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COGNITIVE THERAPY, WORKING MEMORY TRAINING, AND THE TREATMENT OF METHAMPHETAMINE USE DISORDER – A FUNCTIONAL MRI STUDY.

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Table of Contents

Abstract

Background: In recent years, methamphetamine use disorder (MUD), which is associated with adverse outcomes and represents a significant public health burden, has become highly prevalent in Cape Town, South Africa. Protracted methamphetamine (MA) use has been linked with neural dysfunction and working memory deficits. Although current treatments have shown limited efficacy in addressing MUD, recent evidence indicates the potential of utilizing tailored brief cognitive therapy programs and working memory training to improve outcomes. The current study aims to investigate the potential impact of brief cognitive therapy and using working memory training as an adjunct in the treatment of MUD.

Methods: Participants were recruited from an in-patient drug rehabilitation centre in Cape Town. The sample (n = 26) consists of male patients (between the ages of 18–50) diagnosed with MUD. MUD patients were randomly split into 2 groups that received 4 weeks of treatment, i.e. treatment as usual (cognitive therapy only (NT) (n= 12)) and cognitive therapy with working memory training (CT) (n = 14). Neuroimaging and psychological data were collected from participants pre- and post- intervention to assess the relative impact of said interventions.

Results: Behavioural outcome measures and the n-back working memory task adapted for fMRI were measured and compared pre- and post- intervention. No significant differences were present between groups prior treatment on behavioural measures, demographic measures, and fMRI activity. The brief cognitive therapy appeared to reduce depression and impulsivity scores over the course of the intervention, with scores slightly lower in the CT group. An FDR corrected whole-brain repeated measures ANOVA on the main effect of group indicated significant activation in the left posterior cingulate, left anterior cingulate, and left lingual gyrus. Post hoc t-tests were then conducted to follow up the group main effect and significant differences under FDR correction were observed in the NT group (in contrast to the CT group) indicating significantly more activity in the left superior temporal gyrus, left insula, right posterior declive, and right lingual gyrus. Significant differences were also observed under FDR correction on a posthoc test on the CT group (in contrast to the NT group) indicating significantly less activity in the left lingual gyrus, left posterior declive, and right cuneus.

Conclusions: The findings tentatively suggest that the working memory training adjunct may have slightly enhanced working memory maintenance brain function relative to the treatment as usual group post-intervention. The evidence also suggests that there may have been inefficient neural functioning in the treatment as usual group during the working memory task compared to the group receiving the working memory training adjunct. The results demonstrated that brief cognitive therapy treatment did somewhat reduce depressive symptoms and impulsivity in this study, with indications of subtle treatment gains in the cognitive training group. Overall, the current study (despite numerous limitations) provides preliminary and tentative evidence of the possible benefits of brief term cognitive therapy and the potential promise of using working memory training as a treatment adjunct.

Keywords: methamphetamine; addiction; working memory training; working memory; brief cognitive therapy; fMRI; cognitive training; cognitive therapy.

Introduction

Methamphetamine (MA) is a highly potent psychostimulant substance and its abuse represents a significant public health burden locally and globally with particularly deleterious effects on individuals who abuse it and the communities they inhabit (Anglin et al., 2000; Courtney & Ray, 2014; Panenka et al., 2013). The global and local prevalence of MA use is disturbingly high, with the *United Nations Office on Drugs and Crime* (UNODC) (2016) reporting MA use as the second most frequently used substance globally, after cannabis, with approximately 25 million users worldwide and recent estimates predicting further growth (Courtney & Ray, 2014; Panenka et al., 2013; United Nations Office on Drugs and Crime, 2016). Such estimates are consistent with estimates in the Western Cape, where MA use has become increasingly prevalent in adolescents and young adults, with consistent reports of widespread use corroborated by recent community studies, school surveys, and clinical admission studies (Parry et al., 2011). Indeed, there has been a substantial increase of users reporting MA as a primary or secondary drug of abuse during admissions to drug rehabilitation clinics and locals hospitals around Cape Town–with an estimate of 0.3% of patients admitted in 2002 reporting primary or secondary use of MA increasing to 46% patients admitted in 2006 (Plüddemann et al., 2013).

Recent research indicates that while the prevalence of MA abuse remains relatively high in Cape Town, the proportion of individuals seeking treatment for MA abuse declined substantially between 2006 to 2011 (Weybright et al., 2016). Studies have indicated that although many methamphetamine-dependent users in Cape Town report the desire to receive treatment or overcome their dependency, this population tends to possess little awareness of available treatments and face substantial social and economic barriers to access treatment. Many users report perceiving available treatments as ineffective, inappropriate, or in some cases, even abusive, engendering a sense of hopelessness (Meade et al., 2015; Myers et al., 2014, 2018). These reports reflect current evidence which suggests that - i) some clinical facilities provide low-quality treatment and need to be monitored and evaluated; ii) there is a possible mismatch between community needs and treatment service provision; and iii) it is necessary to facilitate treatment engagement and psychosocial education to increase treatment retention and completion (Meade et al., 2015; Myers et al., 2014, 2018).

The socioeconomic context of many MA users also represents a substantial barrier to recovery as the use of MA is rife in South African communities and appears to forms a key activity in many of the social interactions among peer networks of MA users in such communities (Meade et al., 2015; Myers et al., 2014, 2018). MA use has a long history of being associated with violence and criminality (Anglin et al., 2000; Cartier et al., 2006; McKetin et al., 2014; Scott et al., 2007; Watt et al., 2014). In South Africa, in communities with high rates of MA there is a greater risk of neglect, criminality and physical violence and sexual abuse (Parry et al., 2011; Watt et al., 2014). All of these factors are likely to further exacerbate social disintegration and economic decline in these communities (Kapp, 2008; Watt et al., 2014).

Recent evidence suggests that numerous behavioural changes associated with violent behaviour in MA users (including depressive symptoms and aggressive tendencies) are attributable to impairments in social cognition (Homer et al., 2008; Kim et al., 2011; Payer et al., 2011; Sanvicente-Vieira et al., 2016). Chronic MA use has been associated with neurotoxicity and damage in the PFC, a key region implicated in socio-cognitive functioning (Kim et al., 2011). Indeed, a recent study on MA users in Cape Town, found that MA users typically present with affective dysregulation (Uhlmann et al., 2016). As such, intervention strategies should cater to these affective and socio-cognitive difficulties by focusing on improved stress management, personal, and social function. Furthermore, it is also necessary to provide interventions which are cost-effective and short-term to minimise the burden placed on MA users (Homer et al., 2008; Kim et al., 2011; Payer et al., 2011; Sanvicente-Vieira et al., 2016; Uhlmann et al., 2016).

Neuroimaging studies have provided evidence that indicates that cognitive training can improve self-regulation and lower rates of addiction (Verdejo-Garcia, 2016; Vinogradov et al., 2012) by effectively influencing brain processes involved in various types of psychopathology, including addiction (Keshavan et al., 2014; Verdejo-Garcia, 2016; Vinogradov et al., 2012). In particular, recent evidence has indicated that computerized working memory training (WMT) holds promise as a treatment adjunct for substance use disorder (SUD) (Bickel, Moody, et al., 2014). This is important considering that neuropsychological deficits in executive function and working memory (WM) are particularly common in methamphetamine use disorder (MUD) (Scott et al., 2007). As such, cognitive training arguably represents a relatively harmless and cost-effective adjunct that could possibly boost treatment effects and thus hopefully lower local levels of addiction.

Given the high prevalence of global and local MUD and evidence that suggests that there will likely be a sustained demand and need for the treatment of methamphetamine-dependent individuals in South Africa, it is necessary to conduct more research on MA abuse and it’s treatment in the South African context. As such, this thesis evaluates the potential impact of a pilot study which implemented WMT as adjunct to an established brief cognitive therapy (BCT) intervention in Cape Town, using measures of brain function and behaviour in abstinent MUD patients relative to patients receiving treatment as usual. The present thesis thus aims to evaluate the relative impact of BCT with and without WMT on the treatment of abstinent MUD patients for a previously conducted pilot study (Brooks et al., 2016; Brooks, Wiemerslage, et al., 2017), as well as describe behavioural and neuroimaging outcomes from this study. Before describing the study itself, I will first review the literature on the neurophysiological and neurocognitive effects of methamphetamine use. Thereafter, I will briefly review the neuroimaging studies on methamphetamine use disorder. Then, a detailed review of the neuroscience of WM is provided to highlight its crucial role in neurocognitive function. This is followed by a description of recent relevant literature on the utility, efficacy, and potential of BCT in the treatment of SUD. In the final part of the introduction to this study, I will examine the use of WMT as an adjunct in the treatment of SUD.

Review of neurophysiological and neurocognitive effects of methamphetamine use

MA’s primary mechanisms of action are based on the release of norepinephrine, serotonin, and dopamine. Most research has focused on MA’s capacity to modulate dopamine release, given its key role in reward and reinforcement processes of the central nervous system (London et al., 2015; Panenka et al., 2013; Scott et al., 2007). MA stimulates the release of monoamines, whilst simultaneously inhibiting the metabolism of monoamines, resulting in the accumulation of excessive monoamines in the synapse. The release of monoamines effects the major dopaminergic (i.e., mesolimbic, mesocortical, and nigrostriatal), serotonergic, and noradrenergic (i.e., medial basal forebrain, hippocampus, and prefrontal cortex (PFC)) pathways in the brain. After MA consumption, the resultant activation of dopamine pathways is typically associated with euphoric effects, while increased noradrenergic neurotransmission is associated with arousal, memory consolidation, and cognitive processing. Serotonergic pathway hyper-activity following acute MA use is associated with respiration, sexual drive, reward, and pain perception (Courtney & Ray, 2014; London et al., 2015; Panenka et al., 2013; Scott et al., 2007).

The acute effects of MA consumption are dependent on the intake method and dose. Generally low-to-moderate MA doses result in short-term alterations in cognitive and affective functioning, including - euphoria, enhanced energy, alertness, feelings of increased physical and mental capacity, elevated self-esteem, increased libido, increased productivity, as well as increased performance in measures of visuospatial performance, sustained attention, and reaction time (Courtney & Ray, 2014; Hart et al., 2012; Nordahl et al., 2003; Scott et al., 2007). Higher doses, such as those involved in binges (common among chronic MA users), may result in dysphoric symptoms and disturbed cognitive and affective functioning. Binge use is associated with insomnia, increased stereotypy, irritability, heightened anxiety, confusion, fatigue, and impaired concentration. In some cases, effects of binge use include increased, unprovoked aggression, abnormal motor functioning, skin-picking, paranoid ideations, delusions (e.g. formication & parasitosis), and hallucinations (Courtney & Ray, 2014; Hart et al., 2012; Nordahl et al., 2003; Scott et al., 2007).

Methamphetamine use disorder (MUD) refers to the diagnosis of SUD with the primary substance of abuse being identified as MA (American Psychiatric Association, 2013). Patients diagnosed with MUD are characterized by a chronic pattern of MA abuse and dependence (Barr et al., 2006; Potvin et al., 2018). MA is characterized by its high lipid solubility, enabling MA to efficiently and rapidly cross in large doses across the blood-brain barrier (Nordahl et al., 2003). This increased speed of transmission across the blood-brain barrier in stimulants has been linked to the substance's addiction potential during early exposure, particularly with respect to its effect on dopaminergic circuitry, as it disrupts the baseline reward saliency of a healthy brain and thus the expectations of reward in MA users. That is to say, the intake speed of MA into the brain is linked to drug-use reinforcement through its effect on the reward system (Volkow, Fowler, Wang, & Swanson, 2004). This is likely further reinforced by the extended half-life of MA, which is on average approximately 6-12 hours (Courtney & Ray, 2014; Nordahl et al., 2003; Panenka et al., 2013; Rusyniak, 2013; Scott et al., 2007).

Given that the frequent and extended use of MA can result in the depletion of presynaptic monoamine stores, down-regulation of monoamine receptors, and neurotoxicity, all of this can exacerbate the significant psychiatric withdrawal symptoms that typically result after cessation from regular use (Courtney & Ray, 2014; Nordahl et al., 2003; Panenka et al., 2013; Rusyniak, 2013; Scott et al., 2007). MA withdrawal is characterized by severe dysphoria, which is often akin to depressive symptomology and/or affective dysregulation that is typically persistent over two weeks, or more, including - anhedonia, hypersomnia, fatigue, agitation, anxiety, aggression, difficulty concentrating, suicidality, and intensive cravings. Indeed, global metabolic activity in MA users resembles that seen in patients with major depression disorder. The severe and protracted withdrawal from MA thus represents a substantial impediment to recovery from MA dependence (Courtney & Ray, 2014; Nordahl et al., 2003; Panenka et al., 2013; Rusyniak, 2013; Scott et al., 2007).

Craving in addiction is arguably, in part, a reflection of the decreased stimulation of dopamine reward pathways evident after chronic MA use (Volkow et al., 2004, 2012). MA's reinforcing effects lie in its ability to imitate and surpass the intensity and duration of dopamine increases triggered by the phasic firing of cells which are typically induced by exposure to naturalistic reward stimuli (e.g. images of food). Large and rapid increases in dopamine are the likely mechanism by which dopamine encodes the saliency of objects and events. MA craving has been observed to persist for up to 5 weeks of abstinence, with users most vulnerable to relapse within the first two weeks (Volkow et al., 2004, 2012).

Long-term chronic MA abuse has been linked to numerous deficits in cognitive processes including WM, episodic memory, executive function, information processing, psychomotor function, language, attention, and cognitive flexibility (Courtney & Ray, 2014; Dean et al., 2013; Kohno et al., 2014; Panenka et al., 2013; Scott et al., 2007). Although these effects are in general moderate in size (Hart et al., 2012) some MA users are at risk of substantial impairment, with current estimates suggesting that approximately 40% present with global neuropsychological deficits (Scott et al., 2007). These deficits are particularly likely to present themselves in complex cognitive tasks, as well as socio-emotional tasks (e.g. keeping track of a conversation, working in a group, or learning from a lecture) than simpler tasks (e.g. household chores or basic activities of daily living) (Dean et al., 2013; Scott et al., 2007). As such, not only are MA users prone to undergo mild cognitive decline (Courtney & Ray, 2014; Dean et al., 2013; Kohno et al., 2014; Nordahl et al., 2003; Panenka et al., 2013; Scott et al., 2007), but are also more likely to face unemployment and numerous interpersonal problems, related to socio-cognitive deficits (Homer et al., 2008; Scott et al., 2007; Weber et al., 2012). Nevertheless, protracted abstinence has been associated with relative improvements from these deficits in neurocognitive functioning, which may reflect some degree of recovery (Courtney & Ray, 2014; Dean et al., 2013; Kohno et al., 2014; Nordahl et al., 2003; Panenka et al., 2013; Scott et al., 2007).

Thus far, the neurophysiological and neurocognitive processes associated with MA use have been reviewed to provide a summary of the impact of acute and chronic MA use. This section indicates the substantial neurocognitive and neurophysiological impairment associated with chronic use as well as examined craving and withdrawal in MUD. To further understand the impact of MUD and situate the present experiment in the neuroimaging literature, the subsequent section will review pertinent functional and structural magnetic resonance imaging (MRI) literature on MUD.

MRI studies of Methamphetamine use disorder.

Functional magnetic resonance imaging (fMRI) is a non-invasive methodological tool that measures patterns of activity and connectivity in the brain by measuring changes in the local oxygenation of blood (Buxton, 2013; Poldrack et al., 2011). The magnitude of the venous blood oxygenation level dependent (BOLD) signal represents an indirect measure of neuronal activity, serving to reflect changes in regional blood flow, volume, oxygenation, and energy (e.g. glucose) consumption (Buxton, 2013; Soares et al., 2016). In a typical fMRI sequence, approximately 100-1000 3D MRI brain images are acquired, with each image consisting of approximately 100,000 voxels (i.e. uniformly spaced volumes, the foundational unit of MRI images) (Lindquist & Wager, 2014). During the course of an MRI scan, participants are typically requested to perform a specific task or experience an induced behaviour/psychological state while multiple images are acquired in order to form a time series (Lindquist & Wager, 2014). These tasks are generally designed to vary stimuli systematically (typically between alternating conditions of stimulus and rest) to elicit participant neural activity, so as to observe activation differences which indicate which neural areas are associated with the targeted function (e.g. WM). These images are acquired to observe BOLD contrasts over time, that is the differences in MR image intensity between the features, in this case, neural regions, of the brain images, or a particular region of interest (Jezzard & Clare, 2001; Lindquist & Wager, 2014; Stroman, 2016). All of which allows us to begin assessing differences in brain activity between different conditions in a controlled manner which is typically measured using experimental designs that suit the constraints of fMRI.

fMRI studies have demonstrated changes in neuronal function associated with chronic MA use, including impairments in frontal-striatal activation and connectivity between PFC areas during decision-making tasks (London et al., 2015). Current evidence indicates that current stimulant users consistently show impairments in functional activation of the striatum, orbitofrontal cortex (OFC), medial frontal cortex (MFC), and anterior cingulate cortex (ACC) during risky decision-making tasks. Supporting this, differences have also been observed in gray matter volumes between controls and 3-week abstinent methamphetamine users, with smaller volumes of ACC, DLPFC, OFC, superior temporal cortices, and hippocampus in controls (London et al., 2015). Deficits in decision making have been associated with addiction and likely contribute to addiction vulnerability. In decision-making tasks, activation of the right DLPFC has been associated with choices that result in larger future rewards despite short-term losses, as opposed to ventral striatal activation, which has been linked to seeking out short-term rewards. This pattern of activation is consistent with the fact that MA users typically exhibit hyperresponsivity in the ventral striatal area to rewards, but hypoactivity in the rDLPFC during decision making (Kohno et al., 2014).

Prior studies have also noted the neurotoxic effect of chronic MA use on the dorsal striatum structure. The ventral striatum is involved in both reward and motivational salience processes, while the dorsal striatum is considered to link reactive cognitive control to behavioural guidance, enabling online behavioural regulation in response to salient stimuli (Peters et al., 2016). Indeed, there is evidence that the structural abnormalities of the dorsal striatum in chronic MA use are associated with conditioned responses (e.g., to drug cues) and habitual drug use among MA users (Chang et al., 2007; Jedynak et al., 2007; Wang et al., 2012). This may arguably reflect evidence that indicates the shift from controlled (associated with the ventral striatum and PFC) to habitual (i.e., dorsal striatum and amygdala) drug taking that unfolds in the progression of SUD (Brooks, Funk, et al., 2017; Everitt, 2014). This suggests that the major deficits associated with reinforcement processes in response to naturalistic reward cues (eg. sex, food) that have been observed in MUD are largely influenced by impairments in the reward and saliency networks in response to the excessive incentivization of drug related cues. Such reward related impairments are significantly influenced by impairments in emotional regulation and cognitive control, which, as will be argued in further detail later, are fundamentally related to relative impairments in WM function (Brooks et al., 2016; Volkow et al., 2003). Indeed, the well-established PFC regulation of limbic regions also further provide a basis for the link between WM and emotional regulation, (Golkar et al., 2012; Ochsner & Gross, 2005; Wager et al., 2008), and thus, decision making. Indeed, individuals with higher developed WM capacities have been demonstrated to better regulate and exert control over affective experiences (Schmeichel et al., 2008; Schmeichel & Demaree, 2010) and working memory training has been linked to improvements in the regulation of affective experience (Pe et al., 2013; Schweizer et al., 2013; Takeuchi et al., 2014).

The literature reviewed thus far highlights the negative impact of MUD on the structure and function of reward and salience networks and how such impairments may be related to deficits in decision making that are associated with addiction vulnerability and habitual drug use. It is also consistent with claims that WM impairments are linked to poor decision making in SUD patients due to deficits in response inhibition to a previously rewarding stimuli (e.g., a drug cue) alongside hypersensitivity to reward. Indeed, numerous studies have indicated that SUD patients, including MUD patients, have been found with substantial impairments in WM and cognitive control (Bechara & Martin, 2004; Brooks, Funk, et al., 2017; Houben et al., 2011; Nordahl et al., 2003; Potvin et al., 2018; Scott et al., 2007; Zhong et al., 2016). This suggests that WM may play a substantial role in addiction processes and that working memory training may hold promise in bolstering treatment adherence. As such, the subsequent section provides a relatively detailed review of the neuroscience of WM, with a focus on Brooks' extended WM model (Brooks, 2016; Brooks, Funk, et al., 2017).

The Neuroscience of Working Memory

WM is a relatively flexible theoretical construct that refers to a domain-general capacity that facilitates the activation and temporary storage, or retention, of mental representations of information (typically sampled from the external environment) in consciousness, to be processed or manipulated in service of multiple cognitive processes, including prediction, planning, and action execution (Baddeley, 2012; Carruthers, 2013; Moser et al., 2017; Postle, 2006). WM is typically conceptualized as a multi-component system that engages several brain areas including a) the dorsolateral PFC, associated with encoding, attentional salience, and the manipulation of information, (b) the dorsal anterior cingulate cortex, associated with error detection and performance monitoring, and (c) the parietal cortex, associated with information storage and attentional control (Moser et al., 2017). WM is typically understood as involving fronto-striatal and fronto-parietal networks and their interaction with brain regions associated with the sensory properties of the content of WM (Baddeley, 2012; Carruthers, 2013; Moser et al., 2017; Postle, 2006). This section will review the evidence on the neuroscience of WM, with an emphasis on these circuits, to provide an overview of the core neurobiological mechanisms underlying WM function. This will serve as context for a subsequent neurocognitive account of WM.

Prefrontal cortical function and working memory

The PFC has been characterised as functioning in a hierarchal manner where brain areas within this region are structurally and functionally differentiated caudally (posterior) to rostrally (anterior), from the PFC to the frontopolar cortex, or from conceptualization to action, respectively. Rostral areas are considered to be at the top of the neurally organized hierarchy as structurally such areas have lower laminar differentiation at the columnar level, allowing for widespread connections to other brain regions. Caudal areas, on the other hand, have a higher degree of laminar differentiation and are well developed but have limited connections, and thus are mostly restricted to neighbouring neural regions (D'esposito & Postle, 2015). The organization of the PFC in this regard indicates that the abstraction levels of goals or task rules peak rostrally and decrease caudally (Constantinidis & Klingberg, 2016; D'esposito & Postle, 2015; Eriksson et al., 2015). On the other hand, several metanalyses have demonstrated regional specificity with the left PFC implicated predominantly in verbal WM while the right PFC is implicated more in spatial WM (Nee et al., 2013; Owen et al., 2005; Wager & Smith, 2003). The PFC is theorized to function using higher order representations of task contingencies, rules, and abstract representations of categories, critical for the temporal mediation of events that are contingent upon each other. Moreover, the PFC is understood to exert executive control over the neural regions where relevant information is stored via top-down signalling that serves to either enhance or suppress relevant information and impact the likelihood of the successful representation of such information in a competing system (Constantinidis & Klingberg, 2016; D'esposito & Postle, 2015; Eriksson et al., 2015).

Fronto-parietal brain networks in working memory

The parietal cortex is heavily implicated in WM and numerous analyses have found that activity in the fronto-parietal lobes predict current WM capacity (Eriksson et al., 2015) and parietal activity increases are positively associated with WM load (Constantinidis & Klingberg, 2016). Indeed, recent magnetoencephalography (MEG) and electroencephalogram (EEG) research on the delay period in WM found that frontal activation increasingly couples with parietal activation over time and the degree of synchronicity between these two regions increases the likely total volume of information successfully maintained in WM (Constantinidis & Klingberg, 2016). In cases where task load exceeds WM capacity, the medial temporal lobe, associated with binding and relational processing in WM, is activated. Contrastingly, parietal load effects, associated with the storage of irrelevant or distracting information, are negatively associated with basal ganglia activity (Constantinidis & Klingberg, 2016). Together, these findings highlight the differential response of the brain as a function of aspects of load in WM.

The parietal cortex also plays a significant role in both visual and verbal WM; for example, the superior parietal cortex is associated with the executive aspects of WM – i.e., attentional control. Indeed, visuospatial WM is associated with activity in the middle frontal gyrus, inferior frontal gyrus, intraparietal cortex, and superior frontal gyrus, while verbal WM is associated with activation in the superior temporal, ventral prefrontal, and left inferior parietal cortices (Constantinidis & Klingberg, 2016; Eriksson et al., 2015; Moser et al., 2017). Recent evidence indicates that one of the primary functions of the parietal cortices, in particular, is the encoding and maintenance of retrospective sensory information, and the facilitation of attentional shifts to adapt to such low level contextual changes (e.g., sensory stimuli/ attention-shift within WM). The frontal cortices, on the other hand, are associated with maintaining prospective action planning and high level hierarchal contextual updating (e.g., change of a rule/manipulation of content within WM) (Mackey & Curtis, 2017; Nee & Brown, 2013).

Fronto-striatal brain networks in working memory

The basal ganglia and thalamus are implicated, on a structural and functional level, with future WM function (Eriksson et al., 2015), while basal ganglia and prefrontal activity have also been demonstrated to be positively associated with WM function. Basal ganglia involvement, particularly of the striatum, is common in WM tasks – the striatum serves as a gating mechanism by regulating the updating and maintenance of representations in the PFC. Reduced striatal dopamine levels diminish the capacity to update PFC representations resulting in more rigid and distractor-resistant representations (Constantinidis & Klingberg, 2016; Eriksson et al., 2015; Moser et al., 2017). Perhaps this provides one explanation for why individuals with low functioning WM struggle to inhibit distracting information compared to high functioning individuals, as they are slower at disengaging attention from irrelevant information. Indeed, the gatekeeping function of the frontal-striatal regions and dopaminergic mechanisms may represent one probable source of such capacity limitations in WM. As the striatum acts as a gating mechanism that regulates the updating and maintenance of PFC representations, it is likely that damage to it or related dopaminergic connections (e.g. through extended MA use) will diminish WM capacity (Constantinidis & Klingberg, 2016; Eriksson et al., 2015; Moser et al., 2017).

The dopaminergic modulation of the frontal-striatal circuitry is critical to WM function with substantial evidence supporting the notion that dopamine availability is predictive of WM function. D2 receptors are found in their highest concentrations in the PFC and striatum and these receptors have been linked to cognitive flexibility. These representations are modulated by the phasic release of dopamine from D2 receptors to gate signals for switching, encoding, and updating in WM (D'esposito & Postle, 2015). D1 receptors (predominantly located in the PFC (Durstewitz & Seamans, 2002; Takahashi et al., 2012)), on the other hand, mediate the tonic release of dopamine that facilitates the representational stability of information stored in WM -i.e., robust online maintenance of information and resistance to distraction. Dopamine thus acts as a gating signal to the PFC with an apparent functional opponency between the stability and malleability of WM representations, governed by relative dopamine release in the PFC and the striatum (D'esposito & Postle, 2015). The active maintenance of information or mental representations that serves as the core process constitutive of WM has consistently been linked to persistent activity generated by neurons in the PFC, with evidence to suggest that functional activity in the PFC is associated with the fidelity of such representations. Persistent activity is theorized to be generated by the reverberating discharges within a network of interrelated neurons in the PFC, and between the PFC and other relevant brain areas (including, the parietal cortex, inferior temporal cortex, insula, basal ganglia, mediodorsal nucleus of the thalamus, and other subcortical regions). It has been suggested that such persistent activity in the PFC provides high dimensional representations that serve to sustain the sensory features of information maintained in WM (Constantinidis & Klingberg, 2016; D'esposito & Postle, 2015; Eriksson et al., 2015).

Models of working memory function

WM thus arguably emerges from the dynamic interaction of several brain regions. Indeed, numerous connectivity analyses indicate co-temporal activity in the sensory regions and the PFC, parietal cortex, striatum, and medial temporal lobe associated with WM function (D'esposito & Postle, 2015; Eriksson et al., 2015). Furthermore, Diffusion Tensor Imaging research indicates that the integrity of white matter pathways connecting the prefrontal, parietal, and temporal cortices are significantly associated with WM performance (D'esposito & Postle, 2015; Eriksson et al., 2015). In fact, the overall integration of connectivity into separate networks and the synchronicity at several frequencies between frontal, parietal and visual areas, is positively associated with WM capacity in healthy adults (D'esposito & Postle, 2015; Eriksson et al., 2015). Thus, short- and long-range neural oscillations underlying the synchronization of activity among distributed brain regions are critical for WM maintenance processes. With this in mind, it is likely that any item maintained in WM will be encoded in a highly distributed manner and will conform to the general principles of distributed information storage. The integration of this distributed information is achieved by long- and short-range recurrent connections amongst the various relevant regions active during WM (D'esposito & Postle, 2015; Eriksson et al., 2015). The structural and functional neural mechanisms underlying WM enable the temporary storage, organization, and manipulation of salient or relevant information in memory occurring concurrently with the dynamic engagement with other information (Brooks, 2016). WM is thus understood to facilitate the short-term maintenance of information (typically representations of stimuli) in the absence of sensory input. This capacity arguably serves as a basis for the subjective experience of the varying degrees of cognitive control that emerge out of the neural capacity to flexibly toggle between cognitive and affective states. WM acts as a global workspace that selectively attends and manipulates information, and in a sense sets the stage of the emerging conscious experience of effectively or ineffectively exerting cognitive control in processes such as focusing on a target or shifting between cognitive and affective states (Brooks, 2016; D'esposito & Postle, 2015; Eriksson et al., 2015).

In the classic WM model, the central executive, associated with prefrontal networks, presides over three subordinate systems - the phonological loop, visuospatial sketchpad, and the episodic buffer. The central executive is associated with sustained attention or focus, the division of attention between two or multiple streams, switching between these tasks or streams, and the central executive's interaction with long-term memory. The phonological loop is a relatively modular limited short-term store concerned with language which maintains information through the use of vocal or subvocal rehearsal strategies (typically repetitive and conscious) to consolidate beliefs and thus is likely involved in cognitive ruminations. The phonological loop is compromised of the articulatory loop that is involved in language production (Broca's region) and the acoustic store which facilitates language comprehension (Wernicke's region) (Baddeley, 2012; Brooks, Funk, et al., 2017). The phonological loop interacts with the visual semantic networks affiliated with the visuospatial sketchpad, or the dual visual streams, concerned with "where" (dorsal) and "what" (ventral) in perception and action. The dorsal stream begins at V1 (primary visual cortex), and projects to the parietal cortex, enabling individuals to conceive of themselves and their beliefs within time and space. On the other hand, the ventral stream also begins at V1, projecting to the temporal auditory cortex, insular cortex (i.e. interoception) and hippocampus (i.e. memory), providing a foundation for sensible concrete visual perception in the mind of an individual. Finally, the episodic buffer, which interacts with the phonological loop and visuospatial sketchpad functions via the hippocampal-amygdala network located near the medial temporal cortex (Baddeley, 2012; Brooks, Funk, et al., 2017). The episodic buffer refers to a limited buffer store holding integrated episodes or chunks in a multidimensional code between WM components whilst simultaneously linking WM with perception and long-term memory. Evidence suggests that the hippocampal-amygdala network is central to the mesolimbic reward and motivation pathways, interacts with the PFC and is involved with attributing salience to influence attentional systems and top-down modulation of bottom-up processes. Retrieval from this buffer requires conscious access, where it is assumed that consciousness serves as a binding mechanism of stimulus features into perceptible objects (Baddeley, 2012; Brooks, Funk, et al., 2017).

Extended model of working memory

Brooks argues that the model of WM can be further enhanced by integrating elements of Global Workspace Theory and Bayesian probabilistic inference (Brooks, 2016; Brooks, Funk, et al., 2017). As such, this extended account will be reviewed below as it informs and supports the working memory training included in this pilot intervention. It is argued that the brain is a collection of distributed specialized networks and consciousness is associated with a global workspace of the brain serving to integrate the competing and joint input of various networks (including unconscious networks) which serve as the context or background (including affective and motivational states) that shape and constrain events in consciousness. In this framework, the central executive could be related to the executive control network which focuses on goal-related cognitions and functions in dynamic opposition to the default mode network, which focuses on internal states and self-monitoring overall. The updating of conscious perception with internal and external stimuli emerges from background unconscious processing which is mediated hierarchically by executive processes (Brooks, 2016; Brooks, Funk, et al., 2017). That is, conscious perception accommodates input from temporary sensory processes that are modulated by priority maps and contextual constraints concerning the self, others, the external environment, and unconscious processes (e.g. self-concepts, memories, discourse, and impulses).

It is argued that the central executive, though influenced by competing conscious and unconscious processes, typically guides decision making in the face of uncertainty according to three primary principles. Activation of prefrontal regions and the hippocampus (engaging episodic nonconscious salient memories) are arguably governed by the likelihood principle, that is based on prediction error and evaluative inferences concerning present experience in relation to prior experiences of the likelihood that an event will occur. The PFC, insular cortex, and basal ganglia process stimuli or beliefs to determine their salience, in part, in terms of the familiarity (determined by frequentism[1]) of the stimuli/belief, integrating this prior experience with current beliefs concerning the stimuli/belief and its likelihood. Finally, belief systems are thirdly in part influenced through Bayesian probabilistic inferences via the frequency of exposure to events and their outcomes, which serve to update the predictions and action tendencies formulated in the face of the present uncertainty implicated in decision making. This

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[1] According to Brooks (2016) and Brooks et al. (2017) frequentism is term which forms part of the Bayesian Brain framework for describing how a particular region integrates information from multiple cues. As such Frequentism is based on using prior experience and the probability that an event will occur to determine selection. In frequentism, the frequency of an event or phenomenon occurring is the determining principle of what motivates attributing it with salience (Brooks, 2016; Brooks et al., 2017).

can be related to the process of epistemic foraging for information that is influenced by prior beliefs and occurs in the face of uncertainty in order to facilitate the generation of the most accurate predictions that reduce error and the unnecessary expenditure of energy. Bayesian probabilistic inferences thus provide a model of how individuals may integrate multiple sources of information in the present and prior knowledge to update online probabilistic inferences concerning the environment and the agent to guide decision making (Brooks, 2016; Brooks, Funk, et al., 2017). According to this model, WM can be understood as a process of evidence accumulation in a temporally structured hierarchy which serially samples information or epistemically forages from the environment. Ongoing representations of belief or predictions under uncertainty are influenced by the probabilistic modelling of previous beliefs (and related policies) averaged out (with saliency), and this evidence accumulation over time serves to update beliefs and subsequent policies crucial for decision making (Parr & Friston, 2017). This suggests to some extent that background cognitive and neural processes may shape WM function, as at any given moment various brain regions actively compete for conscious access such that negative emotional states, unconscious biases, and physiological processes (e.g. appetite or illness) can perturb or impact WM function. Thus it has been suggested that the salience network may play a central role in addiction processes as cognitive biases and prior experiences related to the dysfunctional state, that is SUD may unconsciously shape WM processes over engaging with novel information or attempts at conscious (Brooks, 2016; Brooks, Funk, et al., 2017).

WM has been argued to be a part of the core pathology of the addiction, with evidence from a recent meta-analysis indicating that significant deficits were predominantly present in the verbal WM domain of SUD patients (Bechara & Martin, 2004; Brooks et al., 2016). With evidence to suggest that mentally rehearsing cognitive strategies may be harder for SUD patients in the face of distraction, Brooks et al. (2017) has suggested that the employment of verbal WM strategies may help curtail impulsive behaviours that lead to the switch towards habitual use and withdrawal. Both cognitive therapy (which focuses on cognitive strategies in treatment) and WMT represent different means of addressing these issues in MUD. As such, the following sections will thus review BCT, the psychological intervention implemented in this secondary data analysis study, and then consider the value of integrating WMT as an adjunct to bolster treatment response.

Brief Term Cognitive Therapy, and the promise of Dialectical Behavioural Therapy

The psychotherapy treatment intervention under investigation in this study has been tailored by the treatment centre into a program which could be considered a form of brief term cognitive therapy (BCT) that utilizes elements of dialectical behaviour therapy (DBT), including the use of DBT related skills programs. The section below provides a brief review of some of the evidence for the utility of brief cognitive behavioural therapies, dialectical behavioural therapy, and DBT skills programs in the treatment of MUD.

Cognitive Behavioural Therapy (CBT) treatments are typically time limited in nature and aim for significant clinical improvements and symptom reduction within 10-20 sessions (i.e., 10-20 weeks). In CBT, psychological dysfunction is conceptualized in terms of learning mechanisms, information processing, and the principles of operant and classical conditioning. CBT is predicated upon the postulate that distortions in information processing (or irrational cognitions or assumptions or biases) concerning the self and external environment underlie various psychological problems. CBT adopts an empirical approach to human behaviour that bases itself on the use of active dialogue between the therapist and patient (i.e., Socratic dialogue) to deal with issues, with a focus on challenging and reformulating maladaptive cognitions into increasingly adaptive cognitions (Hazlett-Stevens & Craske, 2002). CBT is a focused treatment approach that targets specific symptoms and behaviours in the presenting psychological case. Patients typically receive psychoeducation and undergo a process of cognitive restructuring through the therapeutic process and the use of experiential tasks that encourage patients to test their dysfunctional beliefs and learn by experimentation and experience. Treatment typically involves teaching coping skills to help patients respond more effectively to future scenarios related to the presenting psychological issue (Hazlett-Stevens & Craske, 2002; Robins & Chapman, 2004).

Several attempts have been made to further streamline and enhance the efficacy of CBT so as to increase affordability and further treatment access by reducing the number of CBT treatment sessions. Thus, CBT interventions that consist of less than 10 sessions are considered brief cognitive behavioural therapy (Hazlett-Stevens & Craske, 2002). Brief cognitive therapies have shown promise in the treatment of several psychiatric conditions, such as obsessive-compulsive disorder (Baxter et al., 1992; Bolton et al., 2011), post-traumatic stress disorder, phobias

(Paquette et al., 2003; Straube et al., 2006), depression (Du et al., 2016), and substance use disorder (including MUD) (Longabaugh & Morgenstern, 1999; Sobell et al., 1995; Straub et al., 2014). For example, brief CBT has demonstrated efficacy in obsessive-compulsive disorder with treatment response associated with decreased metabolism in the right caudate nucleus (Baxter et al., 1992). Decreased activity in the RDLPFC and parahippocampal areas was observed in association with symptom reduction after BCT for phobias (Paquette et al., 2003). Indeed, a recent study of brief (group) CBT over 5 weeks, observed functional connectivity differences between depressed patients and controls; connectivity was smaller in patients in the cognitive control network (DLPFC, TPJ) and salience network (dACC, insula) at pre-intervention. At post-intervention the depressed patients showed significantly stronger activation and connectivity between the two networks indicating increasingly similar brain function to controls. Such changes in connectivity were associated with symptom reduction over the course of the intervention (Straub et al., 2017). In another study, participation in a 4-week group CBT for depression was associated with increased grey matter volume in the right middle frontal gyrus, which was related to a decrease in negative bias in information processing, and changes in the functional connectivity between the insula and middle frontal gyrus. This change in functional activity was associated with a decrease in the salience of negative stimuli post treatment (Du et al., 2016).

Brief cognitive therapies have been adapted and abbreviated to increase the efficiency and reach of CBT by reducing the number of treatment sessions, utilizing group sessions as the primary format instead of individual therapy, and utilizing self-help materials, bibliotherapy, computer-assisted therapy programs, and skills workshops (Bolton et al., 2011; Hazlett-Stevens & Craske, 2002; Sijbrandij et al., 2007; Straub et al., 2014). In these treatments, a greater burden is placed on the patient, who is encouraged and directed to play a more active role in the therapeutic process, which involves the patient taking some responsibility in engaging with the necessary therapeutic material (Hazlett-Stevens & Craske, 2002). The current study investigates a BCT that utilizes an abbreviated version of dialectical behaviour therapy (Robins et al., 2001; Robins & Chapman, 2004) by integrating some of its principles and workshops into its implementation.

Dialectical Behaviour Therapy

Dialectical Behaviour Therapy (DBT) is a third wave behavioural therapy that has demonstrated substantial empirical success in the treatment of borderline personality disorder (BPD) and suicidal symptoms (Panos et al., 2014). Originally formulated to treat BPD, DBT is a comprehensive therapeutic program that facilitates skills training in conjunction with psychotherapeutic treatment and intensive case management (Robins et al., 2001; Verheul et al., 2003). Typically, DBT based interventions aim to decrease symptom presentation and severity, as well as increase behavioural control and emotional regulation in patients (Goodman et al., 2014; Robins et al., 2001; Schnell & Herpertz, 2007; Verheul et al., 2003). Recent evidence shows that interventions that solely utilized DBT skills training workshops have demonstrated moderate success in the treatment of several psychological disorders (e.g. depression, binge-eating, and attention hyperactivity/deficit disorder) (Valentine et al., 2015). Accordingly, it has been argued that it could be used effectively as a transdiagnostic treatment for emotional dysregulation in psychological disorders (Neacsiu et al., 2014).

Interestingly, there appears to be substantial overlap between BPD and MUD patients in dysfunctional brain activation and emotional dysregulation, suggesting that DBT based interventions (tailored to enhance cognitive control and emotional regulation) may hold promise in the treatment of MUD (Goodman et al., 2014; Schmitt et al., 2016; Schnell & Herpertz, 2007). Indeed, several studies have shown significant functional changes in the overlapping brain regions in BPD patients undergoing DBT. For example, a small pilot 12-week (10 sessions per week) DBT based intervention provided preliminary evidence of decreased functional activity to salient negative stimuli in the right caudal anterior cingulate, posterior cingulate cortex, temporal cortex, and left insula in BPD patients, suggesting improved emotional regulation post-treatment. Contrastingly, reductions in HRF modulation in the left amygdala and bilateral hippocampi were also observed post-treatment, suggesting decreased emotional reactivity (Schnell & Herpertz, 2007). An overall reduction in amygdala activation was later replicated in a larger sample in a different study, indicating improvements in affect regulation (Goodman et al., 2014). This evidence may suggest that similar changes in brain activation may be possibly expected after MUD patients receive a DBT-based treatment.

A recent review on the efficacy of psychotherapeutic treatments for MUD has demonstrated that the CBT interventions have demonstrated some efficacy, with even brief CBT interventions demonstrating minor positive treatment responses (Lee & Rawson, 2008). Unfortunately, despite the promise of DBT based interventions, with evidence of the efficacy of DBT in treating SUD, and MUD in particular (Dimeff et al., 2000; Dimeff & Linehan, 2008; Linehan et al., 1999, 2002; van den Bosch et al., 2002), to the best of my knowledge there are no neuroscientific studies of DBT in treating MUD. As such, this study is interested in evaluating whether WMT treatment intervention may show promise in improving the treatment outcomes of MUD patients given its therapeutic inflection towards the principles of DBT and its use of DBT skills training workshops, with the hope that it possibly enhances the treatment effects of a typical brief term cognitive therapy. Moreover, given that DBT already sets the explicit precedent of developing skills in the treatment process, integrating skills training alongside therapy, it is arguably particularly compatible with using WMT as an adjunct. In the next section, this thesis will examine the literature on WMT to highlight its potential as a treatment enhancing adjunct to the established and adapted brief term cognitive therapy intervention being investigated in this thesis.

Working Memory Training as a Treatment Adjunct

Impulsivity and attentional and WM deficits are commonly found in SUDs (Goldstein & Volkow, 2011; Paulus et al., 2008; Verdejo-García et al., 2008) and are predictors of poor treatment outcomes - e.g. relapse in marijuana, nicotine, alcohol, MA, and cocaine dependence (Aharonovich et al., 2006, 2008; Gowin et al., 2014; Stevens et al., 2014, 2015; Weber et al., 2012). In addition, SUD is also typically associated with lower cognitive control, impaired self-regulation, and poorer WM performance relative to healthy controls. Conversely, WM function has been observed to increase after prolonged abstinence in patients diagnosed with SUDs (Brooks, 2016; Brooks, Funk, et al., 2017; Goldstein & Volkow, 2011; Kalivas, 2008).

The dopaminergic circuits, which underlie WM, have been argued to contribute to the development of addiction. Prefrontal dopaminergic dysfunction might underlie variations in cognitive control, particularly in terms of the verbal strategies implicated in future goals and the modulation of distracting stimuli during WM in SUD patients. Indeed, evidence from recent meta-analyses indicate that adults with SUD present with particularly significant deficits in verbal WM. These deficits are in part attributed to a failure to employ verbal rehearsal strategies typically used to inhibit impulsive behaviour during recreational and controlled use, leading to habitual use. This is in line with numerous neuroimaging studies and models of addiction (Brooks, 2016; Brooks, Funk, et al., 2017; Goldstein & Volkow, 2011; Kalivas, 2008).

Neuroimaging evidence from studies on SUD have also indicated that patients' WM behavioural performance is often commensurate with healthy controls. However, this is may be accompanied by inefficient and compensatory neural processing that are perhaps related to the recruitment of the default mode network in the presence of higher cognitive loads (Brooks et al., 2016). There is evidence for significant structural and functional differences in brain areas often associated with the WM network (including the frontal-striatal, parietal, insular, and cerebellar regions) in numerous SUDs (including MA), with alterations often observed in the PFC (and its related dopamine system) given its moderating function over other areas associated with WM (Brooks et al., 2016). This suggests that treatment interventions ought to target WM and salience networks, particularly the frontal-striatal regions, in SUDs, with some arguing that WMT in particular may hold promise (Bickel et al., 2011; Brooks, Funk, et al., 2017; Constantinidis & Klingberg, 2016; Houben et al., 2011; Olesen et al., 2004).

Recent evidence suggests WMT can help improve rates of delayed gratification in addiction (predominantly stimulant addiction) by strengthening cognitive control (Bickel et al., 2011). This is particularly important because numerous studies have found that steeper delay discounting is related to poor treatment outcomes in patients with SUD(Sheffer et al., 2012; Stanger et al., 2012; Stevens et al., 2014, 2015). Furthermore, impairments in decision making in MA users have been associated with WM deficits that are directly implicated in aspects of executive function, which in turn, are related to a predilection towards risky and stimulus-driven behaviours in MA users and misinterpretations of social interactions that result in negative social interactions (Bechara & Martin, 2004; Cui et al., 2015; Hinson et al., 2003; Kohno et al., 2014). Interestingly, recent research found that relapse in MUD was predicted by the hypoactivation of prefrontal, parietal, and insular cortical regions during a decision-making task (Kohno et al., 2014). On the other hand, WM capacity has also been positively related to the self-regulation of affective processes, with individuals with higher WM capacity tending to exert better control over their emotional experiences (Schmeichel et al., 2008; Schmeichel & Demaree, 2010). Arguably this is important because, the ability to update and reappraise emotionally relevant information (with more neutral or positive interpretations) in WM is crucial in facilitating the successful regulation of emotional experience (Pe et al., 2013). Indeed, recent research has shown that 4 weeks of WMT improved the mood of healthy participants. The participants showed decreases in negative emotions (i.e., anger, depression, and fatigue) as well as decreases in brain activity in the left posterior insula (related to anger) and the left frontoparietal area (a key area in substance disorders) (Takeuchi et al., 2014). Another study on healthy controls showed improvements in emotional regulation with the use of an affective variant of WMT, emotional WMT, and this was reflected in increased activity in the frontoparietal network and subgenual anterior cingulate cortex (relative to placebo) (Schweizer et al., 2013). All of which suggests that WMT has potential as a fruitful adjunct for the treatment of MA, consistent with recent recommendations that 1) improving overall cognitive function should be a target in MUD treatment (Zhong et al., 2016) and 2) computerized WMT should be used as an adjunct to supplement SUD treatment (Bickel, Moody, et al., 2014). Accordingly, the use of WMT as an adjunct to BCT for MUD patients will form the focus of this thesis.

A pilot neuroimaging study on adjunct working memory training for MUD

WMT using the n-back task has been recently shown to improve impulse control in adolescents at risk for alcoholism (Weiland et al., 2012) and has shown promising results in aiding the treatment of alcohol abuse disorders (Houben et al., 2011). Additionally, n-back training may have particular use for SUDs, as it has been demonstrated to increase DLPFC activity, functional connectivity in the frontoparietal executive network, and dopamine release in the striatum, all of which have been shown to be reduced in SUD and relevant to treatment response (Verdejo-Garcia, 2016).

While Brooks' group conducted the first pilot intervention in South Africa to examine the neural and neuropsychological effects of WM training in patients receiving treatment for MUD, the remaining fMRI pilot study data needs to be further analysed. The pilot utilized an adapted computerized version of the n-back task (a well-known visuospatial WM task using simple letter targets) called "Curb Your Addiction (C-Ya)" based on Dr. Brooks' research with Fontera DigitalWorks for the WMT (Brooks et al., 2016; Brooks, Wiemerslage, et al., 2017). So far, published data on the pilot study has demonstrated that after 4 weeks of treatment as usual (TAU) (BCT only; n=15), MUD males exhibited increased grey matter volumes in the mesolimbic reward regions, including areas such as the bilateral putamen (extending to the amygdala and hippocampus) and reduced left middle temporal gyrus, right post-central gyrus, and left insula cortex volume (Brooks et al., 2016). Greater improvements in impulsivity and self-regulation in the WMT group (i.e. BCT with WMT adjunct; WMT; n=20) were linked to findings of significantly greater grey matter volume increases in the bilateral putamen and reductions in the bilateral cerebellar volumes. At follow up, right DLPFC volumes were greater in high WM accuracy MUD patients (irrespective of group). While high accuracy BCT only patients showed reductions in bilateral cerebellar volumes and increases in bilateral putamen volumes, high accuracy WMT patients presented with right cerebellar volumes as well as larger left putamen and right DLPFC volumes. High WM performance in the WMT group was linked to increased orbitofrontal and right middle frontal cortex grey matter volumes. These results arguably contribute to the empirical evidence of the capacity of WMT to induce neuroplasticity and suggest that WMT can aid in the process of normalizing fronto-striatal function and structure in the treatment of MUD (Brooks et al., 2016).

In the neuropsychological analysis of the Brooks et al. (2017) study, a 35% average learning rate was observed in the WMT group. This indicated the mean learning rate of the participants on the WMT task administered as an adjunct during the pilot intervention. This rate corresponded to statistically significant improvements in mood, cognitive control, and impulsivity, relative to the treatment as usual group. This suggested that C-Ya WMT fostered small but significant improvements as an adjunct, and thus may hold promise in possibly reducing relapse and improving cognition in MUD patients with neuropsychological deficits (Brooks, Wiemerslage, et al., 2017).

The current study will seek to supplement these results by conducting a secondary data analysis on the n-back task fMRI data from the pilot intervention described in Brooks et al. (2016, 2017), with the goal of determining whether the pilot intervention had an impact on the brain activity underlying WM in MUD. No differences between groups (i.e., cognitive therapy with working memory training (CT) group and cognitive therapy only (NT) group) will be anticipated at baseline. It is expected that WMT will improve brain function during WM maintenance, as well as mood and behavioural outcome measures, relative to BCT alone.

Aims

1. *Behavioural Response*

   1.1. To examine whether there are any pre- and post- treatment differences in MUD patients' behaviour (impulsivity, self-regulation, and WM) after 4 weeks of brief cognitive therapy.

   1.2. To examine whether there are any pre- and post- treatment differences in MUD patients' behaviour (impulsivity, self-regulation, and WM) after 4 weeks of modified brief cognitive therapy.

   1.3. To compare MUD patients' behavioural response to modified brief cognitive therapy, relative to standard brief cognitive therapy.

2. *Mood Response*

   2.1. To examine whether there are any pre- and post- treatment differences in MUD patients' mood (anxiety and depression) from 4 weeks of brief cognitive therapy.

   2.2. To examine whether there are any pre- and post- treatment differences in MUD patients' mood (anxiety and depression measures) from 4 weeks of modified brief cognitive therapy.

   2.3. To compare MUD patients' mood response to modified brief cognitive therapy, relative to standard brief cognitive therapy.

3. *BOLD Response*

   3.1. To examine whether there are any pre- and post- treatment differences in MUD patients' BOLD activation (on the n back task) from 4 weeks of brief cognitive therapy.

   3.2. To examine whether there are any pre- and post- treatment differences in MUD patients' BOLD activation (on the n back task) from modified brief cognitive therapy.

   3.3. To compare MUD patients' BOLD response to modified brief cognitive therapy, relative to standard brief cognitive therapy.

Hypotheses

1) Overall, both groups (cognitive therapy with cognitive training (CT) & cognitive therapy only – i.e., treatment as usual (NT)) will show lowered depression and anxiety scores, lowered impulsivity, and improvements of self-regulation, WM accuracy, and executive function. These improved outcomes will be more prominent in the WM training group relative to the NT group.
2) There will be no differences between groups at baseline in WM performance and associated brain activation.
3) There will be differences in n-back associated brain activity between groups post-intervention, particularly in the basal ganglia, cingulate cortex, prefrontal cortex, insular cortex, and cerebellum.
4) In the CT group, at follow up, there will be increased n-back associated brain activity (relative to the NT group) in the dorsolateral PFC, and frontoparietal executive areas, and cingulate cortex, suggesting increased n-back associated brain activity in the cognitive control and inhibitory networks supporting WM function.

Methodology

Study design

The current study is a secondary data analysis based on previously collected data from a pilot study (HREC: 554/2012). The current study employs a quasi-experimental repeated measures research design, and assesses neuroimaging, cognitive neuropsychological, and clinical outcomes following a psychotherapeutic treatment intervention (Stangor, 2014). This intervention served as a pilot to test participants currently receiving BCT treatment for MUD and BCT treatment for MUD with WMT as an adjunct. The functional magnetic resonance imaging (FMRI) component of this study employs a block design given its efficacy and sensitivity in detecting differences between conditions (Poldrack, Mumford, & Nichols, 2011). The N-Back WM task was administered during the fMRI scan in alternating blocks - a) 0back (simple letter detection), b) brief rest intervals, and c) 1Back (WM maintenance). This study will compare differences in brain activation between baseline and follow-up scan sessions, as a function of their treatment conditions (CT & NT). It is important to note that, although the original study did include controls, they are not of interest for the purposes of this study, the focus of which is differences between MA treatment groups, pre- and post- the psychotherapeutic intervention. As such, the sample description will be restricted to patients diagnosed with MUD.

Sample

A total of 41 male MUD patients (between the ages of 18–50) were initially recruited for the study from January 2013 to September 2014 in Cape Town, South Africa. These were in-patients were diagnosed as SUD patients with MA as the primary substance of abuse and attended a local clinic (Brooks et al., 2016). Out of the 41 participants assessed for eligibility during the enrolment period, 5 participants were excluded due to being unable to meet the inclusion criteria, resulting in a total of 36 participants being included in the study. Of these, 15 participants were randomly assigned to treatment as usual condition (NT) (participants received the standard BCT) and 21 participants were randomly assigned to the cognitive training condition (CT) (participants who received standard BCT as well as WMT). The NT group provides a contrast to allow us to control for standard treatments effects on the brain and investigate more specific isolated changes that may possibly result from WMT (Brooks et al., 2016).

Following that, a total of 3 NT participants and 7 CT participants were also excluded from the sample at follow up. Of these participants, several were excluded prior to the analyses due to the following reasons - drop-out prior to follow-up (n = 4) and poor task engagement (n = 4) and equipment malfunction, resulting in the failure to record the log file for the scanner task (n = 2). After all this, the final sample consisted of 26 male participants diagnosed with a MUD, with a total of 14 patients in the CT group and 12 patients in the NT group (Please see the Consolidated Standards of Reporting Trials (CONSORT) diagram in Figure 1). These participants were scanned (using MRI and fMRI for both structural and functional data) pre- and post- intervention. All participants provided informed consent.

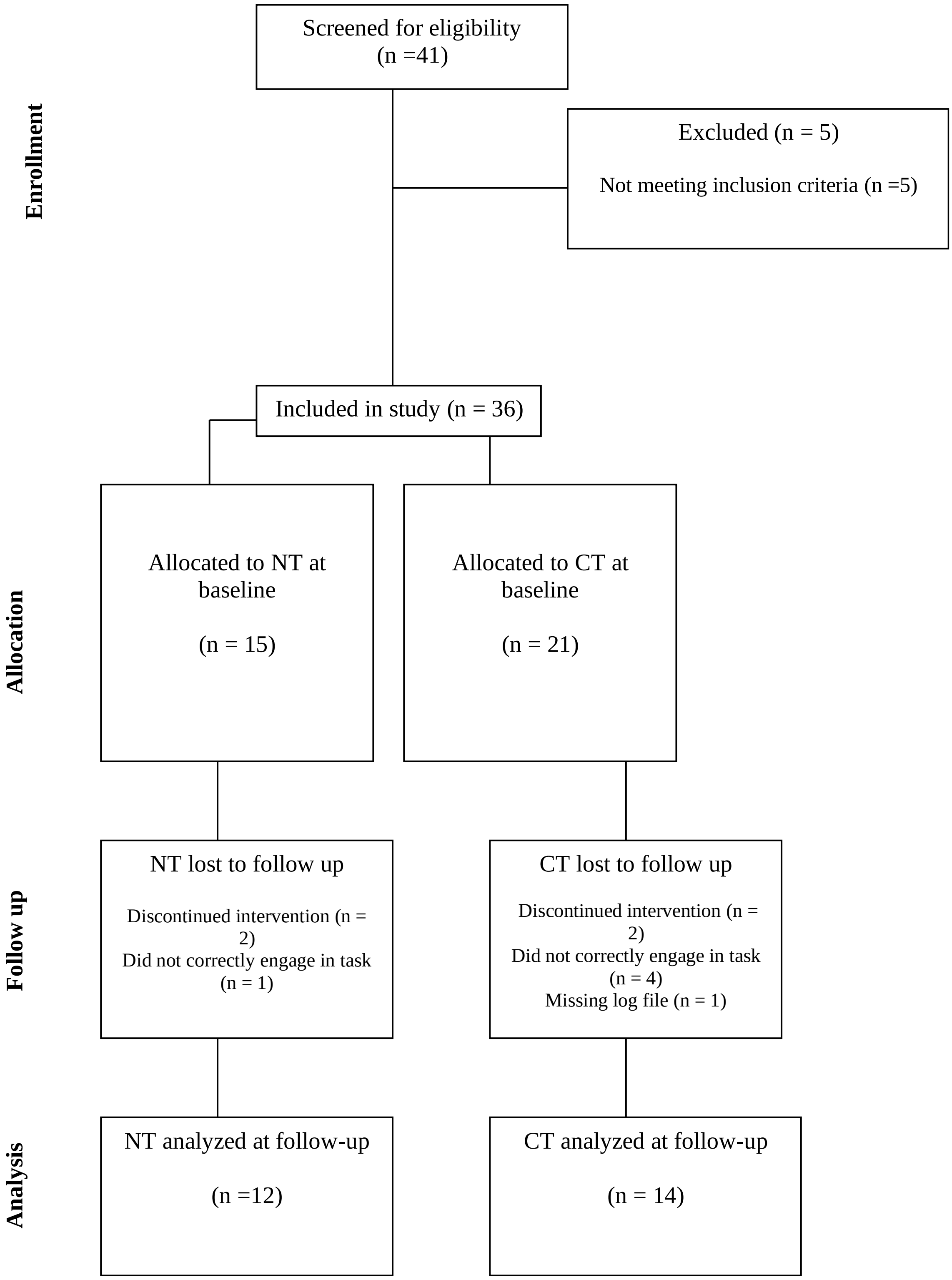

Figure 1. CONSORT Diagram of Pilot Study
CONSORT diagram describing how methamphetamine use disorder (MUD) participants were recruited to either the treatment as usual (NT) group or cognitive training (CT) group. Brain imaging data (structural and functional magnetic resonance imaging) was at baseline and follow-up in NT & CT groups.

Recruitment Procedure

Participants were selected from an admissions list generated by clinicians in the second week of admission to an inpatient drug rehabilitation facility. Potential participants with a primary MUD diagnosis were specifically identified and targeted by clinical staff that recruited patients at the clinic and delivered detailed summaries to prospective participants based on the information leaflets that were provided by the research team. Thereafter, a qualified clinical researcher delivered informed consent and initiated interested participants into the study. Thereafter, the SCID-IV (Structured Clinical Interview for Diagnosis of DSM-IV disorders) was administered by a trained professional clinical researcher to screen for comorbidities (e.g. anxiety and depression) and confirm a MUD diagnosis (First et al., 2002). MA use was measured firstly at clinical interview by qualified psychologists, and then during the study phase by a qualified psychiatrist who administered the SCID-IV. Selection of the MA use group was facilitated via admission lists by clinicians in the second week of admission to the in-patient clinic. In-patients were typically polysubstance users, or other primary substance users (e.g., heroin or cocaine) and so researchers were required to wait for participants whose primary substance of use was MA, as identified by the clinical staff. Participants were clearly informed that they were under no obligation to participate (they could drop out at any time), there were no adverse consequences to abstaining (their treatment would remain unaffected), and access to the WMT application (used for the WMT) could be provided at their convenience independent of the experiment once the study was complete. Participants were also informed that their information would be anonymized and secured to ensure their personal information remains confidential.

Inclusion and exclusion criteria

Only participants that clinicians judged to have the capacity to consent were allowed to enrol into the study. The inclusion/exclusion criteria for participation were as follows: i) MA was the primary substance of use; ii) no history of alcohol dependence, although participants were permitted to have concomitant cannabis/methaqualone use and/or infrequent alcohol use (determined through clinical screening); iii) no current or previous history of psychosis; iv) no current serious clinical diagnoses[2]; v) no prescribed medication during study, vi) minimum of 2 weeks abstinence from MA us and vii) aged between 18 and 50 years, inclusive. In addition, participants were required to be right-handed, HIV negative, possess no metal implants, have

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[2] as confirmed by clinical staff in an admission interview.

no significant physical impairments or illnesses (e.g. blindness, tuberculosis, and etc.), and no neurological conditions (e.g. epilepsy, stroke, dementia, and etc.).

Ethics

The study fully complied with the latest version of the Declaration of Helsinki at the time (World Medical Association, 2009) as well as the South African Good Clinical Practice Guidelines. All participants were reimbursed for their participation in accordance with UCT ethical guidelines. One benefit of this study is that the MA users involved in the CT group could potentially witness an improvement in their response to treatment. Those who were part of the NT group during the experiment or declined participation were provided with the opportunity to access the cognitive training application after the study.

The WMT (based on the n-back task) was administered via Curb Your Addiction, a computer application with no aversive stimuli or known negative side effects. Indeed, it is a simple game involving responding to targets (letters) with a button click. The research team administered no clinical intervention to any participant, although participants received treatment at the in-patient facility. Our experiment did not pose any risk or interference to treatment, and participants were free to stop the cognitive training at any point across the intervention.

Functional magnetic resonance imaging has a good safety record, with minimal adverse side effects on the brain and the body (Jezzard & Clare, 2001; Soares et al., 2016). Though it is slightly cold and noisy during the scan, all participants were given blankets and ear protection to protect them. Participants were informed they could opt out of the scan at any point by pressing a panic button during the scan. All participants were also informed that they could leave the experiment at any time without consequence. All safety procedures were fully explained to the participants and adhered to during the MRI scan (e.g. removing any metal items in clothing). Additionally, if any abnormal brain artefacts were observed during the scanning procedure, the researchers were set up to first alert the head of radiology, to provide a second opinion, and if the artefact was confirmed, the participant's primary medical practitioner was informed (as ethical procedure requires).

All participant information was held in a confidential manner (e.g. with a Unique Identification Code, in password protected computer files). All paper copies of participant information were kept in locked files in accordance with UCT procedures. All electronic information was stored on an encrypted, password protected hard drive. 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 concerning each participant was only accessible to authorised members of the research team, and thus the data analysed in this thesis has remained anonymous. The project worked closely with the Cape Universities Brain Imaging Centre (CUBIC) at Tygerberg Hospital, and the rehabilitation centre to ensure that it fully adhered to local emergency care and insurance procedures for research-related injury. The researchers will provide all participants with a summary of findings from our study as well as any publications emerging from this work (by sending via email or letter, on request).

Research Procedures and Data Collection Methods

Overview of Procedure

The initial 2 weeks of the program were regarded as an induction period for patients - no contact was allowed between the research team and patients during this period (see Figure 2). Researchers were allowed to conduct the cognitive training and data collection for over 4 weeks after the induction period. Both groups completed baseline and follow-up questionnaires. At the baseline of the WMT intervention (week 3), participants completed a demographic questionnaire and battery of validated psychological questionnaires to determine levels of self-reported impulsivity, self-regulation, anxiety, and depression at the clinic. From that point, CT, also received 30-minutes of daily supervised WMT over 4 weeks (excluding weekends) as an additional adjunct to the BCT. At the 4-week WMT follow-up session (week 6), NT and CT groups repeated the questionnaire battery again. At the end of their participation in each study session, all participants from the baseline session received R150 food vouchers and all those participants that completed the 4-week follow-up session received additional R150 food vouchers. As the final 2 weeks of the programme were devoted to preparing patients for their reintegration into society, no contact from the researchers was permitted.

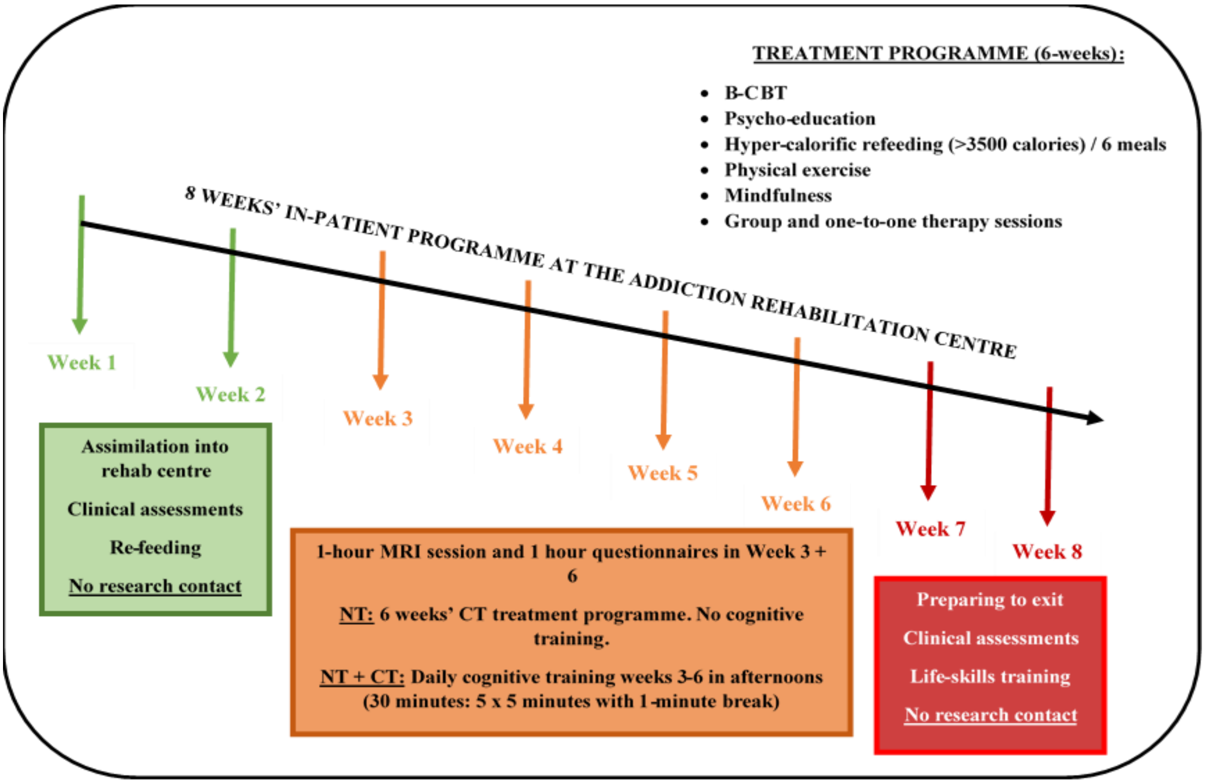

Figure 2 - Graphic Outline of Treatment Plan
The following graphically depicts an outline of the treatment plan that both treatment groups undertook. It details specific information regarding what was involved in the treatment program as well as the different parts of it. To see more detail regarding the treatment plan please refer to appendix E.

Treatment Interventions

Brief Cognitive Therapy

Patients were recruited from an inpatient drug rehabilitation clinic in the city of Cape Town. The programme at the clinic was 8 weeks in duration, during which patients were provided 6 meals daily (i.e. breakfast, lunch, supper, and 3 snacks). The treatment program involved daily 1-hour sessions of BCT based on utilizing the principles of dialectical behaviour therapy over eight weeks. Notably, this treatment intervention utilized DBT based workshops typically aimed to provide skills training in group-sessions, during individual therapy, via telephone coaching, and as part of a therapist consultation team. Typically, 4 sets of skills are considered behavioural outcomes during dialectical behaviour therapy, namely a) mindfulness, b) distress tolerance, c) interpersonal effectiveness and d) emotion regulation (Linehan et al., 1999; Robins et al., 2001; Shearin & Linehan, 1994). Patients were also given access to participate in both physical and leisure activities (please see the treatment schedule attached in the appendix E).

Curb Your Addiction - Working Memory Training Adjunct

WM capacity was specifically targeted as an adjunct in this pilot study because it is associated with enhanced cognitive control, affection regulation, and suppression (Brooks, Wiemerslage, et al., 2017). This study used the computer-based WM task called Curb Your Addiction (C-Ya) developed based on Dr. Brooks' research with Fontera DigitalWorks [www.fontera.com]. Copies of the software were available on request (after the study).

C-Ya is a version of the n-back task modified with a distracting peripheral background mosaic that mimics peripheral distraction in real life (to see a few images of the application itself, please see Figure 3). The n-back task requires participants to respond to a specified target letter as single letters consecutively and randomly present on screen (Kirchner, 1958). In the present study, the letter 'X' was the target of '0-back'; the '1-back' target aimed for a response if the current letter was identical to the '1 before'; the '2-back' target required a response when the current letter was identical to '2 before' and '3 before' for '3-back'. Targets were identified and responded to by pressing a space bar on a computer keyboard. In the present study the standard levels 0-back, 1-back, 2-back, and 3-back were used for training.

Previously findings concerned with WM training impact on neural function indicated that on average 80% was the highest accuracy score attained (Olesen et al., 2004). This was used as a guideline for the progression of participants through the training. During WMT in this study, participants began on the lowest level (i.e., 0-back) and completed 30 min daily until they achieved a minimum of 80% accuracy on that level. Once participants reached the 80% threshold on a particular level (e.g., 0-back), they were assigned the next level (e.g., 1-back) to complete the following day. If participants were unable to achieve 80% on a new level, they were required to continue from the previous level until they achieved 80%. Accuracy scores were calculated using the following algorithm: [1−((number of commissions + number of omissions) / total possible correct)] × 100 (Miller et al., 2009), where commissions were responses to non-target letters; omissions were failures to respond to a target, and total possible correct referred to the total target letters (Miller et al., 2009).

Participants in the CT group were required to engage in the task 5 times a week (i.e. daily) for 4 weeks (i.e. maximum 20 sessions) in addition to receiving BCT. Patients completed this daily 30-minute computerized WMT in a classroom in the clinic. Their pre- and post- test WM maintenance performance on the task whilst in the scanner was utilized to link WM maintenance performance to functional activity in the brain.

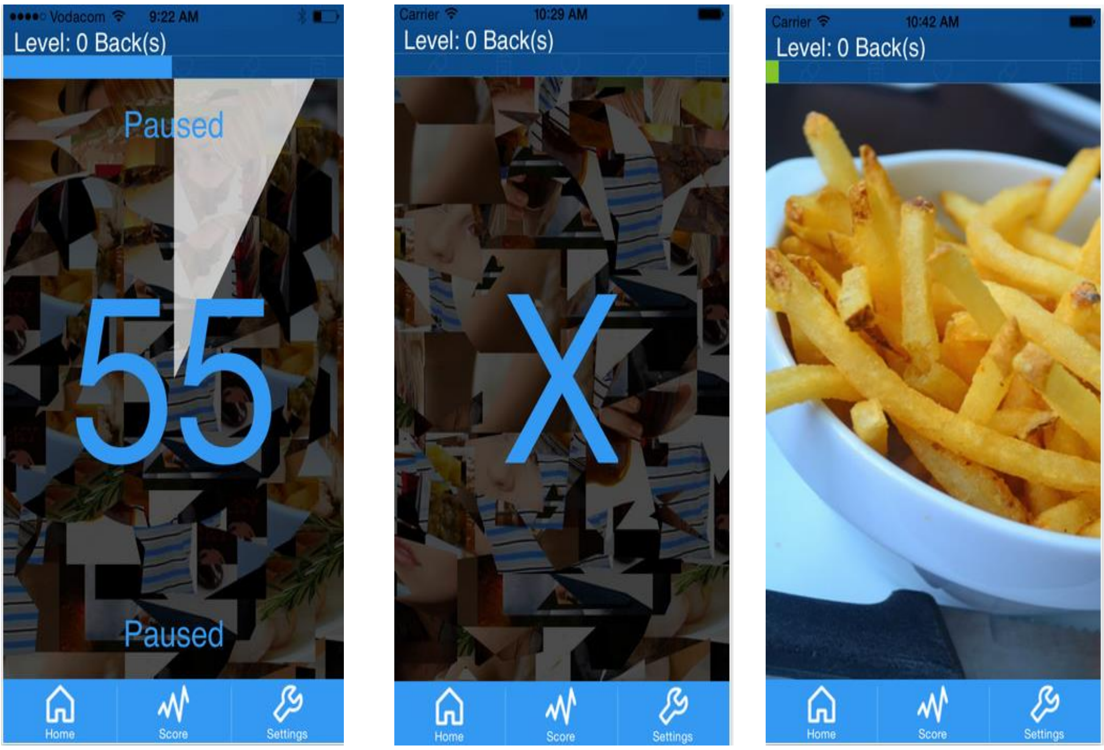

Figure 3 - Snapshots of C-Ya Application

The following pictures in the figure depict different scenes involved in the C-Ya application including, the 60 second count down, the "X" that is displayed during the 0back task, and an example of one of the complete images that is used in the mosaic backgrounds that serves to mimic the peripheral distraction of real life.

Neuropsychological, Clinical, and Behavioural Measures

Listed below are brief descriptions of the various instruments utilized in the study – these were assessed both pre- and post- intervention.

Structured Clinical Interview for Diagnosis of DSM-IV disorders (SCID-IV)

The SCID-IV is an established clinical screening instrument that includes numerous items that comprehensively screen for psychiatric conditions - e.g., substance abuse, mood, thought, anxiety, eating, and psychotic disorders (First, Spitzer, Gibbon, & Williams, 2002).

Hospital anxiety and depression scale (HADS)

The HADS is an established 14-item self-report questionnaire used to assess the patients' levels of anxiety and depression throughout the intervention. The HADS is divided into the depression (7 items) and anxiety (7 items) subscales. Items are rated on a 4-point scale (0, 1, 2, 3) in terms of severity, with a maximum score of 21 for both anxiety and depression. In this scale, the score indicates symptom severity - 0–7 is ‘normal’, 8–10 is ‘borderline’, 11-15 is ‘significant’, and 16 ≥ is ‘severe’ (Zigmond & Snaith, 1983). This scale has demonstrated efficacy in the assessment of symptom severity in clinical populations (Bjelland et al., 2002).

Barratt impulsivity scale (BIS-11)

The BIS is a 30-item self-report questionnaire and represents one of the most established and commonly used measures to assess impulsivity (Stanford et al., 2009). Items are scored on a four-point scale (rarely/never, occasionally, often, almost always/always) and form the basis of 6 first order factors (i.e. cognitive complexity, attention, perseverance, motor, self-control, and cognitive instability) and 3-second order factors (attentional, motor, and non-planning) (Patton et al., 1995). This scale has been empirically demonstrated to have reliability across diverse populations (Vasconcelos et al., 2012).

Self-Regulation Questionnaire (SRQ)

The SRQ is an established 63-item questionnaire designed to assess an individual's general capacity to self-regulate or regulate behaviour to achieve desired or beneficial future outcomes. Recent research suggests that this construct is particularly germane to substance abuse (Brown et al., 1999; Carey et al., 2004). This scale has been empirically verified to possess good internal consistency and reliability in a large sample of young adults (Carey et al., 2004). Based on the items, the SRQ measures 7 factors of self-regulation: a) receiving relevant information, b) evaluating information and comparing it to norms, c) triggering change, d) searching for options, e) formatting a plan, f) implementing the plan, and g) assessing the plan's effectiveness. SRQ scale items are scored on a 5-point scale (i.e. strongly disagree, disagree, unsure, agree, strongly agree) and participants were asked to respond based on how well each statement described them (Brown et al., 1999; Carey et al., 2004).

Working memory accuracy (n-back task)

Every participant completed the n-back task (during fMRI) for 12 min pre- and post-intervention to measure their performance (and thus WM function) on the task across the intervention. The relevant commission and omission errors were recorded to a log file and an index of accuracy was calculated according to the aforementioned algorithm (Miller et al., 2009).

Blocked Design in Functional Magnetic Resonance Imaging

In many fMRI studies – including the current study - that employ tasks as a means to operationalize a behavioural or cognitive process, the way in which tasks are designed and implemented as a function of time is crucial. To appropriately observe neural activity, conditions in a task must be systematically varied in order to observe any potential variation of signal intensity in the voxels of MRI images (Buxton, 2013; Soares et al., 2016; Stroman, 2016). As such, it is necessary to acquire a time series of images in order to observe these variations in signal intensity during the performance or engagement of behaviour/cognitive process (e.g. task/event) of interest compared to the baseline functioning of the brain. In this study, participants engaged in a block-design task, which in general consists of the presentation of a series of stimuli as a series of varying blocks of time, or epochs, where typically the stimuli involved in the task-conditions (the task) are presented in different blocks, with one of the simplest and prototypical designs following an A-B-A-B recurring type of pattern where condition A represents the baseline or rest block, and the B represents the task block (Buxton, 2013; Soares et al., 2016; Stroman, 2016).

In the current experiment, the n-back task design employs the A-B-A-C pattern in a recurring fashion (e.g., A-B-A-C-A-B-A-C-A-B-A-C), where A represents task condition 1, B represents baseline, and C represents condition 2 (this will be discussed in greater detail in the sections below). Typically, the varying blocks (task vs. baseline) alternate by fixed time periods (e.g. each block lasts 10-30s) of presentation while brain images are acquired. For example, in the current experiment, 2D-EPI images sequentially sample different slices of the brain, acquiring approximately 20 EPI images per second covering the whole brain with 3mm thick 2D slices in approximately 3s, such that each of the dynamic full brain images acquired are 3s apart – please see Figure 3 (Buxton, 2013; Soares et al., 2016; Stroman, 2016). Analysing this involves correlating the measured time series for each voxel in each model with the reference model function defined by the block design. It is usually assumed that the model function is a delayed and smoothed estimate of the block design given the slow duration of the haemodynamic response function (Buxton, 2013).

The general linear model (GLM) is commonly employed to test hypotheses based on fMRI data. It assumes that the time course of a voxel is a linear integration of a scaled estimate of the model function that includes expected signal, as well as random noise (e.g. random fluctuations in MR signals, scanner drift, magnetic susceptibility differences between physiological tissues, physiological noise (e.g. participant motion/respiration) (Buxton, 2013;

Stroman, 2016). A block design thus allows the statistical analysis of fMRI images in a meaningful way that has been credited with good statistical power, signal amplitude, and rigour.

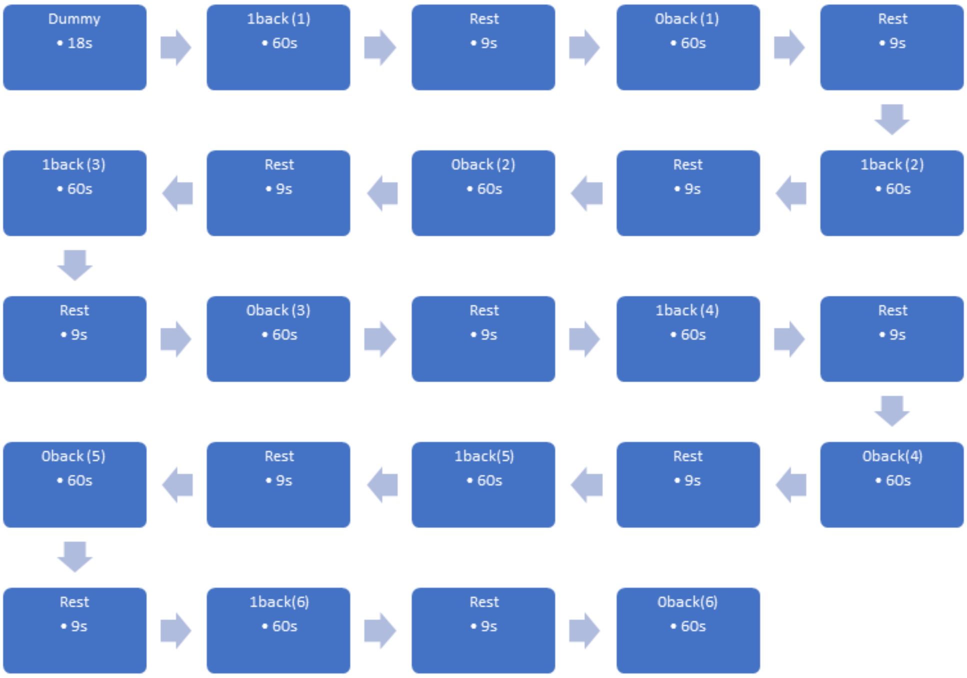

Figure 4 - Outline of N-back Task Design
This figure graphically depicts the different conditions of the n back working memory task (i.e., 0back, 1back, & rest) administered during the fMRI scan and the time frame of each condition.

Working Memory Task Design During Scan

Our laboratory used a version of the n-back task restricted to the 0-back and 1-back levels of the n back task, and which may therefore be considered testing the maintenance of information held in WM systems (Heany et al., 2019). This is in contrast to levels 2-back and higher, which are understood to additionally involve manipulation of the information load sustained in WM. The version of the n-back task used in this study has been successfully used by several laboratories, both in and out the scanner (Hur et al., 2017; Meule, 2017; Rac-Lubashevsky & Kessler, 2016; Ragland et al., 2002). The maintenance of WM in the task has been linked to the inferior parietal gyrus, DLPFC, right ventrolateral PFC, and left lingual gyrus, key regions of interest in MA use (Heany et al., 2019).

Participants were thus required to complete numerous blocks of this two-level letter variant n-back task including - 0-back (respond to presentation of “X” letter) and 1-back (respond to a letter if it is a repetition of the letter presented immediately before) during an fMRI scan (please see Figure 4). The order of the characters (i.e., alphabetic letters) displayed were randomized in each block (and throughout the task). Each of the 1-back and 0-back conditions were administered six times with a rest period between each task condition. Each 1-back and 0-back block consisted of 20 letters, each presented for 1,5 seconds followed by a 1,5 second delay for responses, alongside 9s long rest periods. The total task duration in the scanner was approximately 14 minutes. E-prime (2.0) presentation software was used to present the n-back task during the scan. Participants viewed the task on a mirror attached to the radiofrequency head coil and were requested to respond by pressing a button on the MRI compatible keypad provided.

Data Acquisition Parameters

FMRI scans were acquired at Cape University Brain Imaging Centre (CUBIC) at Tygerberg Hospital, Cape Town, South Africa. The images were acquired using a Siemens 3 Tesla Magnetom Allegra Syngo MR 2004A scanner with a 4-channel head coil using a T2* gradient echo sequence (FoV = 200mm; 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 interleaved echo planar images were acquired. Structural images were recorded for normalization and co-registration purposes using a sagittal T1 weighted image, and an 3D-MPRAGE sequence was used in the scan (TR=2.5s; FoV=256mm; voxel size=1x1x1mm) acquiring 160 interleaved slices per full brain image with a thickness of 1mm.

Pre-processing in Functional Magnetic Resonance Imaging

Once fMRI data has been acquired from the MRI scanner it typically undergoes a series of quality control and pre-processing steps that serve to validate statistical model assumptions, control for and remove artefacts and sources of noise, and standardize the locations of brain regions across participants to increase model validity and sensitivity for group analysis. In data analysis it is typically assumed that a) all voxels of a brain image volume were acquired concurrently, and b), that all data in a voxel time series solely consist of signal from the voxel (and not movement related noise). To facilitate group comparisons all participant’s brains are registered to a template (i.e., the standard Montreal Neurological Institute (MNI) template) such that each voxel is located in the same brain region for all participants (Lindquist, 2008; Poldrack et al., 2011; Soares et al., 2016). The fMRI data was pre-processed and analysed with Statistical Parametric Mapping 12 (SPM12). A summarized review of the pre-processing steps necessary (detailed in order) to prepare fMRI data for statistical analysis is provided below:

(i) The use of realignment – for motion correction - to remove and correct for possible movement artefacts which are a common major source of error in functional magnetic resonance imaging. This is necessary as when movement occurs during the scan, the signal from a voxel can become contaminated by the signal of neighbouring voxels effectively undermining the reliability and validity of the data produced as well as potentially introducing partial volume effects. Thus, the accurate estimation of motion is crucial to applying corrections to the data. The first step in motion correction in SPM12 involved estimating the optimum alignment between the input image (fMRI volume) and the target image (mean image of fMRI series). The second step (in this study) involved applying a 6-parameter rigid body transformation to transform the input image to match the target image. It is transformed using parameters concerned with the translation (x, y, and z directions) and rotation (roll, pitch, and yaw) of the image. This process is facilitated by minimizing the differences between two images by determining the parameters which would facilitate the optimum re-alignment of the images. Each brain volume is then resampled through interpolation to produce motion corrected values for the voxels (Lindquist, 2008; Poldrack et al., 2011; Soares et al., 2016). Excessive motion was checked via visual inspection, with the intent of excluding participants who exceeded a motion threshold of 3mm during the task sequence. No participants were excluded for this reason, however.

(ii) The use of co-registration to statistically map the mean functional image to the high spatial resolution structural MRI image. In this experiment, co-registration was performed using an affine transformation in order to align the structural and functional images. Affine transformation involves the transformation of approximately 12 parameters, corresponding to the translation, rotation, scaling, and shearing effects in the images, on the three axes. This is executed with the aim of ensuring that the voxels are consistently and similarly distributed across the same brain structures within subjects (Lindquist, 2008; Poldrack et al., 2011; Soares et al., 2016).

(iii) The use of normalization to statistically map individual brain scan images (the fMRI brain scans acquired) to the standard MNI template. In SPM12, it is typical to use a non-linear transformation. This involves estimating a smooth and high dimensional mapping between the voxels in the input (fMRI brain scans) and template image (MNI template). This mapping is subsequently used to resample the input image and warp it onto the template image. This allows for reasonable consistency between subjects in the spatial positioning of brain structures, allowing for the comparison, analysis, and generalization of brain imaging data to broader populations (Lindquist, 2008; Poldrack et al., 2011; Soares et al., 2016).

(iv) The use of spatial smoothing to remove outliers using 8mm full-width-half-maximum (FWHM) Gaussian filter (Poldrack et al., 2011). This involves the convolution of fMRI images using a gaussian kernel in order to improve inter-subject registration, overcome limitations in the spatial normalization of brain structures (by blurring residual anatomical differences), and potentially reduce random noise (Lindquist, 2008; Poldrack et al., 2011; Soares et al., 2016).

Statistical Analysis

Mood and Behavioural Response Analyses

All statistics were run using SPSS 12. Given that approximately 16 missing item responses[3] were identified from the psychological scales (i.e. self-regulation, impulsivity, anxiety, and depression) collected over the course of the study, multiple imputation was run utilizing the automated function on SPSS 12. Multiple imputation is an effective, flexible, and well-established tool utilized to replace missing values that often occur in clinical studies. In multiple imputation, missing item values for any variable are predicted using the existing values of other variables, where the predicted values replace the missing values, resulting in an imputed data set (Enders, 2017; Wayman, 2003). The process is performed numerous times generating numerous imputed data sets that are evaluated subsequently by the statistical programme to ensure their robustness. This process accounts for missing item data by incorporating more variance resembling the overall sample while accommodating the extant relationships between variables. Substantial evidence suggests that multiple imputation generates robust results in the presence of low sample sizes and missing data, thus representing a practical solution to missing data problems that many behavioural researchers still overlook (Enders, 2017; Wayman, 2003).

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[3] Please see the table in Appendix A

Descriptive statistics were produced for demographic variables. To assess differences between groups on mood and behavioural measures non-parametric Mann-Whitney U tests were performed. Non-parametric procedures were selected based on the relatively small size of the sample for each group, making it harder to assume normality as well as ensure enough power for a t-test (Hart, 2001; Nachar, 2008). To analyse whether there were between subject differences, that is differences between groups on the various behavioural and mood outcome measures over the course of the intervention (i.e. depression, impulsivity, WM capacity, anxiety, self-regulation), repeated measures ANOVA analyses were run. Repeated measures analyses, particularly mixed effects models, are relatively flexible and robust to violations of assumptions that commonly occur in small sample sizes, such as non-normal distributions (Gueorguieva & Krystal, 2004; Oberfeld & Franke, 2013). To assess within subject differences in the treatment groups over time, paired t-tests were run comparing each outcome variable (Hsu & Lachenbruch, 2005) pre- and post- intervention. Within-subject analyses were conducted across the entire sample, as well as within the respective treatment groups. Finally, Mann-Whitney U tests were performed to investigate post-intervention differences between groups (Hart, 2001; Nachar, 2008).

Functional Magnetic Resonance Imaging Analyses

First Level

SPM12 was used for all fMRI data analyses. In the first level, the n-back task was modelled over the two sessions (pre-, post-) of the participants using only the load conditions (0back, 1back). This analysis included all 278 volumes, only modelling the load conditions for the volumes explicitly. This modelling of the data at the single subject level was conducted to define the scan parameters (Lindquist, 2008; Poldrack et al., 2011). Two conditions were created based on these n-back conditions, with onsets following the scan onset times, as depicted in Figure 3. In this diagram each epoch, or block, was a duration of 20 scans respectively. Regressors for movement parameters derived during pre-processing were included as covariates of no interest at the first level to control for potential noise and increase robustness. Contrasts were created at the single subject level concerned with the n-back task (over the intervention – i.e. both sessions), pre-n-back, post n-back, 1back (over intervention), pre-1back, post-1back, 0back (over intervention), pre-0back, post-0back, 1 back > 0back (over intervention), pre-1back > 0back, post-1back > 0back, 1back < 0back (over intervention), pre-1 back < 0back, and post-1 back < 0back. To further elaborate, at the first level analysis in SPM it was specified that each subject attended two sessions and then t-tests were created to produce contrasts that accounted for, in this case, both sessions, the baseline session only, and the follow up session only. As both sessions (i.e., baseline session only & follow up session only) were included in one model at the first level in SPM12, t-tests were performed to extract those specific effects of each session from the rest of the model which included the other session and the motion regressors, thereby controlling for their effects. The last two contrasts were adjusted for the effects of each session, while the contrast that included both sessions implicitly modelled differences between baseline and follow-up scans for each participant.

Second Level

In the second level, the contrasts (i.e. betas) established at the single subject level were utilized to run several group-level models in this study. Given that there was no control group, a contrast group (NT) was used to isolate response to the use of working memory training as a treatment adjunct. To start, simple between group comparisons were run to establish whether there were any differences on WM performance between treatment groups pre- and post-intervention. As such, two sample t-tests were run to investigate group differences in WM function pre- and post-intervention. Thereafter, to investigate possible within subjects' effects, that is to evaluate treatment response over time in each group, paired t-tests were run on 1back, 0back, 1back > 0back, and 1back < 0back contrasts to determine the relative impact of each treatment condition within each group. To investigate whether there were any differences in WM brain function over time in the entire sample, paired t-tests were run (Henson, 2015; Henson & Penny, 2003; Lindquist, 2008).

Repeated measures ANOVAS were then run utilizing sophisticated contrasts in order to accommodate within-subject error, which was modelled using mixed model repeated measures models (McFarquhar, 2019). SPM12's flexible factorial module was employed to test pooled repeated measures ANOVA models that included interaction and main effect terms [2(Group – CT/NT) X2 (Time – Pre, Post) X2 (Condition – 1back; 0back)]. Post-hoc independent samples t-tests were conducted to investigate the specific nature of differences observed in the mixed-effects models. Furthermore, covariates were excluded in order to avoid the risk of reducing the current analyses power by adding additional noise. Doing so thus arguably improves model sensitivity. Corrections for False Discovery Rate were used to control for multiple comparisons in all analyses and reported where relevant. A recent simulation study by Woo (2014) on cluster extent thresholding used in fMRI studies indicated that minimum stringent primary thresholds such as $p > 0.001$ should be used to reduce the possibility of obtaining false positive clusters and ensure that inferences concerning spatial location can be formulated with a degree of confidence. All analyses were conducted in SPM12 (Henson, 2015; Henson & Penny, 2003; Poldrack et al., 2011).

Results

Mood and Behavioural Results

Demographics

The CT group were 28 years old (*SD* = 6.63 on average and were composed of people who identified as belonging to the “coloured” ethnic group (64%), as well as 36% who self-reported not belonging to any specific ethnic group (in the “other” category). Over half (57%) of the CT group possessed pre-matric qualifications and 28% possesses matric qualifications. The average age of the NT group was 29 years (*SD* = 6.62) and consisted of people that identified as coloured (80%), black (10%), and other (10%). Over half (67%) of NT group participants have pre-matric qualifications and 33% have matric qualifications. At baseline, the average duration of substance use (according to patient self-report) was 9.7 years (CT group mean = 9.14 years, SD = 4.81; NT group mean = 10.50 years, SD = 4.18) and the average duration of abstinence from MA use (in weeks) was 3.76 (CT group mean = 3.1 weeks, *SD* = *3.24*; NT group mean = 4.5 weeks¸ *SD* = 2.52) for the entire sample (please see Table 1). No significant differences were observed between CT and NT groups on demographic variables (i.e., - level of education, ethnicity, age, duration of MA use, duration of abstinence, total matter (brain) volume) – please see Table 2.

Table 1. Descriptive Statistics

Groups	**Sample (n=26)**		**NT (n=12)**		**CT (n=14)**	
Measures	***Mean***	***Standard Deviation***	***Mean***	***Standard Deviation***	***Mean***	***Standard Deviation***
HADS-A	7.77	2.82	8.17	2.13	7.43	3.35
HADS-D	5.58	3.3	5.58	2.64	5.57	3.87
BIS	68.96	11.17	69	11.15	68.93	11.53
SRQ	220.46	18.95	220	14.94	220.43	22.4
Ethnicity	2.65	1.33	2.17	0.94	3.07	1.492
Age	28.62	6.19	29	6.62	28.29	6.031
Education	1.31	0.47	1.33	0.49	1.29	0.469
Duration of use	9.77	4.45	10.50	4.84	9.14	4.2
Duration of abstinence	3.78	2.91	4.54	3.24	3.11	2.52
Nback	83.97	17.88	87.43	13.05	81.01	21.22
TMV	1399	110	1403.35	102.91	1395.82	118.78

Notes: This table detailed the summary statistics prior to the intervention. The following abbreviations were used - CT (Cognitive Therapy and Training); NT (Cognitive Therapy only); HADS-A (Hospital Anxiety and Depression Scale - Anxiety); HADS-D (Hospital Anxiety and Depression Scale - Depression); BIS (Barratt's Impulsivity Scale); SRQ (Self-Regulation Questionnaire); and TMV (Total Matter Volume).

Between Subject Differences – Between Groups

Pre-Intervention

Mood Response

No significant differences were observed between CT group and NT group on mood measures (HADS-anxiety and HADS-depression) (please see Table 2).

Behavioural Response

No significant differences were observed between CT group and NT group on behavioural measures - WM accuracy (n back task), BIS-impulsivity, and SRQ-self regulation scores (please see Table 2).

Table 2. Mann-Whitney U - Between Groups Pre-Intervention

Measures	***Mann-Whitney U***	***Wilcoxon W***	***Asym. Sig. (2-tailed)***
Demographic			
Age	80	185	0.84
Education	80	185	0.8
Duration of use	72.5	177.5	0.55
Duration of abstinence	60	165	0.21
Ethnicity	56	134.5	0.07
T.M.V.	68.5	173.5	0.43
Mood			
HADS-A	61	166	0.23
HADS-D	82	187.5	0.94
Behavioural			
BIS	82	160	0.92
SRQ	77	182	0.72
Nback	81	186	0.88

Notes: This table detailed the results of the pre-intervention Mann Whitney U analyses on demographic variables. The following abbreviations were used - HADS-A (Hospital Anxiety and Depression Scale - Anxiety); HADS-D (Hospital Anxiety and Depression Scale - Depression); BIS (Barratt Impulsivity Scale); and SRQ (Self-Regulation Questionnaire) and TMV (Total Matter Volume).

Post-Intervention

Mood Response

No significant differences were observed between the CT group and the NT group on the Mann-Whitney U tests run on post-intervention mood measures - HADS-anxiety and HADS-depression (please see Table 3).

Behavioural Response

No significant differences were observed between the CT group and the NT group on the Mann-Whitney U tests run on post-intervention behavioural measures - WM accuracy, BIS-impulsivity, and SRQ-self regulation (please see Table 3).

Table 3. Mann-Whitney U - Between Groups Post-Intervention

Measures	***Mann-Whitney U***	***Wilcoxon W***	***Asym. Sig. (2-tailed)***
Mood			
HADS-A	61	166	0.23
HADS-D	82	187.5	0.94
Behavioural			
BIS	82	160	0.92
SRQ	77	182	0.72
Nback	81	186	0.88

Notes: This table detailed the results of the post-intervention Mann Whitney U analyses. The following abbreviations were used - HADS-A (Hospital Anxiety and Depression Scale - Anxiety); HADS-D (Hospital Anxiety and Depression Scale - Depression); BIS (Barratt Impulsivity Scale); and SRQ (Self-Regulation Questionnaire).

Within Subject Differences – Entire Sample

Mood Response

A paired t-test that was run on the depression measures (HADS-D) pre (M= 5.57, SD= 3.29) and post (M= 4.04, SD= 2.877) cognitive therapy indicated there was a *significant reduction* in depression symptom severity over time (t (25) = 2.27, p = .032) (Please see Figure 5). A paired t-test on the anxiety measures (HADS-A) pre (M = 7.77, SD = 2.82) and post (M = 6.54, SD = 2.32) cognitive therapy indicated there was a sub-threshold reduction in anxiety symptom severity over time (t (25) = 2.01 p = .06). All results are detailed in Table 4.

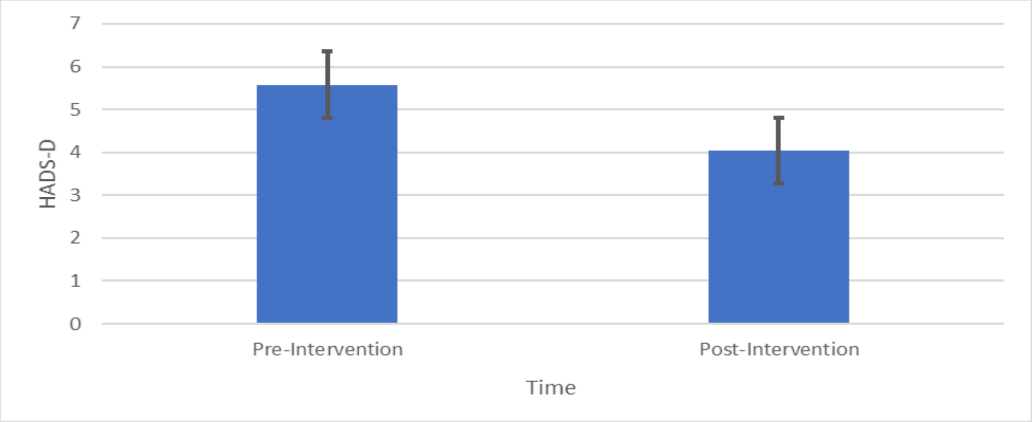

Figure 5 - HADS-D Pre- and Post- Mean Scores & Standard Error

Behavioural Response

A paired t-test on the self-regulation measures (SRQ) pre (M= 220.46, SD= 18.95) and post (M= 222.08, SD= 22.91) cognitive therapy indicated there was no significant difference in self-reported self-regulation over time (t (25) = -.36, p = .73). A paired t-test on the impulsivity measures (BIS) pre (M= 68.96 SD= 11.13) and post (M= 64.77, SD= 10.41) cognitive therapy indicated there was a *significant reduction* in self-reported impulsivity over time (t (25) = 2.12, p = .04) (Please see Figure 6). A paired t-test on the WM accuracy measures (e.g. n back) pre (M= 83.97, SD= 17.87) and post (M= 91.08, SD= 7.75) cognitive therapy indicated there was a sub-threshold improvement in WM over time (t (25) = -2.03, p = .05). Please see all results detailed in Table 4.

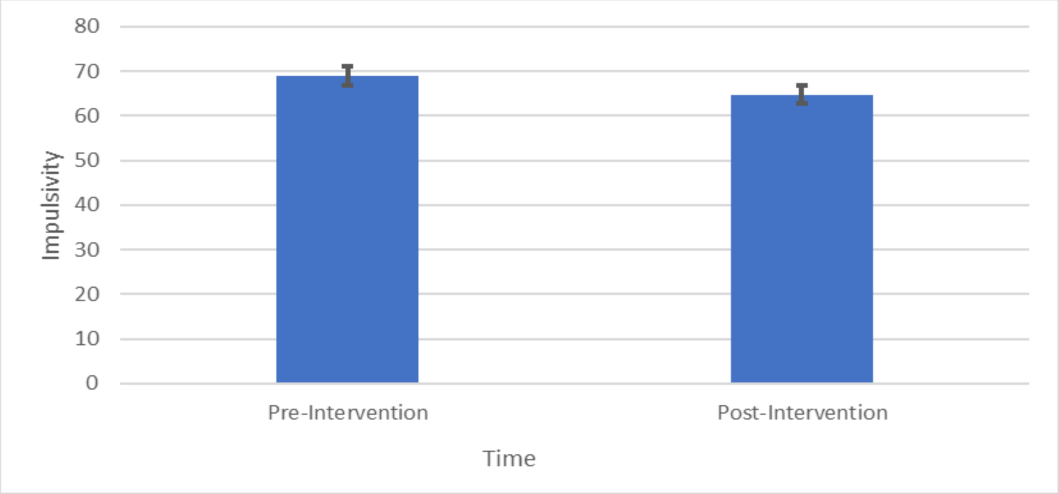

Figure 6 - BIS Pre- and Post- Mean Scores & Standard Error

Table 4. Sample - Paired T-tests

Measure	**Mean**	**Paired Differences**				**t**	**Sig. (2-tailed)**
		Std. Deviation	**Std. Error Mean**	**95% Confidence Interval of the Difference**			
				Lower	**Upper**		
HADS-A	1.23	3.13	0.61	-0.03	2.49	2.01	0.06
HADS-D	1.54	3.46	0.68	0.14	2.93	2.27	0.03
BIS	4.19	10.07	1.97	0.13	8.26	2.12	0.04
SRQ	-1.62	23.16	4.54	-10.97	7.74	-0.36	0.73
Nback	-7.10	17.86	3.50	-14.32	0.11	-2.03	0.05

Notes: This table details the results of the paired samples t-tests run on measures of the entire sample. The following abbreviations were used - HADS-A (Hospital Anxiety and Depression Scale - Anxiety); HADS-D (Hospital Anxiety and Depression Scale - Depression); BIS (Barratt Impulsivity Scale); and SRQ (Self-Regulation Questionnaire). The df = 25 for all comparisons.

Within Subject Differences – Within Groups

Cognitive Therapy Only – Treatment as Usual (NT)

Mood Response

Paired t-tests were run on the HADS-A & HADS-D scores of NT patients to evaluate whether there were any potential differences in anxiety and depression scores pre- and post-intervention. No significant differences were observed. Please see Table 5 for further information.

Behavioural Response

Paired t-tests were run on the WM accuracy, impulsivity, and self-regulation scores of NT patients to evaluate whether there were any potential differences pre- and post- intervention. No significant differences were found. Please see Table 5 for further information.

Table 5. Cognitive Therapy Only - Paired Samples Tests

Measure	**Mean**	**Paired Differences**				**t**	**Sig. (2-tailed)**
		Std. Deviation	**Std. Error Mean**	**95% Confidence Interval of the Difference**			
				Lower	**Upper**		
HADS-A	1.67	3.28	0.95	-0.42	3.75	1.76	0.12
HADS-D	1.25	2.96	0.85	-0.63	3.13	1.46	0.17
BIS	2.42	12.02	3.47	-5.22	10.05	0.70	0.50
SRQ	2.25	21.33	6.16	-11.31	15.81	0.37	0.72
Nback	-6.48	12.79	3.69	-14.60	1.65	-1.75	0.11

Notes: This table details the results of the paired samples t-tests run on measures from the Cognitive Therapy Only group. The following abbreviations were used - HADS-A (Hospital Anxiety and Depression Scale - Anxiety); HADS-D (Hospital Anxiety and Depression Scale - Depression); BIS (Barratt Impulsivity Scale); and SRQ (Self-Regulation Questionnaire). The df = 11 for all comparisons.

Cognitive Therapy with Cognitive Training (CT)

Mood Response

Paired t-tests were run on the HADS scores of CT group patients to evaluate whether there were any potential differences in anxiety and depression scores pre- and post- intervention. No significant differences were observed. Please see Table 6 for further information.

Behavioural Response

Paired t-tests were run on the WM accuracy, impulsivity, and self-regulation scores of CT group patients to evaluate whether there were any potential differences pre- and post-intervention. A significant difference was found on BIS scores, indicating a significant reduction in impulsivity in the CT group post-intervention ($p = 0.02$, $t = 2.61$). Please see Table 6 for further information.

Table 6. Cognitive Therapy with Cognitive Training - Paired Samples Test

Measure	Mean	Paired Differences				t	Sig. (2-tailed)
		Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference			
				Lower	Upper		
HADS-A	0.86	3.06	0.82	-0.91	2.62	1.05	0.31
HADS-D	1.79	3.92	1.05	-0.48	4.052	1.70	0.11
BIS	5.71	8.20	2.19	0.98	10.45	2.65	0.02
SRQ	-4.93	24.92	6.66	-19.32	9.46	-0.74	0.47
Nback	-7.64	21.78	5.82	-20.21	4.93	-1.31	0.21

Notes: This table details the results of the paired samples t-tests run on measures from the Cognitive Therapy with Cognitive Training group. The following abbreviations were used - HADS-A (Hospital Anxiety and Depression Scale - Anxiety); HADS-D (Hospital Anxiety and Depression Scale - Depression); BIS (Barratt Impulsivity Scale); and SRQ (Self-Regulation Questionnaire). The df = 13 for all comparisons.

Change in mood and behavioural outcomes between groups over time

Mood Response

Depression

A repeated measures ANOVA with a Greenhouse-Geisser correction showed that mean depression (HADS-D scores) differed significantly between time points [F (1, 24) = 4.81, p < 0.04], but not between groups [F (1, 24) = 0.07, p < 0.79]. The interaction between group and depression (over time) was not significant [F (1, 24) = 0.15, p < 0.70], indicating that there was insignificant evidence of group differences over time. Post hoc tests using the Bonferroni correction revealed that depression reduced by an average score of 1.52 after treatment (p < 0.04) and this reductive effect appeared to be larger in the cognitive training group than cognitive therapy only group, despite not reaching significance (Figure 7).

Anxiety

A repeated measures ANOVA with a Greenhouse-Geisser correction showed that mean anxiety (HADS-A scores) did not differ significantly between time points [F (1, 24) = 4.12, p < 0.05], nor between groups [F (1, 24) = 0.17, p < 0.69]. The interaction between group and anxiety (over time) was not significant [F (1, 24) = 0.026, p < 0.87], indicating that there was insignificant evidence of group differences over time (Figure 8).

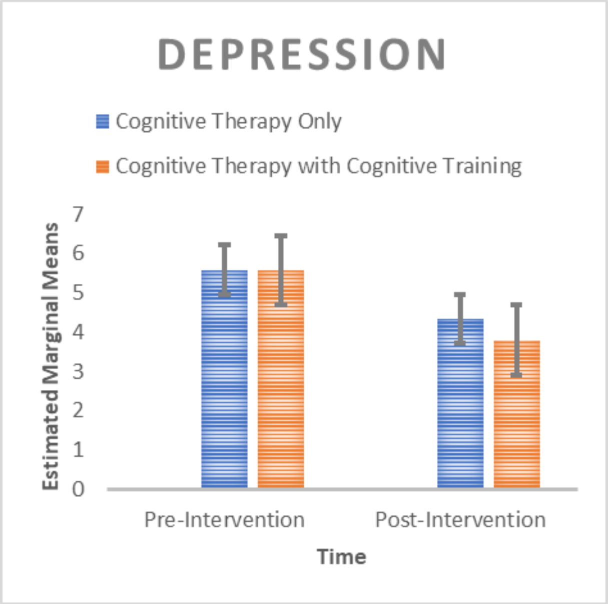

Figure 7 – Depression Repeated Measures ANOVA Bar Graph with Standard Error

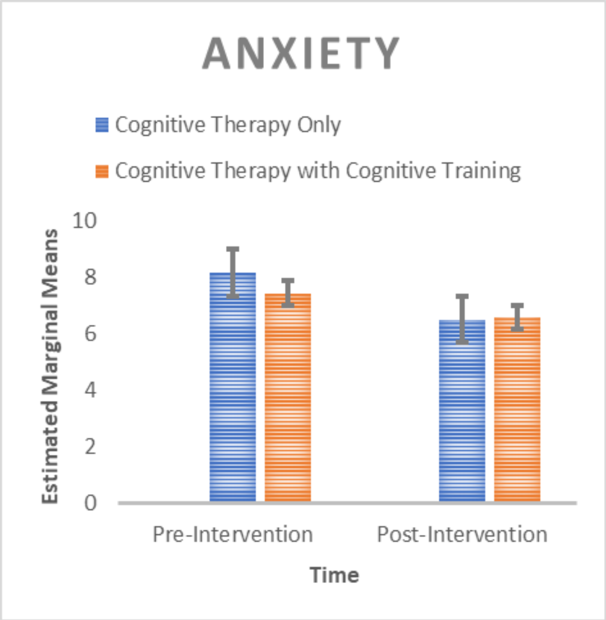

Figure 8 – Anxiety Repeated Measures ANOVA Bar Graph with Standard Error

Behavioural Response

Self-Regulation

A repeated measures ANOVA with a Greenhouse-Geisser correction showed that mean self-regulation did not differ significantly between time points [F (1, 24) = 0.09, p < 0.77], nor between groups [F (1, 24) = 0.25, p < 0.62]. The interaction between group and self-regulation (over time) was not significant [F (1, 24) = 0.42, p < 0.52], indicating that there was insignificant evidence of group differences over time (Figure 9).

Working Memory Accuracy (N-back fMRI task)

A repeated measures ANOVA with a Greenhouse-Geisser correction showed that mean WM accuracy did not differ significantly between time points [F (1, 24) = 3.88, p < 0.06], nor between groups [F (1, 24) = 0.16, p < 0.08].The interaction between group and WM accuracy (over time) was not significant [F (1, 24) = 0.02, p < 0.87], indicating that there was insignificant evidence of group differences over time (Figure 10).

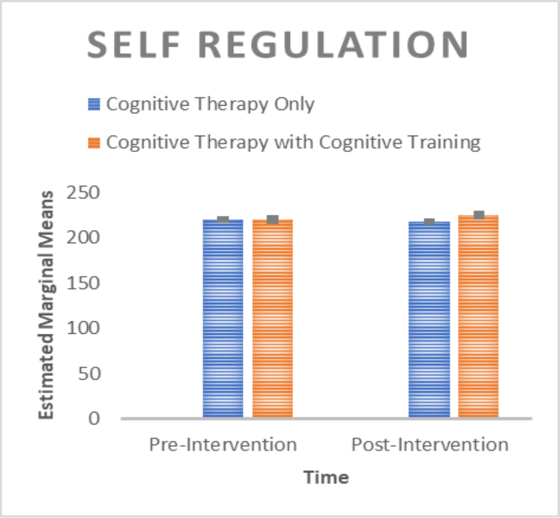

Figure 9 – Self-Regulation Repeated Measures ANOVA Bar Graph with Standard Error

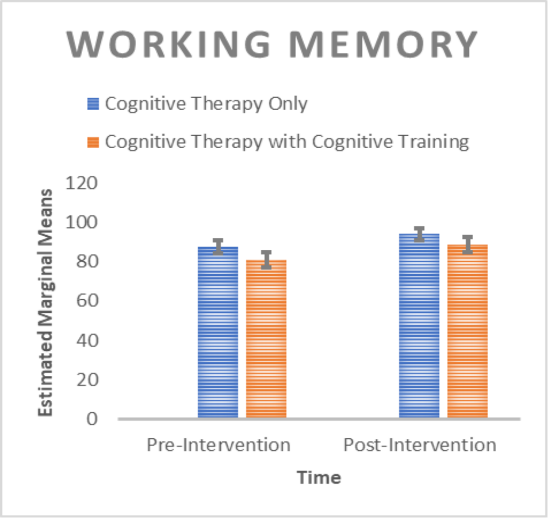

Figure 10 - Working Memory Repeated Measures ANOVA Bar Graph with Standard Error

Impulsivity

A repeated measures ANOVA with a Greenhouse-Geisser correction showed that mean impulsivity did not differ significantly between time points [F (1, 24) = 4.16, $p < 0.05$], nor between groups [F (1, 24) = 0.204, $p < 0.66$]. The interaction between group and impulsivity (over time) was not significant [F (1, 24) = 0.68, $p < 0.42$], indicating that there was insignificant evidence of group differences over time (Figure 11).

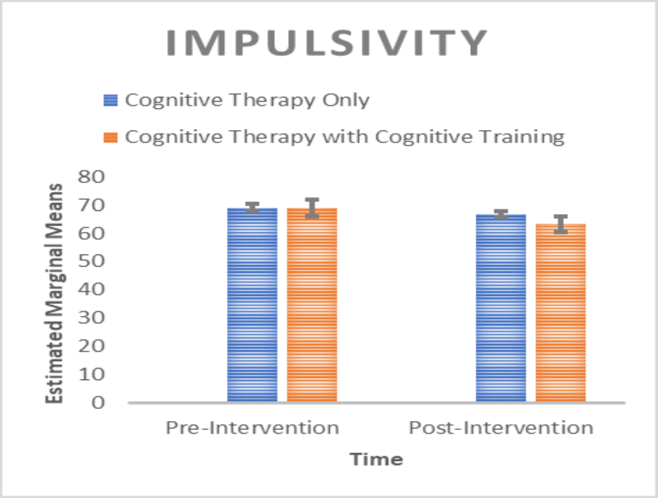

Figure 11 - Impulsivity Repeated Measures ANOVA Bar Graph with Standard Error

fMRI Analyses

Within Subject Analyses – Paired T-tests

Cognitive Training (CT) Group

Whole brain paired t-tests were conducted on contrasts based on the levels of the n back task (e.g., 0back, 1back, 1back < 0back, 1back > 0back). There was no evidence of significant activity observed in the CT group for any of these contrasts between pre- and post-intervention.

Cognitive Therapy Only (NT) Group

Whole brain paired t-tests were conducted on contrasts based on the levels of the n back task (e.g., 0back, 1back, 1back < 0back, 1back > 0back). There was no evidence of significant activity observed in the NT group for any of these contrasts between pre- and post-intervention.

Between Subject Comparisons – T-tests

Pre-Treatment

No significant effects were observed between groups after running ANOVAS on the 0back, 1back, 1back < 0back, and 0back > 1back contrasts at pre-treatment.

Post-Treatment

No significant effects were observed between groups after running ANOVAS t-tests on the on the 0back, 1back, 1back < 0back, and 0back > 1back contrasts at post-treatment.

Whole Brain Repeated Measures ANOVAs

TimexConditionxGroup Interaction

No significant effect was observed after running a whole brain repeated measures ANOVA (using flexible factorial in SPM12) model of the experiment, assessing whether any differences may be observed as a function of an interaction between model terms for time (pre, post), group (CT, NT), and condition (0back, 1back).

TimexCondition Interaction

No significant interaction effects were observed between terms for time and n-back condition after running a whole brain repeated measures ANOVA (using flexible factorial in SPM12).

TimexGroup Interaction

No significant effects were observed after running a repeated measures ANOVA (using flexible factorial in SPM12) model on the potential interaction between the two respective intervention groups and time points.

ConditionxGroup Interaction

No significant effects were observed when attempting to assess whether there is an interaction between treatment group and n back condition after running a whole brain repeated measures ANOVA (using flexible factorial in SPM12) on those interaction terms.

Condition Main Effect

No significant effects were observed after running a repeated measures ANOVA (using flexible factorial in SPM12) model on the main effect of condition.

Group Main Effect

Whole-brain repeated measures ANOVA on the main effect of group, that is the differences between the cognitive training and the cognitive therapy groups indicated significant activation with FDR correction in a cluster encompassing the following areas of peak activation - left posterior cingulate, left anterior cingulate, and left lingual gyrus across both pre- and post- intervention scans (see Table 7 and Figures 12, 13, 14, & 15). Less activation was apparent in the CT group relative to the NT group in these regions.

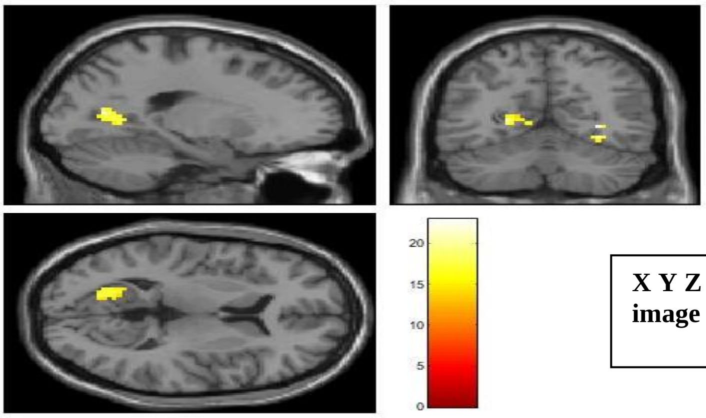

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Figure 12 - Repeated Measures Group Main Effect
Notes: The following figure represents a contrast image depicting significant FDR corrected activation in the left posterior cingulate, left anterior cingulate, and left lingual gyrus.

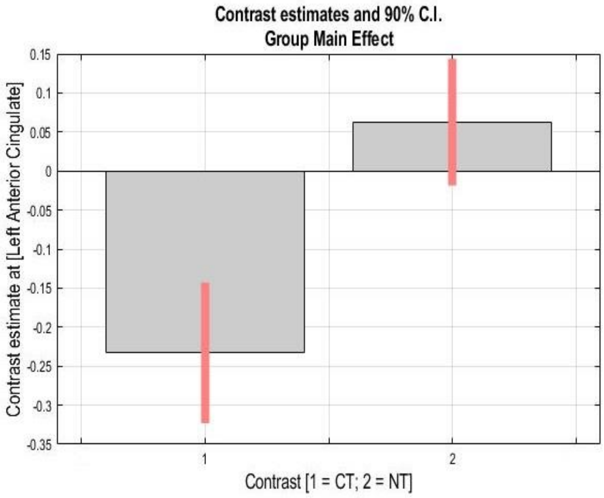

Figure 13 - Group Main Effect Left Anterior Cingulate Contrast estimates
Notes: The following figure depicts the contrast estimates and confidence intervals of the significant activation in the left anterior cingulate for each treatment group.

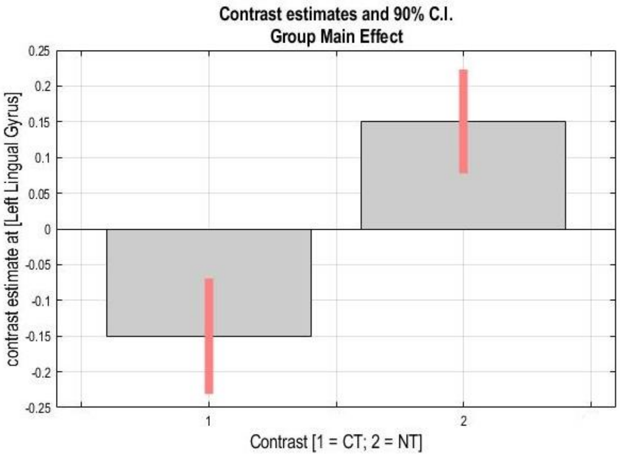

Figure 13 - Group Main Effect Left Lingual Gyrus Contrast Estimates
Notes: The following figure depicts the contrast estimates and confidence intervals of the significant activation in the left lingual gyrus of each treatment group.

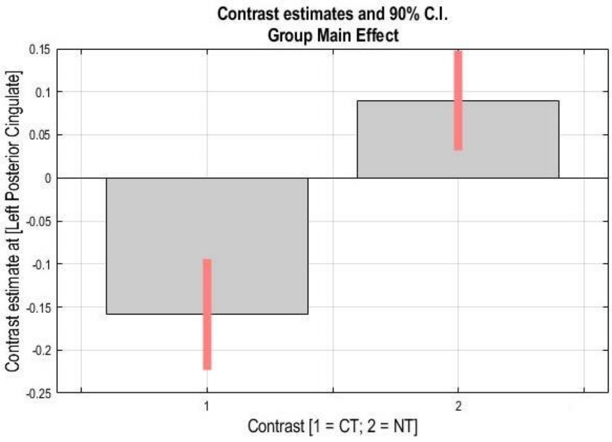

Figure 14 - Group Main Effect Left Posterior Cingulate Contrast Estimates
Notes: The following figure depicts the contrast estimates and confidence intervals of the significant activation in the left posterior cingulate of each treatment group.

Group Main Effect - Post-hoc T-tests

$CT_{Group} > NT_{group}$

A post-hoc t test (used to assess the direction of the effect between the two groups) based on the group main effect indicated significant differences in activity were detected under FDR-correction on the contrast $\mathrm{CT}_{\mathrm{Group}}$ > $\mathrm{NT}_{\mathrm{Group}}$ indicating significantly less activity in the $\mathrm{CT}_{\mathrm{Group}}$ in a cluster containing the left lingual gyrus, left posterior declive, and right cuneus (please see Table 7 and Figure 16).

CT_{Group} < NT_{group}

Post-hoc t tests on group main effect indicated that there were significant differences under FDR correction on the contrast CT_{Group} < NT_{Group} indicating significantly greater activity activity in the NT_{Group} in a cluster containing the left superior temporal gyrus, left insula, right posterior declive, and lingual gyrus (please see Table 7 and Figure 17).

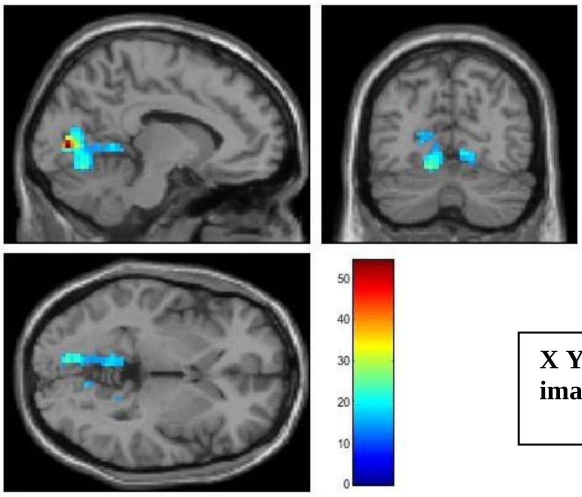

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Figure 16 - Repeated Measures Posthoc t-test CT > NT
Notes: The following figure represents a contrast image depicting significant FDR corrected activation in the left lingual gyrus, left posterior declive, and right cuneus.

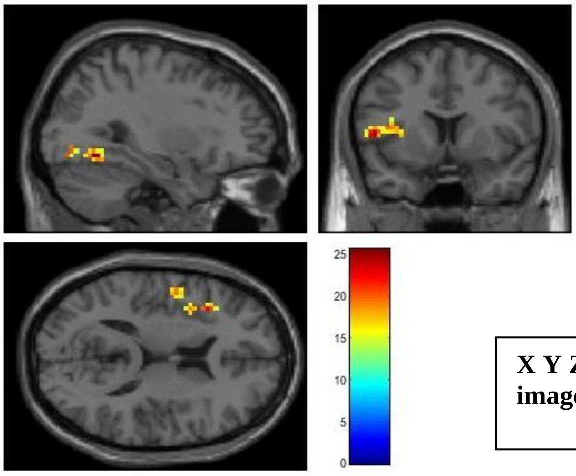

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Figure 17 - Repeated Measures Posthoc t-test CT < NT
Notes: The following figure represents a contrast image depicting significant FDR corrected activation in the left superior temporal gyrus, left insula, right posterior declive, and lingual gyrus.

Time Main Effect

No significant effects were observed on an uncorrected repeated measures model of the main effect of time.

Table 7. Repeated Measures ANOVA Models

Cluster				**Brain Co-ordinates**	
p (FDR)	**k**	**F/t**	**Z**	**x, y, z**	**Region**
Group Main Effect					
0.02	64	22.22	3.76	-19, -68,11	Left Posterior Cingulate [Brodmann area 30]
		20.67	3.65	-22, -59,5	Left Lingual Gyrus [Brodmann area 18]
		16.06	3.28	-13, -50,2	Left Anterior Cingulate [Brodmann area 10]
Posthoc T-test – Ntgroup > CTgroup					
0.003	94	25.60	3.97	-50,7, 5	Left Superior Temporal Gyrus [Brodmann area 22]
		24.11	3.88	-38, 19, 18	Left Insula [Brodmann area 13]
		20.58	3.64	-38, 7, 11	Left Insula [Brodmann area 13]
0.02	54	25.20	3.95	31, -62, -11	Right Posterior Declive
		22.76	3.79	28, -81, -8	Right Lingual Gyrus [Brodmann area 18]
		18.59	3.49	22, -87, -4	Right Lingual Gyrus [Brodmann area 19]
Posthoc T-test - CTgroup > NTgroup					
0.00	274	54.25	5.15	-10, -81, 2	Left Lingual Gyrus [Brodmann area 18]
		30.47	4.24	-13, -71, -14	Left Posterior Declive
		27.72	4.09	9, -81, 8	Right Cuneus [Brodmann area 17]

Notes: The following table details the results of statistically significant repeated measures ANOVA models conducted through the use of the flexible factorial model on the fMRI data in SPM12. The analyses were conducted using FDR-correction to identify significant clusters of activation.

Discussion

This study aimed to investigate the use of WMT as an adjunct to brief term cognitive therapy for MUD. Participants were divided into two groups, those receiving standard brief cognitive therapy (or treatment as usual) and those receiving modified brief cognitive therapy with WM cognitive training as an adjunct. Behavioural outcome measures and the n-back WM task adapted for fMRI were measured and compared pre- and post- intervention. Prior to treatment, no statistically significant differences in brain activity and behavioural and demographic measures were observed between groups.

FDR-corrected findings were observed in the repeated measures ANOVA model, indicating a statistically significant group main effect on the fMRI n-back task. This was further investigated in this study using post-hoc tests. No main effects of load and time, or interactions between any main effects tested, were detected. The behavioural and neuroimaging findings of this study will be discussed below, followed by a description of limitations of the study.

Neuroimaging findings

In the current study, statistically significant differences (FDR corrected) in activation were observed in a cluster containing the left posterior cingulate, left lingual gyrus, and left anterior cingulate for the main effect of group of the repeated measures ANOVA. Subsequently, a post-hoc t-test was performed to determine the direction of the difference between the brief cognitive training and modified cognitive training groups. Statistically significant activation was observed in a posthoc test in the NT group than the CT group in the left superior temporal gyrus, left insula, right posterior declive, and right lingual gyrus. Contrastingly less activation was observed in the posthoc test in the CT group than the NT group in the left lingual gyrus, left posterior declive, and right cuneus. The relevant observed brain activity will be discussed below. This will start with a review of the regions which were found to overlap between the group main effect and posthoc t-tests as they are consistent with each other and then move to the remaining regions identified in the posthoc t-tests which were not implicated in the group main effect.

Statistically significant activation was also observed in the lingual gyrus between groups, with the group main effect indicating less activation in cognitive training group relative to treatment as usual during the n back task. Posthoc tests further indicated more lingual gyrus activity in the treatment as usual group, while the cognitive training group were observed to have less relative activity. The lingual gyrus has been directly implicated in the process of WM maintenance (Heany et al., 2019). Given that the cognitive training group were observed to have less activation on the n back task relative to the treatment as usual group, it could suggest that the treatment as usual group likely need to harness more neural activation to perform the same processes as the cognitive training group. This may suggest that relative to the treatment as usual group, cognitive training may have improved the efficiency of WM maintenance brain function in the sample of MA patients (Brooks, 2016; Brooks et al., 2016; Constantinidis & Klingberg, 2016; Leech and Sharp, 2013; Schweizer et al., 2013; Takeuchi et al., 2014).

Posterior cingulate cortex (PCC) activation was observed as a group main effect, suggesting that there was a difference in activity between treatment groups – with less activity in the cognitive training group relative to treatment as usual. Although there was little evidence for an interaction between session and treatment group on WM-related brain activation, and thus the hypothesis that cognitive training will change brain function in performing a WM task demands was not supported, the fact that a main effect of group was observed despite groups being equivalent with respect to brain response at baseline suggests that the WMT adjunct did have some effect on brain activity underlying WM function. With that in mind, the possible implications of group differences observed in this study are discussed below.

The PCC is implicated as a key region involved in arousal and awareness, with relatively high levels of PCC metabolism and functional activity being associated with normal conscious states. The established function of PCC has been linked to internally directed cognition (including the retrieval of episodic and semantic memories), particularly within the ventral PCC and retrosplenial cortex. The PCC arguably plays an active role in controlling the balance between an external and internal focus of attention (Leech & Sharp, 2013). The PCC has also been linked to environmental change detection and increases in regional activation have been observed during tasks that involve attentional bias towards highly motivated targets. Activity in the dorsal PCC is modulated by attentional states: increased activity while in anticipation of an external cue to action (e.g. repeated letter in the n-back task) and reduced activity once action is initiated and attentional focus is required (Leech and Sharp, 2013). The dorsal PCC has been linked to cognitive control and is involved in the detection and response to environmental events that may require changes in behaviour and are not present within the current cognitive schema or repertoire (Leech and Sharp, 2013). On the whole, changes in arousal are represented by shifts in activation throughout the posterior cingulate, while shifts in the balance between internal/external attention and breadth of focus are associated with more regional changes in activity and connectivity. The n-back requires a narrow external focus, where subjects are rapidly presented with novel information that needs to be retained in WM and utilized in decision making. This is associated with increased activation of the dorsal attention network and fronto-parietal control network (FPCN), alongside deactivation in both the dorsal and ventral PCC (Leech and Sharp, 2013).

Given that the participants in the cognitive training group were more acquainted with the task, having received WMT for four weeks, the decreased activation observed in the left posterior cingulate of this group may possibly represent greater attentional focus (relative to the group receiving treatment as usual) in anticipation of the highly motivated or salient letter cue in the n-back task. It may also possibly reflect lower attentional demands in the cognitive training group, given their task familiarity. It is also possible that the cingulate activations are in response to the cognitive conflict that emerges in participants required to selectively maintain information in WM while updating other information (Murty et al., 2011). This result may also potentially reflect enhanced internally directed cognition (in the retrieval of the relevant letter) in the cognitive training group relative to the treatment as usual group during WM (Leech and Sharp, 2013).

Greater activity in the PCC during in the treatment as usual group (in contrast to cognitive training group) may also reflect the increased activity utilized in the region to anticipate and facilitate the detection and response to changes in the visual environment. Moreover, given that the process of WM maintenance implicated in the 0back and 1back conditions arguably requires sustained attention and response control (Leech & Sharp, 2013; Miller et al., 2009), and also involves familiarity and recognition based performance (Jaeggi et al., 2010), increased activity in the treatment as usual group relative to the cognitive training may thus potentially be indicative of inefficient function in attentional networks or the fact that the task was relatively unfamiliar to the treatment as usual group and thus more novel and salient (Leech and Sharp, 2013).

Greater ACC activity in the group receiving treatment as usual relative to the cognitive training group during the n back task may arguably reflect inefficient functioning in response selection and conflict monitoring (Lenartowicz and McIntosh 2005). Different forms of WMT have been linked to improvements in the function and structure of the ACC, as well as fronto-striatal circuits, reversing some of the effects that would likely result from sustained MA abuse (Brooks, 2016; Brooks et al., 2016; Constantinidis & Klingberg, 2016; Schweizer et al., 2013; Takeuchi et al., 2014). Indeed, neuronal structural integrity within the ACC has been linked to the regulation of conflict monitoring mechanisms and control of goal-directed behaviour and can be compromised by long-term MA dependence (Salo et al., 2007). Injury to this brain region is typically a function of exposure to high dosages of MA to the brain, which can result in long-term neuroplastic changes in the dopaminergic system. This is particularly significant for the ACC given its relatively high concentration of dopamine innervation. MA is neurotoxic to dopaminergic fronto-striatal brain regions (e.g. the striatum, PFC, and anterior cingulate cortex) and typically results in corresponding cognitive deficits, including within selective attention, cognitive control, and WM function in MA-abusing subjects (Salo et al., 2007). As such abnormal ACC function may result in dysregulated goal-directed behaviour in MA users given their greater impulsivity, that is the perseveration implied by the recurrent and impulsive use of MA despite clear evidence of negative outcomes (Salo et al., 2007).

The increased ACC activity observed in the group receiving treatment as usual relative to the cognitive training group during the n back task may therefore possibly reflect inefficient response selection and conflict monitoring (Lenartowicz & McIntosh, 2005). Consequently, this could also reflect inefficient control over goal-directed behaviour during the task (Lenartowicz & McIntosh, 2005). The aforementioned evidence on the link between WMT and ACC function and structure appears somewhat consistent with the decrease in ACC activation observed in the cognitive training group (relative to the treatment as usual group). This would also arguably be in line with the fact that the treatment as usual group did not receive working memory training which would have likely reversed the deleterious effects of sustained MA use on the ACC. These results may also be consistent with the differences observed in impulsivity between groups post-intervention, as although the differences were not significant between groups, a paired t-test of the entire sample indicated significant reduced impulsivity post-treatment, and an exploratory observation of the mean BIS scores post-intervention revealed a trend of improvements in impulsivity that were slightly better in the cognitive training group, as would be expected. This provides preliminary evidence that the cognitive therapy had a positive impact on impulsivity, and that the adjunct WMT likely improves impulsivity more than therapy alone.

The salience network has also been demonstrated to influence PCC activity and task dependent changes in activity in response to unexpected bottom up cues to change behaviour (e.g. - the “X” in the 0back condition). The insula has been linked - in this salience network – to the co-ordination of brain activity in response to unexpected events and implicated in external attentional focus (Leech and Sharp, 2013). Together the anterior insula and dorsal PCC compose a neural system that regulates attentional focus (Leech and Sharp, 2013). It has been argued that some of the cognitive deficits observed in the early abstinence period are associated with insular dysregulation in MA users (Volkow et al., 2003). This possibly explains the statistically significant increased activation in the insula observed in the post hoc test on the group receiving treatment as usual, as it is arguably a reflection of the increased insular dysfunction during abstinence that impacts the treatment as usual group whom are required to regulate attentional focus during the task (Salo et al., 2007).

Posthoc tests indicated greater left superior temporal gyrus activation in the treatment as usual group compared to the cognitive training group during the n back task. Left superior temporal gyrus has been implicated in verbal WM, while prior working memory training studies have observed brain structure alterations in the superior temporal regions at follow up. Activity in left superior temporal gyrus has been noted to be consistently linked in language-based tasks (Takeuchi et al., 2011). In addition, the superior temporal gyrus has also been linked to short term memory (Buchsbaum et al., 2001; Leff et al., 2009; Takayama et al., 2004). Evidence has indicated that the left superior temporal gyrus may be involved in the articulatory loop which allows the storage of verbal information (Takeuchi et al., 2011). All of which perhaps suggests that the maintenance of WM representations in the treatment as usual group required more activation in the superior temporal gyrus, as a compensatory mechanism, thereby allowing equivalent performance as the cognitive training group on the n back task.

The post hoc test conducted to investigate the group main effect further indicated less cuneus activity in the cognitive training group than in the treatment as usual group during the n back task. Bilateral activation in cuneus has been observed in previous fMRI studies on WM; with stronger activation being linked to high-workload conditions (Lagopoulos et al., 2007; Tomasi et al., 2006). Interestingly, findings from a recent EEG study suggests that a power increase in the alpha frequency band within the cuneus may reflect WM maintenance function. This alpha power increase may also reflect the active inhibitory control of the cuneus as a task-irrelevant area. The alpha oscillations are considered to serve as an active filtering mechanism, such that the alpha activity may reflect the suppression of processing in visual areas - in this case the cuneus (Michels et al., 2008). Contrastingly, it has been proposed that disengagement or deactivation of the cuneus frees up the cognitive resources needed in the PFC for optimum performance on WM tasks. As such, one possibility is that less cuneus activation in the cognitive training group may indicate that the cognitive training group did not need to suppress their cuneus to control for task irrelevant activation, and thus would likely have more cognitive resources for optimum performance on the n back task (Michels et al., 2008).

Finally, statistically significant de-activation in the posterior left declive of the cognitive training group and increased activation of the posterior right declive in the treatment as usual group was observed. The declive is located within the vermis of the cerebellum. Cerebellar involvement has been linked to the timing and execution of complicated cognitive processes (Murty et al., 2011), particularly in the production of a timed motor response and error prediction (Dreher & Grafman, 2002). The present evidence is consistent with previously published evidence in this cohort of reduced cerebellar volumes in the cognitive training group relative to the treatment as usual group (Brooks et al., 2016). This suggests that the differences of activation observed in the present experiment may be related to the working memory training adjunct, and possibly indicates that participants from the cognitive training group likely required less activation of motor circuits to respond (with a button press) to the n back task given their familiarity to the task relative to the treatment as usual group (Dreher & Grafman, 2002; Murty et al., 2011).

Psychological findings

In the behavioural measures, paired t-tests indicated that there was a significant reduction in impulsivity and depression symptoms in the entire sample, providing evidence to suggest that the brief cognitive therapy intervention did have some success in the MA patients. It is also noteworthy that these differences (in impulsivity and depression over time) appeared to be greater in the CT than the NT group, although group differences were not statistically significant. A repeated measures analysis indicated there was a significant improvement in depression symptoms over time. A sub-threshold difference between groups provides preliminary evidence for a greater treatment effect in the CT than NT group. A repeated measures ANOVA between groups on impulsivity, was unable to find evidence for differences over time or between groups. However, again, as was the case for depression scores, the change in impulsivity scores from baseline to follow-up was largest for the CT group, suggesting utilizing cognitive training as an adjunct slightly improved patient outcomes.

Interestingly, the self-regulation measure also showed what appeared to be a substantially higher mean in the cognitive training group post-intervention, compared to the NT group, although the analyses indicated no significant differences were present between groups. Yet it is worth considering a prior study on the neuropsychological and behavioural outcomes of this pilot was based on a larger sample of patients (many of which were excluded in the present study) (Brooks, Wiemerslage, et al., 2017). Brooks found that significant results indicating that feelings of self-control were higher and measures of self-regulation, impulsivity were improved in the CT group relative to NT group between baseline and follow up. This corroborates the present findings and suggests that WMT likely improved self-regulation in this intervention (Brooks, Wiemerslage, et al., 2017). As such, this provides promising preliminary evidence for the utility of WMT as an adjunct in MUD, given the appearance of minor treatment gains over patients only undergoing cognitive therapy. It could be argued that these likely did not reach significance due to the lower power of the current study which did not include all the participants involved in the Brooks study, as it only included individuals who received fMRI scans.

The results also provided evidence to suggest that the brief cognitive therapy had a positive impact in reducing depression and impulsivity. The fact that there was a lower mean score trend in self-regulation post-intervention (in contrast to pre-intervention) in the NT only group is puzzling, as DBT workshops are highly focused on improving affective regulation (Neacsiu et al., 2014). One potential explanation for this finding across the whole sample post-intervention is the fact that the psychotherapeutic experience likely increased the level of insight (Gibbons et al., 2007) across the MUD patients, such that the post-intervention self-regulation reports may reflect more accurate self-assessments of the MUD patients self-regulation capacity. Indeed, the presence of lack of insight is well established in the addiction literature (Goldstein et al., 2009; Volkow et al., 2012) and the development and fostering of insight is typically a common goal in psychotherapy (Gibbons et al., 2007). As such, it is possible that the participants may have underestimated or overestimated their level of functioning at baseline due to this lack of insight. Consequently, undergoing the treatment program likely developed participants insight, such that their scores at post-treatment would arguably have more accurately reflected their actual level of functioning (Gibbons et al., 2007).

Brooks study on the same cohort also indicated that NT participants showed significant improvements in BIS scores over the intervention. Moreover, some SRQ scores were also significantly higher in the NT group (compared to the CT group), indicating at the very least that the current trends in the results are indicative of reduced impulsivity and improved self-regulation capacity in the cohort (Brooks, Wiemerslage, et al., 2017). This suggests that the BCT did impact impulsivity and self-regulation in the participants by appearing to enhance cognitive control as evidenced by improvements in self-control, attention, cognitive stability in the impulsivity (BIS) measure, and planning and implementing in the self-regulation measure. Interestingly, increased cognitive control is perceived through the conscious experience of deliberative and generative inferences that formulate predictions concerning the outcomes of events or goals (e.g. involved in planning and implementing). This perception is posited to be particularly evident under the conditions of cognitive load which require substantive dynamic updating to compensate for and address its demand on working memory (Brooks, Funk, et al., 2017).

Limitations

The present thesis was based on pre-collected data and as such there was little that could be done to avoid the many limitations of the study, but to enumerate and critically evaluate them. Limitations to the current pilot study that constrain the interpretation and generalizability of the data are detailed below.

A major limitation of the current study is that only male participants were recruited. This is significant as evidence suggests that females are more likely to present to treatment services with MUD (Weybright et al., 2016) and that there may be different outcomes of WMT as a function of sex (Brooks et al., 2016). Indeed, sex differences have been observed in behavioural and substance addiction (Becker & Chartoff, 2019; Bobzean et al., 2014; Fattore & Melis, 2016; Sanchis-Segura & Becker, 2016), WM (Goldstein et al., 2005; Reed et al., 2017; Saylik et al., 2018; Voyer et al., 2017), treatment response (Carroll & Smethells, 2016), and most significantly, in vulnerability to stimulant use disorder (as estrogen has been linked to having a neuroprotective role in modulating the effects of stimulants on the central nervous system) (Fattore & Melis, 2016; Munro et al., 2006). Indeed, the potential impact of MA abuse on impulsivity and compulsivity are determined by factors associated with sex including neuromodulators (e.g. gonadal hormones) that differentially impact the neuroplasticity of neural circuits (e.g. mesocorticolimbic and reward) by sex (Becker & Chartoff, 2019; Fattore & Melis, 2016; Munro et al., 2006). As such, future WMT studies on SUD should take care to sample females as well in order to assess the differential impact of WMT on treatment outcomes.

The sample size was small, given that this was a pilot study, and this likely impacted the power of the statistical analyses. Indeed, generally, researchers should aim to recruit large enough samples in studies in order to ensure the detection of real effects. Given the small sample size, non-parametric t-tests were used on most of the analyses of the behavioural data as these tests do not rely on the assumption of normality (Gueorguieva & Krystal, 2004; Oberfeld & Franke, 2013). Indeed, non-parametric tests do not make assumptions concerning the data that are difficult to test in smaller samples. Contrastingly, though repeated measures analyses are prone to bias given the sample size, they are robust to deviations from normality (Gueorguieva & Krystal, 2004; Oberfeld & Franke, 2013). Moreover, as this study is based on complex multivariate data (including high dimensional MRI scans, demographic variables, and behavioural measures) it may lead to the commission of type II errors – or, reporting false negatives, missing subtle differences, and misreporting true positive results. This is particularly the case when multiple comparisons corrections are implemented (Ashton, 2013; Button et al., 2013; Krzywinski & Altman, 2013). All of which highlights the fact that underpowered neuroscience studies are rampant and can produce estimates that bias the magnitude of effect sizes (Ashton, 2013; Button et al., 2013; Krzywinski & Altman, 2013).

Sample size issues are compounded in neuroimaging, as data require numerous correction processes that are prone to introduce additional variance increasing the probability of error a priori (Button et al., 2013; Oberfeld & Franke, 2013; Poldrack et al., 2011). In contrast, Friston (2012) argues that experiments based on small samples that properly control for false positives are capable of producing treatment effects that likely are larger, quantitatively stronger, than equivalent results in larger samples. These effects are not necessarily inflated, given that the design aims to increase the study´s ability to uncover larger effect sizes, rather than the trivial effects that larger samples are particularly susceptible to producing. However, it is difficult to independently parcel out the error variance or determine whether the inter-subject variability is a by-product of a true effect, or measurement noise (Bacchetti, 2013; Friston, 2013; Krzywinski & Altman, 2013). Indeed, Friston (2012) recommended that the range of an optimal sample size in any neuroimaging study should be between 16-32 subjects. Indeed, increasing sample size does not by itself necessarily ensure that a true effect will be discovered That is why solid theoretical principles and empirical research should shape the kind of comparisons and object of analysis being undertaken so as to constrain the interpretation of the data (Ashton, 2013). Contrastingly, it is typical for neuroimaging studies to have smaller samples, and although this has constraints in terms of ones capacity to generalize to broader populations, it does, all else being equal, decrease the likelihood of reporting trivial false positives in terms of the effect of the intervention (Friston, 2012, 2013).

It is also possible that the task design may have been too limiting to discriminate effectively between WM capacity given only 0back and 1back levels were utilized. This may due to the fact that 0back and 1back levels predominantly rely on WM maintenance, which being an relatively easier activity compared to the higher levels of the n back task may not be demanding enough to detect the negative impact of sustained MA use on WM (Heany et al., 2019). Finally, if the employment of verbal WM strategies may help curtail impulsive behaviours that lead to the switch towards habitual use and withdrawal, the employment of such verbal strategies would likely entail the higher levels of WM function in order to manipulate the almost automatic impulsive cognitions which would arise in the face of drug cues. N-back tasks employing only 0back and 1back conditions would arguably not measure this crucial aspect of WM (Brooks et al., 2016; Goldstein & Volkow, 2011; Kalivas, 2008). It is also worth noting that the present design did not counterbalance the task, and as such may be prone to order effects, which suggest that the effects observed may be biased by the order or the conditions presented in the task rather than the intervention itself (Price et al., 2015).

Future studies should counterbalance the task and include additional n back levels in order to better detect differences in WM function. Furthermore, it may be valuable to utilize two different measures of WM in future intervention studies, as it is difficult to distinguish between whether n-back task performance and brain function altered due to improved performance or increased familiarity with the task itself (Jaeggi et al., 2010; Miller et al., 2009). Inclusion of an additional measure of WM may deal with this issue as well as provide more robust and comprehensive insight into the impact of WMT, that will avoid this potential conflation between learning the task and improvement in WM function itself. That is to say, the serious and rigorous assessment of WMT of particular kind in the future should involve checks for convergent validity with other measures of WM (e.g. Digit Span Backward) that may not rely on recognition-based responses as much (Jaeggi et al., 2010). This is pertinent given the potential risk of conflating learning effects and improvements in cognition in this particular design.

Another limitation of the present study is the fact that it did not employ slice-time correction in processing given its contentious nature, resulting from concern by some that the artefacts in single image can be propagated throughout the time series due to the use of sinc interpolation. This is of particular concern in light of the interactions between slice timing and head motion. Furthermore, it is also been suggested that slice timing has a minimal effect on block designs in particular (Poldrack et al., 2011; Soares et al., 2016).

It is also worth noting that the rest period only was 9s which appears to be an insufficient amount of time for the BOLD signal to return to baseline, suggesting that there may be no true baseline. This could have made it more difficult to detect results, and thus represents a limitation of the design of the task. On the other hand, there are scholars who argue that there is no true baseline in fMRI in general, and one can only determine the relative amount of activity present. Indeed, in one study it was found that the neuronal activity during rest periods (even as short as 3 second periods) can have the effect of reducing, eliminating, or even reversing the sign of activity during a cognitive task (Stark & Squire, 2001).

The use of imputation to account for the participants omitting answering particular items on a few of the scales certainly also could be considered to represent another possible limitation to the current study. Though familiarity and use of multiple imputation is not yet common in many of the behavioural sciences due to misconceptions and reservations surrounding its use (explored in detail in: van Ginkel et al., 2019), it is also important to note the use of multiple imputation for missing data is a well-established and evaluated practice, that can produce unbiased parameter estimates that are robust to deviations from assumptions of normality, and their use has generated acceptable results in the face of low sample sizes or high rates of missing data (Wayman, 2003). Indeed, Enders (2017) argues the use of multiple imputation to deal with missing data (e.g. item-level missing data in questionnaires) is particularly pertinent in clinical research, which has been slow to adopt it. This is likely to be especially pertinent in longitudinal research, such as the current study, due to the risk the bias of systematic selective attrition (Asendorpf et al., 2014). Fortunately, two studies have been previously published on this cohort on structural (alterations in brain volume linked to WMT) and neuropsychological data (clear improvements in behavioural outcomes), helping to partially guide and corroborate the interpretation of the current results (Brooks et al., 2016; Brooks, Wiemerslage, et al., 2017). This particularly important as these pilots were able to include participants excluded in the current study and thus had greater power to find effects of the WMT intervention.

Importantly, that fact that this intervention involved no active control, with only a comparison group, and that researchers were not blind to the study, also represented significant barriers to interpretation in this study. Hence, future studies on WMT should attempt to address these design issues (Creswell & Creswell, 2018). One promising recommendation might be to follow the example of the Bickel et al. (2011) study which subjected both the active and control WMT groups to the same conditions with one crucial difference. The control training used a modified version of the WM program where the correct answers were cued to the participants. This allowed the participants in the control group to be exposed to same stimuli as the experimental group while providing similar responses as the experimental group. Yet given the fact that the control group were cued on the correct answers, participants in the control group were not required to exert effort, or "work" to provide the correct responses (Bickel et al., 2011; Bickel, Koffarnus, et al., 2014).

This difference between the control and experimental group is particularly important given that a recent meta-analysis evaluating design in WMT has previously noted that studies which utilized passive controls in their designs tended to strongly favour the alternative hypothesis (that WMT would lead to transfer and thus improvements in general fluid intelligence) while findings from studies that use active-control groups tended to favour the null hypothesis (WMT would have no effect) (Dougherty et al., 2016). This meta-analysis highlighted the importance of carefully evaluating experimental design, as the choice of the design should not impact or moderate the efficacy of a manipulation (e.g., inclusion of WMT). In this case, the type of control condition you have should not moderate the outcomes of working memory training as if the effect is contingent on the design of the study. This suggests that the effect is dependent on the design of the study, not the experimental manipulation. Furthermore, studies with passive controls, such as the present study are at risk of placebo effects which appear as a training effect as well, as participant expectations may be confounded with whether they engaged in training or not (Dougherty et al., 2016). Though this arguably may not be attributed to the differences in brain activity between groups, it is worth noting, as such design issues make the interpretation of results difficult (Dougherty et al., 2016).

Finally, it is worth noting some strengths of the study. First, this study avoided one significant design flaw that has been present in many studies on MUD, namely the presence of significant differences in variables at pre-intervention which bar comparability between groups (e.g. differences in I.Q.) (Hart et al., 2012). Secondly, this is one of the first studies in South Africa which has sought to evaluate the impact of computerized cognitive training on addiction and thus is considerably innovative within the South African context. Finally, the use of whole brain analyses in this study can be considered a strength. Although focusing on activation in particular regions of the brain or networks, such as the WM network, may provide greater power to detect the impact of WMT in task-relevant brain circuits, such an approach may come at the cost of excluding additional brain regions that may be activated to compensate for inefficient processing due to the negative impact of MA abuse.

Conclusions

Notwithstanding the substantial limitations of this current pilot study, potentially important results were observed between groups in brain function during the n-back task and noteworthy behavioural results were observed post-intervention. The CT group appeared to have less post-intervention activation in the posterior cingulate cortex, anterior cingulate cortex and lingual gyrus during the n-back task relative to the NT group. I have argued that this may reflect enhanced WM maintenance brain function in the cognitive group training group relative to the treatment as usual group. More specifically, cognitive training may have enhanced internally directed cognition (during retrieval) and overall attentional focus in anticipation of highly motivated and salient targets (PCC). On the other hand, increased activity was observed in the cingulate cortex, insula, and cerebellum in the NT group compared to the CT group during the response selection/sustained attention-based condition (0back). Increased activity in the NT group relative to the CT group may potentially be indicative of inefficient function in attentional networks or the fact that the task is relatively unfamiliar to the NT group and thus more novel and salient. Assuming the former, the data suggests that those who solely received cognitive therapy were relatively inefficient at regulating attentional focus, (particularly external attentional focus), response selection, and conflict monitoring, inhibition of distracting information.

Cerebellum activation were also likely linked to differences in familiarity and efficiency, as cerebellar activation likely reflected the increased activity needed for the timing and execution of complicated cognitive processes – e.g. timed motor response and error prediction. These findings suggest that the n back task may have been slightly more challenging to the NT group requiring the additional recruitment of several brain structures relative to the cognitive training group. The results demonstrated that BCT treatment did reduce depressive symptoms and impulsivity in this study, with preliminary indications that there may be subtle treatment gains in the cognitive training group.

Overall, although brain imaging results were limited, they were mostly consistent with the expectations set out in the study, the literature, and the findings of the previous publications of this pilot study. Future research should attempt to replicate this study on a larger sample of MA users of both genders with an active control condition and more levels on the n-back to increase the sensitivity of detecting WM function. Thus, to conclude, the current study provides preliminary evidence of the potential promise of using WMT as adjunct and the benefits of brief term cognitive therapy and therefore reflects a positive contribution to the sparse literature on the psychological treatment of MUD in South Africa.

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Appendix A – Missing Data

Missing Behavioural Data

Participant ID	**Missing Items (total of 16 missing items)**
NT01	BIS item 16 (post-intervention)
NT13	BIS item 24 (pre-intervention); BIS item 11 (post-intervention)
NT02	BIS item 11 (pre-intervention)
NT11	SRQ item 3 (post-intervention)
NT14	SRQ item 52 (post-intervention)
NT16	SRQ item 39 & 40 (pre-intervention)
CT05	SRQ item 23 (pre-intervention)
CT14	SRQ item 5 (pre-intervention)
CT15	SRQ item 4 (pre-intervention); SRQ item 45 (pre-intervention); SRQ item 4 (post-intervention)
CT18	SRQ item 29 (pre-intervention)
CT19	SRQ item 25 (pre-intervention)
CT24	SRQ item 45 (pre-intervention); SRQ item 42 (post-intervention)

Appendix B – fMRI Posthoc T-Test Figures

NT > CT

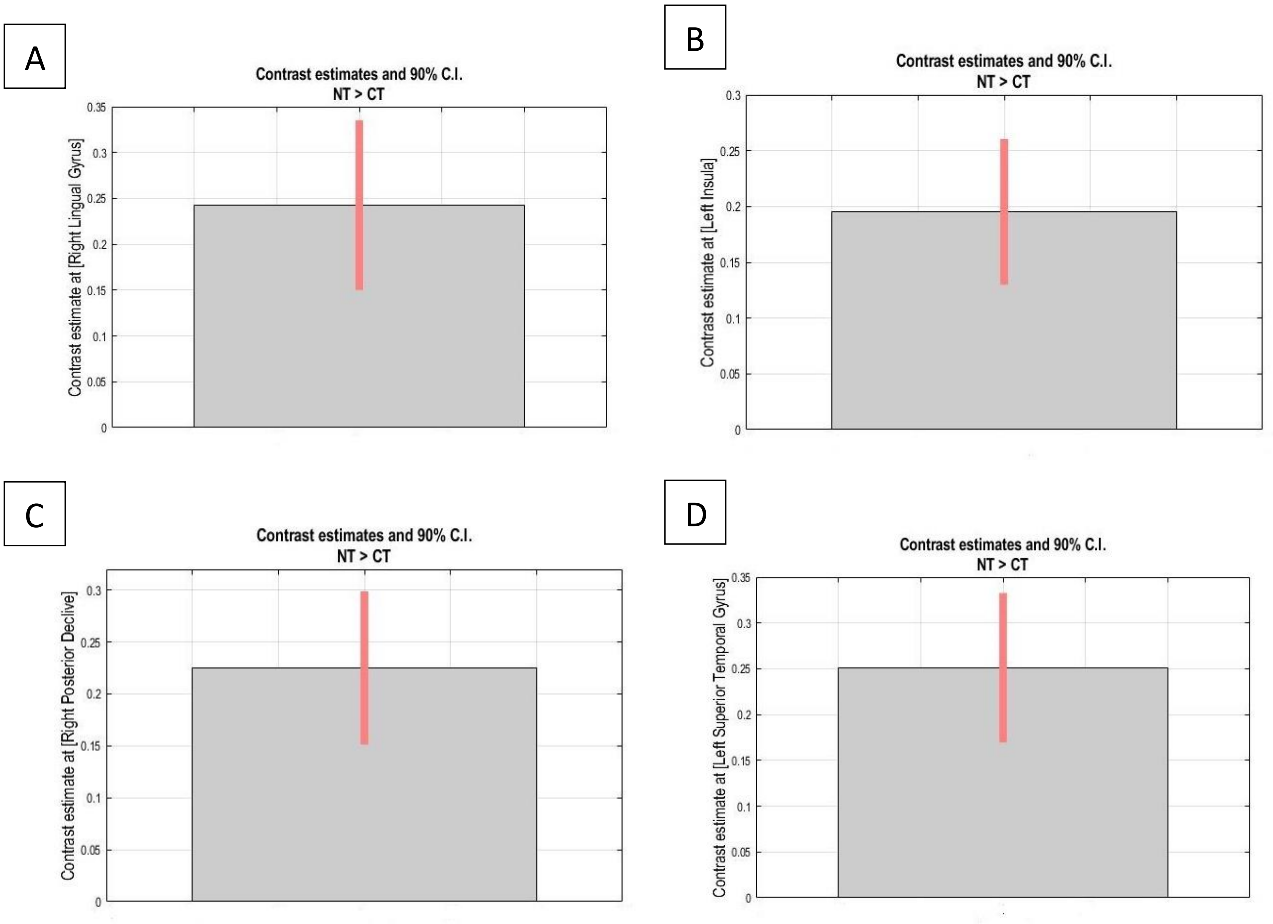

Figure 18 – Repeated Measures Model Posthoc T-Test Contrast Estimate Graphs [NT > CT]

Notes: A - The following figure depicts the contrast estimate and confidence intervals of the significant activation in the right lingual gyrus on the NT > CT contrast. B - The following figure depicts the contrast estimate and confidence intervals of the significant activation in the left insula on the NT > CT contrast. C - The following figure depicts the contrast estimate and confidence intervals of the significant activation in the right posterior declive on the NT > CT contrast. D - The following figure depicts the contrast estimate and confidence intervals of the significant activation in the left superior temporal gyrus on the NT > CT contrast.

CT > NT

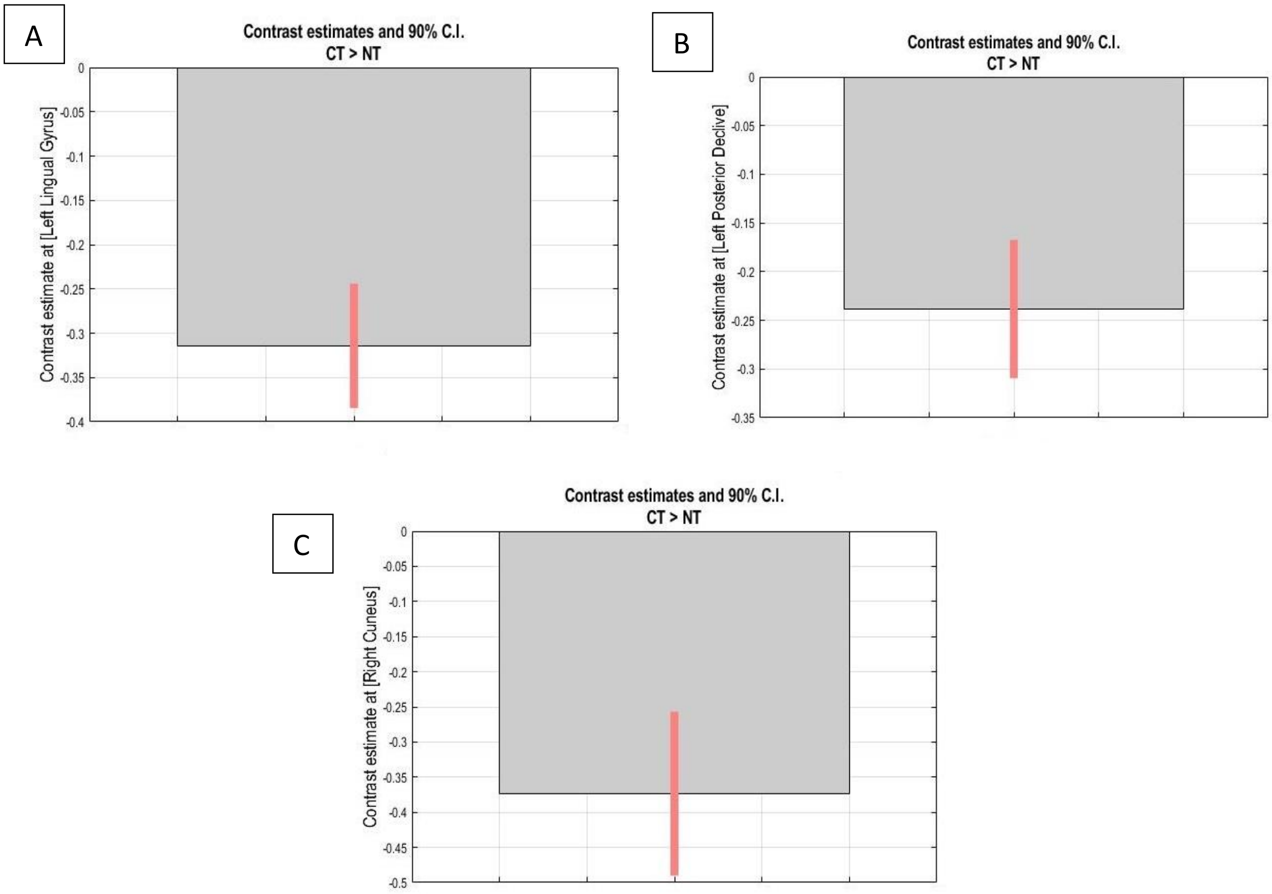

Figure 19 – Repeated Measures Model Posthoc T-Test Contrast Estimate Graphs [CT > NT]
Notes: A - The following figure depicts the contrast estimate and confidence intervals of the significant activation in the left lingual gyrus on the CT > NT contrast. B - The following figure depicts the contrast estimate and confidence intervals of the significant activation in the left posterior declive on the CT > NT contrast. C - The following figure depicts the contrast estimate and confidence intervals of the significant activation in the right cuneus on the CT > NT contrast.

Appendix C– Questionnaire Booklet[4]

Cognitive training and effects on the brain

What level of C-Ya are you on today?

LEVEL: _____

Dr Samantha Brooks

Contact: drsamanthabrooks@gmail.com / 0790311967

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[4] Abridged to only contain relevant scales examined in study.

General Demographics Questionnaire

Name:	
Date of Birth:	
Place of Birth:	
Handedness:	
Claustrophobic?	
Gender:	
Ethnicity:	
Education Level:	
Marital Status:	
Living arrangement:	
Dependents:	
Smoking History:	
Drug History:	
How long taking methamphetamine?	
What was the quantity/frequency?	
How long stopped taking meth?	
Current Medications:	
Medical Conditions:	
Medical History:	
Dietary Style:	
Current drug use:	
Over counter?	
Prescription?	
Illicit?	
Other?	

BARRATT IMPULSIVITY SCALE
(BIS-11)

Directions: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you feel you think and act IN THE LAST FEW DAYS. Read each statement carefully and PLACE A TICK IN THE APPROPRIATE BOX to the right of the statement. Answer quickly and honestly. There are no right or wrong answers.

1 = Rarely/Never 2= Occasionally 3= Often 4= Almost Always

Q.		**1**	**2**	**3**	**4**
1	I plan tasks carefully				
2	I do things without thinking				
3	I make up my mind quickly				
4	I am happy-go-lucky				
5	I don't "pay attention"				
6	I have "racing thoughts"				
7	I plan trips well ahead of time				
8	I am self-controlled				
9	I concentrate easily				
10	I save regularly				
11	I "squirm" at plays or lectures				
12	I am a careful thinker				
13	I plan for job security				
14	I say things without thinking				
15	I like to think about complex problems				
16	I change jobs				
17	I act on "impulse"				
18	I get easily bored when solving thought problems				
19	I act on the spur of the moment				
20	I am a steady thinker				
21	I change where I live				
22	I buy things on impulse				
23	I can only think about one problem at a time				
24	I change hobbies				
25	I spend or charge more than I own				
26	I have outside thoughts when I am thinking				
27	I am more interested in the present than in the future				
28	I am restless at talks or lectures				
29	I like puzzles				
30	I plan for the future				

HOSPITAL ANXIETY AND DEPRESSION QUESTIONNAIRE

(HADS)

HADS : Please circle the number that best represents your view of each underlined statement.

I feel tense or wound up	most of the time 3	a lot of the time 2	Occasionally 1	not at all 0
I still enjoy the things I used to enjoy	definitely as much 3	not quite as much 2	only a little 1	hardly at all 0
I get a sort of frightened feeling as if something awful is about to happen	quite badly 3	not too badly 2	a little 1	not at all 0
I can laugh and as see the funny side of things	as much as I always could 3	not quite so much now 2	definitely not so much now 1	not at all 0
Worrying thoughts go through my mind	a great deal of the time 3	a lot of the time 2	from time to time 1	only occasionally 0
I feel cheerful	not at all 0	not often 1	sometimes 2	a lot 3
I can sit at ease and feel relaxed	definitely 3	usually 2	not often 1	not at all 0
I feel as if I am slowed down	nearly all the time 3	very often 2	sometimes 1	not at all 0
I get a sort of frightened feeling like butterflies in the stomach	not at all 3	Occasionally 2	quite often 1	very often 0
I have lost interest in my appearance	Definitely 3	I don't take so much care as I should 2	I may not take quite as much care 1	I take just as much care as ever 0
I feel restless as if I have to be on the move	Very much 3	quite a lot 2	not very much 1	not at all 0
I look forward with enjoyment to things	As much as ever 3	Rather less than I used to 2	Definitely less than before 1	Hardly at all 0
I get sudden feelings of panic	Very often 3	Quite often 2	Not often 1	Not at all 0
I can enjoy a good book or programme	Often 3	Sometimes 2	Not often 1	Very seldom 0

SELF REGULATION QUESTIONNAIRE (SRQ)

Please answer the following questions by circling the response that best describes how you are.

If you STRONGLY DISAGREE with a statement, circle 1

If you DISAGREE with a statement, circle 2

If you are UNCERTAIN or UNSURE, circle 3

If you AGREE with a statement, circle 4

If you STONGLY AGREE with a statement, circle 5

1. I usually keep track of my progress toward my goals.	1	2	3	4	5
2. My behavior is not that different from other people's.	1	2	3	4	5
3. Others tell me that I keep on with things too long.	1	2	3	4	5
4. I doubt I could change even if I wanted to.	1	2	3	4	5
5. I have trouble making up my mind about things.	1	2	3	4	5
6. I get easily distracted from my plans.	1	2	3	4	5
7. I reward myself for progress toward my goals.	1	2	3	4	5
8. I don't notice the effects of my actions until it's too late.	1	2	3	4	5
9. My behavior is similar to that of my friends.	1	2	3	4	5
10. It's hard for me to see anything helpful about changing my ways.	1	2	3	4	5
11. I am able to accomplish goals I set for myself.	1	2	3	4	5
12. I put off making decisions.	1	2	3	4	5
13. I have so many plans that it's hard for me to focus on any one of them.	1	2	3	4	5
14. I change the way I do things when I see a problem with how things are going.	1	2	3	4	5
15. It's hard for me to notice when I've “had enough” (alcohol, food, sweets).	1	2	3	4	5
16. I think a lot about what other people think of me.	1	2	3	4	5
17. I am willing to consider other ways of doing things.	1	2	3	4	5
18. If I wanted to change, I am confident that I could do it.	1	2	3	4	5
19. When it comes to deciding about a change, I feel overwhelmed by the choices.	1	2	3	4	5
20. I have trouble following through with things once I've made up my mind to do something.	1	2	3	4	5
21. I don't seem to learn from my mistakes.	1	2	3	4	5
22. I'm usually careful not to overdo it when working, eating, drinking.	1	2	3	4	5

23. I tend to compare myself with other people.	1	2	3	4	5
24. I enjoy a routine, and like things to stay the same.	1	2	3	4	5
25. I have sought out advice or information about changing.	1	2	3	4	5
26. I can come up with lots of ways to change, but it's hard for me to decide which one to use.	1	2	3	4	5
27. I can stick to a plan that's working well.	1	2	3	4	5
28. I usually only have to make a mistake one time in order to learn from it.	1	2	3	4	5
29. I don't learn well from punishment.	1	2	3	4	5
30. I have personal standards, and try to live up to them.	1	2	3	4	5
31. I am set in my ways.	1	2	3	4	5
32. As soon as I see a problem or challenge, I start looking for possible solutions.	1	2	3	4	5
33. I have a hard time setting goals for myself.	1	2	3	4	5
34. I have a lot of willpower.	1	2	3	4	5
35. When I'm trying to change something, I pay a lot of attention to how I'm doing.	1	2	3	4	5
36. I usually judge what I'm doing by the consequences of my actions.	1	2	3	4	5
37. I don't care if I'm different from most people.	1	2	3	4	5
38. As soon as I see things aren't going right I want to do something about it.	1	2	3	4	5
39. There is usually more than one way to accomplish something.	1	2	3	4	5
40. I have trouble making plans to help me reach my goals.	1	2	3	4	5
41. I am able to resist temptation.	1	2	3	4	5
42. I set goals for myself and keep track of my progress.	1	2	3	4	5
43. Most of the time I don't pay attention to what I'm doing.	1	2	3	4	5
44. I try to be like people around me.	1	2	3	4	5
45. I tend to keep doing the same thing, even when it doesn't work.	1	2	3	4	5
46. I can usually find several different possibilities when I want to change something.	1	2	3	4	5
47. Once I have a goal, I can usually plan how to reach it.	1	2	3	4	5
48. I have rules that I stick by no matter what.	1	2	3	4	5
49. If I make a resolution to change something, I pay a lot of attention to how I'm doing.	1	2	3	4	5
50. Often I don't notice what I'm doing until someone calls it to my attention.	1	2	3	4	5
51. I think a lot about how I'm doing.	1	2	3	4	5
52. Usually I see the need to change before others do.	1	2	3	4	5
53. I'm good at finding different ways to get what I want.	1	2	3	4	5
54. I usually think before I act.	1	2	3	4	5
55. Little problems or distractions throw me off course.	1	2	3	4	5
56. I feel bad when I don't meet my goals.	1	2	3	4	5
57. I learn from my mistakes.	1	2	3	4	5

58. I know how I want to be.	1	2	3	4	5
59. It bothers me when things aren't the way I want them.	1	2	3	4	5
60. I call in others for help when I need it.	1	2	3	4	5
61. Before making a decision, I consider what is likely to happen if I do one thing or another.	1	2	3	4	5
62. I give up quickly.	1	2	3	4	5
63. I usually decide to change and hope for the best.	1	2	3	4	5

THANK YOU VERY MUCH FOR YOUR TIME AND HELP!

If you have further questions, please do email:

drsamanthabrooks@gmail.com

Appendix D – Consent to Participate in Brain Scan Research Form

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 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 E – Outline of Psychotherapy Treatment Program

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
	Arts/Crafts/Martial Arts	Physical training	Arts/Craft/Games	Relaxation	Arts/crafts	Recreation	Homework
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			
	Balanced lifestyle	Psycho-education	Dealing with boredom	Parenting skills	Arts/crafts		
	Arts/crafts/martial arts	Physical training	Games	Physical training			
6	Group therapy	Group therapy	Group therapy	Group therapy	Group therapy	Therapeutic home visits	Therapeutic home visits
	Talking about drugs	DBT: observe/describe NJ/OM	DBT: observe/describe NJ/OM	DBT: observe/ describe OM/E	Psycho-education		
	Making new friends	Sex and recovery	Taking responsibility	Radical acceptance			
	Repairing relationships	Psycho-education	Taking responsibility	Parenting skills	Skills development		
	Arts/crafts	Physical training	Games	Physical training			
7	Group therapy	Group therapy	Group therapy	Group therapy	Group therapy	Therapeutic home visits	Therapeutic home visits
	Talking about drugs	DBT: Parti/obs/describe	DBT: distress tolerance	DBT: distress tolerance	Psycho-education		
	Refusal skills	Relapse prevention: identifying different types of relapse	Relapse prevention: 8 reasons for relapse	Relapse prevention plan	Skills development		
	Refusal skills	Psycho-education	Relapse prevention plan	Parenting skills			
		Physical training		Physical training			
8	Group therapy	Group therapy	Group therapy	Group therapy	Group therapy/ programme evaluation	Discharge	Discharge
	Talking about drugs	DBT: Change vs. radical acceptance	DBT: Change vs. radical acceptance	DBT: Self-acceptance	Psycho-education		
	Work and recovery	Job searching	CV writing	Discharge planning	Farewells		
	Making informed career choices	Psycho-education	Interview etiquette	Discharge planning			
	Arts/crafts	Physical training	Role playing	Physical training			

Phase One: Orientation (Weeks 1&2); Phase Two: Therapeutic (Weeks 3-6); Phase Three: Discharge (Weeks 7&8).