorsal attentional network) that follow a general trend of reduced within-network and increased between-network connectivity as compared to healthy young adults (Farras-Permanyer et al., 2019; Damoiseaux, 2017). However, given that the age range in the CT sample only spans 23 years (20-43), there may not have been sufficient variability in age to replicate these findings. As discussed below with reference to hypothesis 3, this study did find age to be a significant covariate ($t = 10.81$, $p = 0.001$) in exploratory regression models of average connectivity of the CCNs and DMN across groups. As these networks demonstrate a substantial amount of overlap with the WM network mask, it is interesting that no significant results were demonstrated when modelling age as a predictor of average connectivity using the NeuroSynth WM mask. However, as hypothesis 3 included data from healthy controls and the WM network mask only examined CT participants, it is possible that healthy brains may be altered in dissimilar ways by age in comparison to MA-affected brains. Additionally, it is possible that the larger sample size in hypothesis 3 ($N = 65$) may provide a more accurate representation of, and greater power to detect, an effect of age than that seen in hypothesis 2 ($N = 17$).

As these are exploratory analyses pertaining to a narrow area of investigation (i.e., rsFC of a NeuroSynth-derived WM network in MA users receiving additional WMT during inpatient treatment), comparative research is not known at the time of writing. Given the small sample size and lack of power, it may be presumptuous to attempt to generalise these results to wider populations, and underscores the necessity of further research in this area. However, there exists more context in the literature surrounding the impact of these clinical and demographic variables on rsFC of networks such as the DMN and CCNs. This provides a framework for interpretation of the final hypothesis in this study.

Resting State Functional Connectivity: DMN and CCNs Across Groups

It was hypothesised that intrinsic functional connectivity within and between the DMN and canonical CCNs would differ between MA and HC subject groups. ANOVA results comparing the correlation coefficients of average connectivity values between groups supported this hypothesis, F (2, 63) = 24.54, $p < 0.001$. Between-groups analyses largely supported the scant, yet emerging literature implicating heightened rsFC within and between certain neural networks of people using MA.

Default Mode Network: Within-Network Connectivity. The results of this preliminary investigation appear to align with evidence for hyperconnectivity of intra-network DMN activity (i.e., pairwise combinations between the anterior DMN, posterior cingulate DMN, and precuneal DMN) in people using MA. Support is offered for the notion of hyper-connected, but likely inefficient intrinsic neural connectivity, given the correlations between local hyper-metabolisation of glucose and heighted rsFC in this population (Berman et al., 2008; Aiello et al., 2015, Ipser et al., 2016), as well as other populations with neurological disruption and dopamine depletion, such as people with schizophrenia (Whitfield-Gabrieli et al., 2009), ADHD (Tian et al., 2006), and major depressive disorder (Greiciesus et al., 2007) .

All three pairwise combinations of the DMN exhibited significantly higher average connectivity values in the TAU group when compared to healthy controls (DMN.Ant – DMN.Prec; DMN.Ant – DMN.Pcc; DMN.Prec – DMN.Pcc). The CT group exhibited a similar pattern of elevated within-network DMN connectivity versus the control group, with two being significant (DMN.Ant – DMN.Pcc; DMN.Prec – DMN.Pcc). While this pattern replicates findings in the Ipser et al. (2016) study regarding heighted activity within this task-negative network at rest, this study did not imitate Ipser et al. (2016)'s observation of length of abstinence moderating this effect, as no main effect for abstinence was identified in post-hoc analyses of the model. Potential suppositions for differences between these two similar studies are offered after discussion of the DMN and CCN intra- and inter-network observations of this study.

Interestingly, despite the two patient groups exhibiting no significant difference in duration of abstinence prior to participation (t = -1.16, $p < 0.257$), post-hoc analyses indicated an interaction effect of group (CT or TAU) and abstinence (X^2 = 27.51, $p < 0.001$) on the overall model of connectivity at baseline. When further explored, the DMN.Ant – DMN.Prec pairing was implicated as being significantly impacted by this interaction effect, but, as described in the results section, significant correlations could not be found when outliers (N = 3), as determined by Cook's distance, were removed. As previously mentioned, this may indicate that FATCAT may not be robust to violations of normality with regard to interaction effects in samples of such a small number and/or low power. It is conceivable that the limited sample size in this study introduced an artificial type 1 error in finding significant differences between two relatively similar MA patient groups. While this cannot fully be explained by the present study, future research could explore potential factors affecting intra-network activity of the DMN in MA populations. It is suggested that age should be investigated in these explorations, as exploratory linear models (see Table 7) highlighted age

as a significant (X^2 = 10.81, p = 0.001) covariate impacting average connectivity across groups, and it should be noted that this was the only variable identified by post-hoc tests to significantly affect connectivity in any of the intra-network DMN pairwise combinations (DMN.Ant – DMN.Prec).

Finally, exploratory analyses including race as a binarised variable when modelling connectivity in HC found this to be a significant covariate (X^2 = 6.37, p = 0.011) in the overall model. When further examined with post-hoc testing, the only result of significance could be attributed to the paired network of the anterior and precuneal DMN (DMN.Ant – DMN.Prec), in which being non-white predicted heightened neural connectivity. Due to participant characteristics of this study, race could not be included when modelling connectivity in MA participants, but future research should further examine this demographic variable's interactions with rsFC in both healthy and substance-using populations, as discussed further in the limitations and future research section.

Default Mode Network: Inter-Network Connectivity. When considering inter-network connectivity, the results of this small sample once again echo findings observed in MA populations and samples of other dopamine-depleted conditions, such as Parkinson's disease, ADHD, and schizophrenia (Ipser et al., 2016; Kohno et al., 2014; Delaveau et al., 2010; Castellanos et al., 2008; Whitfield-Gabrieli et al., 2009, Zhou et al., 2007, Jafri, Pearlson, Stevens, & Calhoun, 2008), as well as a sample of healthy participants with acutely-induced reduced dopamine synthesis (Carbonell et al., 2014). While healthy populations typically demonstrate anti-correlation between the DMN and so-called task-positive networks (i.e., the CCNs) (Fox et al., 2005; Fox et al., 2009), the current MA sample demonstrated hyperconnectivity between the DMN and CCNs when compared to healthy controls. In the TAU group, three of the pairwise combinations with significantly higher average connectivity values than HC involved networks of the DMN and frontoparietal

regions (DMN.Ant – Fpr.Left; DMN.Ant – Fpr.Right; DMN.Prec – Fpr.Right), with an additional one trending towards significance (DMN.Prec – Fpr.Left). These indications are useful, as they highlight the increased connectivity between the bilateral frontoparietal networks and the anterior and precuneal portions of the DMN network. While the TAU group did not demonstrate elevated connectivity coefficients between the posterior cingulate DMN and CCNs, one pairwise network in the CT group revealed significantly higher connectivity values than HC (DMN.Pcc – Fpr.Left). Despite the small sample size, these results support previous findings (Ipser et al., 2016; Kohno et al., 2014) suggesting that individuals with MUD display abnormalities of connections between the DMN and CCNs. It would be valuable to replicate these results in a study with a larger sample size in order to further expand these tentative findings of increased connectivity between elements of the DMN and frontoparietal networks, and determine whether research with larger statistical power yields differing results when considering the posterior cingulate DMN and its interactions with the frontoparietal networks.

In terms of covariates and inter-network connectivity between the DMN and CCNs, post-hoc analyses of exploratory linear regression models found level of education and duration of drug use to have a significant impact on these pairwise networks. Across all three groups, a significant negative relationship between education and connectivity was observed in five combinations of networks. These all involved connectivity between DMN and CCNs, such that not completing secondary school was associated with greater connectivity. As there was no interaction effect between group and level of education, it would appear that this effect applies to both HC and MA subjects. However, it is crucial to bear in mind that only one HC participant did not complete their secondary schooling, and as a result, this may not accurately represent education's effect on the connectivity of the groups – that is, in addition to obtaining higher levels of education, the HC group had not been affected by MA use. In

other words, what is noteworthy in these analyses is that in this sample, the anterior DMN network's relationship with bilateral frontoparietal networks as well as the salience network, and the left frontoparietal network's interaction with the posterior cingulate DMN demonstrated increased positive connectivity in participants with lower levels of education.

With regard to drug duration, a main effect on connectivity was discovered in exploratory multivariate models, and post-hoc analyses once again implicated DMN – CCN connectivity as sources of the variance: all five significant results could be attributed to DMN – CCN network connections. Unexpectedly, increased duration of drug use had an inverse relationship with connectivity coefficients in all significant pairwise combination. As the increase in neural network connectivity is associated with MA-use sequelae, one might predict that an increased duration of drug use may produce compounding heightening effects on rsFC, but this is not supported by this study's results. Conversely, Ipser et al. (2016) found no significant association between duration of drug use and connectivity in both MUD and MA-associated psychosis (MAP) participants. Thus, it is imperative that further research into the relationship between duration of drug use and intrinsic functional connectivity of people with MUD is explored, with specific reference to inter-networking of the anterior and posterior cingulate DMN and frontoparietal and salience CCNs.

Cognitive Control Networks. Analyses of between-network connectivity of the CCNs also revealed a pattern in this MA sample of inflated connectivity rates as compared to healthy controls. Pairwise combinations of the left frontoparietal networks with their contralateral counterpart and the salience network respectively comprised the majority of (between-CCN) significant results of the TAU group compared to HC (Fpr.Left – Fpr.Right,; Fpr.Left – Sal), as well as yielding the only significant inter-network CCN results in the CT group compared to HC (Fpr.Left – Fpr.Right). The TAU group demonstrated one other significant pairing compared to HC: that of the dorsal attention and salience networks. In all

cases, the average connectivity coefficients between these networks were significantly higher in the MA participants than the HC participants. The only pairwise combination between CCNs found to be affected by additional covariates in post-hoc multivariate linear models was the left and right frontoparietal pairing being impacted by level of education (Fpr.Left – Fpr.Right). In this case, not completing secondary schooling was associated with increased connectivity between these two networks. These results stand in contrast to those demonstrated in Ipser et al. (2016), in which inflated connectivity between CCNs was not demonstrated in MUD relative to healthy controls.

Although it may be expected that two studies (the present study and Ipser et al., 2016) investigating rsFMRI in DMN and CCN networks in MA users from Cape Town, South Africa, might produce highly consistent results, it has been shown that this was not the case. However, participant characteristics between these two studies differed in a number of ways, which may offer some insight into these dissimilarities. While Ipser et al. (2016) included users with a history of MAP as a group of investigation, MAP candidates were actively excluded from the parent study of this research (Brooks et al., 2016). Variables associated with MUD participants were also distinctive, such that means of abstinence in MA groups in the current study were almost triple that of Ipser et al. (2016)'s MUD (not including MAP) participants. Mean duration of drug use, as measured in years, was roughly one standard deviation (of both studies' data) higher in MUD participants of the current study as compared to Ipser et al. (2016).

Collectively, the results observed in hypothesis 3 add to the growing literature implicating hyper-connectivity of neural networks, specifically the CCNs and DMN, in drug users (Krmpotich et al., 2013; Ma et al., 2010; Wang et al., 2017). The present study identified significantly elevated connectivity coefficients, particularly within the DMN and its inter-network connections with CCNs, in people receiving treatment for MUD when

compared to HC. As well as SUD populations, this hyperconnectivity of intra- and inter-networks, particularly with reference to DMN and frontal networks has been observed in a number of conditions involving sub-optimal neural health, including traumatic brain injury and multiple sclerosis (for a review, see Hillary et al., 2015). This is not to say that the entire brain will demonstrate hyperconnectivity following neurological disruption, but rather that neural resources are usurped from certain networks as others are upregulated as a compensatory response to maintain network connectivity (Hillary et al., 2015)

Although all results of significance in this study highlighted hyperconnectivity of rsFC in patient populations, it should be noted that an absolute consensus of inflated rsFC in substance abuse does not exist in the literature. Indeed, in contrast to the results of this study, Meunier et al. (2012) found significantly reduced rsFC of the orbitofrontal cortex with dorsomedial cortex in stimulant-dependent users. Additionally, Geng et al. (2017) found decreased rsFC in elements of both the salience and default mode networks in non-treatment-seeking cocaine users relative to control and treatment-seeking cocaine groups. However, it should be noted that urine tests of Meunier et al. (2012)'s sample of cocaine and methamphetamine users revealed cannabis, benzodiazepines, tricyclic antidepressants, and morphine at the time of testing. As rsFMRI was scanned at a single timepoint, the acute effects of these substances on rsFC cannot be discounted. Moreover, it should be noted that although cocaine and MA are both stimulants, they are not identical in the manner in which they act upon the central nervous system. Thus, results are not interchangeable, as demonstrated by these differences in findings between the two substances and their effects on rsFC.

Limitations and Directions for Future Research

As mentioned throughout the study, the small sample size is a fundamental limitation of this research. Power analyses using RStudio revealed that with the current sample size, the

statistical power of the study falls short of the recommended threshold of power of 0.80 as per Cohen (1988), even when considering large effect sizes.

Given the nature of secondary analysis, a number of limitations with regard to available data were encountered, and should be noted. For instance, data on the amount and frequency of MA use in the MA groups were missing or inconsistently coded in the original data (Brooks et al., 2016). These covariates would have been of interest in multivariate linear models in the current study, but unfortunately could not be included. Future research may offer additional insights into the potential proportional associations between the amount of MA use and resting state functional connectivity over time and treatment methods.

When running statistical analyses, it should be noted that the original coding of the education variable was required to be recoded from a six-level categorical scale of highest level of education (no matric, matric, Bachelor's degree, Honours degree, Master's degree, and Doctoral degree) into a binary variable ('no matric' and 'matric plus'). Statistically sound analyses could not be run with the original unequal distribution of data across groups, as noted in the Results section. Future research should attempt to match HC and patient participants on this basis, perhaps using a continuous variable such as years of education to better understand these effects. Firstly, this could reduce potential confounds within the study. Additionally, it is important that rsFC in MA users with higher levels of education are included in future research. Wang et al. (2017) demonstrated that MA users with higher levels of education showed significantly lower risk of cognitive impairment than their counterparts with low levels of education. It would be valuable to investigate this proposed protective effect of higher education in MA users to evaluate how it may impact rsFC.

Similarly, the original coding of the categorical race variable had five levels (white, black, coloured, Indian, and other) but was recoded into a binary variable of white and non-white for the same reason. As race was statistically significant in the between-groups chi-

squared analysis of demographic variables at baseline, further analyses of race as a five-level variable would not prove to be statistically reliable or appropriate. However, as race is a factor of interest in such a study due to the demographic history of MA use, a model using a two-factor variable of white versus non-white was included in analyses, but only for HC, as detailed in the Results section. It is important to note that it is likely that it is not race, per se, that is the sole root of differences in rsFC. It is probable that race acts as a proxy for other factors such as socioeconomic status and level of education. Poverty and unemployment, factors associated with increased likelihood of substance abuse (Ramlagan et al., 2010), disproportionately affect the non-white population of South Africa (Gradin, 2013). This is particularly important, given the urgency of the MA crisis and unequal economic status across races in the South African context (Gradin, 2013). Unfortunately, data on employment and total household income was not collected in the parent study. It is possible that these unexplored factors may play a role in substance abuse behaviours, as well as be associated with differences in intrinsic functional brain connectivity, but were not disentangled from race. In order to extricate the true nature of differences between HC and people abusing drugs, future research should aim to include diverse racial representation across all groups in order to achieve a more comprehensive understanding of the extent to which the relationship between race and rsFC is mediated by these extraneous factors..

The aforementioned issues can be associated with an additional limitation related to the parent study: namely, the matching of participants. Although all participants were male, and no significant differences in age were found between groups, participants were not equivalent with respect to other variables such as race, education, and household income. As the nature of the original study was a pilot investigation, it is understandable that participant matching on the basis of multiple variables may not have been possible at the time. However, the significantly greater rsFC in the TAU group as compared to the CT group in

two pairwise combinations involving the precuneal DMN (DMN.Prec – DMN.Pcc and DMN.Prec – DMN.Ant) may further indicate that these two groups were not equivalent at baseline. It should be noted that in future, stringent matching criteria may provide a clearer view of the effects of MA use and forms of treatment.

A final limitation associated with statistical analyses for this study could be identified with regard to the univariate pre-screening of covariates, as described in Table 8. Some may view this as model over-fitting and raise concerns about sample-specific variability and decreased opportunities for replication. Ideally, a priori specification of covariates rather than univariate testing would have taken place, with specific hypotheses detailing the covariates of interest. However, the lack of significant results in the initial expected hypothesis resulted in the necessity for exploratory studies. Unfortunately, the small sample size precluded using more than one or two variables as covariates at a time in modelling. This, therefore, necessitated identification of suitable covariates, perceived to be most informative, for analysis. Additionally, a perceived issue was that the inclusion of covariates that were not associated with the outcome of interest then adding it to a model is likely to increase noise, rather than signal. If the variable does predict the outcome (even if there are no group differences) then by including it in the model information that is not being investigated is accounted for, and theoretically increases the difference between groups.

Another set of limitations may have arisen from the clinical assessment of ability to take part in the study. For ethical reasons, it was deemed necessary to evaluate whether potential participants in were able to take part in the study without their treatment being negatively affected. However, it is possible that this process may have: (1) been affected by individual clinician bias, and (2) introduced a bias of higher-functioning individuals taking part in the study by excluding less severely affected people. Although these procedures were

put in place to protect participants and maximise treatment efficacy, this should be kept in mind when considering the results of this study.

As a recommendation for future research and in light of the need for randomised, controlled trials, it should be noted that practice effects should be considered in future. In this study, WMA data (as measured by the 3-back condition of C-Ya) was only available for CT participants. As such, only within-group considerations of change in WMA were evaluated. However, if future research aims to compare between-groups WMA of CT and TAU participants, it will be necessary to take potential practice effects into account. If the CT group were to engage with the WMA measure on a daily basis as part of the intervention, while the TAU group only used it for testing purposes at pre- and post-treatment, then between-groups differences may be partially attributable to practice effects, instead of the intervention.

As a further consideration for future research, a limitation of the current study exists in the form of the lack of an independent measure of response to treatment. When conceptualising the scope of this study, the intention of including measures of symptom severity scores and/or executive functioning tasks along with the neuroimaging data as an additional independent indicator of response to treatment was discussed. However, there was concern about the oversaturation of analyses in such a small sample size. In future, the inclusion of additional measures could improve our understanding of why significant post-intervention improvements in WMA were not demonstrated in the treatment groups. These could include measures such as the Barratt Impulsivity Scale, desire for drug, perceived feelings of self-control, the Hospital Anxiety and Depression Survey, and the Self-Regulation Questionnaire. It would be helpful to examine these correlations with WMA within the MA group as a whole to better understand predictors of response.

Conclusion

This study analysed data from a parent study that examined VBM and neuropsychological outcomes of people in treatment for MUD, contrasted with HC (Brooks et al., 2016, 2017), and sought to conduct exploratory analyses of this data using rsFMRI. Despite substantial limitations regarding sample size and availability of data, this study offers glimpses of insight into previously unexplored realms of literature regarding rsFMRI in MA inpatient populations. This was conducted through analyses of clinical, demographic, and performance on WM task differences between healthy and MA-using subjects; the relationships between these covariates and rsFMRI of a WM network in people receiving additional cognitive training during inpatient treatment for MUD; and differences of rsFC between and within DMN and CCNs between healthy and MA-using participants.

WMA measures using 0- and 1-back conditions were undifferentiated between-groups at baseline and within-groups pre- and post-intervention. However, the CT group demonstrated a significant change in post-intervention scores of WMA when evaluating performance on the 3-back condition. This offers support for recent research suggesting that easier conditions of the N-back task may not reliably test all aspects of WM function. Although not significant after correcting for multiple comparisons, results tentatively suggest that rsFC of WM networks may be predictive of baseline WMA (3-back) in this sample.

As aligned with the limited research in the field, this sample demonstrates hyperconnectivity within and between intrinsic functional connectivity CCNs and DMN of MA users. This was particularly evident with reference to intra- and inter-networks involving the DMN, as well as inflated activity of the bilateral frontoparietal networks. Main effects of age, level of education, and duration of drug use were found to influence rsFC in this sample. An interaction effect of group and abstinence was also observed, but post-hoc

analyses demonstrated that this was no longer apparent when outliers in the sample were removed.

As the sample size and thus, statistical power, of this study is small, it should be noted that these are preliminary investigations and further research is crucial for unravelling the complexities of rsFC associated with MUD. This study provides a platform for evaluating future research opportunities by identifying gaps in the literature regarding the impact of clinical and demographic variables on rsFC in MA users. While the lack of similar research may be seen as a barrier in terms of interpreting this data, it should also be viewed as an opportunity to replicate this research in the future with a larger sample size in order to create a clearer and more comprehensive picture involving these exploratory findings.

Reference List

Aiello, M., Salvatore, E., Cachia, A., Pappatà, S., Cavaliere, C., Prinster, A., ... & Quarantelli, M. (2015). Relationship between simultaneously acquired resting-state regional cerebral glucose metabolism and functional MRI: a PET/MR hybrid scanner study. *Neuroimage, 113,* 111-121.

Alfonso, J., Caracuel, A., Delgado-Pastor, L., & Verdejo-García, A. (2011). Combined goal management training and mindfulness meditation improve executive functions and decision-making performance in abstinent polysubstance abusers. *Drug and Alcohol Dependence, 117*(1), 78–81. https://doi.org/10.1016/j.drugalcdep.2010.12.025

Allen, E., Erhardt, E., Damaraju, E., Gruner, W., Segall, J., Silva, R., … Calhoun, V. (2011). A Baseline for the Multivariate Comparison of Resting-State Networks. *Frontiers in Systems Neuroscience*, *5*(2011), 2. https://doi.org/10.3389/fnsys.2011.00002

Bae, S.C., Lyoo, I.K., Sung, Y.H., Yoo, J., Chung, A., Yoon, S.J., K… Renshaw, P.F. (2006). Increased white matter hyperintensities in male methamphetamine abusers. *Drug and Alcohol Dependence. 81*(1), 83–88.

Banich, M. T., & Compton, R. J. (2011). *Cognitive neuroscience (3rd ed.)*. Cengage Learning.

Barr, A., Panenka, W., Macewan, G., Thornton, A., Lang, D., Honer, W., & Lecomte, T. (2006). The need for speed: an update on methamphetamine addiction. *Journal of Psychiatry & Neuroscience : JPN*, *31*(5), 301–313.

Beatty, E. L., Jobidon, M. E., Bouak, F., Nakashima, A., Smith, I., Lam, Q., ... & Vartanian, O. (2015). Transfer of training from one working memory task to another: behavioural and neural evidence. *Frontiers in Systems Neuroscience*, *9*, 86.

Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nature Neuroscience, 8*(11), 1458–14563. https://doi.org/10.1038/nn1584

Bechara, A., & Martin, E. (2004). Impaired decision making related to working memory deficits in individuals with substance addictions. *Neuropsychology, 18*(1), 152–162. https://doi.org/10.1037/0894-4105.18.1.152

Berman, S., Voytek, B., Mandelkern, M., Hassid, B., Isaacson, A., Monterosso, J., … London, E. (2008). Changes in cerebral glucose metabolism during early abstinence from chronic methamphetamine abuse. *Molecular Psychiatry*, *13*(9), 897–908. https://doi.org/10.1038/sj.mp.4002107

Bickel, W., Yi, R., Landes, R., Hill, P., & Baxter, C. (2011). Remember the future: working memory training decreases delay discounting among stimulant addicts. *Biological Psychiatry*, *69*(3), 260–265. https://doi.org/10.1016/j.biopsych.2010.08.017

Bickel, W., Moody, L., & Quisenberry, A. (2014). Computerized working-memory training as a candidate adjunctive treatment for addiction. *Alcohol Research*, *36*(1), 123–126. Retrieved from http://search.proquest.com/docview/1685862582/

Bischoff-Grethe, A., Connolly, C., Jordan, S., Brown, G., Paulus, M., Tapert, S., … Grant, I. (2017). Altered reward expectancy in individuals with recent methamphetamine dependence. *Journal of Psychopharmacology, 31*(1), 17–30. https://doi.org/10.1177/0269881116668590

Bledowski, C., Kaiser, J., & Rahm, B. (2010). Basic operations in working memory: Contributions from functional imaging studies. *Behavioural Brain Research, 214*(2), 172–179. https://doi.org/10.1016/j.bbr.2010.05.041

Brecht, M., & Herbeck, D. (2014). Time to relapse following treatment for methamphetamine use: A long-term perspective on patterns and predictors. *Drug and Alcohol Dependence, 139*, 18-25.

Brooks, S. J., Burch, K. H., Maiorana, S. A., Cocolas, E., Schioth, H. B., Nilsson, E. K., ... & Stein, D. J. (2016). Psychological intervention with working memory training increases basal ganglia volume: a VBM study of inpatient treatment for methamphetamine use. *NeuroImage: Clinical*, *12*, 478-491.

Brooks, S., Funk, S., Young, S., & Schioth, H. (2017). The role of working memory for cognitive control in anorexia nervosa versus substance use disorder. *Frontiers In Psychology, 8,* 1651. https://doi.org/10.3389/fpsyg.2017.01651

Brooks, S. J., Wiemerslage, L., Burch, K. H., Maiorana, S. A., Cocolas, E., Schiöth, H. B., ... & Stein, D. J. (2017). The impact of cognitive training in substance use disorder: the effect of working memory training on impulse control in methamphetamine users. *Psychopharmacology*, *234*(12), 1911-1921.

Carbonell, F., Nagano-Saito, A., Leyton, M., Cisek, P., Benkelfat, C., He, Y., & Dagher, A. (2014). Dopamine precursor depletion impairs structure and efficiency of resting state brain functional networks. *Neuropharmacology*, *84*, 90-100.

Carney, T., Myers, B., Louw, J., Lombard, C., & Flisher, A. (2013). The relationship between substance use and delinquency among high-school students in Cape Town, South Africa. *Journal of Adolescence, 36*(3), 447–455. https://doi.org/10.1016/j.adolescence.2013.01.004

Castellanos, F. X., Margulies, D. S., Kelly, C., Uddin, L. Q., Ghaffari, M., Kirsch, A., ... & Milham, M. P. (2008). Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. *Biological psychiatry*, *63*(3), 332-337.

Chang, L., Cloak, C., Patterson, K., Grob, C., Miller, E., & Ernst, T. (2005). Enlarged striatum in abstinent methamphetamine abusers: A possible compensatory response. *Biological Psychiatry*, *57*(9), 967–974. https://doi.org/10.1016/j.biopsych.2005.01.039

Chen, G., Saad, Z.S., Britton, J.C., Pine, D.S. & Cox, R.W. (2013). Linear mixed-effects modeling approach to FMRI group analysis. *NeuroImage*, *73*, 176–190.

Choi, J., Lim, G., Chen, Y., & Jenkins, B. (2018). Abstinence to chronic methamphetamine switches connectivity between striatal, hippocampal and sensorimotor regions and increases cerebral blood volume response. *NeuroImage*, *174*, 364–379. https://doi.org/10.1016/j.neuroimage.2018.02.059

Chomchai, C., & Chomchai, S. (2015). Global patterns of methamphetamine use. *Current Opinion in Psychiatry*, *28*(4), 269-274.

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed). Hillsdale, N.J: L. Erlbaum Associates.

Cole, M., & Schneider, W. (2007). The cognitive control network: Integrated cortical regions with dissociable functions. *NeuroImage*, *37*(1), 343–360. https://doi.org/10.1016/j.neuroimage.2007.03.071

Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., & Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. *Nature Neuroscience*, *16*(9), 1348.

Constantinidis, C., & Klingberg, T. (2016). The neuroscience of working memory capacity and training. *Nature Reviews Neuroscience*, *17*(7), 438–43849. https://doi.org/10.1038/nrn.2016.43

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, *3*(3), 201-215.

Courtney, K., & Ray, L. (2014). Methamphetamine: An update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. *Drug and Alcohol Dependence*, *143*(1), 11–21. https://doi.org/10.1016/j.drugalcdep.2014.08.003

Damoiseaux, J. (2017). Effects of aging on functional and structural brain connectivity. *NeuroImage*, *160*, 32–40.

Delaveau, P., Salgado-Pineda, P., Fossati, P., Witjas, T., Azulay, J. P., & Blin, O. (2010). Dopaminergic modulation of the default mode network in Parkinson's disease. *European Neuropsychopharmacology*, *20*(11), 784-792.

Daumann, J., Koester, P., Becker, B., Wagner, D., Imperati, D., Gouzoulis-Mayfrank, E., & Tittgemeyer, M. (2011). Medial prefrontal gray matter volume reductions in users of amphetamine-type stimulants revealed by combined tract-based spatial statistics and voxel-based morphometry. *NeuroImage*, *54*(2), 794–801. https://doi.org/10.1016/j.neuroimage.2010.08.065

Dawe, S., Davis, P., Lapworth, K., McKetin, R., 2009. Mechanisms underlying aggres- sive and hostile behavior in amphetamine users. *Current Opinion in Psychiatry 22*, 269–273.

Dean, A. C., Groman, S. M., Morales, A. M., & London, E. D. (2013). An evaluation of the evidence that methamphetamine abuse causes cognitive decline in humans. *Neuropsychopharmacology*, *38*(2), 259-274.

Elkashef, A., Vocci, F., Hanson, G., White, J., Wickes, W., & Tiihonen, J. (2008). Pharmacotherapy of methamphetamine addiction: An update. *Substance Abuse, 29(*3), 31–49. https://doi.org/10.1080/08897070802218554

Ersche, K. D., Jones, P. S., Williams, G. B., Smith, D. G., Bullmore, E. T., & Robbins, T. W. (2013). Distinctive personality traits and neural correlates associated with stimulant drug use versus familial risk of stimulant dependence. *Biological Psychiatry, 74*(2), 137–144.

Esteban, O., Blair, R., Markiewicz, C., Berleant, S., Moodie, C., Ma, F., … Gorgolewski, K. (2016). *Poldracklab/Fmriprep: 1.0.0-Rc5*. Zenodo. https://doi.org/10.5281/zenodo.996169

Farras-Permanyer, L., Mancho-Fora, N., Montalà-Flaquer, M., Bartrés-Faz, D., Vaqué-Alcázar, L., Peró-Cebollero, M., & Guàrdia-Olmos, J. (2019). Age-related changes in resting-state functional connectivity in older adults. *Neural Regeneration Research, 14*(9), 1544.

Fernández-Serrano, M., Pérez-García, M., & Verdejo-García, A. (2011). What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance? *Neuroscience and Biobehavioral Reviews*, *35*(3), 377–406. https://doi.org/10.1016/j.neubiorev.2010.04.008

Fassbender, C., Lesh, T., Ursu, S., & Salo, R. (2015). Reaction Time Variability and Related Brain Activity in Methamphetamine Psychosis. *Biological Psychiatry*, *77*(5), 465–474. https://doi.org/10.1016/j.biopsych.2014.07.028

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences*, *102*(27), 9673-9678.

Fox, M. D., Zhang, D., Snyder, A. Z., & Raichle, M. E. (2009). The global signal and observed anticorrelated resting state brain networks. *Journal of neurophysiology*, *101*(6), 3270-3283.

Geng, X., Hu, Y., Gu, H., Salmeron, B. J., Adinoff, B., Stein, E. A., & Yang, Y. (2017). Salience and default mode network dysregulation in chronic cocaine users predict treatment outcome. *Brain*, *140*(5), 1513-1524.

Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry*, *159*(10), 1642-1652.

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature reviews neuroscience*, *12*(11), 652-669.

Gonçalves, P., Ometto, M., Bechara, A., Malbergier, A., Amaral, R., Nicastri, S., … Cunha, P. (2014). Motivational interviewing combined with chess accelerates improvement in executive functions in cocaine dependent patients: A one-month prospective study. *Drug and Alcohol Dependence, 141*, 79–84. https://doi.org/10.1016/j.drugalcdep.2014.05.006

Gonzales, R., Mooney, L., Rawson, R.A., 2010. The methamphetamine problem in the United States. *Annual Review of Public Health, 31*, 385–398.\

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., ... & Schatzberg, A. F. (2007). Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biological psychiatry*, *62*(5), 429-437.

Gradin, C. (2013). Race, poverty and deprivation in South Africa. *Journal of African Economies*, *22*(2), 187-238.

Guerra-Carrillo, B., Mackey, A., & Bunge, S. (2014). Review of resting-state fMRI: A window into human brain plasticity. *The Neuroscientist, 20*(5), 522–533. https://doi.org/10.1177/1073858414524442

Halpin, L., Collins, S., & Yamamoto, B. (2014). Neurotoxicity of methamphetamine and 3,4-methylenedioxymethamphetamine. *Life Sciences*, *97*(1), 37–44. https://doi.org/10.1016/j.lfs.2013.07.014

Hart, C. L., Marvin, C. B., Silver, R., & Smith, E. E. (2012). Is cognitive functioning impaired in methamphetamine users? A critical review. *Neuropsychopharmacology, 37*(3), 586-608.

Henry, B., Minassian, A., & Perry, W. (2010). Effect of methamphetamine dependence on everyday functional ability. *Addictive Behaviors*, *35*(6), 593–598. https://doi.org/10.1016/j.addbeh.2010.01.013

Herman-Stahl, M. A., Krebs, C. P., Kroutil, L. A., & Heller, D. C. (2007). Risk and protective factors for methamphetamine use and nonmedical use of prescription stimulants among young adults aged 18 to 25. *Addictive Behaviors*, *32*(5), 1003-1015.

Hillary, F. G., Roman, C. A., Venkatesan, U., Rajtmajer, S. M., Bajo, R., & Castellanos, N. D. (2015). Hyperconnectivity is a fundamental response to neurological disruption. *Neuropsychology*, *29*(1), 59.

Hoffman, W., Schwartz, D., Huckans, M., McFarland, B., Meiri, G., Stevens, A., & Mitchell, S. (2008). Cortical activation during delay discounting in abstinent methamphetamine dependent individuals. *Psychopharmacology, 201*(2), 183–193. https://doi.org/10.1007/s00213-008-1261-1

Homer, B., Solomon, T., Moeller, R., Mascia, A., DeRaleau, L., & Halkitis, P. (2008). Methamphetamine Abuse and Impairment of Social Functioning: A Review of the Underlying Neurophysiological Causes and Behavioral Implications. *Psychological Bulletin*, *134*(2), 301–310. https://doi.org/10.1037/0033-2909.134.2.301

Howells, F., Uhlmann, A., Temmingh, H., Sinclair, H., Meintjes, E., Wilson, D., & Stein, D. (2014). 1H-magnetic resonance spectroscopy (1H-MRS) in methamphetamine dependence and methamphetamine induced psychosis. *Schizophrenia Research*, *153*(1-3), 122–128. https://doi.org/10.1016/j.schres.2014.01.029

Ipser, J. C., Uhlmann, A., Taylor, P., Harvey, B. H., Wilson, D., & Stein, D. J. (2018). Distinct intrinsic functional brain network abnormalities in methamphetamine-dependent patients with and without a history of psychosis. *Addiction Biology*, *23*(1), 347-358.

Jafri, M. J., Pearlson, G. D., Stevens, M., & Calhoun, V. D. (2008). A method for functional network connectivity among spatially independent resting-state components in schizophrenia. *Neuroimage, 39*(4), 1666-1681.

Jan, R., Kydd, R., & Russell, B. (2012). Functional and Structural Brain Changes Associated with Methamphetamine Abuse. *Brain Sciences*, *2*(4), 434–482. https://doi.org/10.3390/brainsci2040434

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). FSL. *Neuroimage*, *62*(2), 782-790.

Jernigan, T., Gamst, A., Archibald, S., Fennema-Notestine, C., Mindt, M., Marcotte, T., … Grant, I. (2005). Effects of methamphetamine dependence and HIV infection on cerebral morphology. *American Journal Of Psychiatry, 162*(8), 1461–1472. https://doi.org/10.1176/appi.ajp.162.8.1461

Karila, L., Weinstein, A., Aubin, H., Benyamina, A., Reynaud, M., & Batki, S. (2010). Pharmacological approaches to methamphetamine dependence: a focused review. *British Journal of Clinical Pharmacology, 69*(6), 578–592. https://doi.org/10.1111/j.1365-2125.2010.03639.

Keshavan, M., Vinogradov, S., Rumsey, J., Sherrill, J., & Wagner, A. (2014). Cognitive Training in Mental Disorders: Update and Future Directions. *American Journal Of Psychiatry, 171*(5), 510–522. https://doi.org/10.1176/appi.ajp.2013.13081075

Kirchner, W.K., 1958. Age differences in short-term retention of rapidly changing information. *Journal of Experimental Psychology, 55* (4), 352–358.

Krmpotich, T., Tregellas, J., Thompson, L., Banich, M., Klenk, A., & Tanabe, J. (2013). Resting-state activity in the left executive control network is associated with behavioral approach and is increased in substance dependence. *Drug and Alcohol Dependence, 129*(1-2), 1–7. https://doi.org/10.1016/j.drugalcdep.2013.01.021

Kohno, M., Morales, A. M., Ghahremani, D. G., Hellemann, G., & London, E. D. (2014). Risky decision making, prefrontal cortex, and mesocorticolimbic functional connectivity in methamphetamine dependence. *JAMA Psychiatry*, *71*(7), 812-820.

Kohno, M., Okita, K., Morales, A. M., Robertson, C. L., Dean, A. C., Ghahremani, D. G., ... & London, E. D. (2016). Midbrain functional connectivity and ventral striatal dopamine D2-type receptors: link to impulsivity in methamphetamine users. *Molecular Psychiatry*, *21*(11), 1554.

Kohno, M., Loftis, J., Huckans, M., Dennis, L., Mccready, H., & Hoffman, W. (2018). The relationship between interleukin-6 and functional connectivity in methamphetamine users. *Neuroscience Letters*, *677*, 49–54.

Kruskal, W. H., & Wallis, W. A. (1952). Use of ranks in one-criterion variance analysis. *Journal of the American Statistical Association*, *47*(260), 583-621.

Levene, H. (1961). Robust tests for equality of variances. *Contributions to probability and statistics*, 279-292.

Li, X., Su, H., Zhong, N., Chen, T., Du, J., Xiao, K., ... & Zhao, M. (2020). Aberrant Resting-State Cerebellar-Cerebral Functional Connectivity in Methamphetamine-Dependent Individuals After Six Months Abstinence. *Frontiers in Psychiatry*, *11*, 191.

London, E. D., Kohno, M., Morales, A. M., & Ballard, M. E. (2015). Chronic methamphetamine abuse and corticostriatal deficits revealed by neuroimaging. *Brain Research*, *1628*, 174-185.

Ma, N., Liu, Y., Li, N., Wang, C. X., Zhang, H., Jiang, X. F., ... & Zhang, D. R. (2010). Addiction related alteration in resting-state brain connectivity. *Neuroimage*, *49*(1), 738-744.

Malcolm, R., Myrick, H., Li, X., Henderson, S., Brady, K. T., George, M. S., & See, R. E. (2016). Regional Brain Activity in Abstinent Methamphetamine Dependent Males Following Cue Exposure. *Journal of Drug Abuse, 2*(1), 16. https://doi.org/10.21767/2471-853x.100016

Martin, J.H. (2012). *Neuroanatomy text and atlas (4th ed.).* McGraw-Hill Education.

Mars, R. B., Neubert, F. X., Noonan, M. P., Sallet, J., Toni, I., & Rushworth, M. F. (2012). On the relationship between the "default mode network" and the "social brain". *Frontiers in Human Neuroscience, 6*, 189.

Maxwell, J., & Brecht, M. (2011). Methamphetamine: Here we go again? *Addictive Behaviors, 36*(12), 1168–1173. https://doi.org/10.1016/j.addbeh.2011.07.017

McClure, S., & Bickel, W. (2014). A dual-systems perspective on addiction: contributions from neuroimaging and cognitive training. *Annals of the New York Academy of Sciences, 1327*(1), 62–78. https://doi.org/10.1111/nyas.12561

Meade, C., Towe, S., Watt, M., Skinner, D., Myers, B., Kimani, S., … Pieterse, D. (2015). Addiction and barriers to treatment in a sample of community-recruited methamphetamine users in a South African township. *Drug and Alcohol Dependence, 146*, e37–e37. https://doi.org/10.1016/j.drugalcdep.2014.09.472

Melby-Lervåg, M., Redick, T., & Hulme, C. (2016). Working memory training does not improve performance on measures of intelligence or other measures of "far transfer": Evidence from a meta-analytic review. *Perspectives on Psychological Science, 11*(4), 512–534. https://doi.org/10.1177/1745691616635612

Meredith, W., Jaffe, J., Ang-Lee, J., & Saxon, J. (2005). Implications of chronic methamphetamine use: a literature review. *Harvard Review of Psychiatry, 13*(3), 141–154. https://doi.org/10.1080/10673220591003605

Meunier, D., Ersche, K. D., Craig, K. J., Fornito, A., Merlo-Pich, E., Fineberg, N. A., ... & Bullmore, E. T. (2012). Brain functional connectivity in stimulant drug dependence and obsessive–compulsive disorder. *Neuroimage*, *59*(2), 1461-1468.

Miller WR, Brown JM. Self-regulation as a conceptual basis for the prevention and treatment of addictive behaviors. In: Heather N, Miller WR, Greely J, editors. Self-control and the addictive behaviours. Sydney: Maxwell Macmillan; 1991. pp. 3–79.

Monterosso, J.R., Ainslie, G., Xu, J., Cordova, X., Domier, C.P., & London, E.D. (2007). Frontoparietal cortical activity of methamphetamine-dependent and comparison subjects performing a delay discounting task. *Human Brain Mapping, 28* (5), 383-393.

Moszczynska, A. (2016). Neurobiology and clinical manifestations of methamphetamine neurotoxicity. *The Psychiatric Times*, *33*(9), 16–18.

Mushanyu, J., Nyabadza, F., & Stewart, A. G. R. (2015). Modelling the trends of inpatient and outpatient rehabilitation for methamphetamine in the Western Cape province of South Africa. *BMC Research Notes*, *8*(1), 797.

Nestor, L., Ghahremani, D., Monterosso, J., & London, E. (2011). Prefrontal hypoactivation during cognitive control in early abstinent methamphetamine-dependent subjects. *Psychiatry Research: Neuroimaging*, *194*(3), 287–295. https://doi.org/10.1016/j.pscychresns.2011.04.010

Oh, J., Lyoo, I., Sung, Y., Hwang, J., Kim, J., Chung, A., … Song, I. (2005). Shape changes of the corpus callosum in abstinent methamphetamine users. *Neuroscience Letters*, *384*(1), 76–81. https://doi.org/10.1016/j.neulet.2005.04.082

Olesen, P.J., Westerberg, H., Klingberg, T., 2003. Increased prefrontal and parietal activity after training of working memory. *Nature Neuroscience, 7* (1), 75.

Parry, C. D., Myers, B., Morojele, N. K., Flisher, A. J., Bhana, A., Donson, H., & Plüddemann, A. (2004). Trends in adolescent alcohol and other drug use: findings from three sentinel sites in South Africa (1997–2001). *Journal of Adolescence*, *27*(4), 429–440.

Panenka, W. J., Procyshyn, R. M., Lecomte, T., MacEwan, G. W., Flynn, S. W., Honer, W. G., & Barr, A. M. (2013). Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings. *Drug and Alcohol Dependence*, *129*(3), 167-179.

Paulus, M., Tapert, S., & Schuckit, M. (2005). Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. *Archives of General Psychiatry, 62*(7), 761–768. https://doi.org/10.1001/archpsyc.62.7.761

Peltzer, K., Ramlagan, S., Johnson, B., & Phaswana-Mafuya, N. (2010). Illicit Drug Use and Treatment in South Africa: A Review. *Substance Use & Misuse*, *45*(13), 2221–2243. https://doi.org/10.3109/10826084.2010.481594

Petersen, I., & Lund, C. (2011). Mental health service delivery in South Africa from 2000 to 2010 : one step forward, one step back. *South African Medical Journal, 101*(10), 751–757. https://doi.org/10.7196/SAMJ.4841

Plüddemann, A., Myers, B. J., & Parry, C. D. (2008). Surge in treatment admissions related to methamphetamine use in Cape Town, South Africa: implications for public health. *Drug and Alcohol Review*, *27*(2), 185-189.

Plüddemann, A., Flisher, A., Mcketin, R., Parry, C., & Lombard, C. (2010). Methamphetamine use, aggressive behavior and other mental health issues among

high-school students in Cape Town, South Africa. *Drug and Alcohol Dependence, 109*(1-3), 14–19. https://doi.org/10.1016/j.drugalcdep.2009.11.021

Potvin, S., Pelletier, J., Grot, S., Hébert, C., Barr, A., & Lecomte, T. (2018). Cognitive deficits in individuals with methamphetamine use disorder: a meta-analysis. *Addictive Behaviors, 80,* 154-160.

Rac-Lubashevsky, R., & Kessler, Y. (2016). Decomposing the n-back task: An individual differences study using the reference-back paradigm. *Neuropsychologia, 90,* 190-199.

Raichle, M. E. (2015). The brain's default mode network. *Annual Review of Neuroscience, 38,* 433-447.

Ramlagan, S., Peltzer, K., & Matseke, G. (2010). Epidemiology of drug abuse treatment in South Africa. *South African Journal of Psychiatry, 16*(2), 40–49. https://doi.org/10.4102/sajpsychiatry.v16i2.172

Research Imaging Institute, UTHSCSA (2013). *Multi-image Analysis GUI.* Research Imaging Institute, University of Texas Health Science Center. http://rii.uthscsa.edu/mango/index.html

Roos, A., Jones, G., Howells, F., Stein, D., & Donald, K. (2014). Structural brain changes in prenatal methamphetamine-exposed children. *Metabolic Brain Disease, 29*(2), 341–349. https://doi.org/10.1007/s11011-014-9500-0

Rusyniak, D. (2013). Neurologic manifestations of chronic methamphetamine abuse. *The Psychiatric Clinics of North America, 36*(2), 261–275. https://doi.org/10.1016/j.psc.2013.02.005

RStudio Team (2020). *RStudio: Integrated Development for R. RStudio*, PBC, Boston, MA. http://www.rstudio.com/.

Sabrini, S., Wang, G., Lin, J., Ian, J., & Curley, L. (2019). Methamphetamine use and cognitive function: A systematic review of neuroimaging research. *Drug and Alcohol Dependence*, *194*, 75–87. https://doi.org/10.1016/j.drugalcdep.2018.08.041

Salo, R., Fassbender, C., Buonocore, M., & Ursu, S. (2012). Behavioral regulation in methamphetamine abusers: An fMRI study. *Psychiatry Research: Neuroimaging*, *211*(3), 234–238. https://doi.org/10.1016/j.pscychresns.2012.10.003

Salo R., & Fassbender C. (2011) Structural, Functional and Spectroscopic MRI Studies of Methamphetamine Addiction. In Carter C., Dalley J. (eds), *Brain Imaging in Behavioral Neuroscience.* (pp. 321-364). Springer, Berlin, Heidelberg

Salo, R., Nordahl, T., Galloway, G., Moore, C., Waters, C., & Leamon, M. (2009). Drug abstinence and cognitive control in methamphetamine-dependent individuals. *Journal of Substance Abuse Treatment*, *37*(3), 292–297. https://doi.org/10.1016/j.jsat.2009.03.004

Scott, J., Woods, S., Matt, G., Meyer, R., Heaton, R., Atkinson, J., & Grant, I. (2007). Neurocognitive effects of methamphetamine: A critical review and meta-analysis. *Neuropsychology Review*, *17*(3), 275–297. https://doi.org/10.1007/s11065-007-9031-0

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., ... & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience*, *27*(9), 2349-2356.

Shapiro, S. S., & Wilk, M. B. (1965). An analysis of variance test for normality (complete samples). *Biometrika*, *52*(3/4), 591-611.

Shipstead, Z., Redick, T., & Engle, R. (2012). Is working memory training effective? *Psychological Bulletin, 138*(4), 628–654. https://doi.org/10.1037/a0027473

Soares, J., Magalhães, R., Moreira, P., Sousa, A., Ganz, E., Sampaio, A., … Sousa, N. (2016). A hitchhiker's guide to functional magnetic resonance imaging. *Frontiers in Neuroscience, 10,* 515. https://doi.org/10.3389/fnins.2016.00515

South African Community Epidemiology Network on Drug Use, 2014. *Monitoring Alcohol, Tobacco and Drug Abuse Treatment Admissions in South Africa (Phase 37*). Retrieved from http://www.mrc.ac.za/sites/default/files/attachments/2016-06-28/SacenduReportJune2015.pdf

South African Community Epidemiology Network on Drug Use, 2018. *Monitoring Alcohol, Tobacco and Drug Abuse Treatment Admissions in South Africa (Phase 43*). Retrieved from http://www.samrc.ac.za/sites/default/files/attachments/2018-11-05/SACENDUBriefPhase43.pdf

South African Community Epidemiology Network on Drug Use, 2019. *Monitoring Alcohol, Tobacco and Drug Abuse Treatment Admissions in South Africa* (Research Update). Retrieved from http://www.samrc.ac.za/sites/default/files/attachments/2019-03-04/SACENDUupdateJan2019.pdf

Stevens, L., Verdejo - Garcia, A., Goudriaan, A., Roeyers, H., Dom, G., & Vanderplasschen, W. (2014). Impulsivity as a vulnerability factor for poor addiction treatment outcomes: a review of neurocognitive findings among individuals with substance use disorders. *Journal of Substance Abuse Treatment*(1), 58–72. https://doi.org/10.1016/j.jsat.2014.01.008

Stoneberg, D. M., Shukla, R. K., & Magness, M. B. (2018). Global methamphetamine trends: an evolving problem. *International Criminal Justice Review*, *28*(2), 136-161.

Sutherland, M. T., McHugh, M. J., Pariyadath, V., & Stein, E. A. (2012). Resting state functional connectivity in addiction: lessons learned and a road ahead. *Neuroimage*, *62*(4), 2281-2295.

Taylor, P.A., & Saad, Z.S. (2013). FATCAT: (An Efficient) Functional and Tractographic Connectivity Analysis Toolbox. *Brain Connectivity 3*(5):523-535.

Taylor, P. A., Chen, G., Cox, R. W., & Saad, Z. S. (2016). Open environment for multimodal interactive connectivity visualization and analysis. *Brain connectivity*, *6*(2), 109-121.

Thanos, P., Kim, R., Delis, F., Rocco, M., Cho, J., & Volkow, N. (2017). Effects of chronic methamphetamine on psychomotor and cognitive functions and dopamine signaling in the brain. *Behavioural Brain Research*, *320*, 282–290. https://doi.org/10.1016/j.bbr.2016.12.010

Thompson, P. M., Hayashi, K. M., Simon, S. L., Geaga, J. A., Hong, M. S., Sui, Y., ... & London, E. D. (2004). Structural abnormalities in the brains of human subjects who use methamphetamine. *Journal of Neuroscience*, *24*(26), 6028-6036.

Tian, L., Jiang, T., Wang, Y., Zang, Y., He, Y., Liang, M., ... & Zhuo, Y. (2006). Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. *Neuroscience letters*, *400*(1-2), 39-43.

United Nations Office on Drugs and Crime, 2012. *World Drug Report.* Retrieved from https://www.unodc.org/documents/data-and analysis/WDR2012/WDR_2012_web_small.pdf

United Nations Office on Drugs and Crime, 2013. *World Drug Report.* Retrieved from https://www.unodc.org/unodc/secured/wdr/wdr2013/World_Drug_Report_2013.pdf

United Nations Office on Drugs and Crime, 2014. *World Drug Report.* Retrieved from https://www.unodc.org/documents/AnnualReport2014/Annual_Report_2014_WEB.pdf

United Nations Office on Drugs and Crime, 2016. *World Drug Report.* Retrieved from https://www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf

Valls-Serrano, C., Caracuel, A., & Verdejo-Garcia, A. (2016). Goal management training and mindfulness meditation improve executive functions and transfer to ecological tasks of daily life in polysubstance users enrolled in therapeutic community treatment. *Drug and Alcohol Dependence*, *165*, 9–14. https://doi.org/10.1016/j.drugalcdep.2016.04.040

Van Den Heuvel, M. P., & Hulshoff Pol, H. E.(2010). Exploring the brain network: a review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology*, *20*(8), 519-534.

Vearrier, D., Greenberg, M., Miller, S., Okaneku, J., & Haggerty, D. (2012). Methamphetamine: History, Pathophysiology, Adverse Health Effects, Current Trends, and Hazards Associated with the Clandestine Manufacture of Methamphetamine. *Disease-a-Month*, *58*(2), 38–89. https://doi.org/10.1016/j.disamonth.2011.09.004

Verdejo-Garcia, A. (2016). Cognitive training for substance use disorders: Neuroscientific mechanisms. *Neuroscience and Biobehavioral Reviews*, *68*, 270–281. https://doi.org/10.1016/j.neubiorev.2016.05.018

Vincent, J. L., Kahn, I., Snyder, A. Z., Raichle, M. E., & Buckner, R. L. (2008). Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *Journal of Neurophysiology*, *100*(6), 3328-3342.

Vinogradov, S., Fisher, M., & de Villers-Sidani, E. (2012). Cognitive training for impaired neural systems in neuropsychiatric illness. *Neuropsychopharmacology*, *37*(1), 43.

Vocci, F. J. (2008). Cognitive remediation in the treatment of stimulant abuse disorders: A research agenda. *Experimental and Clinical Psychopharmacology*, *16*(6), 484–497.

Volkow, N.D., Fowler, J.S., Wang, G.J., Shumay, E., Telang, F., Thanos, P.K., Alexoff, D. (2010). Distribution and pharmacokinetics of methamphetamine in the human body: clinical implications. *PLoS One, 5*(12).

Wang, T. Y., Fan, T. T., Bao, Y. P., Li, X. D., Liang, C. M., Wang, R. J., ... & Lu, L. (2017). Pattern and related factors of cognitive impairment among chronic methamphetamine users. *The American Journal on Addictions*, *26*(2), 145-151.

Watt, M. H., Meade, C. S., Kimani, S., MacFarlane, J. C., Choi, K. W., Skinner, D., ... & Sikkema, K. J. (2014). The impact of methamphetamine ("tik") on a peri-urban community in Cape Town, South Africa. *International Journal of Drug Policy*, *25*(2), 219-225.

Weafer, J., Van Hedger, K., Keedy, S., Nwaokolo, N., & de Wit, H. (2019). Methamphetamine acutely alters frontostriatal resting state functional connectivity in healthy young adults. *Addiction Biology*, e12775. https://doi.org/10.1111/adb.12775

Wesley, M., & Bickel, W. (2014). Remember the future II: Meta-analyses and functional overlap of working memory and delay discounting. *Biological Psychiatry*, *75*(6), 435-448.

Weybright, E. H., Caldwell, L. L., Wegner, L., Smith, E., & Jacobs, J. J. (2016). The state of methamphetamine ('tik') use among youth in the Western Cape, South Africa. *South African Medical Journal*, *106*(11), 1125-1128.

Whitfield-Gabrieli, S., Thermenos, H. W., Milanovic, S., Tsuang, M. T., Faraone, S. V., McCarley, R. W., ... & Seidman, L. J. (2009). Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proceedings of the National Academy of Sciences*, *106*(4), 1279-1284.

Wilcoxon, F. (1945). *Individual comparisons by ranking methods. Biometrics Bulletin 1* (6), 80–83.

Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C., & Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods*, *8*(8), 665-670. doi: http://dx.doi.org.ezproxy.uct.ac.za/10.1038/NMETH.1635

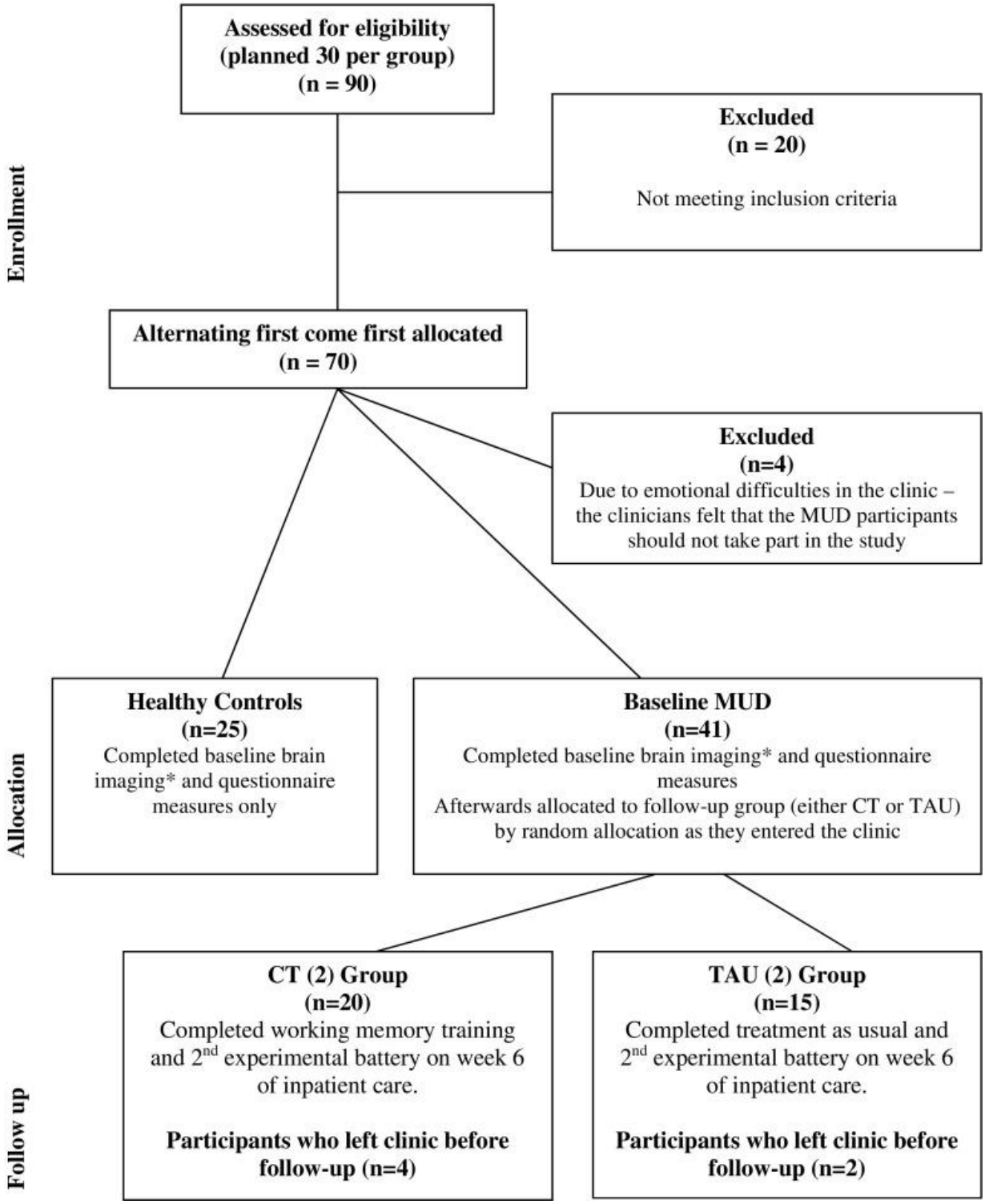
Zhong, N., Jiang, H., Du, J., Zhao, Y., Sun, H., Xu, D., … Zhao, M. (2016). The cognitive impairments and psychological wellbeing of methamphetamine dependent patients compared with health controls. *Progress in Neuropsychopharmacology & Biological Psychiatry*, *69*, 31–37. https://doi.org/10.1016/j.pnpbp.2016.04.005

Zhou, Y., Liang, M., Tian, L., Wang, K., Hao, Y., Liu, H., ... & Jiang, T. (2007). Functional disintegration in paranoid schizophrenia using resting-state fMRI. *Schizophrenia Research*, *97*(1-3), 194-205.

Zillmer, E., Spiers, M., & Culbertson, W. (2008). *Principles of neuropsychology (2nd ed.).* Belmont, CA: Cengage Learning.

Appendices

Appendix A: CONSORT Diagram – Parent Study Design



Appendix B: Treatment Programme at Maitland Treatment Centre

Supplementary Table – Timetable of patient treatment plan at the inpatient rehabilitation centre in Cape Town, South Africa. Of note, daily timeline is represented as beginning at first cell of each daily column (e.g. from 8am after breakfast until 5pm before supper).

Week	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
1	Admission of new patients	Overview of programme and expectations/taking responsibility	Who am I?	Drug addiction and other mental illnesses	Dealing with boredom	Martial Arts/therapeutic duties	Homework
	Psycho-education	Boundaries and consequences	Patterns of use and completion of DUDIT	Setting of goals	Psycho-education	Step work	Diary writing
	Motivation for treatment	Exploring the meaning of fraternization	Importance of recreational activities	Discussion and completion of individual development plan	Arts and crafts	Therapeutic duties	Life histories
	Personal hygiene	Psycho-education	Arts and craft games	Healthy eating habits	Arts and crafts	Physical training	Quiet time
	Art/crafts/Martial Arts	Physical Training	Games/arts and crafts	Physical training	Arts and crafts	Recreation	Recreation
2	Reflection on Week 1	Trust building exercise	Cycle of change	Mindfulness exercise	DBT	Martial arts/therapeutic duties	Homework Diary writing
	Talking about drug effects and withdrawal symptoms	Giving and receiving feedback	Introduction to DBT	Talking about drugs – triggers and cravings	Psycho-education	Step work	Life histories
	Psycho-education	Culture of addiction	Respect for self and respect for others	Relapse justification	Arts/crafts	Therapeutic duties	Quiet time
	Feelings vs. thoughts	Psycho-education	Arts/Craft/Games	Physical training	Arts/crafts	Physical training	Recreation
3	Group therapy	Group therapy	Group therapy	Group therapy	Group therapy	Martial arts/therapeutic duties	Homework
	Talking about drugs	DBT: emotional model	DBT: emotional mind	DBT: emotional mind	Psycho-education	Step work	Diary writing
	Motivation for recovery	Active listening	Communication skills	Giving and receiving feedback		Therapeutic duties	Life histories
	Relaxation	Psycho-education	Giving and receiving feedback	Styles of communication	Arts and crafts	Physical training	Visitations
	Arts/crafts/ martial arts	Physical training	Games	Physical training		Recreation	Recreation
4	Group therapy	Group therapy	Group therapy	Group therapy	Group therapy	Martial arts/therapeutic duties	Homework
	Talking about drugs	DBT: 3 minds, rational mind	DBT: 3 minds, rational mind	DBT: balanced mind	Psycho-education	Step work	Diary writing
	Assertiveness training	Anger management	Conflict management	Parenting skills	Arts/crafts	Therapeutic duties	Life histories
	Styles of communication and role play	Psycho-education	Problem solving	Parenting skills		Physical training	Visitations
	Arts/crafts/ martial arts	Physical training	Games	Physical training		Recreation	Recreation
5	Group therapy	Therapeutic outing	Group therapy	Group therapy	Group therapy	Therapeutic home visits	Therapeutic home visits
	Talking about drugs	Therapeutic outing	DBT: Roleplay	DBT: Balanced mind	Psycho-education		
	Spirituality	What is stress?	Managing stress	Parenting skills			

Appendix C: Informed Consent Form - Parent Study

Brain responses during MRI scan in those who use methamphetamine (MA) or "tik".

You are asked to participate in a research study conducted by:

Prof. Dan J. Stein: dan.stein@uct.ac.za
Dr. Samantha J. Brooks: drsamanthabrooks@gmail.com

Department of Psychiatry and Mental Health, University of Cape Town.

Your participation in this study is entirely voluntary. Please read the information below and ask questions about anything you do not understand, before deciding whether or not to participate.

You have been asked to participate in this study because we would like to try to better understand the brain processes that help a person to control their drug addiction. To do this we need to recruit both healthy participants who have never used methamphetamine (MA or "tik"), and people who are currently undergoing early-stage treatment for MA addiction. All participants will receive a food voucher for each brain scan.

- **PURPOSE OF THE STUDY**

It is currently unclear how drug addiction and specific ways of thinking are associated with brain functions. In other fields of neuroscience (e.g. eating disorders), it seems that a specific way of thinking is linked to a better ability to have greater self-control over our cravings. This was of thinking is linked to a specific brain region. With this knowledge in mind, we want to use a simple "brain game" that uses this part of the brain to try to strengthen self control, so that treatment for drug addiction might work better. Also, if this works, people with a tendency to want to take drugs can use this simple brain game at home, to help strengthen their resolve not to start taking the drug again.

- **PROCEDURES**

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

a) If you are currently receiving treatment for MA addiction, we will at first ask you to come to the brain scan facilities at the hospital, and take part in a completely safe brain scan (an MRI). We will make arrangements to collect you from and return you to the clinic.

b) One month before attending the hospital for a second brain scan, we will ask some of you who are residents at a local treatment facility for MA addiction, to do a daily training on a computer, involving a fun brain training task. This task requires that participants look at the computer screen, and press a button when the current letter on the screen is the same as one shown before. Clinicians and researchers at the treatment facility will support us in helping you to learn this task.

c) Some of you who are receiving treatment for MA addiction will not do this task before the brain scan, but will be offered the chance to do it after the brain scans.

d) If you are a healthy control who is not receiving treatment for MA addiction, with no previous lifetime history of drug abuse, we will provide you with directions to the brain scan facilities, or will help with your transport if it is difficult for you. You will not be required to do any brain training before the scan, but will do the same task during one brain scan.

e) Before going into the brain scanner at the clinic, all participants will first be asked some basic questions about their general feelings on the day, as well as basic information about age, education etc.

f) The task inside the scanner will then be fully explained to you by a researcher. It will be the same task that the people attending the clinic for MA addiction will be trained to do. But all participants will be given a full explanation of the task before entering the scanner. Simply, all participants will see letters appearing on a screen in front of them in the scanner. They will be given a button box to press when the current letter on the screen is the same as the one shown before. Therefore, participants must try to concentrate as hard as possible on the sequence of the letters. The total time in the brain scanner will be approximately half an hour.

g) At the end of the brain scan all participants will be given a questionnaire booklet to complete within an hour at the hospital.
h) Those who take part in the brain training programme while attending the clinic for MA addiction will be invited back to the hospital for a second brain scan one month later.
i) All participants will receive a food voucher for each brain scan that they participate in.
j) If a participant feels uncomfortable at any time during any part of this study (both inside and outside the brain scan), they are free to withdraw at any time, and their personal or medical rights will not be affected. All data collected from participants will remain completely confidential at all times. Participants can receive information about the results of our study by contacting us on the emails given above.

- **POTENTIAL RISKS AND DISCOMFORTS**

There are no dangers in taking part in an MRI scan. It is one of the safest ways currently to measure what is going on inside the brain. However, some people find the brain scan a little noisy, and sometimes a little cold. To account for this, we will provide ear plugs and a blanket to keep you warm. 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 indicate to us by pressing the button. There will be radiologists and researchers close by to assist you at all times.

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

It is highly likely, based on results from previous research, that doing brain training in this way will alter the way your brain functions, in a healthy way, so that you can use more self-control in general, or to lower drug taking. However, this is not yet known. Hopefully, you will be participating in a study that provides evidence for this. If this is shown, your participation in this study will help to improve the lives of many people who currently battle with drug addiction.

- **COMPENSATION FOR PARTICIPATION**

We will provide a food voucher for each brain scan you attend.

- **CONFIDENTIALITY**

Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission or as required by law. Confidentiality will be maintained in the following ways:

a) Paper-based records will be kept in a secure location and only accessible to people involved in the study
b) Computer-based records will only be available to people involved in the study through the use of access privileges and passwords
c) People involved in the study will be required to sign statements agreeing to protect the security and confidentiality of identifiable information
d) Personal identifiers will be removed from research-related information
e) We will use codes for all questionnaires that we collect, using the initials of the participant and the date of scan (and whether it is a second scan). We will not write your name on the questionnaires

- **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 to which you are otherwise entitled. You may also refuse to answer any questions you do not want to answer. 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 fully inform you of the outcome of our study if you wish. 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:

Dr Samantha Brooks: drsamanthabrooks@gmail.com OR:
Human Research Ethics Committee: Tel. 021 406 6338; email: sumayah.ariefdien@uct.ac.za

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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.

_____
Printed Name of Subject

_____ _____
Signature of Subject Date

_____ _____
Signature of Witness Date

Appendix D: WM Network WMA (3-back) Post-hoc Analyses

Pairwise Clusters	*t*	*p*
Parietal – DLPFC	1.29	0.216
Parietal – Front.R	0.23	0.824
Parietal - dACC	1.25	0.231
Parietal – Front.L	0.61	0.549
Parietal - Cerebellum	-0.49	0.630
Parietal – Ant.In	1.44	0.171
Parietal – Precentral	2.21	0.044
DLPFC – Front.R	0.95	0.356
DLPFC – dACC	1.37	0.192
DLPFC – Front.L	0.72	0.484
DLPFC – Cerebellum	-0.73	0.478
DLPFC – Ant.In	0.72	0.483
DLPFC – Precentral	2.39	0.316
Front.R – dACC	1.63	0.125
Front.R – Front.L	0.93	0.369
Front.R – Cerebellum	-1.83	0.088
Front.R – Ant.In	1.40	0.183
Front.R – Precentral	1.42	0.177
dACC – Front.L	1.80	0.095
dACC – Cerebellum	1.03	0.319
dACC – Ant.In	2.87	0.124
dACC – Precentral	2.32	0.036*
Front.L – Cerebellum	0.40	0.699
Front.L – Ant.In	0.27	0.790
Front.L – Precentral	1.06	0.309
Cerebellum – Ant.In	2.50	0.026
Cerebellum – Precentral	-1.12	0.280
Ant.In – Precentral	1.25	0.232

Appendix E: Original and Adjusted Results of Table 6 ANOVA

Paired Networks	Between-Group Differences: ANOVA (df = 2, 63)					
	+CT – HC		+TAU – HC		+TAU – CT	
	Standard	FDR-adjusted	Standard	FDR-adjusted	Standard	FDR-adjusted
Dan – DMN.Prec	0.493	0.609	0.780	0.862	0.731	0.873
Dan – DMN.Pcc	0.611	0.712	0.416	0.513	0.205	0.634
Dan – DMN.Ant	0.811	0.864	0.276	0.362	0.193	0.634
Dan – Fpr.Left	0.936	0.936	0.883	0.883	0.941	0.981
Dan – Fpr.Right	0.070†	0.147	0.077†	0.147	0.898	0.981
Dan – Sal	0.273	0.382	0.037*	0.082†	0.267	0.635
DMN.Prec – DMN.Pcc	<0.001*	0.007*	0.001*	0.007*	0.022*	0.231
DMN.Prec – Fpr.Right	0.095†	0.181	0.010*	0.029*	0.272	0.635
DMN.Prec – Sal	0.823	0.864	0.185	0.299	0.129	0.635
DMN.Pcc – Sal	0.415	0.544	0.875	0.883	0.559	0.873
DMN.Ant–DMN.Prec	0.060†	0.147	<0.001*	0.007*	0.005*	0.105
DMN.Ant – DMN.Pcc	<0.001*	0.007*	<0.001*	0.007*	0.380	0.798
DMN.Ant. – Fpr.Left	0.032*	0.112*	0.011*	0.028*	0.533	0.874
DMN.Ant – Fpr.Right	0.049*	0.147	0.004*	0.016*	0.245	0.634
DMN.Ant – Sal	0.185	0.278	0.472	0.551	0.622	0.873
Fpr.Left – DMN.Prec	0.064†	0.147	0.039*	0.082†	0.702	0.873
Fpr.Left – DMN.Pcc	0.003*	0.016*	0.235	0.353	0.111	0.634
Fpr.Left – Fpr.Right	0.001*	0.007*	0.003*	0.015*	0.981	0.981
Fpr.Left – Sal	0.022*	0.092†	0.009*	0.029*	0.596	0.873
Fpr.Right – DMN.Pcc	0.161	0.161	0.110	0.193	0.723	0.873
Fpr.Right – Sal	0.123	0.123	0.275	0.362	0.749	0.873

Note: The table presents group differences at baseline in correlation coefficients after adjusting for subject motion. Original p-values of between-group differences are presented alongside FDR-adjusted p-values. ANOVA results of significance ($p < 0.05$) are marked with an asterisk (*). ANOVA results trending towards significance are marked with a dagger (†).