# Executive Functioning in Methamphetamine Psychosis

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DECLARATION

I, the undersigned hereby declare that the work contained in this thesis is my own original work and that I have not previously in its entirety or in part submitted it at any other university for a degree. Each contribution to, and quotation in, this dissertation for work or works of other people has been cited and referenced.

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# ABSTRACT

An association between methamphetamine dependence and neurocognitive impairment has long been established. However, there are a number of research gaps. First, while evidence suggests that the primary cognitive domains affected in methamphetamine dependence are executive functions; previous research fails to employ a comprehensive battery of executive functioning tests. Second, there is little research investigating the specific neuropsychological impairments associated with methamphetamine psychosis in particular. Third, ADHD is highly co-morbid with substance dependence. Symptoms of ADHD were therefore investigated as possible confounders in this study. Fourth, few studies of methamphetamine dependence have explored relationships between neuropsychological data and cortical thickness data; the current study therefore investigated this further. The current study employed a neuropsychological test battery to compare executive functioning across three groups; a methamphetamine dependent group without psychosis (*n* = 20), a methamphetamine dependent group with psychosis (*n* =19) and a healthy control group (*n* = 20); demographically matched. Brain images were acquired using a Siemens Magnetom Allegra 3T system with a high-resolution, T1-weighted, 3D-multiecho MPRAGE sequence with the following scan parameters: TR=2530ms; graded TE=1.53, 3.21, 4.89, 6.57ms; flip angle=7°; FOV=256mm; slice thickness=1mm; 160 slices; and acquisition duration of 10.49 min. Cortical thickness was assessed employing a surface-based cortical reconstruction and automatic labelling tool in the FreeSurfer software package. Four executive domains were identified and evaluated, namely decision making and impulsivity; inhibitory control and set-shifting; attention and working memory; and verbal fluency. One-way ANOVAs were conducted in order to assess differences between groups. Analyses indicated significant between group differences on most tasks of executive functioning. Overall the methamphetamine psychosis (MA+) group performed more poorly than the methamphetamine non-psychosis (MA-) group and the controls (NC). Statistically significant between-group differences were observed on inhibitory control and set-shifting ($p < .001$), attention and working memory ($p = .006$), and on tasks of generativity ($p < .001$). Spearman's correlational analyses revealed that in general, executive impairment was associated with cortical thinning of frontal regions in the MA+ group and cortical thickening of frontal regions in the MA- group. This may be reflective of a compensatory response to methamphetamine toxicity in the MA- group. In conclusion, executive functioning was significantly impaired in the MA- group and even more so in the MA+ group. Symptoms of ADHD were not found to be significantly correlated with executive functioning data. Therefore executive dysfunction is more likely the result of MA toxicity than a pre-existing ADHD disorder.

An improved understanding of the neuropsychology and neuroanatomy of methamphetamine dependence may ultimately contribute to the clinical management of these individuals.

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# CHAPTER ONE: INTRODUCTION

The current study aims to address four gaps that have been identified in the existing research conducted on the neuropsychological sequelae of methamphetamine (MA), and particularly of methamphetamine-induced psychosis. Here we introduce these gaps before moving to review the literature. First, I introduce the lack of comprehensive data available on executive functioning (EF) in MA. Second, given the association between MA and substance-induced psychotic disorder, I then identify the dearth of research available comparing individuals who develop psychosis to those who do not develop psychosis on neuropsychological task performance, particularly in the South African context. Third, I discuss the co-morbidity of ADHD and MA-dependence and the relationship between these two disorders in terms of EFs as ADHD is a potential confounder in my data. Finally, I discuss the prefrontal brain regions that mediate these EFs and the value that the current research will add to existing knowledge on this topic.

An association between methamphetamine dependence and neurocognitive impairment has long been established. A meta-analysis of the neuropsychological consequences associated with MA-dependence found that these involve a variety of cognitive domains, including executive functions, memory, motor skills, language and information processing speed, and visuo-constructional abilities (Scott et al., 2007). Executive functions involve the management of cognitive process and include reasoning, planning and problem solving; memory is the ability to store and remember information; motor skills refer to the ability to perform a sequence of movements; language refers to the ability to communicate, both verbally and written; Information processing refers to the ability to interpret incoming information; visuo constructional abilities involve the coordination of fine motor skills with visuospatial abilities. The largest impairments in MA have been found on tasks of executive functions, (Scott et al., 2007). However, many studies test “executive functions” by means of either a single task of response inhibition (Salo et al., 2007), two tasks of response inhibition (McCann et al., 2008) or simply one task of working memory and one task of decision making (Gonzalez, Bechara & Martin, 2007). Thus detailed research on the specific domains of executive functions (EF) such as attention and working memory, decision making and impulsivity, inhibition and mental flexibility, is lacking. The current study attempts to address this gap by employing a comprehensive battery of EF tasks, focusing in particular on the executive domains of decision making and impulsivity, inhibition and set shifting, attention and working memory, as well as verbal fluency.

Of further importance, is the substance-induced psychotic disorder (SIPD) resulting from MA use. This psychotic state experienced by MA-dependent individuals is characterized by auditory, visual and/or tactile hallucinations and persecutory ideation (McKetin, McLaren, Lubman & Hides, 2006; Srisurapanont et al., 2003). Relatively little research to-date has been conducted on methamphetamine-induced psychotic disorder and particularly little research has been conducted on the neuropsychological deficits associated with MA psychosis, particularly in comparison with MA dependent individuals without a history of psychosis, and particularly in the South African context. The current study attempts to address this gap in the literature by comparing neuropsychological functioning, specifically executive functioning, in MA-dependent individuals with and without psychosis.

MA dependence and attention-deficit/hyperactivity disorder (ADHD) are commonly comorbid conditions. It is notable that similar executive dysfunction to that seen in MA dependence is seen in ADHD. Certainly, ADHD is a risk factor for substance abuse and the progression to dependence is quicker in individuals with ADHD than those without ADHD (Jaffe et al., 2005). In particular, ADHD individuals use MA more frequently than those without ADHD (Jaffe et al., 2005). Whether this is due to the "self medication hypothesis" is not entirely evident. Nevertheless, it is also possible that MA may lead directly to impairments in executive function (Jaffe et al., 2005; Matsumoto, Kamijo, Yamaguchi, Iseki, & Hirayasu, 2005). ADHD is therefore a confounding factor when investigating executive functioning in substance use disorders. There is, however, relatively little data investigating whether the executive impairments observed in MA may be due to a pre-existing disorder such as ADHD, or due to the neurotoxic effects of the drug. While establishing causality is not the aim of this cross-sectional study, I do aim to investigate the relationship between ADHD and executive impairment in our MA dependent sample.

Previous research investigating methamphetamine dependece, neuropsychological functioning, and brain imaging has examined either regional cerebral blood flow (Chang et al. 2002), morphometric changes (Chang et al. 2005) or conducted fMRI studies investigating performance of single cognitive tasks (Monterosso et al. 2007; Paulus et al. 2002, 2003). Thompson et al. (2004) mapped regional brain abnormalities and correlated this data with memory performance. However, there are few studies that have performed such correlational analyses between MRI and neuropsychological data.

No such studies, to my knowledge have correlated executive functioning data with cortical thickness data in methamphetamine dependence, and particularly methamphetamine psychosis. I therefore aim to address this gap.

In particular, I aim to correlate executive functioning data with cortical thickness data of the frontal cortex as EFs are mediated by the prefrontal cortex (PFC). Three main areas of the PFC have been identified; namely the orbitofrontal cortex (OFC) the dorsolateral prefrontal cortex (DLPFC), and the anterior cingulate cortex (ACC), mediate decision making and emotion regulation, working memory and mental flexibility, and response inhibition, respectively (Verdejo-Garcia, Bechara & Recknor, 2006). *Figure 1* below is a diagrammatic representation of how the frontal regions and associated executive functions have been divided in this thesis. Given that response inhibition and impulsivity are closely linked, as are response inhibition and attention; this schematic is intended as an initial heuristic. I discuss this further in the following literature review

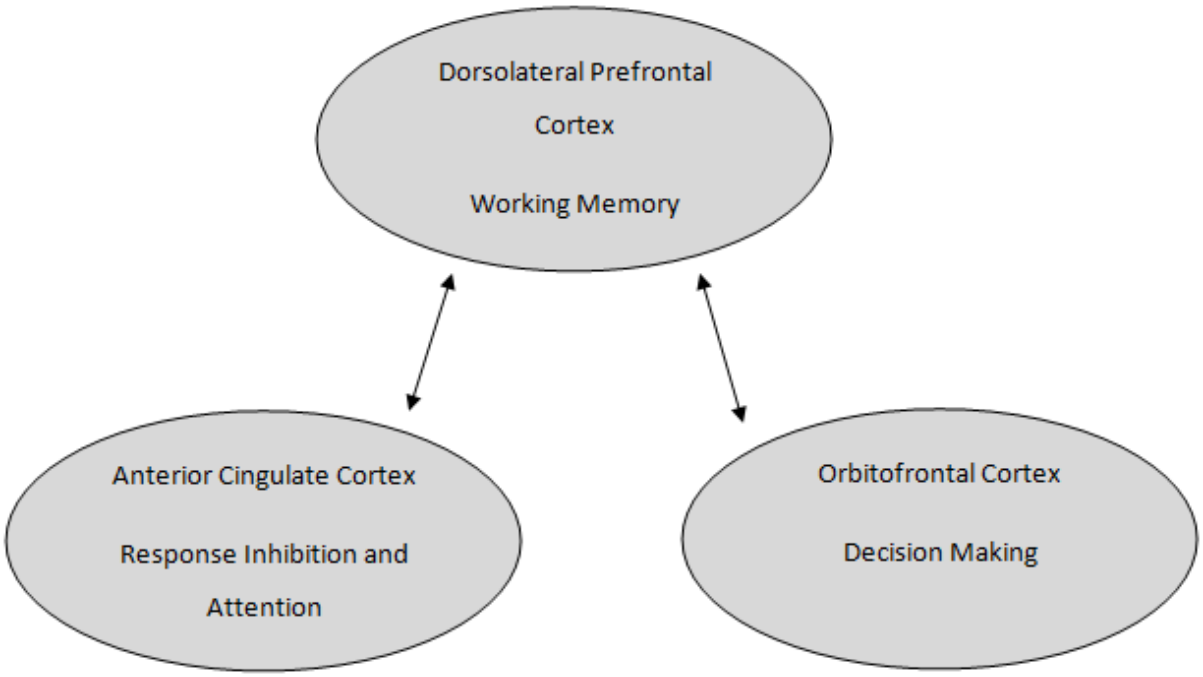


*Figure 1.* Diagramatic Representation of the relationship between executive functions and the prefrontal cortex

In summary, this study will focus on addressing these key gaps in existing research. Firstly we will investigate executive functioning of individuals who are dependent on MA. We will be using a

comprehensive battery of tests investigating four executive functioning domains, namely, decision making and impulsivity, attention and working memory, inhibition and set-shifting, and verbal fluency. Secondly, we will be comparing those individuals who are dependent on MA and do not develop MA psychosis to those who do develop MA psychosis. Thirdly, we will be investigating the co-morbidity of ADHD and MA in our sample. And finally, we will investigate the frontal brain regions that mediate executive functioning in our sample of MA dependent individuals. The literature investigating these four core components will now be reviewed in order to provide background regarding previous research findings.

# CHAPTER TWO: LITERATURE REVIEW

This chapter begins with a brief background and history of MA, before discussing some statistics specific to South Africa. While this is not an epidemiological study and therefore details of previous research conducted is not provided here, the background and history provide a rationale for investigating MA further in the South African context. The literature relevant to the four core components of the current study will then be discussed in more detail. First, we will discuss the neuropsychological effects of MA, particularly executive functions. Second, we discuss the frontal cortex sub-regions that mediate EFs. Third we briefly discuss the co-morbidity between ADHD and MA. Lastly, we review the literature relevant to methamphetamine-induced psychosis. The following methods have been used to identify relevant literature for this chapter: (1) searching the MEDLINE, PUBMED, PSYCHARTICLES and PSYCHINFO databases; (2) exploring the reference list of peer-reviewed journal articles already located; and (3) following up suggestions from colleagues working in this field. The literature search was confined to English publications in peer-reviewed journals. Where unpublished works were encountered such as interviews and unpublished reports, these have also been included. This chapter will then conclude with the specific aims and hypotheses of the current study.

## METHAMPHETAMINE: BACKGROUND

### A Brief History of Methamphetamine

MA is sometimes referred to as “Hitler’s Drug” (Leggett, 2003: p. 34) as it was allegedly used by the Nazis as a means of assisting soldiers in combat. Although MA was first synthesized in Japan in the late 1800s, it was not widely used until World War II (Leggett, 2003) where German military personnel used it in order to combat fatigue and increase alertness (Scott et al. 2007). It was also given to Japanese civilian factory workers in military support industries to increase productivity (Anglin et al., 2000). After the war, the first epidemic of widespread abuse occurred between 1945 and 1957 where a surplus of Army stock flooded the market. In 1954 the number of MA abusers in Japan was estimated at 550 000 people, 10% of whom reported symptoms of MA-induced psychosis. MA use then subsided for a while as new laws were introduced in response to the increase in crime and homicides linked to MA. MA use then later spread among blue collar workers, students,

housewives and office workers, leading to the second epidemic which began in 1970 to the present day (Anglin et al., 2000).

In South Africa, the first methamphetamine (or 'tik" as it is locally known) manufacturing operation was discovered by the police in 1998. No other such operations were found until 2001 when 10 MA laboratories were discovered, nine in Gauteng and one in Woodstock in Cape Town. In 2003 a shift was seen where the majority of cases were then found in the Western Cape, including multiple seizures in Mitchell's Plain and other areas on the Cape Flats; most of which involved pure methamphetamine powder (Leggett, 2003).

## Methamphetamine Use in South Africa

According to SACENDU (as cited by Leggett, 2003), treatment demand for MA addiction also increased during that time. In the first half of 2002, there were only three patients in treatment for MA dependence in Cape Town out of a total 1600 patients in rehab for drug addiction. This increased to 13 in the second half of 2002 and to 35 in the first half of 2003 (Leggett, 2003).

MA use in South Africa has significantly increased in the last decade, particularly in areas on the Cape Flats, such as Mitchell's Plain in the Western Cape Province (Kapp, 2008; Leggett, 2003; Plüddemann, Myers & Parry, 2007; Simbayi et al., 2006), with 42% of drug abusers in Cape Town in 2006 using methamphetamine as their primary drug of choice (Pluddemann, Myers & Parry, 2007). A report compiled by the Medical Research Council of South Africa (MRC; Pluddemann, Myers & Parry, 2007), indicated that the number of patients with MA as their primary or secondary substance of abuse increased dramatically from 2003 to 2006. The authors of that report found that out of the total number of patients treated at over 25 specialist treatment centres for any substance (including alcohol, cannabis, mandrax, heroin or cocaine), 6 % of them were MA users in 2003. This number increased to 49% in 2006 (Pluddemann, Myers and Parry, 2007).

In a more recent report by SACENDU (South African Community Epidemiology Network on Drug Use; Dada et al., 2012), data were collected across 23 specialist treatment centres in Cape Town and it

was found that methamphetamine remains the most common primary substance of abuse. The drastic increase in MA use that was seen between 2003 and 2006 is not reflected over the period 2007 – 2012. In the first half of 2007, 41% of patients used MA as their primary substance of abuse. This decreased to 36% in the second half of 2007. In the first half of 2011, 35% of patients used MA as their primary substance of abuse. This increased to 39% in the second half of 2011. Moreover, Plüddemann, Dada and Parry (2013) observed a significant decline in the number of adolescent patients reporting methamphetamine as their primary substance of abuse between 2006 and 2011. However, a similar trend was not observed in adults. Over the same period, a gradual but significant increase was observed regarding the number of adults reporting methamphetamine as their primary substance of abuse (Plüddemann, Dada & Parry, 2013). This indicates that the plateau of numbers could be due to the decrease in number of adolescent users; however, the number of adult users continues to increase.

Despite this apparent plateau, MA is still the most common substance of abuse, with numbers far exceeding those for heroin, cocaine, ecstasy, dagga, mandrax and even alcohol (Dada et al., 2012). Drug abuse is currently thought to cost South Africa R20-billion per year (Benadie, 2012; in press). These statistics are alarming given the highly addictive nature of MA and its devastating consequences. Long term MA abuse or dependence can result in a variety of medical and psychiatric sequelae, impairment in occupation and social functioning, and particularly neuropsychological impairment (Scott et al., 2007).

## Clinical Effects of Methamphetamine

Methamphetamine (MA) is a highly addictive psycho-stimulant drug that acts on the central nervous system (CNS) and results in the release of monoamine neurotransmitters, which includes dopamine, norepinephrine and serotonin. The marked increase in dopamine levels result in the “high” experienced by individuals who use the substance (Ernst, Chang, Leonido-Yee & Speck, 2000). In order to reproduce the same intense feeling of pleasure, after dopamine stores have been depleted, a higher dose of MA is required. Long term high dose use of MA results in a severe depletion of dopamine, leading to depression, fatigue, and anhedonia. MA is then needed in order for the brain to produce enough dopamine for the individual to feel normal; hence, the highly addictive nature of the drug (Barr et al., 2006).

In addition, MA has a substantially greater elimination half-life than other psycho-stimulant drugs, such as cocaine. This leads to behavioural and psychological effects that last significantly longer than other drugs (8-13 hrs for MA v. 1-3 hrs for cocaine; Barr et al., 2006; Scott et al., 2007). The effects from smoking MA are instantaneous and result in a number of acute effects on the sympathetic branch of the autonomic nervous system, including hypertension, tachycardia, hyperthermia, increased breathing rate, and constriction of blood vessels. Scott et al. (2007) adds to these acute effects feelings of euphoria and alertness, increased libido and a decrease in appetite. These acute effects can last anything between 4 and 24 hours (Ernst et al., 2000). Chronic use, which involves binge use where the drug is administered repeatedly over a few hours or even days, can lead to highly elevated blood concentrations of the drug (Scott et al., 2007). Moreover, due to the relatively high lipid solubility of MA, the drug is transferred rapidly across the blood-brain barrier (Barr et al., 2006). As a result, long term exposure to MA may result in profound impairments in both the neurobiology and structure of the brain, leading to both psychiatric and neuropsychological consequences (Scott et al. 2007). While "the mechanisms responsible for amphetamine-induced neurotoxicity have not been fully identified" (Berman, O'Neill, Fears, Bartzokis, & London, 2008: p. 196), it is accepted that this neurotoxicity has been associated with various neuropsychological deficits (Nordahl, Salo, & Leamon, 2003) as well as particular abnormal behaviours such as psychoses, amongst others (Chang, Alicata, Ernst & Volkow, 2007; Ernst, Chang, Leonido-Yee, & Speck, 2000; Jacobs, Fujii, Schiffman & Bello, 2008).

In summary, a brief background of MA has been provided. We now move to review the literature on the four core components of the current study in more detail. We start by reviewing the literature on the neuropsychological effects of MA and we specifically include an extensive section reviewing the literature on executive functioning. Included in this section is a discussion of the frontal cortex sub-regions mediating executive functioning. We then review the literature on the psychiatric associations with MA. The co-morbidity between MA and ADHD will also be discussed.

# THE NEUROPSYCHOLOGICAL DEFICITS ASSOCIATED WITH METHAMPHETAMINE AND OTHER STIMULANTS

Methamphetamine, cocaine, and other drugs that alter the monoaminergic system, can have a significant effect on behavioural and cognitive processes even in the absence of psychosis (Fernández-Serrano, Pérez-García, & Verdejo-García, 2011; Nordahl, Salo & Leamon, 2003). Specifically psychoactive substance use is associated with neuropsychological deficits in certain cognitive domains. Moreover, stimulant dependence (cocaine, methamphetamine, ecstasy, and to a lesser extent nicotine and caffeine) is associated with greater neuropsychological impairment than alcohol, cannabis or opioid dependence (see van Holst & Schilt (2011) for a review). Some of these associations are clearer than others. A number of review articles investigating the neurocognitive effects of various substances are discussed below. These articles shed light on what is currently known and what needs further investigation.

Spronk, van Wel, Ramaekers & Verkes, (2013) conducted a systematic review of studies on the acute and long-term effects of cocaine on cognitive functioning. These authors also performed several meta-analyses to compare the magnitude of cognitive effects across different domains. All studies published after 2003 were included in the review with a total of 14 acute studies and 63 long-term studies. The following cognitive domains were investigated; attention, response inhibition, memory, learning, psychomotor performance, cognitive flexibility and decision making. Results from the acute studies indicated that cocaine intoxication is associated with improved functioning in response inhibition as well as functions that involved a speed component in psychomotor tasks. Long-term cocaine use, however, was associated with impairments in most cognitive domains. The most significant impairments were found on tasks of sustained attention, response inhibition, memory, reward-based decision making and psychomotor performance (Spronk et al., 2013).

The neuropsychological profiles of MA and cocaine are similar (Spronk et al., 2013). While the acute effects of single low doses of MA may include improved cognition, long term exposure to MA may lead to neuropsychological deficits across several domains (Barr et al., 2006). Fernández-Serrano et al. (2011) conducted a systematic review of the literature examining specific versus generalized effects of a number of drugs of abuse and their associated neuropsychological effects. Articles published between 1999 and 2009 were included in their review. Since most drug users are polysubstance users, few studies were reviewed investigating ‘pure’ samples where participants used mostly one substance. No studies of ‘pure’ cocaine users were found to meet their inclusion

criteria. Three studies investigating the neuropsychological effects of MA were included. These three studies are discussed below.

Volkow et al. (2001; as cited in Fernández-Serrano et al., 2011) conducted a PET imaging study investigating dopamine-transporter-binding and neuropsychological impairment in 5 MA abusers before and after a 12 – 17 month period of abstinence. Retest of cognitive functions showed mild, but non-significant improvements in gross motor skills and episodic memory, but persistent impairments on fine-grained psychomotor function and executive-based interference during memory encoding. Moon et al. (2007; as cited in Fernández-Serrano et al., 2011) investigated verbal and visual episodic memory in 19 MA dependent participants with a mean abstinence of 1.79 years and 18 non-drug using control participants. It was found that long term abstinent MA users showed no impairments on tests of verbal memory, but impairments were observed on tests of visual memory. In a more recent study, Salo et al. (2009; as cited in Fernández-Serrano et al., 2011) investigated differences in performance on the Stroop task between three participant groups; a recently abstinent group (mean abstinence of 2.6 months), a long-term abstinent group (mean abstinence 31.5 months) and a non-drug using control group. Results indicated that recently abstinent participants showed greater impairments in response inhibition when compared to both long-term abstinent participants and non-drug using controls. This indicates that response inhibition skills may be recovered with increased duration of abstinence.

Similar results were observed by Johanson et al. (2006). The authors investigated brain function in abstinent MA users using neuroimaging and cognitive assessment. Cognitive functions of 16 MA users were compared to those of 18 healthy controls. These cognitive functions were assessed using a variety of tasks. Estimates of IQ were obtained using the vocabulary and block design subtests of the Wechsler Adult Intelligence Scale (WAIS) III (Wechsler, 1997). Motor performance was measured using the finger tapping task, the grooved pegboard and the Digital Symbol Substitution Test (DSST; (Wechsler, 1997). The California Verbal Learning Test (CVLT; Delis et al., 1987) and the Paired Associates Learning (PAL) task from Cambridge Automated Neuropsychological Assessment Battery (CANTAB) were used to assess explicit memory. Working memory was evaluated using 3 subtests of the CANTAB: the Spatial Working Memory (SWM) task, the Delayed Match to Sample (DMS) task and the Rapid Visual Information Processing (RVIP) task. The standard Trail Making Tests (parts A and B; Reitan, 1958) as well as two word generation lists were used to assess executive function. Two executive function tasks from the CANTAB were also used: the Intradimensional/Extradimensional shift task which is a measure of an individual's ability to attend

to specific attributes of compound stimuli and to shift that attention when required, and the Stockings of Cambridge task which is a test of spatial planning. MA users had to meet the criteria for amphetamine dependence in the past, but had to be in at least early partial remission, with no methamphetamine use for at least 3 months. The authors failed to find significant differences on several neuropsychological domains. No differences were observed with regards to motor function, one of the two measures of explicit memory, executive functions or working memory. The authors suggested that this was partially due to the length of abstinence; that ranging between 3 months and 10 years, with an average of 3 years. Length of abstinence should therefore be minimized in order to identify neuropsychological deficits (Johanson et al., 2006).

Importantly, however, a meta-analysis examining the neuropsychological domains affected by MA use noted significant impairments (Scott et al. 2007). The meta-analysis analyzed 18 studies all published prior to January 2007, including 487 participants with methamphetamine abuse/dependence and 464 normal control participants. The authors identified contradictory results when investigating the acute effects of MA. While some studies found that MA enhanced cognitive functioning, other studies reported cognitive deficits associated with acute administration. In terms of the long term effects of MA, however, the authors found significant deficits regarding several different cognitive processes, including episodic memory, executive functions (e.g., response inhibition, novel problem solving), complex information processing speed, and psychomotor functions. These dysfunctions likely reflect alterations in frontostriatal and limbic circuits. Smaller effects were evident in attention, working memory, language, and visuoconstruction.

A number of single studies investigating the neuropsychological effects of MA have also emphasized inconsistencies (see Simon 2000; Chang, 2002; Gonzalez, 2004; Johanson et al., 2006); and discussed the various methodological factors which may contribute to these. Firstly, limited studies have used a comprehensive neuropsychological battery in order to assess functioning across a number of neuropsychological domains. Moreover, many of these limited studies make use of a variety of divergent tests within their batteries and this may have contributed to inconsistent results. Secondly, the studies have varied in terms of their sample demographics and the drug use characteristics of their participants. While some studies include treatment-seeking participants where the range of length of abstinence is wide (see Johanson et al., 2006), other studies include participants who are currently using the drug (see Simon et al., 2000). Results are also confounded by numerous common psychiatric (ADHD and depression) conditions (Scott et al., 2007) and various other comorbidity profiles. In particular, comorbid ADHD is not well characterized.

In addition, further research is required particularly in the area of impulsivity and decision making within the MA-dependent population (Scott et al., 2007). This population has a tendency to display risky decision-making and impulsivity. Therefore Scott et al. (2007) suggests a relationship between decision-making and executive aspects of working memory deficits. Further suggestion is made that the combined deficits of working memory and decision-making may predispose MA users toward further risky behaviours such as needle-sharing and unprotected sex. This highlights the importance of examining such deficits in future studies (Scott et al., 2007).

In summary, a wide range of neuropsychological domains may be impaired in MA, the most severe of those being executive functions. However, no research to-date has investigated executive functions comprehensively. The current study therefore aims to address this short-coming, by examining deficits in not only working memory or decision-making, but a comprehensive list of executive domains. Executive functioning in MA will now be discussed in detail together with the frontal cortex sub-regions that mediate these functions.

## Executive Functions and Related Brain Regions

"The executive functions of human cognition are among the most interesting processes" (Stuss & Alexander, 2000, p. 289), and may be what defines us as uniquely human (Stuss & Levine, 2002). Executive functions include all processes of cognitive control; they are attentionally demanding and are involved in goal-directed behavior (Garavan & Hester, 2007). Executive functions can be divided into inhibition and set-shifting, due to their reliance on attentional processes (Stuss & Levine, 2002) attention and working memory (Awh, Vogel & Oh, 2005), and impulsivity and decision-making (Monterosso & Ainslie, 1999). Certainly, these domains are interrelated; inhibition and set-shifting both require aspects of attention (Stuss & Levine, 2002) and working memory (Chambers, Garavan & Bellgrove, 2009), and poor decision-making has been associated with working memory deficits (Bechara & Martin, 2004). However, all these processes involve the frontal lobes, particularly, the prefrontal cortex (PFC). Disruptions to the prefrontal cortex can lead to a number of pathological conditions with cognitive, emotional, behavioural or affective manifestations such as addiction (Goldstein, Volkow, Wang, Fowler, & Rajaram, 2001) or ADHD or even schizophrenia (Fuster, 2008). The relationship between executive function domains and addiction is complex. Cognitive process such as inhibitory and attentional control, behavior monitoring and memory play a significant role in

dependence risk (Garavan & Hester 2007), as does decision making (Noël, Bechara, Dan, Hanak, & Verbanck, 2007).

Substance dependence is therefore often associated with impairment on tasks of executive functions, particularly those relying on different systems within the prefrontal cortex (PFC; Verdejo-García, Bechara, Recknor & Pérez-García, 2005; Verdejo-García, Rivas-Pérez, López-Torrecillas & Pérez-García, 2006), such as decision making and working memory (Gonzalez, Bechara & Martin, 2007). Moreover, evidence suggests that MA can result in impairments in executive functions. Barr et al. (2006, p. 306) suggests that the "most consistent and severe changes (in MA abusing individuals) include specific impairments in working memory, attention, and executive functions". It has been hypothesized that these specific impairments were found "due to the denser dopaminergic innervation of neural circuits that sub-serve these cognitive processes, including dopamine-rich fronto-striatal thalamo-cortical pathways" (Woods, Rippeth, Conover et al., 2005; as cited in Barr et al., 2006, p. 306). These impairments differ depending on which one of three systems of the PFC have been affected; the dorsolateral prefrontal cortex (DLPFC; Bechara, H. Damasio, and A. Damasio, 2000; Verdejo-García, Bechara, Recknor & Pérez-García, 2006; Verdejo-García, Rivas-Pérez, López-Torrecillas & Pérez-García, 2006); the orbitofrontal cortex (OFC; Bechara, H. Damasio, and A. Damasio, 2000; Verdejo-García, Bechara, Recknor & Pérez-García, 2005; Verdejo-García, Rivas-Pérez, López-Torrecillas & Pérez-García, 2006); or the anterior cingulate cortex (ACC; Verdejo-García, Bechara, Recknor & Pérez-García, 2005; Verdejo-García, Rivas-Pérez, López-Torrecillas & Pérez-García, 2006). These three systems of the PFC in relation to the four domains of executive functioning, including verbal fluency, and substance dependence will now be discussed.

### *Verbal Fluency*

Our study combines verbal fluency with executive functions due to the fact that verbal fluency is negatively affected by a lack of cognitive control and has been associated with damage to the left frontoparietal cortices, anterior PFC, and insula (Gläscher et al., 2012).Verbal fluency or generativity consists of both category or semantic fluency and letter or phonemic fluency and is generally considered a measure of language production. While verbal fluency is not commonly considered an executive function it has been suggested that phonemic fluency is reliant on executive functions (Spreen & Straus, 2008; as cited in Neill, Garvich & Rossell, 2013) and therefore more difficult than semantic fluency due to the fact that it requires a higher level of skill (Neill, Garvich & Rossell, 2013).

It has further been suggested that performance on a semantic fluency task requires intact executive functions, including task maintenance, working memory, monitoring and inhibition (Lezak et al., 2004; as cited in Neill, Garvich & Rossell, 2013). There has been much debate in the literature about the possibility that semantic fluency is dependent more on executive than semantic skills (Doughty and Done, 2009; Neill, Garvich & Rossell, 2013).

Doughty and Done (2009) conducted a systematic review and a series of meta-analyses examining semantic memory in schizophrenia. The authors collected 91 articles published prior to October 2007 that investigated semantic memory in schizophrenia patients using a variety of semantic memory tasks such as naming, word-picture matching, verbal fluency, associations, priming and categorization. Their results indicated that semantic memory was affected in schizophrenia. They further noted that the decline in semantic knowledge in schizophrenia may not explain the semantic memory impairment adequately. The authors suggest that this may be due to the executive dysfunction that accompanies schizophrenia. Specifically, the meta-analysis that investigated verbal fluency measures supported the position that there is a primary executive impairment in schizophrenia which is responsible for the poor verbal fluency performance. Since the impairments on semantic fluency were similar to those observed on phonemic fluency and category switching, the authors suggest executive dysfunction which translates to problems with retrieval as well as a reduced store of semantic knowledge (Doughty & Done, 2009).

Verbal fluency impairments have been identified in MA dependence (see for example Kalechstein et al., 2003; Simon et al., 2007; Weber et al., 2012). Scott et al. (2007), in their meta-analysis, identified moderate language impairments associated with MA users. The authors suggest that this could be due to the executive deficits observed earlier in the paper. Verbal fluency requires “rule-guided generation of words under time constraints” (Scott et al. 2007, p. 288). Verbal fluency therefore requires intact executive functions and any impairment in verbal fluency could be attributed to problems with executive or cognitive control of search and retrieval strategies and/or reduced processing speeds (Scott et al., 2007).

In an earlier study, Kalechstein et al. (2003) investigated neurocognitive impairment in the initial phases of abstinence in MA dependence. The study included 27 MA dependent participants and 18 normal controls. Participants were tested on a wide range of neurocognitive measures, including

executive functions and fluency, attention and psychomotor speed, learning and memory, and visuospatial skills. The authors found significant impairments on the majority of neurocognitive domains, and of particular interest for our research, verbal fluency in the MA dependent group when compared to the normal control group.

More recently, Simon et al. (2010) evaluated the change in cognitive performance over a one month period during early abstinence from MA use. A group of 27 MA users were compared to 28 normal controls on neurocognitive tests measuring attention and processing speed, learning and memory, working memory, timed tasks of executive functions and untimed tasks of executive functions. A subsample from each group was tested one month later. A group of MA users who maintained abstinence for one month ($n$ = 18) were compared to a group of normal controls ($n$ = 21). Significant differences were found at both points of comparison, indicating no significant improvements in cognition in the first month of abstinence. Particularly, MA users performed worse than normal controls on tasks of verbal fluency.

Verbal fluency has also been associated with a number of psychotic symptoms and has been specifically identified as a predictor of psychosis in high risk patients (Becker et al., 2010). Becker et al. (2010) investigated verbal fluency in patients at high risk of developing psychosis compared to first-episode schizophrenia patients. High risk patients are those who have a history of psychotic-like symptoms or have had a psychotic period that spontaneously subsided in less than a week, a family member with a first degree psychotic disorder, or the presence of a schizotypal personality disorder. The authors found no statistically significant difference between the high risk group and the schizophrenia group patient on verbal fluency (specifically, semantic fluency). However, within the high risk group statistically significant differences were observed between those who did develop psychosis and those who did not develop psychosis. Those who developed psychosis performed worse than those who didn't. Both groups differed significantly from controls. The authors concluded that verbal fluency is impaired before the development of psychosis. It is suggested that verbal fluency is a good predictor of the future development of psychosis in patients who are at high risk (Becker et al., 2010).

In an earlier study, Riley et al. (2000) investigated neuropsychological functioning in a group of first episode schizophrenia patients. The authors compared 40 patients at first presentation of psychotic

symptoms to 22 matched controls on a neuropsychological test battery assessing attention, verbal learning and memory, spatial ability, psychomotor speed, and executive functions. Verbal fluency was included in the executive functions in order to provide a measure of left frontal lobe functioning. Significant differences were observed on some tasks of executive functioning, including verbal fluency (phonemic and semantic) as well as on verbal learning and memory. Specifically, the largest impairments were observed on verbal fluency, particularly semantic fluency.

In summary, there is a strong argument for the approach taken in this thesis, which is to consider verbal fluency an executive function (see for e.g. Becker et al., 2010; Kalechstein et al., 2003; Riley et al., 2000). As emphasized, verbal fluency is negatively affected by poor cognitive control (Gläscher et al., 2012; Scott et al., 2007), an executive function comprising response inhibition and set-shifting. These two components of executive functioning are discussed below.

*Response Inhibition and Set-Shifting*

Impairment on tasks of response inhibition has been noted in MA (Scott et al. 2007). Inhibition refers to the ability to inhibit a thought, feeling or action and is typically assessed using a Stop Signal task, a Go/No Go task (Chambers, Garavan & Bellgrove, 2009; Leland, Arce, Miller & Paulus, 2008; Tekin & Cummings, 2002) or a Stroop task (Chambers, Garavan & Bellgrove, 2009; Garavan & Hester, 2007) or a card-sorting task (Stuss & Levine, 2002), and also draws on working memory (Gläscher et al., 2012). Both response inhibition and set-shifting rely heavily on attentional processes (Stuss & Levine, 2002) and have been associated mainly with the DLPFC and the ACC (Gläscher et al., 2012).

Stop Signal Tasks are widely used to measure response inhibition in clinical populations (Chambers et al., 2009; Padmala & Pessoa, 2010; Sharp et al., 2010). Delays in stop signal reaction times (SSRTs) have been associated with individuals with damage to the right inferior frontal gyrus (IFG), particularly the pars opercularis when compared to a normal control group as well as individuals with left frontal damage (Aron et al., 2003; as cited in Chambers et al., 2009).

However, other studies indicate that impairments on tasks of response inhibition are associated with medial rather than ventral PFC (Dècary & Richer, 1995; Floden & Stuss, 2006; Picton et al., 2007; as

cited in Chambers et al., 2009). Impairments on the Go/No Go task have been associated with excision of the dorsomedial PFC, including the ACC and the supplementary motor area (SMA; Dècary & Richer, 1995; as cited in Chambers et al., 2009). Tekin and Cummings (2002) also suggest that dysfunction in the ACC circuitry results in decreased motivation and response inhibition, particularly on the Go/No Go task.

Stroop tasks are also widely used to measure response inhibition in clinical populations, including drug dependent populations (see Salo, Ursu, Buonocore, Leamon & Carter, 2009). This task essentially requires the individual to ignore irrelevant, distracting information; resulting in slower responses and reduced accuracy (Garavan & Hester, 2007). It therefore relies on selective attention in order to ignore distracting stimuli (Stuss & Levine, 2002). Literature suggests two brain regions associated with impairment on the Stroop Task; the ACC (Bench et al. 1993, Pardo et al. 1990; as cited in Stuss & Levine, 2002) and the DLPFC (Stuss et al. 2001; as cited in Stuss & Levine, 2002).

The WCST also measures aspects of response inhibition. This task relies on attentional switching or set-shifting in order to inhibit perseverative responses. The shifting of responses necessary to succeed on the WCST are regarded as extra-dimensional (i.e. across perceptual dimensions, e.g. from colour to shape) as opposed to intra-dimensional (i.e. shifting within a perceptual dimension, e.g. from red to blue). Extra-dimensional shifting has been associated with the DLPFC (Stuss & Levine 2002).

The Stroop Task and the WCST were also used to investigate cognitive control by Gläscher et al. (2012). Poor performances on response switching and set switching were associated with damage to the ACC. Poor performances on the Stroop Task were associated with damage to the left DLPFC.

In addition, Tekin and Cummings (2002) also suggest that the DLPFC is also involved in problem set shifting and mental flexibility as well as planning behaviour and problem solving. The authors suggest that dysfunction in this circuitry results in an individual unable to direct their attention meaningfully and is easily distracted. These individuals often perform poorly on the WCST which requires set shifting and strategy generation. They also perform poorly on generativity tasks such as verbal and design fluency tasks.

There is evidence that response inhibition is impaired in MA-dependence. Scott et al. (2007) conducted a meta-analysis of the cognitive functions associated with MA and noted significant executive dysfunction, particularly on tasks of response inhibition and set-shifting, specifically the Stroop Task and the WCST. A number of single studies have also identified impaired response inhibition in MA (Kim et al., 2006; Leland et al., 2008; Monterosso, Aron, Cordova, Xu & London, 2005; Salo et al., 2002). For example, Salo et al. (2002) hypothesized in their study that MA-dependent individuals lack the ability to ignore distracting information. The authors used a computerized version of the Stroop Task on a group of MA-dependent individuals (*n* = 8) as well as a control group (*n* = 13) in order to test their hypothesis. Although their sample sizes were small, their participants were recruited according to stringent exclusion criteria, thereby minimizing the effects of co-morbid psychiatric conditions or other substances on results. The authors found that MA-dependent individuals showed slower reaction times than normal controls on interference trials, but not on non-interference trials, indicating a response-selection deficit as a result of an impaired ability to ignore irrelevant information (Salo et al., 2002).

Similarly, Monterosso, Aron, Cordova, Xu & London (2005) measured response inhibition in MA-dependence using a Stop Signal task. The authors had 3 groups of participants; a group of MA-dependent individuals (n = 11) who were abstinent for between 5 and 7 days; and two control groups (one smokers (n = 14) and one non-smokers (n = 29)). Stop Signal reaction times (SSRTs) were significantly slower for the MA-dependent group than the other two control groups. However reaction times for Go trials indicated no statistically significant between group differences, thus indicating no impairment in motor speed. In addition, no significant differences were observed with discrimination errors, indicating no impairment in decision processes. The authors conclude that a specific deficit in inhibition is associated with MA-dependence (Monterosso et al., 2005).

Furthermore, Kim, S. J. et al. (2006) investigated grey matter density changes and performance on the WCST in 29 MA dependent participants and compared this to 20 control participants. The authors found lower grey-matter density in the right middle frontal cortex and more total errors in the WCST in MA abusers compared to controls. A correlation was observed between decreased grey-matter density in the right middle frontal cortex and total errors on the WCST. It was also found that long-term abstinent MA abusers showed less decrease on grey-matter density and fewer errors

than short-term abstinent abusers, indicating that this impairment may be recovered with increased duration of abstinence.

More recently, Kim, Y. T. et al. (2009) conducted a study examining whether MA abusers have cerebral metabolic abnormalities and executive dysfunction. The authors investigated executive functions using the WCST task. Their participants included 24 MA dependent participants and 21 age-matched control participants. All participants underwent resting-state PET imaging and completed a computerized version of the WCST. The authors found that MA dependent participants completed fewer categories and made more Perseverative Errors and Total Errors than normal control participants. Their data suggest that MA participants have dose-dependent frontal hypometabolism and frontal executive dysfunction (Kim, Y. T. et al., 2009).

In addition, Leland et al. (2008) investigated the benefits of predictive cueing on response inhibition in MA-dependence. The authors suggested that an inhibitory response is often preceded by a cue that doesn't necessarily require immediate inhibition. To illustrate this point one could think about the orange traffic light that precedes a red traffic light, warning one to slow down and stop; or a yield sign indicating a potential stop. Cued Go/No Go tasks present stimuli that predict the need to inhibit a response before the Go/No Go stimuli are presented. Both response times and response accuracy are improved on such cued tasks. The authors wanted to determine whether these cues would activate the ACC and therefore result in improved inhibition in MA-dependence. They used a cued Go/No Go task, paired with fMRI, with a group of MA-dependent individuals ($n$ = 17) and a normal control group ($n$ = 16). All participants were male and were all abstinent at the time of scanning. Results indicated two interesting findings. Firstly, MA-dependent individuals showed ACC activation in response to the presented cues predicting the need to inhibit a particular response. Secondly, it was found that the greater the activation of the ACC, the better their inhibitory performance on the trials following the cues. Such results were not observed with the normal control group, indicating that cues did not affect their performance (Leland et al. 2008). This cue-based ACC activation is similar to the error-likelihood hypothesis of Brown and Braver (2005) as participants realized the potential for error in the form of inhibitory failure. This activation is also consistent with the response-conflict hypothesis of Botvinick et al. (2004), given the cues' dual role of either a "Go" stimulus or a "Cue" stimulus, indicating the likelihood of the following trial being a "No Go" trial.

In summary, the ability to inhibit a particular response is impaired in MA dependence. It is evident that the anterior cingulate cortex plays an important role in this ability (Brown & Braver, 2005; Botvinick, Cohen & Carter, 2000; Bush, Luu & Posner, 2000; Gläscher et al., 2012). Therefore any disruptions to this frontal sub-region may result in impairment of response inhibition. However, in tasks where working memory load is increased, greater dorsolateral prefrontal cortex (DLPFC) activation is observed (Hester et al., 2004 as cited in Garavan & Hester, 2007; Tekin & Cummings, 2002). Working memory and particularly attentional control are particularly important in response inhibition and set shifting (Stuss & Levine, 2002). The processes of attention and working memory will now be discussed.

*Attention and Working memory*

Attention and working memory (WM) seems to be impacted in MA (Scott et al. 2007). The processes of attention and working memory are clearly intertwined; however, exactly how these processes interact with each other has been the focus of much research in the field of cognitive neuroscience (Awh, Vogel & Oh, 2005). Selective attention refers to "goal directed focus on one aspect of the environment, while ignoring irrelevant aspects" (Gazzaley & Nobre, 2012, p. 129). Working memory on the other hand refers to "maintenance and/or manipulation of task relevant information in mind for brief periods of time to guide subsequent behaviour" (Gazzaley & Nobre, 2012, p. 129). Awh et al. (2005) suggest that the role of attention is a sort of a "gatekeeper", determining which items will occupy the limited capacity of working memory. The DLPFC plays a significant role in the ability to remember facts over short periods of time i.e. working memory (Bechara et al., 2000). The ACC is also suggested to play a role in working memory processes (Cazalis et al., 2011; Lenartowicz & McIntosh, 2005).

Numerous studies have found WM deficits in MA dependent individuals (Gonzalez, Bechara and Martin, 2007; Chang et al., 2002). For example, Chang et al. (2002) conducted a study investigating the persistent abnormalities in regional cerebral blood flow and cognitive functions in abstinent methamphetamine users. Twenty MA-dependent participants were compared to 20 healthy control participants on tests of neuropsychological functioning. Participants were tested on a computerized battery of focused and sustained attention as well as tests of psychomotor speed, gross motor functioning, verbal memory, and executive functioning. Results indicated that MA-dependent

individuals performed similarly to healthy controls, except on tasks of reaction time that required working memory (WM). Considering that WM has been shown to involve activation of D1 family dopamine receptors (Muly et al., 1998 as cited in Chang et al., 2002), it follows that MA related damage to the dopaminergic neurons may affect WM function (Chang et al., 2002).

More recently, Gonzalez, Bechara and Martin (2007) investigated executive functions of individuals with different self reported "drugs of choice"; including either methamphetamine or alcohol. Seventeen participants identified alcohol as their drug of choice and 16 identified methamphetamine as their drug of choice. These two groups were compared to 19 healthy controls on two tasks; one testing decision making (Iowa Gambling Task) and one testing WM (a delayed non-match to sample task). Results showed that the MA users performed significantly poorer than the alcohol users and healthy controls on the WM task. However, the gambling task did not yield any significant results, except for during the later trials of the task. On analyzing the final few trials, it was found that the MA dependent group and the alcohol users made more bad choices when compared to healthy controls (Gonzalez, Bechara & Martin, 2007). Working memory of MA users, therefore, was more impaired than decision making.

A relationship between working memory and decision making exists. Bechara et al. (2000) saw value in investigating whether the cognitive functions relating to WM were different from those relating to decision making. The authors found that WM was not dependent on intact decision making abilities, but rather, a different relationship was observed. While it is possible to have intact WM in the presence or absence of intact decision making, impairments in WM resulted in impairments in decision making, revealing an "asymmetrically dependent" relationship (Bechara et al., 2000: p. 301).

There is literature suggesting that WM is mediated by the DLPFC (Bechara et al., 2000; Tekin & Cummings, 2002) and the ACC (Lenartowicz & McIntosh, 2005). Certainly patients with damage to the DLPFC have demonstrated working memory impairments. However, few studies have explored the relationship between WM dysfunction and PFC damage in MA dependence. Therefore the current study aims to explore this in further depth.

In summary, attention and working memory deficits have been identified in MA dependence, however, the majority of studies make this conclusion based on single tasks. Furthermore, working

memory seems to be mediated by the DLPFC and possibly the ACC, however, evidence for this relationship in MA is lacking in the literature. The current study aims to address these gaps. Decision making and impulsivity will now be discussed in more detail.

*Decision-Making and Impulsivity*

It has long been established that addiction to substances is associated with impairments in decision-making (Bechara et al., 2001). Decision-making is a complex process that requires consideration of numerous variables (Kennerley & Walton, 2011). A simple decision of where to shop, for example, may require an individual to consider multiple variables before making a decision. The decision is likely to be influenced by a number of factors such as dietary requirements (vegetarian, halaal), dietary goals (saving money, health), food preferences, accessibility etc. It is also likely that the decision you make today is different to the one you made yesterday, or will make tomorrow, depending on your needs and goals. Therefore there is a valuation process that takes place (Kennerley & Walton, 2011). This valuation process needs to be deconstructed in order to measure the constructs of decision-making.

Monterosso, Ehrman, Napier, O'brien & Childress (2001) suggest that there are two main variables that need to be considered when making a decision; delay and risk. The authors investigated three decision making tasks of delay and risk in order to establish whether they examine the same construct. They compared a delay discounting task, a gambling task and the Roger's decision-making task. The authors administered these tasks to 32 cocaine-dependent participants. It was found that performance on the delay discounting task correlated with performance on the gambling task, indicating that these two tasks measure the same construct.

Delay and risk have been consistently associated with frontal brain regions. Specifically, it was suggested by Kennerley and Walton (2011) that people with damage to the ventromedial and orbitofrontal PFC (VMPFC and OFC, respectively) consistently make poor choices such as investing money in risky business ventures. It was further suggested that the ACC also plays a role. While the VMPFC and OFC are involved in determining the incentive value of the decision outcome, the ACC seems to be involved in tracking the history of choices and integrating this with information regarding the current value of the choice. This suggests that the ACC may be necessary for adaptive decision-making.

Relatively recently, Gläscher et al. (2012) conducted a study investigating cognitive functions associated with the PFC, namely cognitive control and decision-making. The authors used voxel-based lesion-symptom mapping in 344 individuals; 165 of which had lesions to the PFC. These individuals were tested on a comprehensive neuropsychological test battery. Four tasks were used measuring cognitive control and one task measuring decision-making was used. The results pertaining to cognitive control were mentioned above. Value-based decision-making and reward learning was measured using the Iowa Gambling Task (IGT). Poor performance on the IGT was associated with damage to the ventral sectors of the medial PFC, lateralized to the left. Performance on this task was also associated with dorsal sectors of the anterior PFC on the right and with the ACC, frontal pole, and the superior and middle frontal gyri, both medially and laterally.

Evidence suggests that stimulant-dependent individuals are less efficient in making-decisions because they do not adequately evaluate the potential consequences of the decision (Paulus, Hozack, Frank, Brown & Schuckit, 2003). However, the precise nature of decision-making deficits in substance abusing populations remains an area of debate (Paulus, Hozack, Frank, Brown & Schuckit, 2003). While some authors argue that substance abusing individuals show an exaggerated response to success (Bechara et al., 2001), others argue that these individuals are less sensitive to negative consequences (Lane and Cherek, 2000). In terms of reward and punishment, it seems as though these constructs are more effective when they are immediate rather than delayed.

In MA, impairments in decision-making have been noted. Gonzalez, Bechara and Martin (2007) investigated working memory and decision making in 33 drug (48%) or alcohol (52%) dependent individuals, and 19 controls. The drug of choice was methamphetamine and participants were at least 14 days abstinent. Decision-making was measured using the Iowa Gambling Task (IGT). Results indicated that MA dependent participants were impaired on both working memory and decision-making tasks and that both impairments were significantly different from alcohol dependent participants and controls.

In a meta-analysis conducted by Scott et al. (2007), mentioned early in this literature review, it was found that few studies included a comprehensive neuropsychological test battery and for this reason, decision-making and impulsivity were not reviewed in their paper. Based on the evidence for such deficits associated with MA (Semple et al., 2005; Hoffman et al., 2006; Gonzalez et al., 2007; Monterosso et al., 2007) the authors suggest that any future studies investigating executive brain functions should specifically include tasks measuring these two constructs (Scott et al., 2007).

Salo (2009; in press) stated, in terms of MA dependence and decision-making, that “impairments in this decision-making ability might make them (MA-dependent individuals) more likely to spend a paycheck on the immediate satisfaction of getting high rather than on the longer-term satisfaction gained by paying rent or buying groceries". This inability to make an informed decision, involving adequate premeditation of the consequences associated with that decision is typical in substance abusing populations. Both economists and psychologists have an active interest in this particular line of research. The general consensus, in terms of decision-making amongst consumers, is that while they may act impatiently today, they prefer, or rather plan, to act patiently in the future. For example, when an individual is given a choice between R10 today or R11 tomorrow, they may choose the smaller immediate amount. However when asked to choose between R10 in a year and R11 in a year and one day, they may choose the larger, slightly delayed amount (McClure, Laibson, Loewenstein, & Cohen, 2004). A similar pattern of behaviour is present in MA users and is referred to as “delay discounting” in the literature. “Delay discounting” refers to a relationship between the delay and the value of the reinforcer.

McClure et al. (2004; p. 504) suggests that the “discrepancy between short-run and long-run preferences (such as those in delay discounting) reflects the differential activation of distinguishable neural systems”. The authors hypothesized that short-run impatience is controlled by the limbic system. Long-run patience on the other hand is controlled by the lateral prefrontal cortex and associated structures. The authors tested their hypothesis by measuring brain activity of normal participants during a task in which they had to make choices between early monetary rewards or delayed monetary rewards. The earlier option had a lower value than the delayed option. The authors assumed that the more difficult the decision, the greater activation of relevant areas of the brain. Their assumptions were confirmed when prefrontal and parietal cortex showed greater activation during difficult decisions than other regions of the brain. Furthermore, they found that limbic and paralimbic cortical structures were involved when making choices of early rewards, rather than delayed rewards. These structures have consistently been associated with impulsive behaviour as well as drug dependence where dopaminergic innervation has been disrupted. Impatient behaviour thus seems to be driven by the limbic system (McClure et al., 2004).

In an earlier investigation of brain structures associated with delay discounting, Paulus et al. (2002) conducted a study examining prefrontal dysfunction in methamphetamine-dependent individuals. A

functional neuroimaging study was carried out in order to determine the relationship between decision-making dysfunction and neural activation in different prefrontal areas. The authors hypothesized that methamphetamine-dependent individuals in early sustained remission show decision making dysfunctions that are related to disrupted activation of the orbitofrontal and dorsolateral cortices. Participants in their study included a group of ten methamphetamine-dependent (M-D) adult males as well as a group of control participants. A structured clinical interview for a DSM-IV diagnosis (American Psychiatric Association, 1994) and the anti social personality disorder (ASPD) segment of the SCID II for personality disorders were conducted on the MD group. Individuals with major depressive disorder, bipolar, schizophrenia, post-traumatic stress, panic, obsessive-compulsive disorder or ASPD as well as individuals exhibiting current signs of withdrawal as indicated by the presence of at least two DSM IV withdrawal signs were excluded from the study. Participants were abstinent from methamphetamine for an average of 22.4 days (+/- 3.5 days), at the time of testing. A two-choice prediction task was administered to all participants to determine the response characteristics in decision-making situations with uncertain outcome as well as a two-choice response task. The main difference between these two tasks is that during the two-choice prediction task, the participant does not know the correct response in advance. The only information that the participant may use to guide their current response is the sequence of previous responses and outcomes. In comparison, during the two-choice response task, the participant knows the correct answer before selecting a response. Magnetic resonance images were obtained from all participants.

Results yielded five main results. Firstly, methamphetamine-dependent participants relative to controls relied more on an outcome-dependent strategy during the two-choice prediction task than the controls. This indicates that MD participants are more driven by the previous outcome of a response than normal control participants. Secondly, as duration of abstinence increased in the MD group, the degree of behavioural difference between these two groups diminished, indicating the possibility that this behaviour change could be temporary. Thirdly, the MD group similarly to controls exhibited task-related activation in bilateral prefrontal, parietal, and insula cortices. However, they showed less inferior prefrontal task-related activation. Fourth, MD participants did not show task-related activation in left prefrontal cortex, bilateral ventromedial prefrontal cortex or right orbitofrontal cortex. These results were expected given that these areas are critical for decision-making. Fifth, it was found that activation in the right orbitofrontal cortex was a good predictor of the duration of methamphetamine use (Paulus et al., 2002). However, given the small

sample sizes of this study (n = 10) and that the samples consisted only of males, the extent to which the results can be interpreted is limited. The authors conclude that immediate outcomes more often drive decision-making behaviour in MA-dependent individuals, relative to controls. MA-dependent individuals also show less task-related activation of the DLPFC and the OFC; this reduced activation was not related to length of abstinence. Therefore, chronic use of MA may lead to long-lasting effects on decision-making, consistent with changes in activity in the OFC (Paulus et al., 2002).

Similarly, Monterosso et al. (2007), conducted research exploring the neuropsychological substrates that underlie performance on a delay discounting task. The clinical literature thus far suggests that the neural substrates that are most likely to play a role in the valuation of delayed rewards involve the ventromedial prefrontal cortex (VMPFC), including the orbitofrontal cortex (OFC). The authors therefore designed a study to investigate the neural basis of delay discounting in MA dependent individuals. The study involved two parts. Firstly the authors assessed delay discounting in a group of MA dependent participants and then compared these results to those of healthy control participants who were not drug-dependent or drug-abusing (with exception to light marijuana abuse). Secondly, the authors used a variant of the task used in the first part of the study for an fMRI component comparing MA-dependent participants (n=12) to the control participants (n=17). It was hypothesized that the MA-dependent group would show greater delay discounting than the control group and that this finding would be paired with “less task-related signal change in the prefrontal cortex in the MA-dependent group” (Monterosso et al. 2007; p. 385). Participants in the MA-dependent group had to meet the DSM IV criteria for MA dependence. Participants were excluded if they met the criteria for any other current axis I diagnoses, except nicotine dependence. Participants were also excluded if they tested positive for any drugs other than MA and marijuana.

Participants performed a delay discounting task outside the scanner which was presented on a computer screen. The task required participants to choose between smaller immediate rewards and larger delayed rewards. Once participants had completed the pre-scanning DD task they then entered the scanner and completed an fMRI choice probe task. Results from the Monterosso et al. (2007) study indicated that MA abusers discounted more often than normal control participants. This difference was apparent even though the control group did not exclude cigarette smokers, a population that is known to exhibit considerably higher levels of delay discounting than non-smoking individuals.

In terms of neural recruitment patterns during the delay discounting task, Monterosso et al. (2007) found robust bilateral recruitment of the intraparietal sulcus (IPS). The authors suggested that this may be due to the fact that the task requires both a calculation component and a response selection component. Participants therefore need to combine the two types of information (delay and amount) and then compare the alternatives in order to make a decision. Lesion and imaging studies suggest that the IPS is involved in numerical calculations. This finding is consistent with McClure et al. (2004) who suggested frontoparietal cortex involvement in choices involving immediate alternatives. Furthermore, the authors also observed activation of the dorsolateral prefrontal cortex (DLPFC). This area of the brain is associated with working memory, a key component of delay discounting.

However, when comparing the two participant groups the authors did not observe reduced task-related activation of the frontoparietal network of MA abusers during the task, as would be expected. They did, however, observe between group differences regarding the hard-choice versus easy-choice paradigms. There were two clusters where these changes were evident; one in the left DLPFC and another in the right posterior parietal cortex. Although these were the only differences that were significant, a similar pattern of signal change was observed in all regions recruited by the task. This pattern of neural activation being greater in response to hard choices than easy choices was generally more robust in control participants than MA abusers. This result is similar to that found by McClure (2004). However, Monterosso et al. (2007) did not observe activation of the limbic and paralimbic systems, as did McClure (2004). A possible reason for this is that the choices used in the Monterosso et al. (2007) study were purely hypothetical and this could have minimized the limbic recruitment in such choices.

The authors performed a correlational analysis between activation and delay discounting. Results did not reveal any relationship between either the hard-choice versus no-choice paradigm or the hard-choice versus easy-choice paradigm and individual level of delay discounting. The latter being of particular interest as this would suggest that the observed group differences in activation, associated with this paradigm, are not in fact related to behavioural group differences in delay discounting of MA abusers. This finding would therefore suggest that the apparent inefficiency in neural response observed in MA abusers is not related to the tendency toward greater delay

discounting (Monterosso et al., 2007). However the authors note that a larger sample size may reveal such a relationship.

More recently, Hoffman et al. (2008) conducted a study investigating neural correlates of delay discounting (DD) in recently abstinent MA-dependent adults. The authors examined the cortical and sub-cortical activity associated with DD in patients recently (2-8 weeks) abstinent from MA and in a matched sample of healthy controls, using fMRI. The authors hypothesized that DD choices would activate the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC) and the posterior parietal cortex (PPC) more than control choices, in both groups. In addition to this they expected that choices of immediate vs. delayed rewards would activate ventral striatum and sub-genual anterior cingulate cortex (ACC). Finally, the authors "hypothesized that increased discounting in the MA group relative to the control group would be reflected in increased activity in the affective circuit due to overvaluation of immediate rewards and decreased activity in the cognitive circuit due to difficulty making comparisons" (Hoffman, 2008; p. 184).

The Hoffman et al. (2008) study included two participant groups; an MA-dependent group (n=19), and a healthy control group (n=17). MA-dependent participants reported using at least 0.5g of MA per day over 5 days per week for the past year. Each participant was interviewed and diagnosed using the Structured Clinical Interview of the DSM-IV (APA, 2000) in order to establish a diagnosis for MA-dependence and confirm the absence of disqualifying psychiatric disorders. The DD task was performed in the fMRI scanner and took the form of a forced-choice block design task. The task consisted of eight DD blocks alternated with 8 magnitude-estimation (ME) control blocks. Each block contained 10 trials resulting in a total of 80 ME and 80 DD trials per run for two runs. DD trials presented the participants with two choices; a delayed reward and an immediate reward. The ME trials, which served as the control condition, consisted of two choices in which either the delay or the reward was held constant. Each participant was presented with 160 immediate and delayed reward pairs in pseudorandom sequence.

Results from their study indicated that MA participants discounted more heavily than the non-drug addicted control participants. Greatest activation was associated with hard DD choices bilaterally in the middle cingulate, posterior parietal cortex (PPC), and the right rostral insula. Control participants displayed more activation than MA participants bilaterally in the precuneus and the right caudate

nucleus, anterior cingulate cortex (ACC), and the dorsolateral prefrontal cortex (DLPFC). Degree of discounting was correlated with the activity in the amygdale, DLPFC, posterior cingulate cortex and PPC. The authors concluded that MA addicted individuals who strongly prefer smaller immediate over larger delayed rewards, activate the dorsal cognitive control system in order to overcome their preference. Amygdala activation during choice of delayed reward was associated a greater degree of discounting. This suggests that heavily discounting MA-dependent individuals may be more responsive to the negative attributes of delayed rewards than non-drug addicted individuals (Hoffman et al., 2008).

While it seems that the majority of studies have indicated that MA-dependent individuals discount more often than controls, the mechanism behind delay-discounting is an area of debate. While McClure et al. (2004) observed limbic and paralimbic activation, Monterosso et al. (2007) did not. While Monterosso et al. (2007) did not observe decreased activation of the fronto-parietal network as one would expect, Paulus et al. (2002) observed less inferior prefrontal task-related activation in MA-dependence. Therefore more clarity on the neural correlates associated with delay-discounting is required, particularly in MA-dependence. The present study aims to investigate the prefrontal brain regions that correlated with executive brain functions in methamphetamine dependence.

It has been hypothesized that delay discounting forms the primary basis of impulsivity (Ainslie, 1975). Impulsivity plays a significant role in both our understanding and the diagnosis of various forms of psychopathology. There is an entire section of the DSM-IV (American Psychiatric Association, 2000) dedicated to impulse-control disorders such as, intermittent explosive disorder, kleptomania and pyromania. Furthermore, impulsivity appears in the diagnostic criteria for a variety of psychiatric disorders such as, borderline personality disorder, antisocial personality disorder, attention deficit/hyperactivity disorder, mania, dementia, bulimia nervosa, and the paraphilias and, of particular importance to the current study, substance use disorders. Therefore research on substance use disorders must take into account the impact of impulsivity on neuropsychological functioning.

Impulsivity is predominant among users of various substances, including alcohol, cocaine and amphetamines. Moreover, it is considered a risk factor for the development of alcohol and substance abuse and dependence and is also a predictor of poorer treatment results for substance-

dependent individuals. Impulsivity is a personality trait that is clinically important in terms of both understanding and intervening with drug users (Semple, Zians, Grant, & Patterson, 2005) as it can lead to a number of maladaptive behaviours such as polysubstance use, binge drug use, unprotected sex, needle sharing and suicidal behaviour (Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2007).

Impulsivity is a multidimensional construct. Traditional personality theories view impulsivity as a thrill or sensation-seeking construct that involves a lack of planning, prompting an individual to act on feelings of the moment without regard for rules and regulations (Whiteside & Lynam, 2001). While Moeller et al. (2001, p. 1784) has provided an appropriate definition of impulsivity as "a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to themselves or to others", there still remains little consensus among researchers regarding the definition and measurement of impulsivity (Semple et al., 2005).

Semple et al. suggested that in 2005 there were few studies that examined the relationship between MA and impulsivity. The authors concluded that this relationship needed further investigation, given the clinical implications. They suggested that patient screening and assessment of impulsivity could identify patients who are at risk of developing a substance use disorder or are likely to engage in high risk sexual behaviour. This knowledge could also assist drug treatment or rehabilitation programs as well as intervention programs aimed at reducing high risk sexual behaviours. The authors therefore decided to explore this relationship further in a sample of 385 males and females currently using MA. They examine impulsivity in terms of personal and social resources, substance use, sexual risk behaviour, and psychiatric health. The authors hypothesized that participants who scored high on self-report measures of impulsivity would also have fewer personal and social resources, consume larger amounts of MA, exhibit high risk sexual behaviours and exhibit worse psychiatric health. Results showed that two background characteristics were shown to be associated with high levels of impulsivity namely, age and education. Younger participants and less educated participants were shown to have higher levels of impulsivity. A positive relationship was also observed between quantity of MA used and impulsivity. Higher doses of MA were associated with higher levels of impulsivity. The high impulsivity group also had significantly more sex partners and significantly more unprotected sex acts than the low impulsivity group. A strong positive correlation was also noted between depression and impulsivity. The authors proved that substance using

individuals show high levels of impulsivity that are linked with various other negative factors associated with substance use. The current study therefore aims to explore impulsivity further using a delay discounting task.

In summary, there is evidence for an association between MA dependence and decision making deficits. However, Scott et al. (2007) suggests this relationship needs further investigation. There also exists debate around the exact nature of decision making deficits in MA and it is for these reasons that we will investigate this further. Decision-making has been assessed either using a gambling task or a delay discounting task. Our aim is to include a variety of tasks in our study in order to fully assess the nature of decision-making deficits in our sample. Furthermore, the OFC and ACC have been found to mediate decision-making. However, cortical thickness of these frontal sub-regions has not been investigated in relation to executive functioning in MA dependence. The current study aims to address this gap. We now move to review, briefly, the literature on the relationship between impulsivity, ADHD and methamphetamine.

## THE RELATIONSHIP BETWEEN IMPULSIVITY, ADHD, AND METHAMPHETAMINE

Impulsivity is one of three distinct characteristic of attention deficit/hyperactivity disorder (ADHD), together with hyperactivity and inattention. Individuals who are diagnosed with ADHD are at increased risk for substance use disorder (SUD; Biederman et al., 1998; Matsumoto et al., 2005; Wilens et al., 1997). Biederman et al. (1998) found that ADHD is associated with a twofold increased risk for SUD. This association has numerous clinical, scientific and public health implications (Wilens et al. 1997). Clinically, early detection of developing drug dependence in high risk ADHD adolescents could lead to effective early intervention strategies. Thus, preventive programs could be developed, aimed at adolescents with ADHD, years before the onset of SUD (Wilens et al. 1997). Treating adolescent ADHD can therefore help prevent the development of SUD (Wilson et al., 2005). Moreover, ADHD can play a pivotal role in the pathogenesis and maintenance of SUD (Wilson et al., 2005) and evidence suggests high rates of comorbidity between ADHD and MA dependence, in particular (Duarte, Woods, Rooney, Atkinson & Grant, 2011; Jaffe at al., 2005; Obermeit et al., 2013).

The neuropathogenesis of ADHD is not well understood, however, it is presently conceptualized as a disorder resulting from hypoactivity in the dopaminergic systems and possibly an imbalance in the noradrenergic systems (Biederman, 2005; di Michele et al., 2005). Therefore, neuropsychological disturbances would be characteristic of an underlying fronto-striatal pathophysiology (Hervey et al., 2004). Moreover, similar to MA, current pharmacologic treatments for ADHD target dopaminergic systems and block the reuptake of dopamine and norepinephrine. As a result, individuals with ADHD may experience more beneficial effects from initial MA use which may then lead to repeated use and thus dependence (Jaffe et al., 2005). It is therefore unknown whether MA use results in a similar symptom profile to ADHD, or whether individuals with these symptoms have a predisposition for MA dependence, due to its initial "self-medicating" effects. It has also been suggested that ADHD is a significant predictor of MA-induced psychosis (Fujii, 2002; Salo et al., 2013). The current study aims to investigate the co-morbidity of MA use and ADHD. We now move to review the literature on the psychiatric associations with MA.

## METHAMPHETAMINE-INDUCED PSYCHOTIC DISORDER

Substance-induced psychotic disorder (SIPD) can be attributed to the use of a variety of legal and illegal substances such as alcohol, cannabis, cocaine, heroin and methamphetamine. SIPD as a result of methamphetamine is associated with chronic, high doses and/or continuous use (see Grant et al., (2011) for a review on MA Psychosis). Dependent methamphetamine users are at a particularly high risk of developing psychosis (McKetin et al., 2006). A study conducted by Srisurapanont et al. (2003) found both positive and (to a lesser extend) negative symptoms associated with MA psychosis. Positive symptoms include delusions, hallucinations and incoherent speech. Negative symptoms include poverty of speech, psychomotor retardation and flattened affect (Srisurapanont et al., 2003). Other psychiatric sequelae associated with MA psychosis include anxiety, paranoia, and delirium. Depression accompanies withdrawal when MA use ceases (Harris & Bakti, 2000 as cited in Scott et al., 2007).

McKetin et al. (2006) examined the prevalence of psychotic symptoms among regular MA users in Australia. The authors found that 18% of their sample showed clinically significant symptoms of psychosis; excluding those with a history of schizophrenia or any other psychotic disorders. This indicates a high prevalence of psychotic symptoms among regular MA users. In addition it was found

that MA abusers were 13 times more likely to develop psychotic symptoms when compared to the general population (McKetin et al., 2006).

Literature examining MA psychosis in South Africa is scarce (Vos, Cloete, Le Roux, Kidd, Jordaan, 2010). The number of psychiatric admissions due to MA use in the Western Cape increased significantly between 2002 and 2006. Vos et al. (2010) completed a retrospective study investigating admission numbers of adult and adolescent substance users in the first half of 2002, compared to those in the first half of 2006. Results indicated zero psychiatric admissions due to MA use in 2002. This number increased in 2006, with a total of 37% of admissions due to MA use. Demographic information obtained from the sample in 2006 indicated that the majority of admissions were male (64%), single (100%), unemployed (93%) and the mean age at admission was 22 years. The authors concluded that MA-related psychiatric hospital admissions reflect an increasing trend; consistent with the reported increase in demand for treatment at community drug treatment centers in Cape Town (Vos et al., 2010).

There are a number of risk factors that influence the development of a psychotic disorder secondary to methamphetamine abuse or dependence. In particular, individuals with a premorbid neurological condition may be at greater risk (Fujii, 2002; Salo et al., 2013). Fujii (2002) examined this hypothesis by reviewing 29 inpatients of Hawaii state hospital for history of traumatic brain injury, learning disabilities, birth complications, or soft neurological signs. It was found that 19 out of 29 inpatients demonstrated one or more of the above during childhood. In particular, a large number of these inpatients were diagnosed with ADHD. Similarly, in a more recent study, Salo et al. (2013) investigated the possibility ADHD-relevant childhood behaviours as a predictor of later MA psychosis in adulthood. The authors included a total of 190 MA using participants in their study; 145 of which reported symptoms associated with MA psychosis and 45 did not. All participants completed the Wender Utah Rating Scale (WURS) which retrospectively assesses ADHD-relevant childhood behaviours and symptoms in adults. The authors found a significant positive correlation between frequency of MA-related psychotic episodes and scores of the WURS (Salo et al., 2013). Previous neurological disorders such as ADHD, therefore, may be a risk factor for developing treatment-resistant psychosis in MA abusers (Fujii, 2002; Salo et al., 2013).

Considering that MA psychosis is often resistant to treatment, patients with this disorder are often misdiagnosed as having schizophrenia (Fujii, 2002). This is because MA psychosis presents similarly to paranoid schizophrenia (Jacobs et al., 2008). These similarities are expected given the effect of MA on dopamine and the dopamine hypothesis of schizophrenia (Baumeister & Francis, 2002). The similarities between the neuropsychological profiles of both paranoid schizophrenia and MA psychosis were investigated by Jacobs et al. (2008), as compromised neurocognition is a core feature of both schizophrenia and MA psychosis (Mesholam-Gately, Giuliano, Goff, Faraone and Seidman, 2009). The authors suggested that while both the literature on the neurocognition of schizophrenia and the literature on the neurocognition of MA dependence had been extensively studied, no studies had been conducted on MA psychosis at that time. The authors therefore compared a group of inpatients with paranoid schizophrenia at a state hospital in Hawaii (n = 19) to a group of inpatients with MA psychosis (n = 20) on a range of neuropsychological tasks including a number of tests of executive functioning, such as the Wisconsin Card Sorting Task, the DKEFS colour word interference subtest. This is the first such study comparing these two population groups. The authors found no significant differences between the two groups on any domains of executive functioning. The authors suggest that "the similarities in presentation between MA psychosis and paranoid schizophrenia extend to neurocognition and allude to a common underlying pathophysiology" (Jacobs et al., 2008: p. 102). Therefore the neurocognition of schizophrenia will now be discussed. Given the minimal number of studies investigating the neuropsychological deficits associated with MA psychosis, the evidence presented below may assist in identifying the nature of such deficits.

Mesholam-Gately et al. (2009) conducted a meta-analysis of neurocognitive findings from 47 studies of first episode schizophrenia published from 1994 to 2008. The meta-analysis used 43 separate samples including 2204 first episode patients and 2775 largely age- and gender-matched control participants. Significant impairments across 10 neurocognitive domains were observed in the samples of first episode schizophrenics. Findings indicated that these impairments observed during first episodes, are similar to those observed in well established illness. The most severe impairments were observed in immediate verbal memory and processing speed. However, neurocognition seemed to be impaired across all 10 domains, indicating generalised neurocognitive impairment. Executive functions were assessed using only a few outcome measures of the Wisconsin Card Sorting Task. While significant impairments were observed, it is certainly challenging to draw conclusions based on evidence from just one task of executive functions and studies investigating executive functions using larger neuropsychological test batteries are required. It was noted that general

cognitive ability, as assessed by means of IQ scores, was found to be considerably worse in first episode schizophrenia, when compared to IQ observed before frank illness onset. This indicates a decline in cognition between the premorbid and first episode stages of schizophrenia (Mesholam-Gately et al., 2009). Thus, similar trends may be observed in the onset of MA psychosis.

Executive functioning impairments were also emphasized by Bilder et al. (2000) who conducted a study investigating the neuropsychology of first episode schizophrenia. The authors administered a comprehensive neuropsychological test battery to 94 individuals with first-episode schizophrenia as well as to a group of 36 healthy volunteers. The neuropsychological test battery evaluated the following domains: language, memory, attentional, executive, motor, and visuospatial abilities. Results indicated a relatively non-specific deficit pattern, reflecting disturbances in key systems (mesencephalic, diencephalic, limbic or frontal functional systems). However, statistically significant impairments were found on memory and executive functions, when compared to other domains such as language and visuospatial abilities. Particularly, the most severe deficits were observed on tasks of attention and executive functions (Bilder et al., 2000).

In summary, it has been observed that certain symptoms associated with MA are seen also in schizophrenia (e.g. paranoid delusions). This likely reflects an overlap in underlying mechanisms, and therefore in neuropsychology (Salo et al., 2002). Indeed, it has been observed that the neuropsychological profile of schizophrenia is similar to that observed in MA psychosis (Jacobs et al., 2008). Given that the most severely affected domain in schizophrenia is that of executive functions (Bilder et al. 2000), it may therefore be hypothesized that the most severely affected domain in MA psychosis will also be executive functions. Given the evidence presented above it is also likely that a decline in cognition will be observed in MA psychosis, when compared to MA dependence.

SUMMARY

The literature review has identified four key areas that need further investigation. These are listed and summarized below. A research question pertaining to each section is posed. Specific hypotheses are presented below.

1. Methamphetamine and executive functions

Chronic use of methamphetamine has been associated with neurotoxicity (Barr et al., 2006; Berman et al., 2008; Nordahl et al., 2003; Scott et al., 2007) and structural abnormalities in the brain (Hoffman, 2008; McClure et al., 2004; Monterosso et al., 2007; Paulus et al., 2002). These structural abnormalities result in various neuropsychological sequelae (Barr et al., 2006; Hoffman, 2008; McClure et al., 2004; Monterosso et al., 2007; Paulus et al., 2002; Nordahl, Salo & Leamon, 2003; Scott et al., 2007). Currently, research investigating these neuropsychological sequelae has provided inconsistent results. These studies state different findings with regards to the nature of the neuropsychological impairments. Therefore further research is needed in order to address this issue. Specifically, many studies suggest that executive functions are most often and most severely affected by MA (Barr et al., 2006; Bechara et al., 2001; Chang et al., 2002; Gonzalez, Bechara & Martin, 2007; Paulus, Hozack, Frank, Brown & Schuckit, 2003; Verdejo-García, Bechara, Recknor & Pérez-García, 2005). However, previous studies have based their findings on only one or two tasks of executive functioning. No studies to date have comprehensively explored executive functions in MA dependence. The present study therefore aims to address this shortcoming by investigating executive functions by means of a comprehensive neuropsychological test battery, covering the domains of attention and working memory, decision making and impulsivity, response inhibition, and verbal fluency.

***Research Question: Are executive functions impaired in MA? And if so which of the four domains shows the most severe impairment?***

## 2. Methamphetamine-induced psychotic disorder

Moreover, substance-induced psychotic disorder as a result of MA abuse in an under-researched topic, particularly in South Africa, where prevalence rates and economic costs are high. Specifically, neuropsychological data on this population is South Africa is lacking. The present study aims to address this shortcoming in providing data on the neuropsychological sequelae associated with MA psychosis. Particularly, the study aims to draw on comparisons between MA dependence with a history of psychosis and MA dependence without a history of psychosis in an attempt to improve understanding of these populations from a neuropsychological point of view; thus potentially informing and improving behavioural therapies.

***Research Question: Are executive functions more severely impaired in MA Dependence with a history of psychosis compared to MA Dependence without a history of psychosis?***

## 3. Co-morbidity of ADHD in methamphetamine

Furthermore, given the high comorbidity of ADHD and substance dependence (Biederman et al., 1998; Jaffe et al., 2005; Matsumoto et al., 2005; Wilens et al., 1997; Wilson et al., 2005), the present study aims to investigate the relationship between symptoms of ADHD and executive functioning within MA dependence. ADHD is a potential risk factor for the development of a substance use disorder. Identifying risk factors can aid in identifying high risk groups, and therefore aid in the prevention of MA dependence in South Africa.

***Research Question: Are symptoms of ADHD found to be co-morbid in our MA groups and if so, how do these relate to any executive impairment found?***

4. The correlation between executive functions and prefrontal cortex

Finally, the present study also aims to correlate cortical thickness of frontal cortex sub-regions with neuropsychological deficits, specifically executive dysfunction. Previous research investigating methamphetamine dependence, neuropsychological functioning, and brain imaging has examined either regional cerebral blood flow (Chang et al. 2002), morphometric changes (Chang et al. 2005) or conducted fMRI studies investigating performance of single cognitive tasks (Monterosso et al. 2007; Paulus et al. 2002, 2003). Thompson et al. (2004) mapped regional brain abnormalities and correlated this data with memory performance. However, there are few studies that have performed such correlational analyses between MRI and neuropsychological data. No such studies, to my knowledge have correlated executive functioning data with cortical thickness data in methamphetamine dependence, and particularly methamphetamine psychosis. I therefore aim to address this gap. In addition, there are some inconsistencies in the literature regarding the exact brain structures associated with MA dependence and we aim to add insight here.

***Research Question: Is there a correlation between executive impairment and cortical thickness in our MA sample?***

The above research questions will be answered by investigating a number of specific hypotheses. These are outlined below.

# HYPOTHESES

1. Executive function impairments will be observed in the MA groups compared to healthy controls on the domains of response inhibition and set-shifting, attention and working memory, decision-making and impulsivity, and verbal fluency.

2. The MA-psychosis group will perform worse than both MA-dependent and NC groups on tasks of executive functioning.

3. Decision making and impulsivity are expected to be positively correlated with structural abnormalities in the OFC and the ACC, i.e. greater extent of structural damage in the OFC and the ACC will be associated with more severe impairments on tasks of decision making and impulsivity.

4. Working memory is expected to be positively correlated with structural abnormalities in the DLPFC, i.e. greater extend of structural damage in the DLPFC will be associated with more severe impairments on tasks of WM.

5. Response Inhibition is expected to be positively correlated with structural abnormalities in the ACC, i.e. larger amounts of structural damage in the ACC will be associated with more severe impairments on tasks of response inhibition.

6. Verbal Fluency is expected to be positively correlated with structural abnormalities in the anterior PFC and insula, i.e. greater extend of structural damage in the anterior PFC and insula will be associated with more severe impairments on tasks of verbal fluency.

7. Comorbid ADHD has a negative impact on executive functions in this methamphetamine-dependent sample.

# CHAPTER THREE: RESEARCH DESIGN AND METHODS

## STUDY DESIGN

This empirical study employed a quasi-experimental, controlled design used in order to test specific hypotheses. Quasi-experimental designs are those which employ multiple measures or a control group without randomly assigning participants to groups. Since quasi-experiments are natural experiments, threats to external validity are minimized and generalisability is increased as compared to a laboratory setting (Mouton, 2001). The ability of these designs to establish a cause and effect relationship is dependent upon the degree to which the two groups in the study are equivalent. In this study, participants have been matched as closely as possible in terms of age, gender, level of education, employment status, ethnicity, and language. A battery of validated neuropsychological tests was administered to all participants as well as a number of questionnaires widely used in clinical settings.

The independent variable in this study is related to methamphetamine and is a grouping variable that has three levels, namely, methamphetamine dependence with a history of psychosis i.e., substance induced psychotic disorder (MA+), methamphetamine dependence without a history of psychosis (MA-) and no methamphetamine i.e. healthy control participants (NC) with no history of methamphetamine use. The dependent variables are related to executive functioning, and include measures of impulsivity and decision making, inhibition and set shifting, attention and working memory, and verbal fluency.

Methamphetamine dependence is defined using the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders 4$^{th}$ edition (2000). The substance of choice is from the amphetamine class of substances, specifically methamphetamine. According to the DSM-IV-TR the criteria for substance dependence are as follows:

*A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:*

*(1) tolerance, as defined by either of the following:*
   *a. a need for markedly increased amounts of the substance to achieve intoxication or desired effect*
   *b. markedly diminished effect with continued use of the same amount of the substance*

*(2) withdrawal, as manifested by either of the following:*
   *a. the characteristic withdrawal syndrome for the substance*
   *b. the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms*

*(3) the substance is taken in larger amounts or over a longer period than was intended*

*(4) there is a persistent desire or unsuccessful efforts to cut down or control substance use*

*(5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain smoking), or recover from its effects*

*(6) important social, occupational, or recreational activities are given up or reduced because of substance use*

*(7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance*

(American Psychiatric Association, 2000)

Participants in the clinical groups (methamphetamine groups) had to meet these criteria in order to be eligible to take part in this study. Participants who did not meet these criteria and/or met these criteria for any other substances (with the exception of nicotine and cannabis) were excluded from participation.

In addition, the Methamphetamine Psychosis group of participants had to be diagnosed with substance-induced psychotic disorder. The diagnostic criteria for substance induced psychotic disorder as set out by the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000) are as follows:

A. *Prominent hallucinations or delusions*
B. *There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):*
   *(1) the symptoms in Criterion A developing during, or within a month of, substance intoxication or withdrawal*
   *(2) medication use is etiologically related to the disturbance*
C. *The disturbance is not better accounted for by a Psychotic Disorder that is not substance induced. Evidence that the symptoms are better accounted for by a Psychotic Disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use; the symptoms persist for substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication, or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is other evidence that suggests the existence of an independent non-substance-induced psychotic disorder (e.g., a history of recurrent non-substance-related episodes)*
D. *The disturbance does not occur exclusively during the course of a delirium*

(American Psychiatric Association, 2000)

The dependent variable, executive functioning, has been operationally defined as those functions that are associated with the neural circuits of the prefrontal cortex (PFC). The PFC is strongly correlated with the formulation and monitoring of goal directed actions (Stuss & Knight, 2002; Roberts et al., 1998; as cited by Verdejo-Garcia, Bechara & Recknor, 2006). There are three functional circuits of the PFC, each arguably relevant to specific executive functions, specifically working memory and mental flexibility (dorsolateral prefrontal cortex), decision making and emotion regulation (orbitofrontal cortex) and response inhibition (anterior cingulate cortex; Verdejo-Garcia, Bechara & Recknor, 2006). We have also added verbal fluency to our battery, given its association with the frontal cortex (Doughty and Done, 2009; Neill, Garvich & Rossell, 2013).

## PARTICIPANTS

Three groups of participants were recruited to take part in this study: a methamphetamine dependent group with a history of psychosis (MA+), a methamphetamine dependent group without a history of psychosis (MA-) and a group of non-substance-dependent/abusing healthy control participants (NC). A total of 175 participants were recruited for this study; approximately 70 participants were judged as eligible to take part; out of which 59 took part. The MA+ and control groups each contained 20 participants and the MA- group contained 19 participants. The remaining 116 participants were either not eligible for the study or chose not to complete participation. Ineligibility resulted from a number of factors including drug dependence other than methamphetamine, co-morbid psychiatric disorders or lack of English proficiency.

Recruitment was carried out through usual clinical activities. Three groups were recruited. First, the methamphetamine dependent group with a history of psychosis (particularly first episode) was recruited from psychiatric in-patient wards at Groote Schuur Hospital, Valkenberg Psychiatric Hospital, Victoria Hospital and Somerset Hospital in Cape Town. These participants met the criteria for an Axis I diagnosis of substance induced psychotic disorder (SIPD) according to the structured clinical interview for DSM-IV (SCID-IV) as well as the DSM-IV criteria for methamphetamine dependence. Their treatment with neuroleptics had not extended past three months at the time of testing. Second, non-psychotic methamphetamine dependent participants were recruited from the Cape Town Drug Counseling Centre and various other drug counseling centers within the Cape Town area that were willing to participate in the study. This sample met the DSM-IV criteria for methamphetamine dependence through use of a SCID-IV. These participants did not, however, meet the criteria for SIPD according to the SCID-IV. Third the healthy control participants were recruited through word of mouth and flyers requesting voluntary participation. These participants did not meet the DSM-IV criteria for methamphetamine dependence or SIPD nor any other psychiatric disorder.

Testing after a period of drug abstinence also decreases the likelihood that the observed cognitive impairment is due to residual drug or withdrawal effects. Since many of our participants were in treatment at the time of testing, many of them were still using the drug at the time. We required that they remain abstinent for seven days prior to testing; however, this was not always the case. Therefore we required that they abstain from using the drug on the day of testing. All participants were recruited according to strict inclusion and exclusion criteria.

Group 1: Methamphetamine dependence with a history of psychosis (MA+)

*Inclusion criteria*

- Chronic diagnosis of MA dependence on the SCID-IV
- History of experiencing psychotic symptoms lasting at least one week in total and associated with methamphetamine use. Psychotic symptoms defined as a minimum score of 3 or more on any one of items P1, P2, P3, and G9 of the PANSS rating scale
- Current drug abstinence (on the day of testing)
- Age range between 18 and 45 years

*Exclusion criteria*

- Substance dependence other than MA (except nicotine and marijuana)
- Lifetime and current diagnosis of psychiatric disorders (with the exception of a substance induced psychotic disorder)
- History of psychosis prior to MA use
- Medical or neurological illness or trauma that would affect the central nervous system,
- Reported history of a seropositive test for HIV
- Severe renal, hepatic, pulmonary, endocrine disease
- Severe head injury
- Lack of fluency in English, as this may impair understanding of testing procedures
- Patients judged to be experiencing substance intoxication or withdrawal delirium

Group 2: Methamphetamine Dependence without a history of psychosis (MA-)

*Inclusion Criteria*

- Chronic diagnosis of MA dependence on the SCID-IV
- Current drug abstinence (on the day of testing)
- Age range between 18 and 45 years

*Exclusion Criteria*

- Substance dependence other than MA (except nicotine and marijuana)
- Lifetime and current diagnosis of psychiatric disorders
- Medical or neurological illness or trauma that would affect the central nervous system,
- Reported history of a seropositive test for HIV
- Severe renal, hepatic, pulmonary, endocrine disease
- Severe head injury
- Lack of fluency in English, as this may impair understanding of testing procedures
- Patients judged to be experiencing substance intoxication or withdrawal delirium

Group 3: Healthy Controls (NC)

*Inclusion Criteria*

- No evidence of any drug dependency on the SCID-IV
- Demographic details resembling those of the methamphetamine dependent samples

*Exclusion Criteria*

- Substance dependence other than nicotine
- Lifetime and current diagnosis of psychiatric disorders

- Medical or neurological illness or trauma that would affect the central nervous system
- Reported history of a seropositive test for HIV
- Severe renal, hepatic, pulmonary, endocrine disease
- Severe head injury
- Lack of fluency in English, as this may impair understanding of testing procedures
- Participants judged to be experiencing substance intoxication or withdrawal delirium

The three comparison groups were matched as closely as possible in terms of age, gender, years of education and social demographics (see *Table 1* and *Figures 1-7* below). Participants received compensation for participating in this study in the form of food vouchers, which could not be exchanged for cigarettes or alcohol. Participants did not receive cash monies for participating in this study. Transport was provided for participants by a professional transport service provider, when necessary.

*Table 1.* Demographic and Clinical Characteristics for Participants Across all 3 Participant Groups

| Variable | MA+ (n = 20) | MA- (n = 19) | NC (n = 20) |
|---|---|---|---|
| Age | 25.45 (7.57) | 24.0 (3.83) | 24.2 (4.32) |
| Gender (M:F) | 16:4 | 17:2 | 14:6 |
| Handedness (R:L) | 20:0 | 16:2 | 19:1 |
| Years of Education | 9.6 (1.43) | 10.68 (2.24) | 12.45 (1.61) |
| IQ (FSIQ) | 74.4 (12.7) | 79.53 (17.46) | 89.65 (16.28) |
| Duration of Abuse (months) | 62.33 (38.9) | 70.7 (29.1) | --- |
| Duration of Abuse (range) | 12 – 144 | 36 – 120 | --- |
| Length of Abstinence (days) | 56.2 (53.18) | 52.56 (62.20) | --- |
| Length of Abstinence (range) | 0 – 180 | 0 – 240 | --- |
| Quantity Used/Week (grams) | 1.4 (1.27)* | 2.97 (2.45)* | --- |
| Quantity Used/Week (range) | 0.25 – 5* | 0.5 – 10* | --- |
| Cigarette smokers % | 95% | 84% | 50% |
| Cannabis users % | 100% | 74% | 45% |

*Note:* For all variables except gender, handedness and ranges, data presented are means with standard deviations in parentheses. MA+ = Methamphetamine dependence with a history of psychosis. MA- = Methamphetamine dependence without a history of psychosis. NC = Normal Controls

*These data were gathered by means of self-report interviews and are included only for interest. No guarantees can be made that these data are accurate. We were therefore reluctant to include 'Quantity' in any statistical analyses, given that the source of such information is questionable.

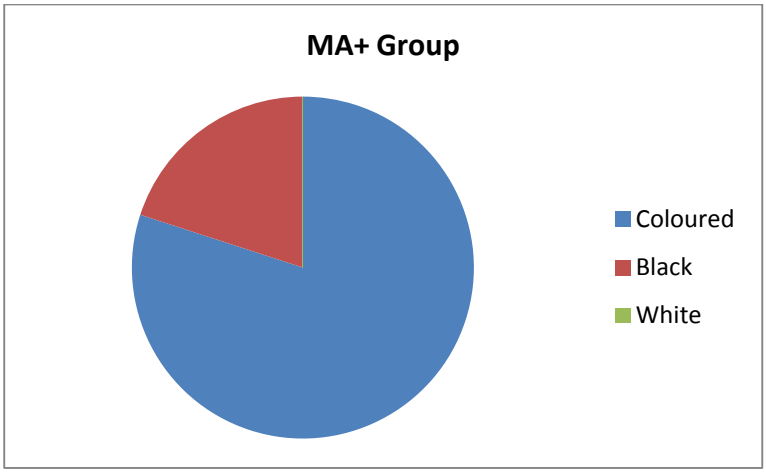


*Figure 2*. Population groups present in the MA+ group

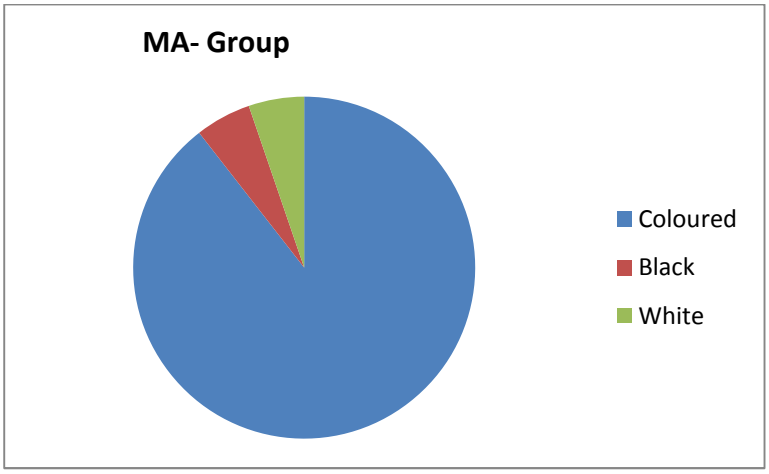


*Figure 3*. Population groups present in the MA- group

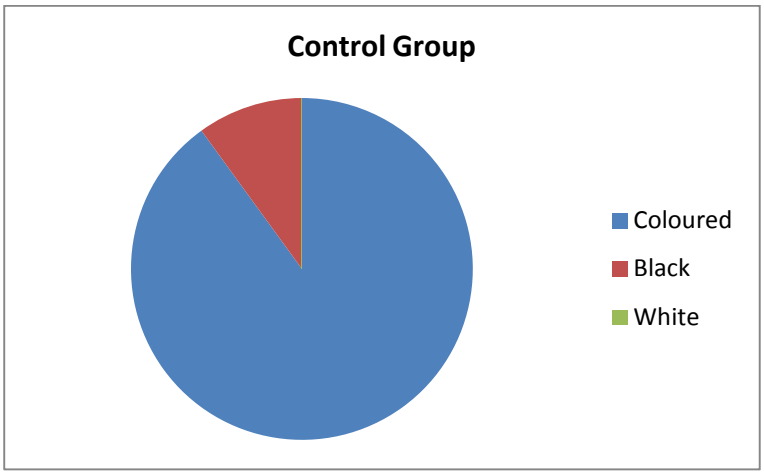


*Figure 4*. Population groups present in the control group

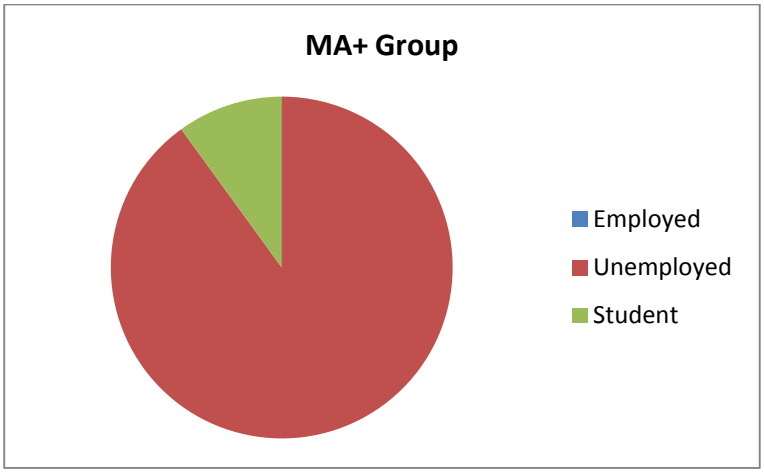


*Figure 5*. Employment status of participants in the MA+ group

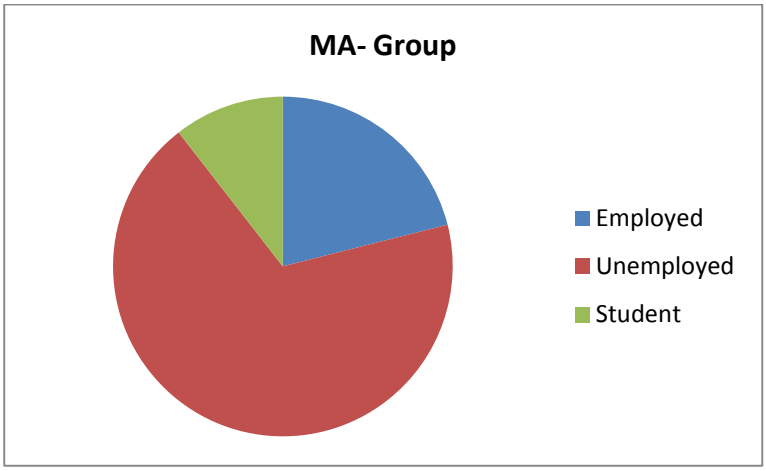


*Figure 6*. Employment status of participants in the MA- group

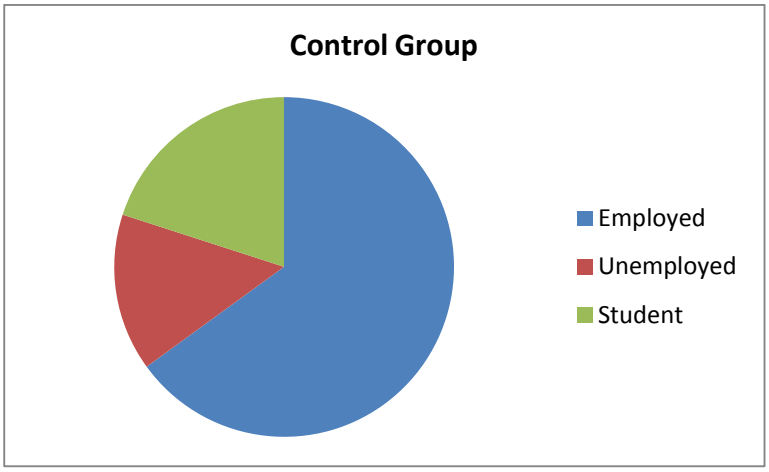


*Figure 7*. Employment status of participants in the control group

# MATERIALS

The following measures were used in the study; screening questionnaire; informed consent sheet; demographics, drug use and pre-morbid mental health questionnaire; structured clinical interview for DSM-IV (SCID-IV); The Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1997) and a neuropsychological test battery including subtests from the CANTAB (Cambridge Cognition) battery and the D-KEFS (Delis, Kaplan & Kramer, 2001), The Stroop Task (Stroop, 1935), a Delay Discounting Task, The Balloon Analogue Risk Taking Task (Lejuez et al., 2002), The Attention Network Task (Fan et al. (2002), Task Switching, and the Wisconsin Card Sorting Task (Psychological Assessment Resources, 2003); and an ADHD self report questionnaire (Burke & Austin, 2010).

## Demographic and Clinical Questionnaires

### *Screening Questionnaire (see Appendix A)*

A screening Questionnaire was used to screen potential participants, either in person or telephonically in order to decide whether they were eligible to participate in the study. Previous head injuries, epilepsy or any other neurological condition would have excluded participants from the study. Information such as handedness, metal implants or pregnancy was necessary information required before conducting the MRI scans.

### *Informed consent sheet (see Appendix B)*

A document detailing the purpose of the study as well as the participant's role in the study was presented to each participant, before the commencement of their participation. Their rights and responsibilities were explained to them. Participants were made aware that they would not be harmed in any way during the study and that they may withdraw without any undue discriminations against them as a result of their withdrawal. Their participation was voluntary and they were informed that all their information would be kept confidential and their identity would be kept anonymous. Participants were required to agree to these terms by signing the informed consent sheet before participation.

*Demographics, drug use and pre-morbid mental health questionnaire* (see *Appendix C*)

Measures of demographics included current age, sex, employment status and number of years of education completed, marital status, number of dependents and dwelling types. Drug use measures included: life-time use of all major drug types and days of drug use in the past month by drug type. Measures of MA use included the participant's main route of methamphetamine administration in the past year, age of first MA use, frequency of MA use in the past year and MA dependence in the past year. A history of mental illnesses was also recorded.

*Structured Clinical Interview for DSM-IV (SCID-IV)*

The SCID-IV is a clinician administered semi-structured interview used to diagnose psychiatric disorders based on the criteria of the Diagnostic and Statistical Manual (Rodriguez 2004). Administration of the SCID will be restricted to the Axis-I psychiatric disorders and Axis-V.

*Positive and Negative Syndrome Scale (PANSS)*

The PANSS is a clinician administered scale that determines positive, negative as well as general psychopathological symptoms (Kay et al., 1987). This scale measures psychotic and general psychopathology on a Likert type continuous scale. As the scale includes general psychopathological measures such as anxiety tension and depression, this scale will also be administered to control groups without a history of psychosis.

*The Wechsler Abbreviated Scale of Intelligence (WASI)*

The WASI is a widely used clinical tool giving an estimate of IQ. It was developed out of the need for a short and reliable measure of intelligence in both clinical and research settings. It is designed for use with individuals aged from 6 – 89 years. The WASI contains four subtests. Two of these are verbal measures, namely vocabulary and similarities, and two of these are performance measures, namely block design and matrix reasoning. Raw scores are obtained from these four sections and then converted into T-scores from which IQ estimates are made. An individual's verbal, non-verbal, and general cognitive functioning can be estimated in approximately 30 minutes through administration of this scale and yields the three conventional verbal, performance and full scale IQ scores. The WASI has been used extensively in research, particularly in clinical populations.

Neuropsychological Test Battery

*The Cambridge Neuropsychological Test Automated Battery (CANTAB)*

The computerized neuropsychological tests in the CANTAB are currently used in more than 50 countries, with a bibliography of over 500 peer-reviewed journal articles. Johanson et al. (2006) have previously used the CANTAB tests in a methamphetamine abusing sample. These widely validated tests allow for quick and accurate assessment of many cognitive domains, with excellent sensitivity. Furthermore, as no reading or verbal responses are required, the CANTAB tests are well suited for cross-cultural administration, particularly valuable for the South African population. Most importantly, the battery was developed with the aid of functional neuroimaging techniques; therefore, the neuroanatomical regions associated with performance on each subtest within the battery have been well defined. All CANTAB tests are administered on a touch screen computer, and are presented in the form of games that the examinee must complete.

The CANTAB battery used in the current study consisted of the Big/Little Circle (BLC) task to assess basic comprehension; decision making and response control subtests including the Affective Go/No Go (AGN) task, the Cambridge Gambling task (CGT), the Information Sampling Task (IST) and the Stop Signal Task (SST); and the executive functions, working memory and planning subtests including the Spatial Span (SSP) task, the Spatial Working Memory (SWM) task and the Reaction Time (RT) task.

*The Big/Little Circle test* assesses comprehension, learning and reversal. This task was used to assess basic understanding of verbal instruction. It was also used to train participants in the general idea of following and reversing a rule, before proceeding to the rest of the CANTAB battery as well as a training task to familiarize participants with using a touch screen. The participants were presented with a series of paired squares, each one containing a circle; one large and one small. Initially the participants were instructed to touch the square containing the smaller of the two circles presented on the screen (see *Figure 8*). Following 20 trials, the participant was then required to change the rule and touch the square containing the larger of the two circles presented for a further 20 trials.

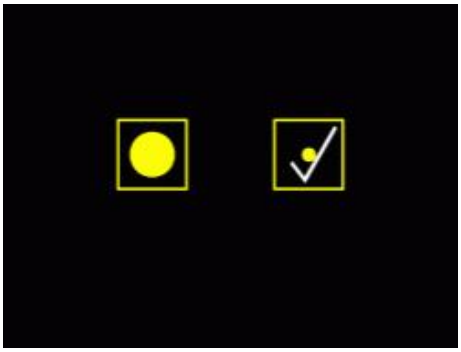

*Figure 8*. The BLC task screen

*The Affective Go/No Go (AGN)* test assesses information processing biases and inhibitory control for positive and negative stimuli. During this test, a series of words were rapidly presented in the centre of the screen. These words were either positive or happy words (for example, “smile”, “stamina”, “terrific”, “optimistic”) or negative or sad words (for example, “dull”, “crying”, “mistake”, “hopeless”). The participant was given a target valence and asked to press the button on the press pad when they saw a word that matched this valence (see *Figure 9*).


*Figure 9*. The AGN task screen (positive valence condition)

Words were displayed one at a time in the centre of the screen. Each word was displayed for 300ms and there was an interval between the words of 900ms. The test consisted of ten 18-word blocks. The first two blocks in each test were practice blocks and were therefore not scored. Affective

cognitive functions are thought to be related to the ventral and medial-prefrontal cortex areas of the brain because of the limbic connections with this region.

*The Cambridge Gambling Task (CGT)* was developed to assess decision making and risk taking behavior outside of a learning context. Relevant information is presented to the participants 'up-front' and there is no need to learn or retrieve information over consecutive trials. On each trial, participants were presented with a row of ten boxes across the top of the screen, some of which were red and some of which were blue. At the bottom of the screen were rectangles containing the words 'Red' and 'Blue'. Participants were required to guess whether a yellow token was hidden in a red box or a blue box by touching the block containing the corresponding word at the bottom of the screen (see *Figure 10*). In the gambling stages, participants began with a number of points, displayed on the screen, and were able to select a proportion of these points (5%, 25%, 50%, 75% or 95%), displayed in either increasing or decreasing order, in a second box on the screen, to gamble on their confidence in this judgment. A stake box on the screen displayed the current amount of the bet.

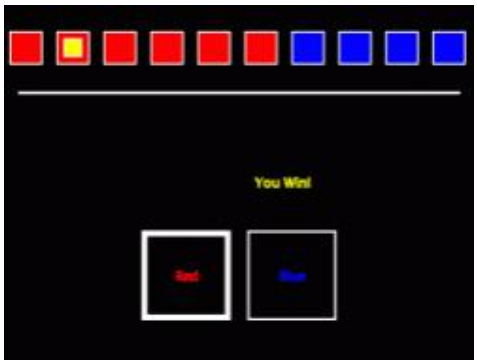


*Figure 10*. The CGT task screen for the decision stage

The task consisted of five stages. The first stage was a decision stage only where participants were required to decide whether a yellow token was hidden in a red box or a blue box and make their choice by touching the appropriate box at the bottom of the screen. The second stage was a training stage for gambling with ascending stakes. The participants had to select their colour choice as well as indicate the amount they chose to bet by touching the stake box at the appropriate time. If the stake box on the screen was not touched, the final value displayed was used. The third stage was a test stage for gambling where the participants' performance was assessed. The fourth stage was a

further training stage for gambling. This time the stakes moved in a descending direction. The fifth stage was another test stage for gambling, with the stakes moving in the same direction as the fourth stage. The participants' performance was assessed here. The likely neural substrate for this task is the orbitofrontal prefrontal cortex.

*The Information Sampling Task (IST)* tests impulsivity and decision making. The IST is designed to measure pre-decisional processing where the participant gathers and evaluates information prior to making a decision. Inadequate reflection means that decisions will be made on the basis of less evidence, and, therefore will reduce the accuracy of the eventual decision. Participants were presented with a 5x5 array of grey boxes on the screen, and two larger coloured panels below these boxes (see *Figure 11*). Participants were informed that they were playing a game for points, which they could win by making a correct decision about which colour is in the majority under the grey boxes. They touched the grey boxes one at a time, which then opened up to reveal one of the two colours shown at the bottom of the screen. Once a box had been touched, it remained open. When the participant had made their decision about which colour was in the majority, they touched the panel of that colour at the bottom of the screen to indicate their choice. After the participant had indicated their choice, all the remaining grey boxes on the screen revealed their colours and a message was displayed to inform the participant whether or not they were correct. The colours changed from trial to trial. There were two conditions: the fixed win condition, in which the participant was awarded 100 points for a correct decision regardless of the number of boxes opened; and the decreasing win condition, in which the number of points that could be won for a correct decision started at 250 and decreased by 10 points for every box touched. In either condition an incorrect decision costs 100 points.

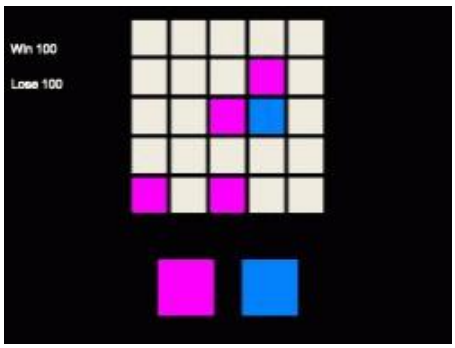


*Figure 11*. The IST task screen showing the training stage

*The Stop-Signal Task (SST)* is a psychological test that measures a person's response inhibition ability. This test consisted of two parts. The task screen showed a white ring, displayed to alert the participant, and then a visual stimulus displayed within the ring after a fixed 500ms delay, consisting of an arrow pointing to the left or to the right (see *Figure 12*). The participant is then introduced to the press pad, and instructed to press the left hand button when they see a left-pointing arrow and the right hand button when they see a right-pointing arrow. The first block consisted of 16 trials for the participant to practice this. During the second part of the task, the participant was told to continue pressing the buttons on the press pad when they saw the arrows, as before, but, if they heard an auditory signal (a beep), they should then withhold their response and not press the button.

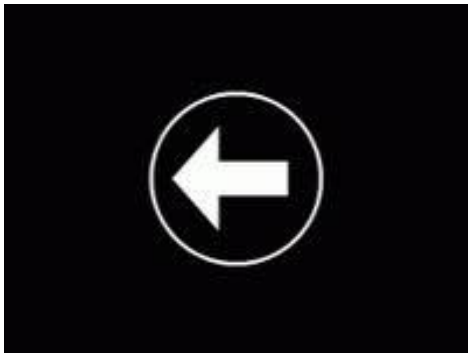

*Figure 12*. The SS task screen

The task consisted of 5 assessed blocks, each block containing 64 trials. Each block was divided into four sub-blocks of 16 trials for analysis purposes only i.e. there were no gaps between these trials and they were not evident to the participant. Each sub-block contained 12 “go” trials with no auditory stop signal delay (SSD) period and four “stop’ trials with an auditory stop signal. The 12 go trials and four stop trials were given in a random order within each sub-block, but all the trials from one sub-block take place before the next sub-block begins. Each sub-block consisted of exactly one stop trial derived from each of four series (staircases), which at the start of the test were as follows: Series 1: 100ms; Series 2: 200ms; Series 3: 400ms; Series 4: 500ms. The timing of the auditory stop signal changes throughout the test, depending on the participant’s previous performances, so that

stopping occurred approximately 50% of the time for each participant. The shorter the SSD, the more likely it is that the participant was be able to hold off responding to the arrow. Note that for some participants the SSD may have become negative: that is, the auditory signal occurred before the onset of the arrow stimulus. The timing of the four series is expected to converge as the test proceeds. At the end of each assessed block, a feedback screen was displayed showing a graphical representation of the participants' performance, which was explained to the participant who was then encouraged to go faster on each trial.

*The Spatial Span (SSP) task* is a computerized version of the Corsi's Blocks task and provides a measure of working memory. A set of white squares was shown to the participant on a computer screen. Some of the squares changed in colour, one by one, in a variable sequence (see *Figure 13*). At the end of each sequence a tone indicated that the participant should touch each of the boxes coloured by the computer in the same order as they were originally presented. The number of squares that change colour ranged from 2 to 9. There were three possible sequences at each level, but as soon as the participant passed a sequence at each level they will immediately progress to the next level, not necessarily performing all three sequences at each level. If all three attempts at a particular level were completed unsuccessfully, the task would terminate. Both the sequence and colour used changed from sequence to sequence to minimize interference.

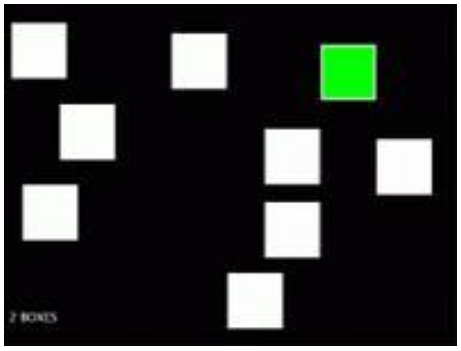

*Figure 13*. The SSP task screen

*The Spatial Working Memory (SWM)* task assesses working memory and strategy use. It tests the participants' ability to retain spatial information and to manipulate remembered items in working memory. It is a self-ordered task which also tests heuristic strategy.

The test began with a number of coloured squares (or boxes) shown on the screen. The aim of the test was to, by process of elimination, find one blue token that the computer had hidden in one of a number of boxes and then fill up an empty column on the right hand side of the screen (see *Figure 14*). Only one token was hidden at a time and the participant was to remember which boxes had tokens inside already and which one had not, as the idea was to refrain from opening a box that had already had a token in it. Touching any box in which a blue token had already been found was an error. The number of boxes was gradually increased from three to eight, thereby increasing in difficulty. The colour and position of the boxes used were changed from trial to trial to discourage the use of stereotyped search strategies. The participant decided the order in which the boxes were searched. The computer determined the number of boxes that should be visited (discounting errors). Performance at the harder levels of this task was enhanced by the use of a heuristic search strategy.

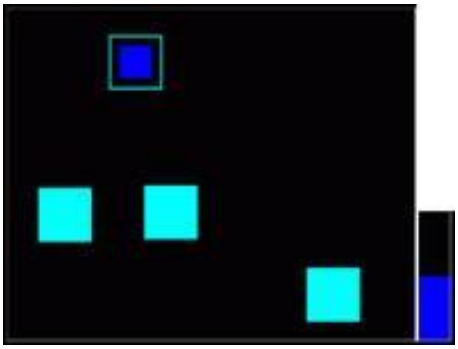

*Figure 14*. The SWM task screen (4 boxes)

*The Reaction Time (RTI) task* provides a measure of response speed and movement in single and 5-choice paradigms. The task was divided into five stages, with each successive stage having increasingly complex response requirements. In the first stage, the participant was required to touch the screen when a yellow spot appeared in the centre of the screen, neither touching too soon nor too late (see *Figure 15*). Once the participant had achieved 5 out of 6 correct, or completed a maximum of 18 attempts, the second stage was introduced. The second stage was the choice reaction task and here the yellow spot may appear in any one of five locations. Again, the participant was trained to a criterion of 5 out of 6 correct, with a maximum of 40 attempts. If the participant failed to achieve the criterion on this stage, the test terminated. Successful participants were then introduced to the press pad. The third stage required the participant to hold down the press pad

button until the yellow spot appears in the centre of the screen, at which time, they would release the button, but they did not have to touch the screen. The fourth stage, again, required the participant to hold down the button of the press pad until the yellow spot appears but this time they had to release the button and then touch the screen. The fifth and final stage required participants to do the same as stage 4 only this time there were five possible locations where the yellow spot may have appeared. The participant had to release the button on the press pad and then touch the screen where the spot was presented.

*Figure 15*. The RTI task screen for the first stage if the RTI task

### *The Stroop Task*

The Stroop task is a classic psychological test of inhibitory control. This task consisted of four trials, each one progressively more difficult than the next. Trial 1 requires participants to read a series of words (“blue”, “red” or “green”), printed in black ink, in random sequence. Trial 2 required participants to name the ink colour of a series of square blocks on the page (again the blue, red or green coloured blocks are printed in random sequence on the page). Trial 3 required participants to name the ink colour of the words (“blue”, “red” or “green”). Here, the word that is printed does not correspond to the colour in which it has been printed; therefore the participant had to inhibit the obvious response of reading the word, as opposed to naming the ink colour in which the word is printed. Trial 4 contained a series of words printed on a page in one of the three colours (blue, red or green). This trial contained 2 rules; if the word did not have a block printed around it, the participant named the ink colour and if the word did have a block around it they then read the word. This trial required participants to not only inhibit typical responses, but they also had to hold the two rules in mind, demonstrating cognitive flexibility. Each trial was timed from start to finish and errors were

recorded (both non-corrected errors and self-corrected errors). Therefore three measures are obtained from this task. This task is a widely validated measure of response inhibition and cognitive control in clinical populations and is also widely used in methamphetamine-dependent populations (Salo, 2009).

*Wisconsin Card Sorting Test (WCST; computerized version)*

The WCST is a neuropsychological test of set-shifting, i.e. the ability to display flexibility in the face of changing schedules of reinforcement. During this task, a number of stimulus cards appeared on the computer screen in front of the participant. The shapes on the cards were different in color, quantity, and design. The computer decided whether the cards were to be matched by color, design or quantity. The participant was then given a card at the bottom of the screen and asked to match it to one of the stimulus cards, thereby forming separate virtual "piles" of cards for each (see *Figure 16*). Once the card had been matched the words "right" or "wrong" appeared on the screen, depending on whether the participant made a correct choice or an incorrect choice. Once that card had been matched and feedback had been given, another card appeared on the screen and again, the participant was required to match it to one of the four at the top of the screen. The participant was not told how to match the cards; however, he or she was told whether a particular match was right or wrong. During the course of the task the matching rules were changed and the time taken for the participant to learn the new rules, and the mistakes made during this learning process were analyzed to arrive at a score.

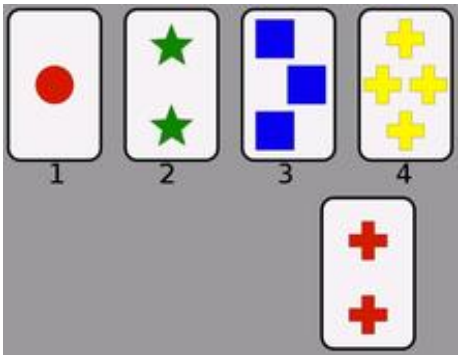


*Figure 16*. The WCST task screen

*Delis-Kaplan Executive Functions System (D-KEFS): FAS and Category Fluency Subtests*

The D-KEFS is a standardized battery of tests, designed to evaluate higher level cognitive functions in both children and adults for both neuropsychological research and clinical utility. Studies of internal consistency revealed the reliability of different sub-tests was largely in the moderate to high range (Delis, Kaplan & Kramer, 2001). The validity of the D-KEFS instruments has been demonstrated in numerous neuropsychological studies completed over the last 50 years (Delis, Kaplan & Kramer, 2001). The D-KEFS assesses vital executive functions such as flexibility of thinking, inhibition, problem solving, planning, impulse control, concept formation, abstract thinking, and creativity in both verbal and spatial modalities. The D-KEFS (FAS and Category Fluency Subtests) is a test of generativity or verbal fluency of both the semantic and phonemic types. Verbal fluency refers to the rate at which an individual can produce words.

The D-KEFS Verbal Fluency subtests are comprised of three conditions: letter fluency (FAS), category fluency, and category switching. The first condition, "Letter Fluency" assesses the fluency with which the participant can generate lexical items while simultaneously observing a number of rules. Participants were required to generate words verbally beginning with a specified letter of the alphabet (F, A, and S), as quickly as possible. Participants had 60 seconds in which to give as many words as they were able to, whilst conforming to three simple rules; (1) they may not say names of people (for example "Frank"); (2) they may not say names of places (for example "France"); and (3) they may not say two or more of the same words with different endings (for example "fun" and "funny"). The higher level functions assessed by this task include initiation, simultaneous processing, systematic retrieval of phonetically similar lexical items and speed of processing. Performance on this task is dependent upon a number of fundamental cognitive components, including vocabulary, spelling ability, and attention. The outcome measure for this task is the total number of correct responses across all three letters (F, A, S).

The second condition, "Category Fluency" required the participant to retrieve and generate words belonging to a designated high-frequency semantic category, i.e. "Boy's Names" and "Animals". Again, participants had 60 seconds to give as many words from these semantic categories as possible. This task is more familiar to participants than generating words that start with a particular letter of the alphabet and therefore higher scores are often observed. The outcome measure for this task is the total number of correct responses across both categories.

The third condition, “Category Switching” assesses the rate at which semantic knowledge can be retrieved as well as cognitive flexibility in shifting between two semantic categories. The combination of fluency and switching in the same task increases the sensitivity of the instrument to frontal dysfunction. This task required the participant to alternate between two different semantic categories, namely “Fruit” and “Furniture”. Participant alternated between these two categories as many times as possible in 60 seconds. The outcome measures for this task was the total number of correct responses.

*Attention Network Task (ANT)*

Attention is a complex cognitive function, dependent on interacting neural systems of the brain. According to the Attention Network Theory, the systems can be subdivided into an alerting or vigilance network, a network of orientation or selection, and an executive or conflict network. Fan, McCandliss, Sommer, Raz & Posner (2002) developed an experimental task called the Attention Network Task (ANT), combining a cue-target and a flanker test to obtain measures of the efficiency and accuracy of the three networks.

During the ANT task participants were shown a series of arrows on a computer screen. A cross was presented in the middle of the screen and the arrows were presented either above or below the cross. Participants were instructed to keep their eyes on the cross throughout the experiment. Five arrows appeared on the screen at the same time and the participant had to respond to the central arrow. The central arrow was surrounded by distracter arrows, displayed in one of three possible conditions; the distracter arrows were pointing in the same direction as the central arrow; the distracter arrows were pointing in the opposite direction to the central arrow; or the distracter arrows did not have arrow heads at all and appeared as solid lines on either side of the central arrow (see *Figure 17*).

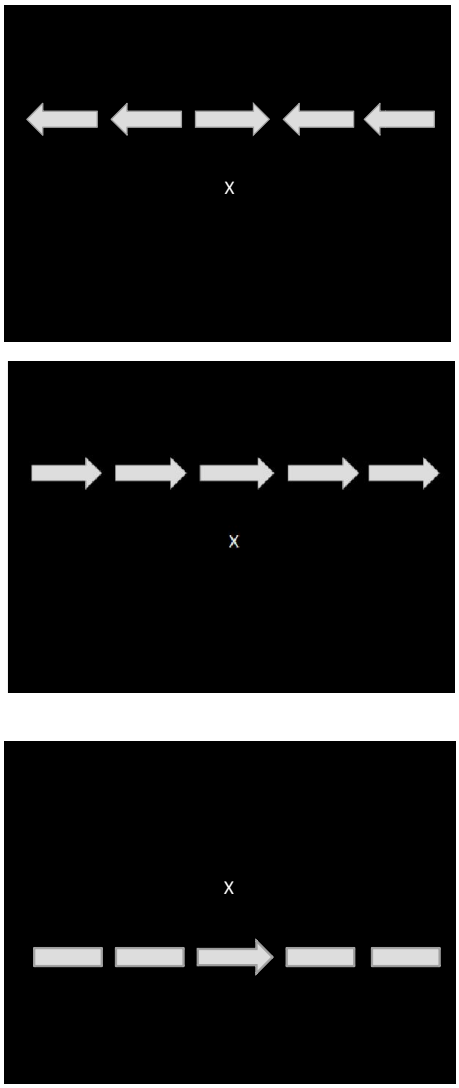


*Figure 17*. The three different task screens for the ANT

*Balloon Analogue Risk Taking Task (BART)*

The BART is a computerised task that serves as a behavioural index of basic risk decision-making. Lejuez et al. (2002) reported favourable convergent and discriminant properties of the BART, indicating convergence with other indices of risk-taking (e.g., gambling), and divergence from impulsivity and anxiety-relevant variables such as anxiety sensitivity. In the BART, a balloon is displayed on a computer screen and participants are instructed to use the left and right arrow keys in order to pump up the balloon (in order to earn points), using the left arrow key and stop pumping

using the right arrow key. Participants earn rewards by blowing up 15 virtual balloons including both red (see *Figure 18*) and blue balloons (see *Figure 19*). Each pump earns the participant 5 points. Each balloon has an explosion threshold that varies from balloon to balloon and which, if reached, results in the loss of all points for that balloon. Therefore, in deciding whether to make each pump, participants weigh the potential gain against the potential risk of losing all the points for that balloon. BART performance provides a more valid and generalizable assessment of risk decision-making than many other standard risk-taking tasks (Lejuez et al., 2002).

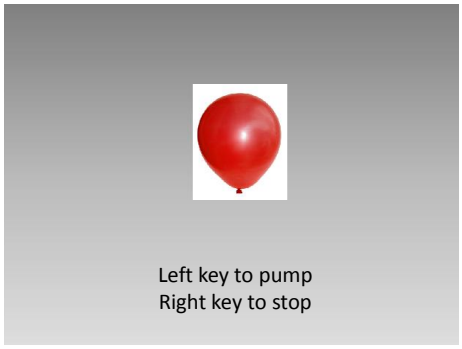


*Figure 18*. The BART task screen representing a non-inflated red balloon

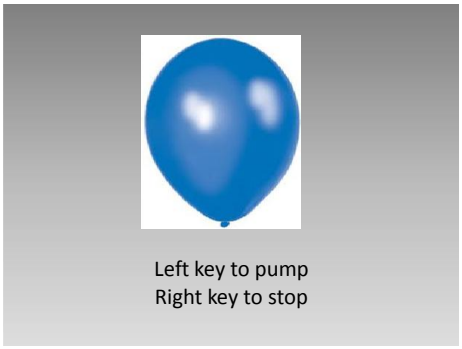


*Figure 19*. The BART task screen representing a partially-inflated blue balloon

### *Task Switching*

Task Switching is a measure of an individual's ability to shift frequently between cognitive tasks. Alternating between two separate tasks places high demands on working memory processes. Task Switching probes the control processes that reconfigure mental resources for a change of task by requiring participants to switch frequently among a small set of simple tasks.

The participant is required to respond to objects on a computer screen depending on cues at the top of the screen (see *Figure 20*). Each cue indicates whether the participant should respond to the colour of the object or the shape of the object (both being displayed in a single image). The colours are red or green (for example, press the left button if the colour is red and the right button if the colour is green), and the shapes are triangles or circles (for example, press the left button if the shape is a triangle and the right button if the shape if a circle). There are a number of practice trials for this task and participants have to score a minimum of 60% in order to proceed to the experimental trials. Feedback is given on practice trials indicating whether the participant was correct or incorrect. This task measures reaction time as the task changes from trial to trial as well as total number of errors.

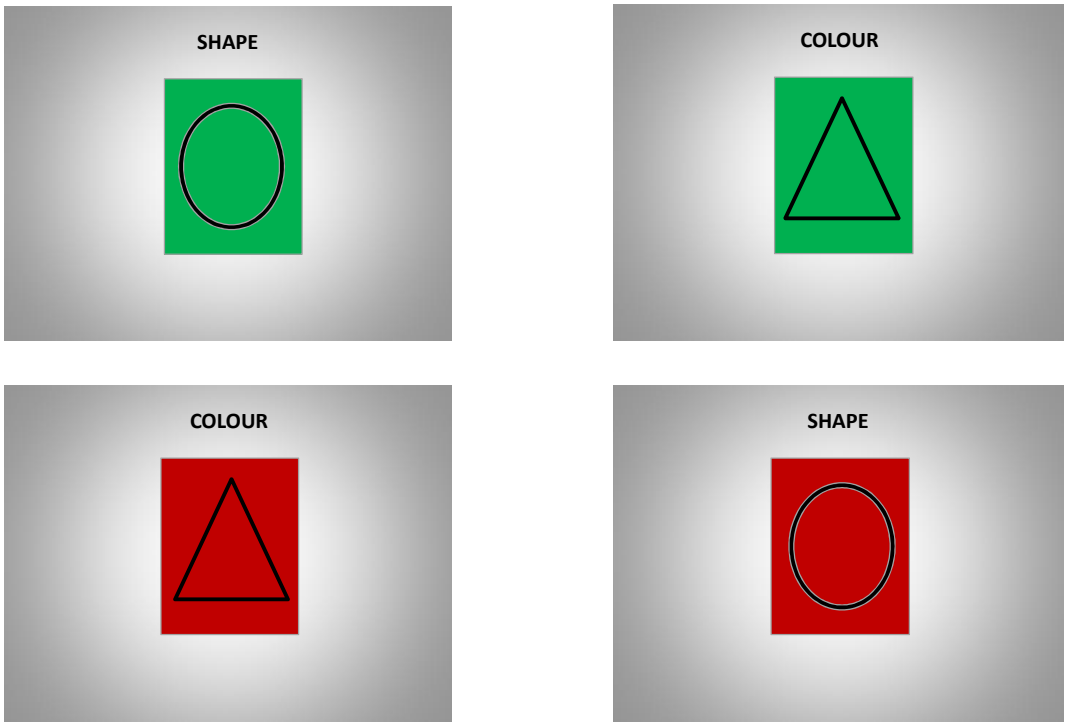


*Figure 20*. The 4 conditions for Task Switching

### *Delay Discounting Task (DDT)*

The Delay Discounting Task is a measure of an individual's tendency to discount rewards that are delayed in time, rather than immediate (thus "Delay Discounting"). This task has been widely studied in methamphetamine-dependent samples (for example see Hoffman et al., 2008; Monterosso et al., 2007; Paulus et al., 2002). It measures the preference for receiving smaller rewards immediately,

versus larger rewards later. Participants are presented with a series of choices regarding money options. For each item, the participant must choose if they would prefer to receive a certain amount of money today, or a larger amount of money later (see *Figure 21*). Although the participant will not be receiving any actual money during this task, it is important that they respond to the questions as if they would actually receive the money options they chose. There are 27 total items on the task. Various scores can be obtained which measure the degree to which the participant "discounts" the delayed rewards.


*Figure 21*. The DD task screen

*ADHD self report questionnaire* (see *Appendix D*)

Burke and Austin (2010) identified the need for a valid self-report measure of adult ADHD for the South African context. The authors therefore designed a scale containing a number of items based on 7 factors yielded through a preliminary pilot study of 402 undergraduate students. This questionnaire is similar to previous questionnaires of adult ADHD, in that it covers items that retrospectively assess symptoms of childhood ADHD, and also covers items on current symptoms of ADHD. However, it is more comprehensive than previous measures in that it covers a wider variety of symptoms, as well as behavioural, cognitive and emotional aspects of ADHD (Burke & Austin, 2010).

This ADHD self report questionnaire contains three sections. The first section contains information relating to the demographic details of the participant, such as age and level of education. The second section contains information pertaining to the participants' childhood. Childhood here refers to between 3 and 17 years of age. This section consists of 39 questions that are based on the DSM-IV

criteria of ADHD. Additional questions are also included, relating to aspects such as the impact of the symptoms, learning disorders and emotional consequences. The third section contains information pertaining to the participants' adulthood. Adulthood here refers to any age over 17 years. This section contains a total of 51 questions; grouped according to cognition (relating to response inhibition, working memory and planning), social interactions, behaviour (specifically impulsivity), and emotion (relating to frustration tolerance). All items on the questionnaire are rated according to the presence and the frequency of a particular symptom. Participants answered the items by circling either a "yes" or "no" response, indicating the presence or lack thereof, of a particular symptom. This gives an indication of the number of symptoms present. If the participant responded "yes" to a particular item, then they had to indicate the frequency of the symptom. This was done on a 5-point Likert-scale, i.e. "Almost Never", "Now and again", "At least once a week", "At least once a day", or "More than once per day". Each item was given a score ranging from 0 – 5; where 0 equals "no" and 5 equals "more than once per day". Rating the items in this way gives an indication of the severity, impact and/or frequency of a symptom (Burke & Austin, 2010).

## PROCEDURE

This study consisted of four phases. A telephonic screening interview (Phase 1) was conducted with those participants who responded to the flyers, and those who were recruited through clinics and hospitals, to ensure that they satisfied the initial inclusion/exclusion criteria. Participants who qualified were tested on three separate days. Screening took place on the first day, during which the SCID-I for Axis I diagnoses was administered by a qualified clinician (Phase 2). The Edinburgh Handedness Questionnaire was also administered during this session. The screening session took place either at Valkenberg hospital or in the Psychiatric Department at Groote Schuur Hospital. If participants were found to be ineligible for the study after the SCID-I, they were compensated for their time by means of food vouchers, but were not invited back for the third and fourth phases of the study. If participants were found to be eligible for the study according to the SCID-I, they were invited back for the MRI scanning session (Phase 3). MRI scans were conducted at the Cape Universities Brain Imaging Centre, CUBIC, using a Siemens Magnetom Allegra 3T system with a high-resolution, T1-weighted, 3D-multiecho MPRAGE sequence with the following scan parameters: TR=2530ms; graded TE=1.53, 3.21, 4.89, 6.57ms; flip angle=7°; FOV=256mm; slice thickness=1mm;

160 slices; and acquisition duration of 10.49 min. Thereafter, participants were invited to the final testing session (Phase 4) where a neuropsychological test battery was administered.

The SCID-IV session took approximately 1-3 hours to complete, depending on which group the participant belonged; the MRI session took approximately 3-4 hours to complete, and the neuropsychological testing session took approximately 4-5 hours to complete. A sample timeline of study events during the neuropsychological testing session is presented in *Table 2* below. All neuropsychological tests were administered in a random sequence to minimize sequence effects. Urine screens were performed on both days of testing to verify drug abstinence.

*Table 2*. Sample Timeline of Study Events for the Neuropsychological Testing Session

| Time (in minutes) from Study Start | Event |
|---|---|
| **00.00** | ADHD Questionnaire |
| **30.00** | CANTAB Battery |
| **100.00** | WASI |
| **140.00** | WCST |
| **160.00** | D-KEFS Verbal Fluency |
| **175.00** | Stroop Task |
| **185.00** | Attention Network Task |
| **200.00** | Balloon Analogue Risk Taking Task |
| **210.00** | Delay Discounting Task |
| **220.00** | Task Switching |
| **240.00** | Debriefing |

# DATA ANALYSIS

## Test Scoring

### *ADHD Self Report Questionnaire*

This questionnaire yields two main scores; a childhood score and an adulthood score. The childhood section contains 39 questions, scored between 0 (no, the thought/feeling/behaviour did not apply to me) and 5 (the thought/feeling/behaviour applied to me more than once per day). This gave a score range of 0 – 195. A higher score indicates more symptoms of childhood ADHD. The adulthood section contains 51 questions pertaining to aspects of the participants' life, namely, "thoughts", "interactions with others", "behaviour", and "feelings", scored in the same manner as the childhood items. This gave a score range of 0 – 255. A higher score indicates more symptoms of adulthood ADHD.

### *Weschler Abbreviated Scale of Intelligence (WASI)*

Rules and criteria for scoring the WASI are provided for each subtest in the scoring manual. The scoring for Block Design and Matrix Reasoning is fairly objective; however, the scoring for Vocabulary and Similarities requires more judgement. Therefore the scoring manual contains sample responses in addition to the general scoring criteria. Responses are scored as 0, 1, or 2, depending on the level of understanding the participant displays. The maximum score obtainable on Vocabulary is 80, from 42 items. The maximum score obtainable on Similarities is 48, from 26 items.

Block Design contains 13 items where the participant is timed on a task requiring them to build a particular pattern out of blocks. Items 1 – 9 allows 60 seconds for completion; items 10 – 13 allows 120 seconds for completion. Items 1 -4 are scored 0, 1, or 2 depending on whether they were completed in the required time on trial 1 (score 2) or trial 2 (score 1) or not correct on trial 1 or 2 (score 0). The maximum score obtainable on Block Design is 71.

Matrix Reasoning contains 35 items plus two practice items. The participant is scored 0 (for an incorrect response) or 1 (for a correct response). The maximum score obtainable on Matrix Reasoning is 35.

All subtests were scored strictly according to the scoring manual guidelines. Raw scores were then converted to T scores, using the tables in Appendix A of the scoring manual that corresponded to the age group of the participant. T scores were then used to look up the corresponding IQ in the IQ table in Appendix A of the scoring manual.

### *Cambridge Neuropsychological Test Automated Battery (CANTAB)*

CANTAB*eclipse* stores all test results directly into a data file which is stored electronically under the ID code created for each participant. For each test the values for a number of outcome measures are automatically calculated and stored in a "Summary Test Results" file for each participant. The outcome measures for the tasks are as follows:

*The BLC* results in five outcome measures, namely; Mean Correct Latency; Percent Correct; Total Correct; Total Errors and Total Attempts. For the purpose of this study, only Percent Correct was recorded. Participants needed to score a total of 100% in order to continue with the neuropsychological tests. If it was found that the participant was not able to follow the instructions, and did not score 100%, the assessment would be discontinued.

*The AGN* yielded four main outcome measures; mean correct latency (positive), mean correct latency (negative), total omissions (positive) and total omissions (negative). These outcome measures are explained in *Table 3* below.

*Table 3*. Outcome Measures for the AGN

| Outcome Measure | Explanation |
|---|---|
| **Mean Correct Latency (positive)** | This is the mean time taken to respond correctly to each target word stimulus in the blocks with targets matching this target type (i.e. positive). |
| **Mean Correct Latency (negative)** | This is the mean time taken to respond correctly to each target word stimulus in the blocks with targets matching this target type (i.e. negative). |
| **Total Omissions (positive)** | This is the total number of missed responses to targets in the blocks with targets matching this target type (i.e. positive). |
| **Total Omissions (negative)** | This is the total number of missed responses to targets in the blocks with targets matching this target type (i.e. negative). |

*The CGT* has six outcome measures; quality of decision making; deliberation time; risk taking; risk adjustment; delay aversion; overall proportion bet. These outcome measures are explained in *Table 4* below.

*Table 4*. Outcome Measures for the CGT

| Outcome Measure | Explanation |
|---|---|
| **Quality of decision making** | This measure is the proportion of trials on which participants chose to gamble on the more likely outcome. |
| **Deliberation time** | This is the mean latency from presentation of the coloured boxes to the participant's choice of which colour to bet on. |
| **Risk taking** | This measure refers to the mean proportion of the current points total that the participant chose to risk on gambling trials for which they had chosen the more likely outcome. |
| **Risk adjustment** | Participants are more likely to gamble larger amounts when the odds are strongly in their favor. This measure refers to the tendency to bet a higher proportion of points on trials where the large majority of the boxes are the colour chosen than when a small number of boxes are of the colour chosen. |
| **Delay aversion** | Participants who are unable or unwilling to wait will bet larger amounts on the descending trials than on the ascending trials. This measure reflects this tendency. It is calculated by subtracting the Risk Taking measure calculated for ascending trials from the Risk Taking measure on descending trials. |
| **Overall proportion bet** | This measure refers to the average proportion of the current points total that the participant chose to risk on each gambling test trial, including trials on which they bet on the less likely outcome as well as trials where both outcomes were equally likely. |

*The IST* yields six outcome measures; mean number of boxes opened per trail; mean P correct; total correct; sampling errors; discrimination errors; and mean box opening latency. These outcome measures are explained by *Table 5* below:

*Table 5*. Outcome Measures for the IST

| **Outcome Measure** | **Explanation** |
|---|---|
| **Mean number of boxes opened per trial** | This measure gives the mean number of boxes opened per trial for the specified win condition. |
| **Mean P (Correct)** | This is the mean of a per-trial probability value over all trials with the specified win condition. The value is the probability that the colour chosen by the participant at the point of decision would be correct, based only on the evidence available to the participant at that time, and assuming each box has a 0.5 probability of assuming a particular colour. |
| **Total Correct** | This is the number of trials for which the participant correctly chose the colour that was in the overall majority for the specified win condition. |
| **Sampling Errors** | This is the number of trials where the participant chose a colour that was not in the overall majority but was in the majority at the point of decision, for the specified win condition. |
| **Discrimination Errors** | This is the number of trials where the participant chose a colour that was not in the majority at the point of decision, for the specified win condition. Even of the colour chosen was revealed to be the correct colour; this is considered to be an error, as the participant made a decision which was not logically based on the evidence available to the participant at the time. |
| **Mean Box Opening Latency** | Box opening latency is the time elapsed between the participant opening a box and then opening a subsequent box, or, for the first box opened, the time elapsed from the start of the trial to the first box opening. This measure calculates the mean of these latencies for the specified win condition. |

*The SST* yields five outcome measures; direction errors; proportion of successful stops; reaction time on go trials; stop signal delay (50%); stop signal reaction time. These outcome measures are explained by *Table 6* below.

*Table 6*. Outcome Measures for the SST

| **Outcome measure** | **Explanation** |
|---|---|
| **Direction Errors** | This occurs when the participant presses the wrong button on the press pad i.e. the left button is pressed when the right button should have been pressed or vice versa. |
| **Proportion of Successful Stops** | This refers to the number of times the participant stopped successfully, divided by the total number of stop signals. |
| **Reaction Time on GO Trials** | This is the reaction time on Go Trials |
| **Stop Signal Delay (50%)** | This is the SSD at which the participant was able to stop 50% of the time. It is calculated as the arithmetic mean of the measured SSD, or failed-stop reaction time if applicable, from completed assessment stop trials. |
| **Stop Signal Reaction Time (SSRT)** | This is an estimate of the length of time between the go stimulus and the stop stimulus at which the participant is able to successfully inhibit their response on 50% of trials. |

*The SSP Task* produced one outcome measure. Span Length is the longest sequence successfully recalled by the participant. The maximum score is 9.

*The SWM Task* produces two outcome measures. “Between Errors” are defined as the number of times a participant revisits a box in which a token has previously been found. This is calculated for trials of four or more tokens only. The second outcome measure is termed “Strategy”. It has been suggested that an efficient strategy for completing this task is to follow a predetermined sequence by beginning with a specific box and then, once a blue token has been found, to return to that box to start the new search sequence. An estimate of the use of this strategy is obtained by counting the number of times the participant begins a new search with a different box for 6- and 8-box problems only. A high score represents poor use of this strategy and a low score equates to effective use.

*The RTI Task* yields two outcome measures. The "Five-Choice Reaction Time" is a measure of the speed with which the participants release the press pad button in response to a stimulus in any one of five locations. Choice reaction time latency is measured in milliseconds and tends towards a positive skew. The "Five-Choice Movement Time" is a measure of the time taken to touch the stimulus after the press pad button has been released in trials where the stimuli has been presented in one of five possible locations. Movement time latency is measured in milliseconds and is usually normally distributed for correct responses.

### *The Stroop Task*

The Stroop Task yields three scores per participant per trial over a total of 4 trials. Errors refer to the total number of errors (that were not corrected by the participant) for a particular trial. Self corrected errors refer to the total number of errors corrected by the participant for a particular trial. Total time refers to the total time a participant took to complete a particular trial, in seconds. Therefore a total of 12 (3 outcome measures x 4 trials) outcome measures were recorded per participant.

### *Wisconsin Card Sorting Task*

The WCST yields a total of 5 outcome measures; number of trials administered; total correct; total errors; perseverative responses; and perseverative errors. These outcome measures are explained in *Table 7* below:

*Table 7*. WCST Outcome Measures

| **Outcome measure** | **Explanation** |
|---|---|
| **Number of Trials Administered** | The total number of trials administered to the participant. Fewer errors in card matching resulted in fewer trials being administered. |
| **Total Correct** | The number of correctly matched cards. |
| **Total Errors** | The number of incorrectly matched cards. |
| **Perseverative Responses** | The number of similar responses made despite knowledge that the previous response was incorrect. |
| **Perseverative Errors** | The number of similar, but incorrect, responses made despite knowledge that the previous response was incorrect. |

*D-KEFS: Verbal Fluency*

Verbal Fluency yielded a total of four outcome measures. Phonemic Fluency includes the total number of words generated by participants over three letters namely F, A, and S. Semantic Fluency includes the total number of words generated over two categories namely Boy's Names and Animals. Category Switching produced one outcome measure; Total Correct Responses which is the total number of correct words generated.

*Attention Network Task (ANT)*

The ANT yielded six outcome measures (see *Table 8* below). These include three Reaction Time measures and three Accuracy measures across three different conditions, namely, Congruent Trials (when all arrows are pointing in the same directions), Non-congruent Trials (when distracter arrows are pointing in the opposite direction to the response arrow) and Neutral Trials (when distracters do not have arrow heads and are simply lines).

*Table 8*. Outcome Measures for the ANT

| | **Trials** |
|---|---|
| **Reaction Time** | Non-congruent Trials |
| | Neutral Trials |
| | Congruent Trials |
| **Accuracy** | Non-congruent Trials |
| | Neutral Trials |
| | Congruent Trials |

*BART*

The adjusted number of pumps across balloons (i.e. the BART score) serves as the primary dependent variable. This adjusted value is defined as the average number of pumps on balloons that did not explode. This score is preferable to the unadjusted average because the number of pumps is essentially constrained on balloons that exploded, thereby limiting between-participant variability in the unadjusted averages below (Bornovalova et al., 2009).

### *Task Switching*

Task Switching produces two outcome measures. These are Total Errors and Reaction Time. Total Errors are the total number of errors made over the test trial. Reaction Time is the average RT over all items on the test trial.

### *Delay Discounting Task*

The Delay Discounting task provides one outcome measure; the total number of discounts by the participant, i.e. the total number of times the participant chose the smaller immediate (monetary) option over the larger delayed (monetary) option.

## Cortical Thickness

The FreeSurfer 5.1.0 software package (http://surfer.nmr.mgh.harvard.edu/) was used to create a three-dimensional model of the cortex surface of each participant and to estimate cortical thickness from the T1-weighted images. Following the automated image processing, a visual inspection of the whole cortex of each individual lead to manual corrections where necessary. Brain surfaces were reconstructed and inflated and cortical thickness values were computed as the shortest distance (mm) between the pial surface and the grey/white matter surface (Dale et al., 1999; Fischl et al., 1999). Mean cortical thickness values for regions of interest in the frontal and cingulate cortex of both hemispheres were calculated (Desikan et al., 2006; Fischl et al., 2004) and exported to SPSS 20.0 for statistical analysis. *Table 9* below indicates the regions of interest examined.

*Table 9*. Frontal regions of interest

| **Left hemisphere** | **Right hemisphere** |
|---|---|
| Caudal anterior cingulate | Caudal anterior cingulate |
| Caudal middle frontal | Caudal middle frontal |
| Lateral orbitofrontal | Lateral orbitofrontal |
| Medial orbitofrontal | Medial orbitofrontal |
| Paracentral | Paracentral |
| Pars orbitalis | Pars orbitalis |
| Pars triangularis | Pars triangularis |
| Pars opercularis | Pars opercularis |
| Precentral | Precentral |
| Rostral Anterior cingulate | Rostral Anterior cingulate |
| Rostral middle frontal | Rostral middle frontal |
| Superior frontal | Superior frontal |
| frontal pole | frontal pole |
| Insula | Insula |

## Descriptive Statistics

All data were checked and cleaned before analyses. Mean scores with standard deviations in parentheses, as well as ranges, are presented under the results sections below, for each dependent variable. Graphical illustrations of means are also presented in the Results chapters that follow.

## Inferential Statistics

One-way ANOVAs were conducted in order to examine between-group differences. Raw scores were used in these analyses for each outcome variable for each executive domain. ANOVA assumptions include equal sample sizes, independence of observations, normal distribution of data, and homogeneity of variance. Our sample sizes were generally equal (see *Table 1*) and the observations

were independent. The assumption of normality was largely upheld (see *Appendix E*) and where the assumption of homogeneity of variance is violated, an adjusted *F* is reported. The homogeneity of variance and normality assumptions can be violated without serious consequences (Howell, 2002), as ANOVA is a relatively robust statistical test. However, in order to compensate for these violations, Kruskal-Wallis non-parametric ANOVA tests were conducted on the data. Results did not differ from those of the parametric one-way ANOVA results; therefore we have chosen to report the parametric one-way ANOVA results in the following results chapters. Due to the exploratory nature of this thesis, we do not want to apply methods that are too stringent and have therefore chosen not to correct for multiple comparisons.

It was our aim to conduct a MANCOVA analysis in order to control for covariates such as age, highest level of education (HLOE) and full scale IQ (FSIQ) estimates. However, our data violated too many assumptions and therefore it was not appropriate to run such analyses. We observed significant differences between our groups in terms of HLOE and FSIQ and our data were not normally distributed.

Composite neuropsychological scores were then computed to reduce the number of variables initially examined. Z-scores for each outcome measure were computed in order to do this. Z-scores are expressed as the distance from the sample mean divided by the standard deviation. These Z-scores were calculated using the mean of the control group. Outcome measures were grouped according to executive domain, as presented in Results Chapters 4, 5, 6 and 7, namely, decision making and impulsivity, inhibition and set-shifting, attention and working memory, and verbal fluency. Cronbach's alphas were calculated in order to establish reliability of the individual outcome measures. Four composite scores were created for each of the four executive domains. One-way ANOVAs were conducted in order to examine between-group differences on the four composite scores. Tests of normality indicated largely normally distributed data, with few violations (see *Appendix E*) and where Levene's test of homogeneity of variance was violated, an adjusted Welch's *F* is reported. Tables of Levene's statistics can be found in *Appendix F*. Specific results are presented under the Results sections.

It was also our aim to run multiple regression analyses in order to establish relationships between neuropsychological data and structural MRI data, however, again too many assumptions were

violated and therefore it was not appropriate to run these analyses. We had far too many variables and too many covariates to run a multiple regression. We investigated potential avenues of reducing our variables, but none of these were successful. Our data were log-transformed in order to improve normality; however, this did not result in normally distributed data. We therefore decided to run Spearman's Rho non-parametric correlational analyses in order to examine the relationship between executive functioning and prefrontal cortical thickness. Specific results are presented under the Results sections.

All statistical analyses were carried out using the SPSS v20 software package (SPSS Inc., Chicago, IL). The statistical significance threshold was set at $\alpha = 0.05$. Details of each individual analysis are presented under the Results chapters below.

## ETHICAL CONSIDERATIONS

The study was conducted in accordance with the guidelines of The Declaration of Helsinki (Edinburgh 2000) and The Medical Research Council of South Africa's guidelines (2002) on the ethical conduct of research studies in humans. The principal investigator ensured that these guidelines were adhered to for the duration of the study.

Informed consent (see *Appendix B*) was obtained in writing from all participants. The participants were informed that all data collected would be kept strictly confidential and that the results of the study would be made public and published without compromising confidentiality. Participants were also ensured of their anonymity throughout the duration of the study. Participation is this study was voluntary and it was made clear to all participants that they were free to refuse to participate, or to withdraw from the study at any point, without prejudice.

In the interest of ethics, no participants were issued with any cash monies; however, time taken to participate was compensated for by means of food vouchers from a local grocery store where no cigarettes or alcohol were to be purchased.

The chapters that follow include the Results and Discussions relating to the research questions identified at the start of this thesis. Chapter Four introduces the four broad domains of executive functions and presents findings relating to these domains. Chapters Five, Six and Seven and Eight expand the results from each domain and investigate each task and its associated outcome measures. Each of these chapters includes a discussion of the results. Chapter Nine presents the results of the correlational analyses between cortical thickness and executive functions. Chapter Ten presents the results of our ADHD questionnaire. Chapter Eleven presents a summary of the results as well as directions for future research and concluding remarks.

# CHAPTER FOUR: EXECUTIVE IMPAIRMENT IN METHAMPHETAMINE

Executive functioning was examined using a number of neuropsychological tasks. These tasks were divided into four domains of executive functioning namely, Decision Making and Impulsivity, Attention and Working Memory, Response Inhibition and Set-Shifting, and Verbal Fluency. Each domain was tested using a number of tasks. Each task contained a number of outcome measures, details of which can be found in the methods section.

In order to reduce the number of variables or outcome measures examined, composite neuropsychological scores were computed. A method described by Ferret, Carey, Thomas, Tapert and Fein (2011) was employed. Outcome measures were grouped into domains based on what each measure was designed to measure. Z-scores were computed for each outcome measure after which average z-scores for each domain were computed. Cronbach's alphas were calculated in order to establish the reliability of each domain. Results indicated Cronbach's alphas of between 0.519 and 0.939, indicating moderate to strong reliability. The Attention and Working Memory domain showed the lowest internal consistency ($\alpha = 0.519$), indicating the possibility that the tests in this domain are not all testing the same function. This may be due to the fact that the tests include "accuracy" measures as well as "reaction time" measures.

Four composite domain scores were derived from the individual neuropsychological tasks as follows:

1. *Decision Making and Impulsivity*: Delay Discounting Task, Balloon Analogue Risk Taking Task, Information Sampling Task, Cambridge Gambling Task.
2. *Attention and Working Memory*: Task Switching, Attention Network Task, Reaction Time, Spatial Working Memory, and Spatial Span.
3. *Response Inhibition and Set-Shifting*: Affective Go/No Go Task, Stop Signal Task, Stroop Task, and the Wisconsin Card Sorting Task.
4. *Verbal Fluency*: Letter Fluency and Category Fluency.

Descriptive statistics for all outcome measures are presented in the tables below. Means with standard deviations in parentheses are presented, as well as ranges. Mean z-scores and standard deviations are also presented for each domain as well as z-score ranges. Cronbach's alphas are presented for each executive domain.

*Table 10*. Executive Functioning Performance within the Decision-Making Composite Domain

| | **Group 1: MA+** (*n* = 20) | | **Group 2**: **MA**- (*n* = 19) | | **Group 3: NC** (*n* = 20) | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Decision Making and Impulsivity α = 0.653** | -1.08 – 0.56 | -0.29 (0.51) | -1.12 – 0.62 | -0.19 (0.40) | -0.63 – 0.73 | 0.001 (0.41) |
| Delay Discounting Task | | | | | | |
| Number of discounts | 13 – 22 | 16.30 (2.27) | 13 – 21 | 16.37 (2.09) | 10 – 14 | 12.15 (1.31) |
| Percentage (%) | 40.74 – 81.48 | 60.00 (9.35) | 48.15 – 77.78 | 60.82(7.44) | 37.04 – 66.67 | 54.26 (11.61) |
| Balloon Analogue Risk Taking Task | | | | | | |
| Number of pumps | 137 – 1108 | 495.39 (252.39) | 272 – 932 | 445.05 (168.38) | 52 – 863 | 401.6 (205.39) |
| Average number of pumps | 3.43 – 27.70 | 12.39 (6.31) | 6.80 – 23.30 | 11.13 (4.21) | 1.30 – 21.58 | 10.04 (5.13) |
| Maximum number of pumps | 7 – 113 | 33.85 (27.13) | 12 – 66 | 25.58 (11.57) | 3 – 92 | 25.45 (20.94) |
| Total points earned | 470 - 3515 | 1700.75 (700.3) | 915 - 3515 | 1648.95 (561.22) | 60 – 3470 | 1494.25 (787.84) |
| Information Sampling Task | | | | | | |
| Win condition fixed | | | | | | |
| Mean no. of boxes opened/trial | 3.8 – 25 | 14.83 (8.00) | 6 – 25 | 14.42 (6.2) | 3.9 – 25 | 12.48 (6.51) |
| Mean P (correct) | 0.52 – 1 | 0.78 (0.15) | 0.65 – 1 | 0.79 (0.11) | 0.58 – 1 | 0.76 (0.13) |
| Total correct | 1 – 10 | 7.9 (2.10) | 7 – 10 | 8.41 (1.06) | 5 – 10 | 7.95 (1.64) |
| Sampling errors | 0 – 4 | 1.05 (1.23) | 0 – 3 | 1.12 (0.86) | 0 – 5 | 1.5 (1.5) |
| Discrimination errors | 0 – 5 | 1.55 (1.7) | 0 – 3 | 0.82 (0.95) | 0 – 4 | 1.15 (1.18) |
| Mean box opening latency | 394.3 – 3793.67 | 1132.50 (849.74) | 421.98 –1116.03 | 1116.03 (671.26) | 368.55 – 8156.25 | 1501.61 (1661.95) |
| Win condition decreasing | | | | | | |
| Mean no. of boxes opened/trial | 1.5 – 25 | 8.93 (6.28) | 5.3 – 25 | 10.13 (4.72) | 4 – 22.9 | 9.26 (4.64) |
| Mean P (correct) | 0.55 – 1 | 0.69 (0.13) | 0.62 – 1 | 0.72 (0.09) | 0.61 – 0.94 | 0.71 (0.08) |
| Total correct | 4 – 10 | 6.75 (1.89) | 6 – 10 | 7.59 (1.12) | 5 – 10 | 7.7 (1.34) |
| Sampling errors | 0 – 5 | 2.25 (1.59) | 0 – 4 | 1.76 (1.14) | 0 – 5 | 2 (1.2) |
| Discrimination errors | 0 – 6 | 1.95 (1.64) | 0 – 3 | 1.06 (0.97) | 0 – 3 | 0.9 (0.97) |
| Mean box opening latency | 335.92 – 5753.47 | 1831.41 (1567.67) | 445 – 1766.88 | 1108.78 (397.91) | 537.98 – 7330.19 | 1606.36 (1484.13) |
| Cambridge Gambling Task | | | | | | |
| Delay aversion | -0.07 – 0.9 | 0.5 (0.33) | 0 - 0.9 | 0.44 (0.28) | 0.03 – 0.77 | 0.41 (0.21) |
| Deliberation time | 1385.61 – 6363.12 | 3367.15 (1332.87) | 1373.73 – 8371.32 | 3217.37 (1571.16) | 1257.7 –11185.69 | 3041.36 (2156.82) |
| Overall proportion bet | 0.31 – 0.94 | 0.57 (0.17) | 0.27 – 0.89 | 0.58 (0.18) | 0.39 – 0.74 | 0.57 (0.11) |
| Quality of decision making | 0.39 – 0.98 | 0.72 (0.23) | 0.3 – 1.00 | 0.74 (0.19) | 0.14 – 1.00 | 0.83 (0.18) |
| Risk adjustment | -2.27 – 2.38 | 0.18 (1.00) | -0.46 – 1.48 | 0.24 (0.49) | -0.63 – 2.27 | 0.86 (0.86) |
| Risk taking | 0.28 – 0.94 | 0.59 (0.18) | 0.26 – 0.94 | 0.61 (0.18) | 0.38 – 0.87 | 0.62 (0.13) |

*Table 11*. Executive Functioning Performance within the Attention and Working Memory Domain

| | Group 1: MA+ **(*n* = 20)** | | Group 2: MA- **(*n* = 19)** | | Group 3: NC **(*n* = 20)** | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Attention and Working Memory α = 0.519** | -1.12 - -0.10 | -0.58 (0.29) | -1.98 – 1.05 | -0.62 (0.66) | -1.03 – 0.44 | -0.01 (0.33) |
| Task switching | | | | | | |
| Errors | 9 – 111 | 61.90 (32.87) | 1 – 264 | 52.84 (63.74) | 1 – 93 | 20.85 (25.36) |
| Average reaction time | 655.88 – 1976.61 | 1220.5 (409.65) | 571 - 1761 | 1104.02 (258.79) | 601.41 – 2255.03 | 1121.32 (467.39) |
| Reaction Time | | | | | | |
| Five choice movement time | 493.25 – 1267.71 | 687.44 (190.37) | 399.29 – 1538.5 | 623.29 (285.11) | 309.62 – 688.25 | 530.09 (113.46) |
| Five choice reaction time | 299.12 - 680 | 375.90 (100.52) | 264.5 – 549.25 | 342.62 (82.49) | 257.88 – 387.75 | 317.73 (38.09) |
| Attention network task | | | | | | |
| Accuracy: | | | | | | |
| Neutral trials | 33.33 – 100 | 87.28 (17.55) | 85.42 – 100 | 97.02 (4.19) | 95.83 – 100 | 99.06 (1.26) |
| Congruent trials | 33.33 – 100 | 87.61 (17.48) | 89.58 – 100 | 97.59 (3.63) | 93.75 – 100 | 99.17 (1.57) |
| Incongruent trials | 10.42 – 100 | 71.42 (29.97) | 68.75 – 100 | 91.56 (7.43) | 87.5 – 100 | 94.89 (3.35) |
| Reaction time: | | | | | | |
| Neutral trials | 432 – 1019 | 649.65 (138.20) | 462 – 803 | 567.74 (93.02) | 425 – 752 | 547.65 (92.37) |
| Congruent trials | 416 – 1037 | 633.35 (135.61) | 420 – 805 | 573.21 (105.63) | 414 – 760 | 543 (88.96) |
| Incongruent trials | 485 – 1030 | 703.25 (138.28) | 528 - 1046 | 671.21 (137.71) | 492 - 795 | 620.2 (80.22) |
| Spatial working memory | | | | | | |
| Between errors | 8 – 75 | 43.70 (20.32) | 1 – 73 | 35.87 (21.78) | 0 – 52 | 20.85 (15.27) |
| Strategy | 30 - 44 | 37.75 (3.71) | 24 - 41 | 34.01 (5.68) | 22 - 43 | 32.1 (6.01) |
| Spatial Span | | | | | | |
| Span length | 2 - 8 | 5.00 (1.49) | 3 - 8 | 5.53 (1.36) | 3 - 9 | 6.05 (1.54) |

*Table 12*.Executive Functioning Performance within the Response Inhibition and Set-Shifting Domain

| | **Group 1: MA+** (*n* = 20) | | **Group 2: MA-** (*n* = 19) | | **Group 3: NC** (*n* = 20) | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Response Inhibition and Set Shifting α = 0.830** | -9.25 - -0.19 | -2.79 (2.58) | -3.31 – 0.48 | -0.67 (1.07) | -0.74 – 0.72 | 0.00 (0.43) |
| Affective Go/No Go task | | | | | | |
| Mean correct latency (positive) | 380.79 – 946.89 | 690.45 (162.60) | 411.67 – 759 | 636.60 (89.93) | 262.55 – 686.25 | 512.47 (98.45) |
| Mean correct latency (negative) | 310 – 872.31 | 649.75 (151.09) | 502.20 – 838.50 | 653.95 (101.98) | 386.90 – 688.33 | 528.63 (79.37) |
| Total omissions (positive) | 2 – 34 | 15.89 (10.76) | 1 – 23 | 10.17 (7.00) | 0 – 22 | 5.22 (5.77) |
| Total omissions (negative) | 4 – 35 | 15.89 (9.7) | 1 – 15 | 8.56 (4.31) | 0 – 16 | 3.50 (3.85) |
| Stop signal task | | | | | | |
| Directions errors on stop/go trials | 0 – 32 | 7.79 (9.25) | 0 – 11 | 3.31 (3.2) | 0 – 7 | 1.72 (2.02) |
| Proportion of successful stops | 0.15 – 0.8 | 0.46 (0.14) | 0.35 – 0.9 | 0.53 (0.14) | 0.28 – 0.82 | 0.5 (0.16) |
| Median correct RT on go trials | 319 – 825 | 564.63 (147.48) | 365.5 – 953 | 589.47 (167.7) | 394.5 – 897 | 552.89 (142.32) |
| SSD (last half) | -186.22–548.25 | 283.81 (231.19) | 72.1 – 708.2 | 366.97 (174.84) | 150.62 – 738.82 | 341.87 (147.28) |
| SSRT (last half) | 113.48 – 588.98 | 280.82 (134.31) | 102.62 – 403.72 | 222.47 (75.41) | 139.92 – 291.92 | 211.02 (44.43) |
| Stroop task | | | | | | |
| Trial 1: Total time | 21 – 43 | 33.00 (9.17) | 18 – 42 | 26.26 (6.61) | 15 – 31 | 22.60 (3.91) |
| Errors | 0 – 4 | 0.74 (1.15) | 0 – 3 | 0.26 (0.81) | 0 – 1 | 0.1 (0.31) |
| Self corrected errors | 0 – 4 | 1.47 (1.39) | 0 – 3 | 0.79 (1.08) | 0 – 1 | 0.1 (0.31) |
| Trial 2: Total time | 31 – 79 | 53.00 (13.96) | 21 – 58 | 37.16 (11.07) | 21 – 53 | 31.10 (6.8) |
| Errors | 0 – 6 | 1.53 (1.9) | 0 – 3 | 0.37 (0.83) | 0 – 3 | 0.15 (0.67) |
| Self corrected errors | 0 – 5 | 2.16 (1.30) | 0 – 5 | 1.58 (1.43) | 0 – 3 | 0.7 (0.92) |
| Trial 3: Total time | 49 – 122 | 81.89 (21.12) | 44 – 105 | 68.84 (16.98) | 37 – 69 | 52.5 (9.53) |
| Errors | 0 – 16 | 3.11( 4.16) | 0 – 5 | 0.84 (1.3) | 0 – 5 | 0.3 (1.13) |
| Self corrected errors | 1 – 13 | 4.42 (3.02) | 0 – 6 | 3.16 (1.86) | 0 – 7 | 1.45 (1.82) |
| Trial 4: Total time | 40 – 230 | 103.68 (57.65) | 47 – 150 | 79.21 (25.41) | 43 – 104 | 59.85 (14.73) |
| Errors | 0 – 21 | 3.58 (6.14) | 0 – 5 | 1.00 (1.33) | 0 – 6 | 0.8 (1.77) |
| Self corrected errors | 0 – 18 | 4.42 (4.54) | 0 – 7 | 2.42 (1.77) | 0 – 5 | 0.9 (1.33) |
| Wisconsin card sorting task | | | | | | |
| Total correct | 44 – 95 | 67.53 (15.09) | 58 – 86 | 74.5 (10.47) | 42 – 83 | 64.23 (11.6) |
| Total errors | 12 – 84 | 47.88 (25.68) | 11 – 70 | 30.58 (18.43) | 8 – 86 | 32.46 (28.91) |
| Perseverative responses | 5 – 77 | 33.00 (22.32) | 5 – 33 | 15 (8.91) | 4 – 66 | 19.54 (20.19) |
| Perseverative errors | 5 – 66 | 28.29 (18.52) | 5 – 29 | 13.67 (7.67) | 4 - 53 | 16.77 (16.22) |

*Table 13*. Executive Functioning Performance within the Verbal Fluency Domain

| | **Group 1: MA+** (*n* = 20) | | **Group 2: MA-** (*n* = 19) | | **Group 3: NC** (*n* = 20) | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Verbal Fluency** | -2.32 – 0.68 | -1.2 (0.70) | -1.79 – 0.64 | -0.73 (0.77) | -1.76 – 1.96 | 0.00 (0.79) |
| **α = 0.939** | | | | | | |
| Phonemic (letter) fluency | | | | | | |
| F | 5 – 22 | 9.58 (4.54) | 4 – 20 | 10.21 (4.72) | 6 – 24 | 14.05 (4.65) |
| A | 4 – 14 | 6.42 (2.85) | 1 – 15 | 7.74 (4.0) | 1 – 26 | 11.4 (5.48) |
| S | 4 – 17 | 8.79 (3.57) | 4 – 18 | 10.95 (4.39) | 3 – 25 | 15.35 (5.07) |
| Total | 14 – 52 | 24.79 (9.46) | 13 – 47 | 28.74 (11.7) | 10 - 75 | 40.80 (13.9) |
| Semantic (category) fluency | | | | | | |
| Animals | 6 – 21 | 13.00 (3.93) | 10 – 25 | 16.84 (4.19) | 12 – 29 | 19.45 (4.51) |
| Boy's Names | 6 – 24 | 13.53 (4.22) | 8 – 27 | 16.58 (4.78) | 12 – 29 | 19.7 (4.87) |
| Total | 12 – 44 | 26.68 (7.77) | 24 – 48 | 34.63 (7.3) | 27 – 58 | 39.15 (8.1) |
| Category switching | | | | | | |
| Total correct responses | 6 - 18 | 11.11 (2.83) | 8 – 19 | 11.95 (2.84) | 10 – 18 | 13.7 (2.11) |

The first set of analyses combined all z-scores from the four composite domains and derived an average in order to create one Executive Functioning score. Descriptive statistics are presented in *Table 14* below and *Figure 22* below.

*Table 14*. Descriptive Statistics for the Executive Functioning Composite Scores

| **Executive Functioning** | **Mean (SD)** | **Range** |
|---|---|---|
| **Group 1: MA+** (*n* = 20) | -1.18 (0.85) | -3.14 - -0.9 |
| **Group 2: MA-** (*n* = 19) | -0.55 (0.51) | -1.69 – 0.22 |
| **Group 3: NC** (*n* = 20) | -0.00 (0.29) | -3.14 -0.59 |

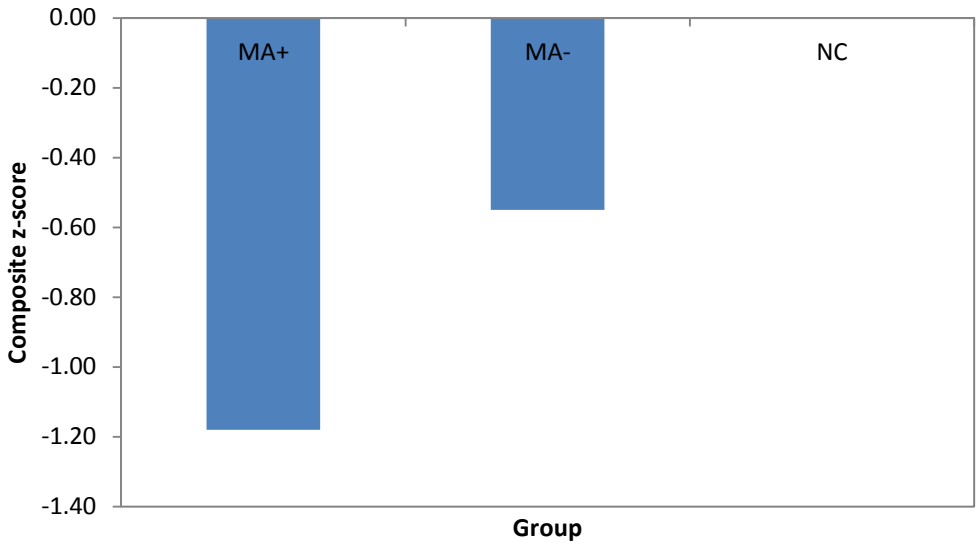


*Figure 22*. Executive Functioning Composite Scores for the 3 Participant Groups

The prediction for this outcome variable was that MA participants would perform worse than control participants. One-way ANOVAs were conducted on these overall "EF" scores in order to establish between-group differences. For the most part, data were normally distributed. Where Levene's test of homogeneity of variance, was violated, Welch's *F* is reported. The groups were more or less equal in size.

The analysis compared EF across all 3 participant groups. Levene's test was significant $F(2, 56) = 13.532$, $p < .001$; therefore the assumption of homogeneity of variance was violated and an adjusted $F$ is reported here. Statistically significant between-group differences were observed, Welch's $F(2, 56) = 22.11$ , $p < .001$. The Games-Howell post-hoc calculation of multiple comparisons was used to shed further light on the data. Statistically significant differences were found between all three participant groups; MA+ and MA- groups ($p = .023$); MA- and NC groups ($p = .001$); and MA+ and NC groups ($p < .001$), respectively, with the most impairment observed in the MA+ group and the least impairment observed in the NC group. The MA- group performed somewhere in between the MA+ and NC groups. Our prediction was therefore confirmed that Executive Functioning is impaired in methamphetamine. Subsequent analyses begin to expand further on this result.

The second set of analyses examined the average z-scores for each of the 4 composite domains; Decision Making and Impulsivity (DM), Response Inhibition and Set-Shifting (RI), Attention and Working Memory (WM) and Verbal Fluency (VF). Descriptive statistics are presented in *Table 15* below and graphically illustrated in *Figure 23* below.

*Table 15.* Descriptive Statistics for the Four Executive Domains

| | **Group 1: MA+ (*n* = 20)** | | **Group 2: MA- (*n* = 19)** | | **Group 3: NC (*n* = 20)** | |
|---|---|---|---|---|---|---|
| | M (SD) | Range | M (SD) | Range | M (SD) | Range |
| **DM** | -0.29 (0.51) | -1.08 – 0.56 | -0.19 (0.40) | -1.12 – 0.62 | 0.001 (0.41) | -0.63 – 0.73 |
| **WM**** | -2.79 (2.58) | -9.25 - -0.19 | -0.67 (1.07) | -3.31 – 0.48 | 0.00 (0.43) | -0.74 – 0.72 |
| **RI**** | -0.58 (0.29) | -1.12 - -0.10 | -0.62 (0.66) | -1.98 – 1.05 | -0.01 (0.33) | -1.03 – 0.44 |
| **VF**** | -1.2 (0.70) | -2.32 – 0.68 | -0.73 (0.77) | -1.79 – 0.64 | 0.00 (0.79) | -1.76 – 1.96 |

*Note: * indicates significance at p < .05; ** indicates significance at p < .001*

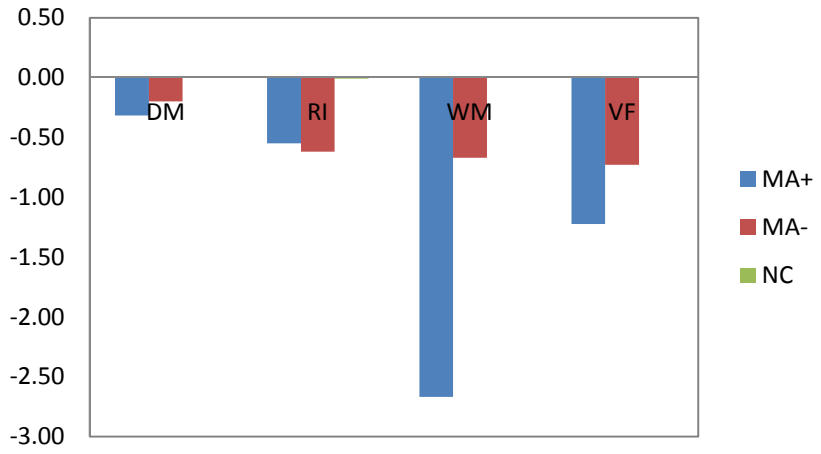


*Figure 23*. Mean Composite z-scores for the 4 Executive Functioning Domains

One-way ANOVAs were conducted on each of the 4 domains in order to establish between-group differences. For the most part, data were normally distributed. Where Levene's test of homogeneity of variance was violated, Welch's *F* is reported. The groups were more or less equal in size.

The analysis compared 4 composite domains across the 3 participant groups. All domains yielded significant between-group differences, except for Decision Making and Impulsivity. These results can be seen in *Table 1*6 below.

*Table 16*. ANOVA Results Summary Table

| | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| **Decision Making and Impulsivity** | | | | | |
| **Between Groups** | .915 | 2 | .457 | 2.332 | .107 |
| **Within Groups** | 10.788 | 55 | .196 | | |
| **Total** | 11.703 | 57 | | | |
| **Response Inhibition and Set-shifting** | | | | | |
| **Between Groups** | 4.607 | 2 | 2.304 | 17.948 | < .001 |
| **Within Groups** | 11.581 | 55 | .211 | | |
| **Total** | 16.189 | 57 | | | |
| **Attention and Working Memory** | | | | | |
| **Between Groups** | 81.739 | 2 | 40.870 | 13.037 | < .001 |
| **Within Groups** | 144.284 | 55 | 2.623 | | |
| **Total** | 226.024 | 57 | | | |
| **Verbal Fluency** | | | | | |
| **Between Groups** | 14.804 | 2 | 7.402 | 12.987 | < .001 |
| **Within Groups** | 31.348 | 55 | | | |
| **Total** | 46.151 | 57 | | | |

Post-hoc analyses were conducted in order to shed further light on where the specific between-group differences were found. Either Tukey's HSD or Games-Howell calculations were used depending on whether an adjusted *F* was reported.

Response inhibition and set-shifting yielded significant between-group differences, Welch's $F(2, 55) = 17.948$, $p < .001$. The Games-Howell calculation of multiple comparisons indicated significant differences between the MA+ and NC groups, $p < .001$ and between the MA- and NC groups, $p = .004$. No significant difference was observed between the MA+ and MA- groups ($p = .975$), indicating that these two groups performed similarly. For this domain, however, the MA- group performed slightly worse than the MA+ group. Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ and MA- groups and Group 2 included the NC group.

Attention and Working Memory yielded significant between-group differences, Welch's $F(2, 55) = 13.037$, $p < 001$. The Games-Howell calculation of multiple comparisons indicated significant differences between the MA+ and NC groups, $p = .001$; the MA- and NC groups, $p = .047$; and between the MA+ and MA- groups, $p = .008$. Results show that the MA+ group performed worse than both the MA- and NC groups, with the NC group performing the best. Tukey's HSD homogenous

subsets revealed two homogenous groups. Group 1 included the MA+ group and Group 2 included the MA- and NC groups.

Verbal Fluency yielded significant between-group differences, $F(2, 56) = 12.987$, $p < .001$. Tukey's HSD calculation of multiple comparisons indicated significant differences between the MA+ and NC groups, $p < .001$, and between the MA- and NC groups, $p = .011$. No significant difference was observed between the MA+ and MA- groups ($p = .119$), indicating that these two groups performed similarly. Both MA groups performed significantly worse than the NC group. Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ and MA- groups and Group 2 included the NC group.

We then combined the two MA groups in order to improve statistical power on the Decision Making and Impulsivity domain. An independent-samples t-test was run in order to establish a between-groups difference. A significant difference was observed between the MA group and the NC group ($p = .035$), where previously we did not observe a significant difference. The MA group showed greater impairment than the NC group.

In summary, statistically significant between groups differences were observed between the three participant groups on Response Inhibition and Set-shifting, Attention and Working Memory, and Verbal Fluency, but not on Decision Making and Impulsivity. However, when the two MA groups were combined, this improved the statistical power of our analyses and a significant difference was observed on tasks of Decision Making and Impulsivity. Our predictions were therefore largely confirmed by our results. These results will now be expanded upon. Subsequent chapters will expand on each of the four executive functions domains, analysing between-group differences for each task. The results will be discussed individually for each domain in Chapters 5, 6, 7, and 8.

# CHAPTER FIVE: DECISION MAKING IMPAIRMENT IN METHAMPHETAMINE

Decision making was assessed using the following four tasks: a Delay Discounting Task, the Balloon Analogue Risk Taking Task, the Information Sampling Task and the Cambridge Gambling Task. The outcome measures for each of these tasks, as explained in the methods section, will be analysed below. Descriptive statistics for each outcome measure for each task are presented in tables and figures below. One-way ANOVAs were conducted in order to establish between-group differences.

## Delay Discounting Task (DDT)

The Delay Discounting Task yielded one dependent variable or outcome measure of interest, namely, total number of discounts. This is the number of times a participant chose the immediate option over the delayed option when given an option of a smaller immediate monetary reward, or a larger delayed monetary reward. Results indicate that, in general, the MA groups discounted more often than the NC group. Descriptive statistics are presented in *Table 17* below and graphically represented in *Figure 24* below.

*Table 17*. Descriptive Statistics for the Delay Discounting Task

| | **Group 1: MA+ (*n* = 20)** | | **Group 2: MA- (*n* = 19)** | | **Group 3: NC (*n* = 20)** | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Number of discounts**** | 13 – 22 | 16.30 (2.27) | 13 – 21 | 16.37 (2.09) | 10 – 14 | 12.15 (1.31) |

*Note: * indicates significance at p < .05; ** indicates significance at p < .001*

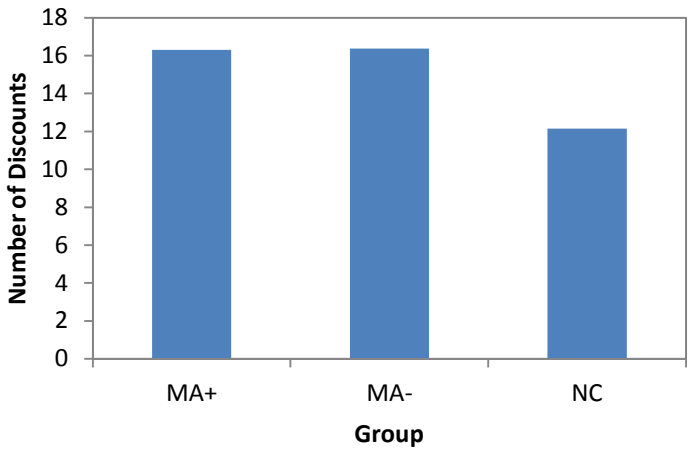


*Figure 24*. Mean Number of Discounts per Group

The prediction for this outcome measure was that MA participants would discount more often and therefore show greater impairment than NC participants. Furthermore, it was predicted that the normal control group would discount less frequently, and therefore show less impairment, than both the MA groups.

One-way ANOVAs were conducted on the data. Levene's test was significant $F(2, 56) = 2.640$, $p = .08$; therefore the assumption of homogeneity of variance was upheld. A statistically significant between-group difference was observed, $F(2, 56) = 30.976$, $p < .001$ (see *Table 17*). Tukey's HSD post-hoc calculation of multiple comparisons revealed a statistically significant difference between the MA+ and NC groups ($p < .001$) and between the MA- and NC groups ($p < .001$). No significant between group differences ($p = .993$) were observed between the MA+ and MA- groups, indicating similar performances between these two groups on the Delay Discounting Task. Both MA groups discounted more often than the NC group. This was further illustrated by a Tukey's HSD analysis that identified the MA+ and MA- groups as a homogenous subset.

*Table 18*. ANOVA Results Summary Table for Number of Discounts

| | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| **Between Groups** | 231.405 | 2 | 115.703 | 30.976 | < .001 |
| **Within Groups** | 209.171 | 56 | 3.735 | | |
| **Total** | 440.576 | 58 | | | |

Balloon Analogue Risk Taking Task (BART)

The BART yielded four dependent variables or outcome measures of interest, namely, total number of pumps, adjusted average number of pumps, maximum number of pumps, and total points earned. Results indicate that, in general, the MA+ group show a greater number of pumps, a greater adjusted average number of pumps and a greater maximum number of pumps than the other two groups. The MA+ group also earned more points than the other two groups. NC participants scored the lowest on all four measures. This trend is what we would expect to find, given that MA users take more risks than non-MA users. Descriptive statistics are presented in *Table 19* below and graphically represented in *Figures 25 - 58* below.

*Table 19.* Descriptive Statistics for the Balloon Analogue Risk Taking Task

| | **Group 1: MA+ (*n* = 20)** | | **Group 2: MA- (*n* = 19)** | | **Group 3: NC (*n* = 20)** | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Number of pumps** | 137 – 1108 | 495.39 (252.39) | 272 – 932 | 445.05 (168.38) | 52 – 863 | 401.6 (205.39) |
| **Average number of pumps** | 3.43 – 27.70 | 12.39 (6.31) | 6.80 – 23.30 | 11.13 (4.21) | 1.30 – 21.58 | 10.04 (5.13) |
| **Maximum number of pumps** | 7 – 113 | 33.85 (27.13) | 12 – 66 | 25.58 (11.57) | 3 – 92 | 25.45 (20.94) |
| **Total points earned** | 470 – 3515 | 1700.75 (700.3) | 915 – 3515 | 1648.95 (561.22) | 60 – 3470 | 1494.25 (787.84) |

*Note: * indicates significance at p < .05; ** indicates significance at p < .001*

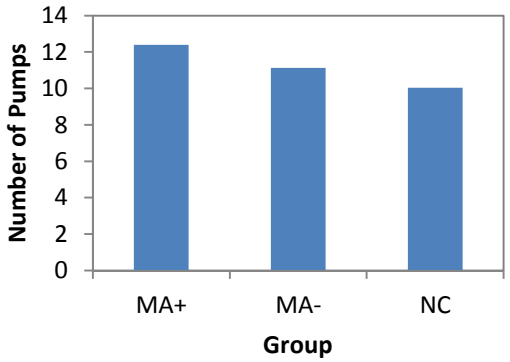


*Figure 25.* Adjusted average Number of Pumps per Balloon

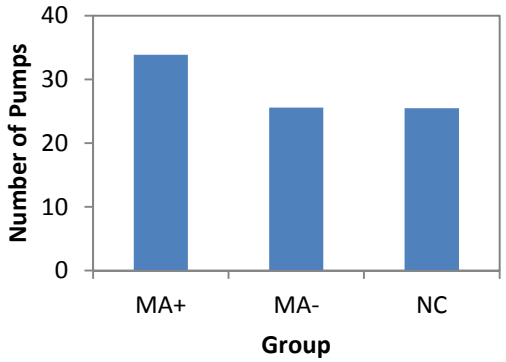


*Figure 26*. Maximum Number of Pumps on a Balloon

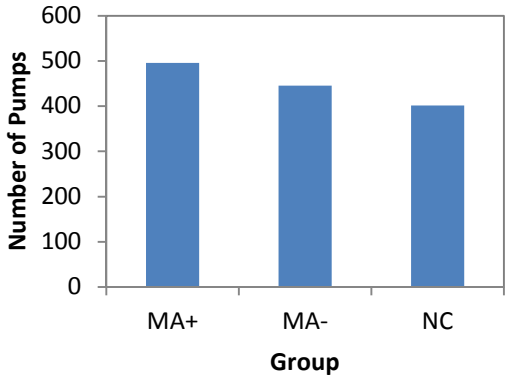


*Figure 27*.Total Number of Pumps

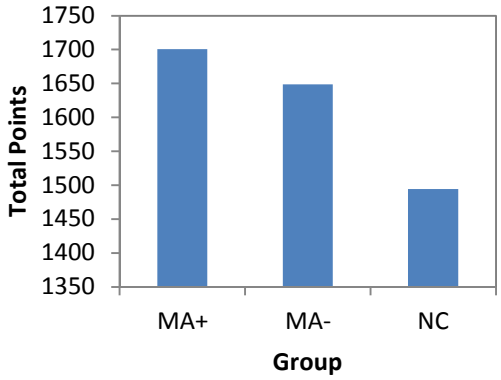


*Figure 28*. Total Points Earned

The prediction for these outcome measures were that MA participants would take more risks than NC participants and therefore show higher numbers of pumps and ultimately earn a larger number of points. Furthermore, it was predicted that the control group would take fewer risks than the MA groups.

While the bar charts above indicate that the MA participants took more risks that the NC participants, none of these group differences were found to be statistically significant. Levene's test for all four outcome variables was not significant. Therefore, the assumption of homogeneity of variance was upheld. No statistically significant between-group differences were observed on any of the outcome measures for the BART (see *Table 20*).

*Table 20.* ANOVA Results Summary Table for the BART

| | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| **Total pumps** | | | | | |
| **Between Groups** | 88714.798 | 2 | 44357.399 | .985 | .380 |
| **Within Groups** | 2522203.947 | 56 | 45039.356 | | |
| **Total** | 2610918.746 | 58 | | | |
| **Adjusted average** | | | | | |
| **Between Groups** | 55.447 | 2 | 27.723 | .985 | .380 |
| **Within Groups** | 1576.377 | 56 | 28.150 | | |
| **Total** | 1631.824 | 58 | | | |
| **Maximum pumps** | | | | | |
| **Between Groups** | 919.089 | 2 | 459.544 | 1.041 | .360 |
| **Within Groups** | 24720.132 | 56 | 441.431 | | |
| **Total** | 25639.220 | 58 | | | |
| **Total Points** | | | | | |
| **Between Groups** | 460517.281 | 2 | 230258.641 | .481 | .620 |
| **Within Groups** | 26780856.447 | 56 | 478229.579 | | |
| **Total** | 27241373.729 | 58 | | | |

## Information Sampling Task (IST)

The IST yielded a total of 12 outcome measures, 6 per condition across 2 conditions. The first condition was a “Fixed Win Condition” and the second condition was a “Decreasing Win Condition”. For each condition there were 6 outcome measures; Mean Number of Boxes Opened Per Trial; Mean P Correct; Total Correct; Sampling Errors; Discrimination Errors; and Mean Box Opening Latency. Explanations of these outcome measures can be found under the Methods section. Results indicated few differences between the groups on this task. Descriptive statistics for the two conditions are presented in *Table 21* below. Four outcome measures, yielding the most interesting results, are graphically illustrated in *Figures 29 - 32* below.

*Table 21*. Descriptive Statistics for the Information Sampling Task

| | **Group 1: MA+ (*n* = 20)** | | **Group 2: MA- (*n* = 17)** | | **Group 3: NC (*n* = 20)** | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Win condition fixed** | | | | | | |
| **Boxes opened/trial** | 3.8 – 25 | 14.83 (8.00) | 6 – 25 | 14.42 (6.2) | 3.9 – 25 | 12.48 (6.51) |
| **Mean P (correct)** | 0.52 – 1 | 0.78 (0.15) | 0.65 – 1 | 0.79 (0.11) | 0.58 – 1 | 0.76 (0.13) |
| **Total correct** | 1 – 10 | 7.9 (2.10) | 7 – 10 | 8.41 (1.06) | 5 – 10 | 7.95 (1.64) |
| **Sampling errors** | 0 – 4 | 1.05 (1.23) | 0 – 3 | 1.12 (0.86) | 0 – 5 | 1.5 (1.5) |
| **Discrimination errors** | 0 – 5 | 1.55 (1.7) | 0 – 3 | 0.82 (0.95) | 0 – 4 | 1.15 (1.18) |
| **Mean box opening latency** | 394.3 – 3793.67 | 1132.50 (849.74) | 421.98 –1116.03 | 1116.03 (671.26) | 368.55 – 8156.25 | 1501.61(1661.95) |
| **Win condition decreasing** | | | | | | |
| **Boxes opened/trial** | 1.5 – 25 | 8.93 (6.28) | 5.3 – 25 | 10.13 (4.72) | 4 – 22.9 | 9.26 (4.64) |
| **Mean P (correct)** | 0.55 – 1 | 0.69 (0.13) | 0.62 – 1 | 0.72 (0.09) | 0.61 – 0.94 | 0.71 (0.08) |
| **Total correct** | 4 – 10 | 6.75 (1.89) | 6 – 10 | 7.59 (1.12) | 5 – 10 | 7.7 (1.34) |
| **Sampling errors** | 0 – 5 | 2.25 (1.59) | 0 – 4 | 1.76 (1.14) | 0 – 5 | 2 (1.2) |
| **Discrimination errors*** | 0 – 6 | 1.95 (1.64) | 0 – 3 | 1.06 (0.97) | 0 – 3 | 0.9 (0.97) |
| **Mean box opening latency** | 335.92 – 5753.47 | 1831.41(1567.67) | 445 – 1766.88 | 1108.78 (397.91) | 537.98 – 7330.19 | 1606.36(1484.13) |

*Note: * indicates significance at p < .05; ** indicates significance at p < .001*

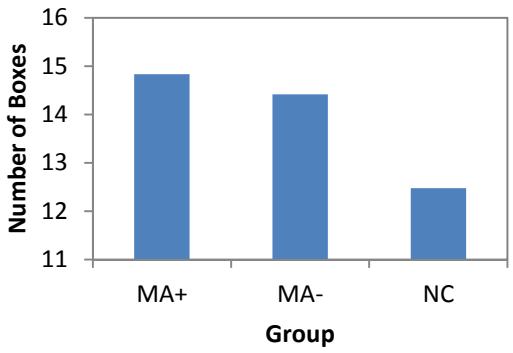


*Figure 29*. Fixed Win Condition: Mean Number of Boxes Opened per Trial

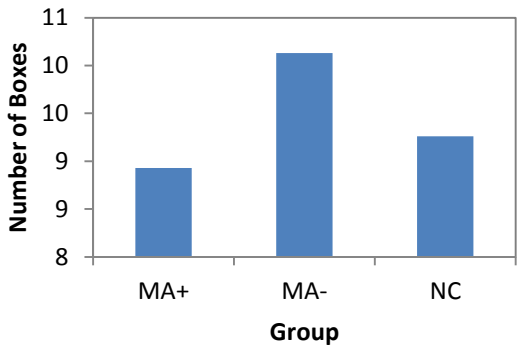


*Figure 30*. Decreasing Win Condition: Mean Number of Boxes Opened per Trial

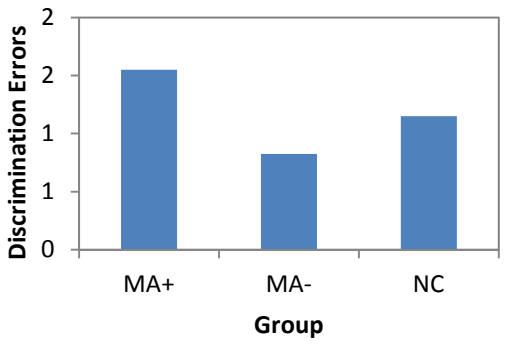


*Figure 31*. Fixed Win Condition: Discrimination Errors

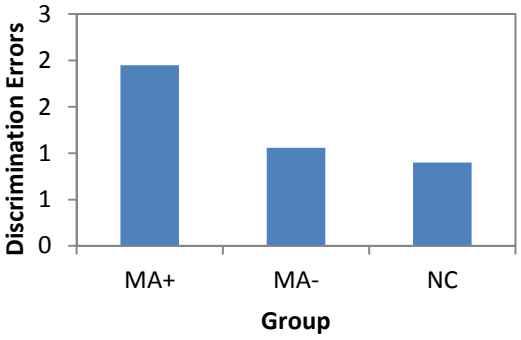


*Figure 32*. Decreasing Win Condition: Discrimination Errors

The prediction for this outcome measure was that MA participants would make decisions based on less evidence i.e. open *fewer* boxes and as a result make more errors than NC participants. It was also predicted that the NC participants would use more evidence to make their decisions i.e. open more boxes, and this would lead to fewer errors. This was not necessarily the case. Interestingly, on the Fixed Win Condition, the MA participants actually opened more boxes than the NC participants. However, on the Decreasing Win Condition, where participants lost points for every box they opened, the MA+ group drastically decreased the number of boxes opened per trail. The other two groups (MA- and NCs) performed similarly to the Fixed Win Condition.

One-way ANOVAs were conducted in order to establish between-group differences. Where the assumption of homogeneity of variance assumption was violated, an adjusted *F* is

reported. Results did not reveal any statistically significant between-group differences on the Fixed Win Condition. ANOVA results are presented in *Table 22* below.

*Table 22*. ANOVA Results Summary Table for the IST Fixed Win Condition

| | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| **Mean number of boxes opened per trial** | | | | | |
| **Between groups** | 62.338 | 2 | 31.169 | .639 | .532 |
| **Within groups** | 2634.917 | 54 | 48.795 | | |
| **Total** | 2697.255 | 56 | | | |
| **Mean P correct** | | | | | |
| **Between groups** | .010 | 2 | .005 | .291 | .748 |
| **Within groups** | .911 | 54 | .017 | | |
| **Total** | .920 | 56 | | | |
| **Total correct** | | | | | |
| **Between groups** | 2.852 | 2 | 1.426 | .504 | .607 |
| **Within groups** | 152.868 | 54 | 2.831 | | |
| **Total** | 155.719 | 56 | | | |
| **Sampling errors** | | | | | |
| **Between groups** | 2.320 | 2 | 1.160 | .748 | .478 |
| **Within groups** | 83.715 | 54 | 1.550 | | |
| **Total** | 86.035 | 56 | | | |
| **Discrimination errors** | | | | | |
| **Between groups** | 4.907 | 2 | 2.453 | 1.380 | .260 |
| **Within groups** | 95.971 | 54 | 1.777 | | |
| **Total** | 100.877 | 56 | | | |
| **Mean box opening latency** | | | | | |
| **Between groups** | 1844550.592 | 2 | 922275.296 | .678 | .512 |
| **Within groups** | 73408142.585 | 54 | 1359410.048 | | |
| **Total** | 75252693.177 | 56 | | | |

Results revealed only one statistically significant between-group difference on the Decreasing Win Condition; all other outcome measures showed no statistically significant between-group differences. ANOVA results are presented in *Table 23* below.

*Table 23.* ANOVA Results Summary Table for the IST Decreasing Win Condition

| | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| **Mean number of boxes opened per trial** | | | | | |
| **Between groups** | 13.854 | 2 | 6.927 | .247 | .782 |
| **Within groups** | 1516.725 | 54 | 28.088 | | |
| **Total** | 1530.579 | 56 | | | |
| **Mean P correct** | | | | | |
| **Between groups** | .012 | 2 | .006 | .556 | .577 |
| **Within groups** | .563 | 54 | .010 | | |
| **Total** | .574 | 56 | | | |
| **Total correct** | | | | | |
| **Between groups** | 10.599 | 2 | 5.300 | 2.344 | .106 |
| **Within groups** | 122.068 | 54 | 2.261 | | |
| **Total** | 132.667 | 56 | | | |
| **Sampling errors** | | | | | |
| **Between groups** | 2.174 | 2 | 1.087 | .606 | .549 |
| **Within groups** | 96.809 | 54 | 1.793 | | |
| **Total** | 98.982 | 56 | | | |
| **Discrimination errors** | | | | | |
| **Between groups** | 12.625 | 2 | 6.312 | 4.073 | .023 |
| **Within groups** | 83.691 | 54 | 1.550 | | |
| **Total** | 96.316 | 56 | | | |
| **Mean box opening latency** | | | | | |
| **Between groups** | 4947030.729 | 2 | 2473515.365 | 1.467 | .240 |
| **Within groups** | 91077984.503 | 54 | 1686629.343 | | |
| **Total** | 96025015.233 | 56 | | | |

Therefore the only statistically significant between-group differences were observed on Discrimination Errors on the Decreasing Win Condition, $F(2,54) = 4.073$, $p = .023$. The Tukey's HSD post-hoc calculation of multiple comparisons was used to shed further light on the data. Statistically significant differences were found between the MA+ and NC groups, $p = .027$. No statistically significant differences were observed between the MA- and NC groups ($p = .921$), or the MA+ and MA- groups ($p = .086$). Tukey's HSD homogenous subsets analysis separated the MA+ and MA- groups on the one hand, and the MA- and NC groups on the other.

These results have not confirmed the prediction that MA participants make choices based on less information than NCs. However, these results do confirm the prediction that MA+ participants make more errors than NC participants.

## Cambridge Gambling Task (CGT)

The CGT yielded a total of six outcome measures; Delay Aversion, Deliberation Time, Overall Proportion Bet, Quality of Decision Making, Risk Adjustment, and Risk Taking. Descriptive statistics are presented in *Table 24* below and graphically illustrated in *Figures 33 - 38* below.

The prediction for these outcome measures were that the MA participants would be more averse to waiting to bet larger amounts (i.e. behave more impatiently), take longer to make choices, show a poorer quality of decision making and more risk taking than NC participants. Furthermore, it was predicted that NC participants would be less averse to waiting to bet larger amounts (i.e. behave more patiently), take less time to make choices, show a better quality of decision making and take less risks that MA participants.

*Table 24*. Descriptive Statistics for the Cambridge Gambling Task

| | Group 1: MA+ (***n*** = **20**) | | Group 2: MA- (***n*** = **18**) | | Group 3: NC (***n*** = **20**) | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Delay aversion** | -0.07 – 0.9 | 0.5 (0.33) | 0 - 0.9 | 0.44 (0.28) | 0.03 – 0.77 | 0.41 (0.21) |
| **Deliberation time** | 1385.61 – 6363.12 | 3367.15 (1332.87) | 1373.73 – 8371.32 | 3217.37 (1571.16) | 1257.7 –11185.69 | 3041.36 (2156.82) |
| **Overall proportion bet** | 0.31 – 0.94 | 0.57 (0.17) | 0.27 – 0.89 | 0.58 (0.18) | 0.39 – 0.74 | 0.57 (0.11) |
| **Quality of decision making** | 0.39 – 0.98 | 0.72 (0.23) | 0.3 – 1.00 | 0.74 (0.19) | 0.14 – 1.00 | 0.83 (0.18) |
| **Risk adjustment*** | -2.27 – 2.38 | 0.18 (1.00) | -0.46 – 1.48 | 0.24 (0.49) | -0.63 – 2.27 | 0.86 (0.86) |
| **Risk taking** | 0.28 – 0.94 | 0.59 (0.18) | 0.26 – 0.94 | 0.61 (0.18) | 0.38 – 0.87 | 0.62 (0.13) |

*Note: * indicates significance at p < .05; ** indicates significance at p < .001*

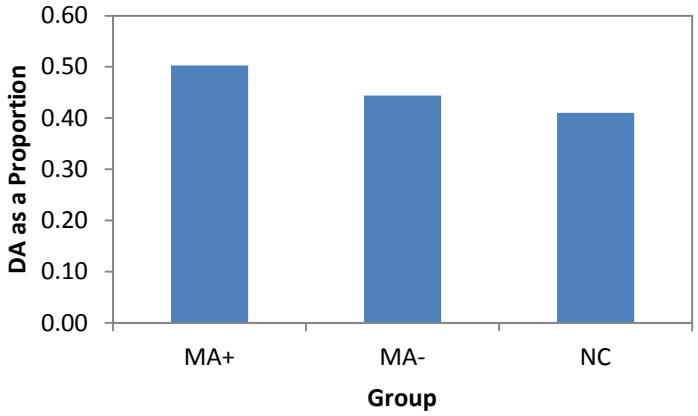


*Figure 33*. Mean Delay Aversion Scores

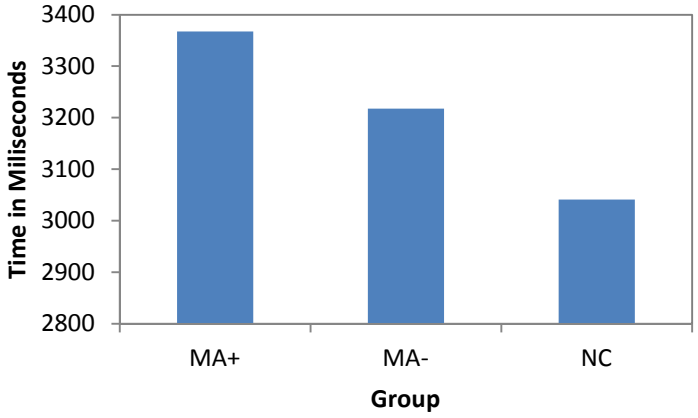


*Figure 34*. Mean Deliberation Time

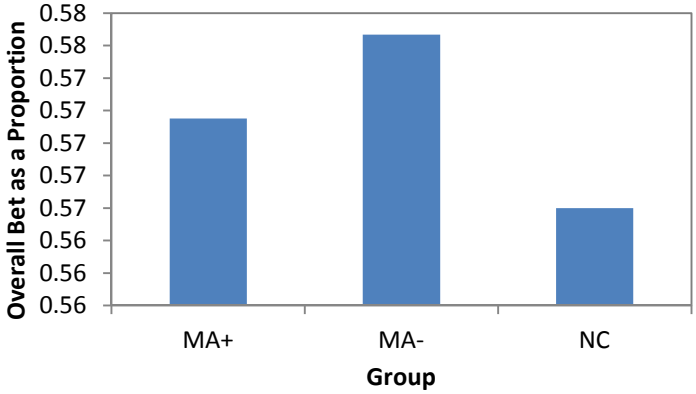


*Figure 35*. Mean Overall Proportion Bet

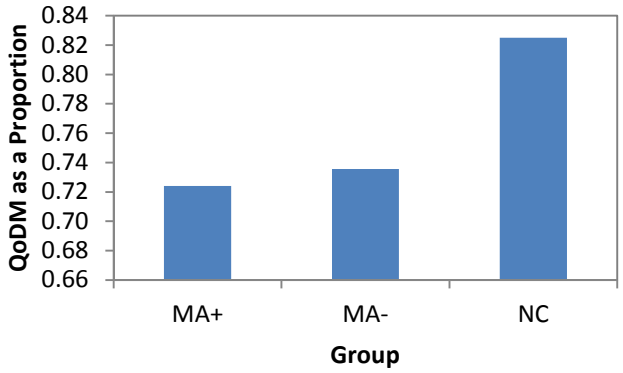


*Figure 36*. Mean Quality of Decision Making Score

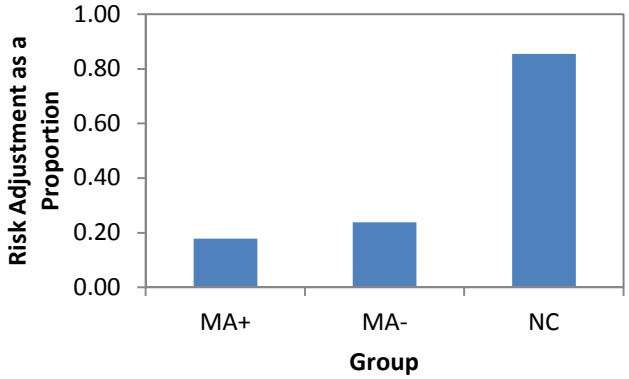


*Figure 37*. Mean Risk Adjustment Score

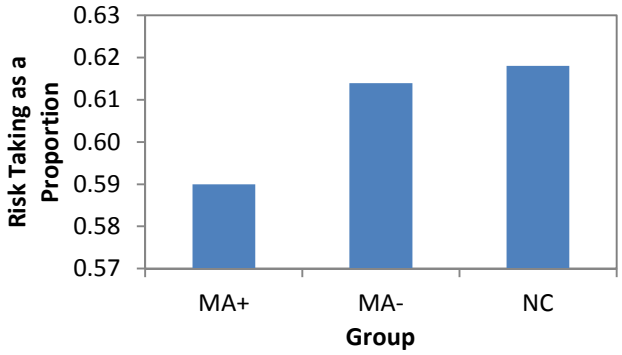


*Figure 38*. Mean Risk Taking Score

The bar charts above illustrate, generally, what we would expect to find. However, only one statistically significant result was observed. The other five outcome measures yielded

statistically non-significant results. Levene's test of homogeneity of variance was generally found to be non-significant; therefore the assumption of homogeneity of variance was upheld.

*Table 25*. ANOVA Results Summary for the CGT

| | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| **Delay aversion** | | | | | |
| **Between groups** | .088 | 2 | .044 | .573 | .567 |
| **Within groups** | 4.248 | 55 | .077 | | |
| **Total** | 4.336 | 57 | | | |
| **Deliberation time** | | | | | |
| **Between groups** | 1063512.228 | 2 | 531756.114 | .178 | .837 |
| **Within groups** | 164105173.007 | 55 | 2983730.418 | | |
| **Total** | 165168685.235 | 57 | | | |
| **Overall proportion bet** | | | | | |
| **Between groups** | .001 | 2 | .001 | .022 | .978 |
| **Within groups** | 1.342 | 55 | .024 | | |
| **Total** | 1.343 | 57 | | | |
| **Quality of decision making** | | | | | |
| **Between groups** | .121 | 2 | .060 | 1.497 | .233 |
| **Within groups** | 2.220 | 55 | .040 | | |
| **Total** | 2.341 | 57 | | | |
| **Risk adjustment** | | | | | |
| **Between groups** | 5.534 | 2 | 2.767 | 4.130 | .021 |
| **Within groups** | 36.849 | 55 | .670 | | |
| **Total** | 42.383 | 57 | | | |
| **Risk taking** | | | | | |
| **Between groups** | .009 | 2 | .005 | .166 | .847 |
| **Within groups** | 1.496 | 55 | .027 | | |
| **Total** | 1.505 | 57 | | | |

The only outcome measure from the CGT to reveal a statistically significant between-group difference was Risk Adjustment, $F(2, 54) = 4.130$, $p = .021$. Tukey's HSD post-hoc tests revealed significant differences between the MA+ and NC groups, p = .031. No statistically significant differences were observed between the MA- and NC groups ($p = .061$), or the MA+ and MA- groups ($p = .973$).Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ and MA- groups and group 2 included the MA- and NC groups.

Combining the two MA groups, in order to improve statistical power had no effect on the Decision Making and Impulsivity tasks. The outcome measures that were not found to be statistically significant in the above analyses remained unchanged by the independent-samples t-test.

In summary, the results from these analyses show significant between-group differences on few outcome measures regarding Decision-Making. Both MA groups discounted more frequently than controls on the DDT. The BART showed no significant between-group differences. The MA+ group committed significantly more errors than the controls on the IST. The MA+ group displayed a higher level of risk than controls on the CGT. Combining the two MA groups did not reveal any further significant results. These results will now be discussed below.

# DISCUSSION

Our hypothesis predicted that Decision-Making would be impaired in methamphetamine dependence. Particularly, it was predicted that the MA groups would perform worse on decision-making tasks than the control participants; indicated by the following: MA+ > MA- > NC. This prediction was partially confirmed by our results.

Our results indicate that certain aspects of decision-making are impaired in MA. In particular, MA participants discounted the value of a higher delayed reward more frequently than control participants, indicating that MA participants may act more impulsively and impatiently than control participants. This finding is consistent with previous research findings that indicate impaired decision-making in general (Bechara et al., 2001; Paulus, Hozack, Frank, Brown & Schuckit, 2003) and an association between MA and delay discounting (Hoffman et al., 2006; Monterosso et al., 2007; Paulus et al., 2002) in particular.

The Balloon Analogue Risk Taking Task did not yield any statistically significant results, contradicting both our hypothesis that this task would identify MA participants as higher risk takers than control participants and previous literature indicating that substance abuse is associated with risky decision making (Bornovalova et al., 2005; Duarte et al., 2011; Lane & Cherek, 2000).

There are a number of factors that could explain this result. Firstly, Bornovalova et al. (2009) suggest that individuals exhibit less risky behaviour when the reward/loss magnitude is large. In other words, the higher the potential reward, the higher the potential loss, and therefore the less risky one is inclined to be. This sheds some light on our findings. Given that our participants earned only 5 points per pump, this reward/loss magnitude could have been too small to illicit the risky behaviour that is associated with substance dependence. It is suggested that future studies consider a larger reward/loss magnitude in order to illicit risky behaviour. Secondly, it is important to note that there are differences between the three participant groups as shown by the bar charts in the results sections above; even though these differences were not statistically significant. Thus, the lack of statistical significance may be due to inadequate sample size.

The Information Sampling Task only yielded one statistically significant result. Results indicated that MA+ participants made more Discrimination Errors during the Decreasing Win Condition than control participants. Discrimination errors are the number of times a participant chose a colour that was not in the majority at the time of making the decision. Therefore MA+ participants made more decisions that were not logically based on the evidence available to them at the time. This is consistent with what we expected in terms of the MA+ participants, and is in agreement with previous literature suggesting that MA impairs decision-making (Clark et al., 2006; Hoffman et al., 2006, 2008; Monterosso et al., 2007; Paulus et al., 2002, 2003).

Furthermore, we would have expected the MA- group to also perform poorly on this task. Although the MA- group performed worse than the control group, these differences were not statistically significant. Clark et al. (2006) found that substance users, both current and abstinent, responded at a lower probability of making correct responses on the IST. Our results only partially reflect this finding, again perhaps reflecting the relatively small sample size. However, these data are consistent with previous work conducted by Passetti et al. (2008) that compared abstinent opiate addicts to non-abstinent opiate addicts on the IST and found no significant differences between their groups on any of the outcome measures. In addition, only one participant from their entire sample was found to be impaired. This may suggest that this task is not sensitive to the decision-making impairments found in opiate addicts (Passetti et al., 2008). Similarly this task may not be a sensitive measure of decision-making in this sample of methamphetamine-dependent individuals.

The Cambridge Gambling Task only yielded one statistically significant result. It was found that MA+ participants scored significantly lower than control participants on Risk Adjustment. There were no statistically significant differences between the MA- participants and the control participants. This indicates that control participants are more likely to bet larger amounts when the odds are strongly in their favour. In other words, they tend to bet a higher proportion of points on trials where the large majority of the boxes are the colour chosen than when a small number of boxes are of the colour chosen. This result is consistent with our prediction for this outcome measure. Passetti et al. (2008) also found similar results when comparing abstinent opiate addicts to non-abstinent opiate addicts on the Cambridge Gambling Task. The authors found that the abstinent addicts scored higher on Risk Adjustment than the non-abstinent addicts. Further to this finding, we would also expect

significant differences on all other outcome measures for this task. However, this was not the case. Our results do however show that the MA+ group was more likely to place bets on trials where the smaller majority of the boxes were of the chosen colour. We conclude that the MA+ group's decisions were therefore more risky than the NC and MA- groups.

In summary, it would appear that certain aspects of decision-making are impaired in our sample of MA dependent participants. We have shown that MA participants are more impulsive than controls as they discount the value of future (delayed) rewards and instead opt for smaller, immediate rewards. MA+ participants in particular have been shown to make poor decisions based on minimal information and also make risky decisions. Scott et al. (2007, p. 287) suggest that this may predispose individuals with methamphetamine-psychosis to "real world" risky behaviours such as needle sharing and unprotected sex. Therefore clinical management of these individuals should address such impairment.

# CHAPTER SIX: RESPONSE INHIBITION IMPAIRMENT IN METHAMPHETAMINE

Response Inhibition was assessed using the following four tasks; the Affective Go/No Go Task; the Stop Signal Task; the Stroop Task, and the Wisconsin Card Sorting Task. The outcome measures for each of these tasks, as explained in the methods section, will be analysed below. Descriptive statistics for each outcome measure for each task are presented in tables and figures below. One-way ANOVAs were conducted in order to establish between-group differences. Repeated-measures ANOVAs were also conducted on some of these data.

## Affective Go/No Go Task (AGN)

The AGN Task yielded four dependent variables or outcome measures, namely, Mean Correct Latency (positive), Mean Correct Latency (negative), Total Omissions (positive) and Total Omissions (negative). Results indicate that, in general, MA participants performed worse than control participants on this task. Descriptive statistics are presented in *Table 26* and graphically represented in *Figures 39 - 40* below. Each outcome measure will be dealt with separately, however, the ANOVA results summary can be found in *Table 27* below.

*Table 26*. Descriptive Statistics for the AGN Task

| | Group 1: MA+ (***n*** **= 19)** | | Group 2: MA- (***n*** **= 18)** | | Group 3: NC (***n*** **= 18)** | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Mean correct latency (positive)**** | 380.79 – 946.89 | 690.45 (162.60) | 411.67 – 759 | 636.60 (89.93) | 262.55 – 686.25 | 512.47 (98.45) |
| **Mean correct latency (negative)** | 310 – 872.31 | 649.75 (151.09) | 502.20 – 838.50 | 653.95 (101.98) | 386.90 – 688.33 | 528.63 (79.37) |
| **Total omissions (positive)** | 2 – 34 | 15.89 (10.76) | 1 – 23 | 10.17 (7.00) | 0 – 22 | 5.22 (5.77) |
| **Total omissions (negative)**** | 4 – 35 | 15.89 (9.7) | 1 – 15 | 8.56 (4.31) | 0 – 16 | 3.50 (3.85) |

*Note: * indicates significance at p < .05; ** indicates significance at p < .001*

*Table 27.* ANOVA Results Summary for the AGN

| | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| **Mean correct latency (positive)** | | | | | |
| **Between groups** | 305766.495 | 2 | 152883.248 | 10.217 | < .001 |
| **Within groups** | 778130.797 | 52 | 14964.054 | | |
| **Total** | 1083897.293 | 54 | | | |
| **Mean correct latency (negative)** | | | | | |
| **Between groups** | 183847.110 | 2 | 91923.555 | 6.880 | .002 |
| **Within groups** | 694782.128 | 52 | 13361.195 | | |
| **Total** | 878629.238 | 54 | | | |
| **Total omissions (positive)** | | | | | |
| **Between groups** | 1056.309 | 2 | 528.154 | 7.884 | .001 |
| **Within groups** | 3483.401 | 52 | 66.988 | | |
| **Total** | 4539.709 | 54 | | | |
| **Total omissions (negative)** | | | | | |
| **Between groups** | 1440.793 | 2 | 720.397 | 16.555 | < .001 |
| **Within groups** | 2262.734 | 52 | 43.514 | | |
| **Total** | 3703.527 | 54 | | | |

The prediction for the outcome measure Mean Correct Latency (mean time taken to respond) was that MA participants would perform at a slower rate than NC participants on both the positive and negative items. This prediction was largely confirmed as illustrated by *Figure 39* below. As shown, the MA groups performed more slowly on both positive and negative items, compared to the NC group.

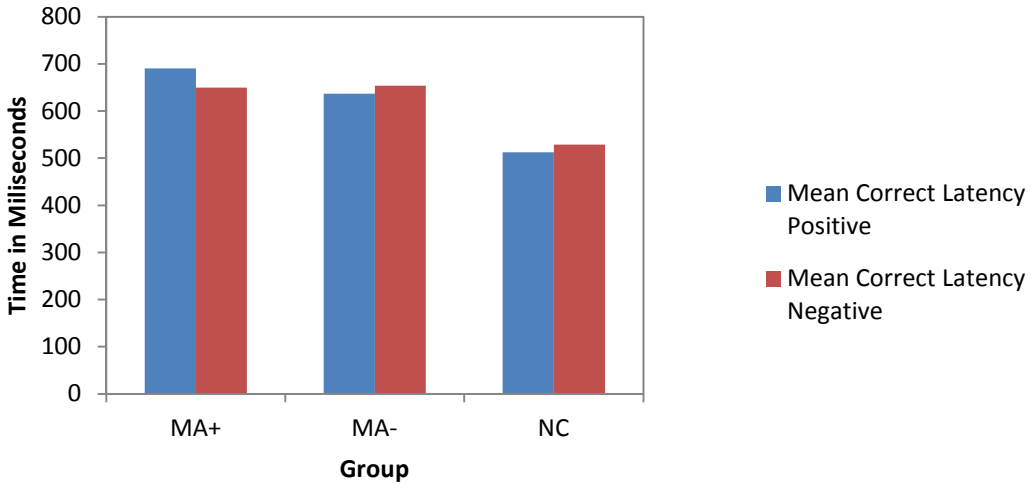


*Figure 39.* Mean Correct Latency Scores for Positive and Negative Items

A one-way ANOVA was conducted to compare the three group means. Levene's test for Mean Correct Latency (positive) was significant $F(2, 52) = 6.263$, $p = .004$; therefore the assumption of homogeneity was violated, and an adjusted $F$ is reported here. A statistically significant between-group difference was found, Welch's $F(2, 52) = 11.294$, $p < .001$. The Games-Howell calculation of multiple comparisons was used to shed further light on the data. Statistically significant differences were found between the MA+ and NC groups ($p = .001$); and between the MA- and NC groups ($p = .001$). No statistically significant between group differences were observed between the MA+ and MA- groups ($p = .381$). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ group and group 2 included the MA- and NC groups.

Levene's test for Mean Correct Latency (negative) was significant $F(2, 52) = 2.804$, $p = .070$; therefore the assumption of homogeneity of variance was violated, and an adjusted $F$ is reported here. A statistically significant between-group difference was found, Welch's $F(2, 52) = 6.88$, $p = .002$. The

Games-Howell calculation of multiple comparisons was used to shed further light on the data. Statistically significant differences were observed between the MA+ and NC groups ($p$ = .013); and between the MA- and NC groups ($p$ = .001). No statistically significant differences were observed between the MA+ and MA- groups ($p$ = 993). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ group and group 2 included the MA- and NC groups.

The prediction for the outcome measure Total Omissions (incorrect responses) was that the MA participants would show more omissions than NC participants, for both positive and negative items. This prediction was confirmed as illustrated by *Figure 40* below. As shown, the MA+ group scored a higher number of omissions than the MA- and NC groups, with the NC group scoring the least number of omissions, for both positive and negative items.

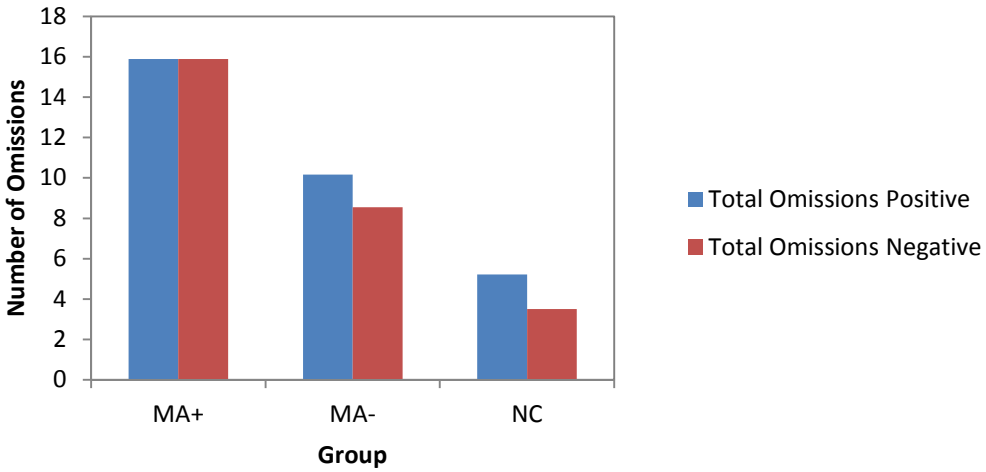


*Figure 40*. Total Omissions of Positive and Negative Items

A one-way ANOVA was conducted in order to compare the three group means. Levene's test for Total Omissions (positive) was significant $F(2, 52) = 7.221$, $p$ = .002; therefore the assumption of homogeneity of variance was violated, and an adjusted $F$ is reported here. A statistically significant between-group difference was found, Welch's $F(2, 52) = 7.747$, $p$ = .002. The Games-Howell calculation of multiple comparisons was used to shed further light on the data. A statistically significant difference was observed between the MA+ and NC groups ($p$ = .002). The differences between the MA- and NC groups ($p$ = .068) and between the MA+ and MA- groups ($p$ = .148) were

not statistically significant. Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ and MA- groups and group 2 included the MA- and NC groups.

Levene's test for Total Omissions (negative) was significant $F(2, 52) = 12.336$, $p < .001$; therefore the assumption of homogeneity of variance was violated, and an adjusted $F$ is reported here. A statistically significant between-group difference was found, Welch's $F(2, 52) = 16.067$, $p < .001$. The Games-Howell calculation of multiple comparisons was used to shed further light on the data. Statistically significant differences were observed between the MA+ and MA- groups ($p = .016$); between the MA+ and NC groups ($p < .001$); and between the MA- and NC groups ($p = .002$). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ and MA- groups and group 2 included the MA- and NC groups.

## The Stop Signal Task (SST)

The SST yielded five outcome measures, namely, Direction Errors on Stop and Go Trials, Proportion of Successful Stops (last half), Median Correct RT on Go Trials, Stop Signal Delay (last half), Stop Signal Reaction Time (last half). Most of the outcome measures have yielded the expected differences between the groups; however they are not all necessarily statistically significant. Descriptive statistics are presented in *Table 28* below and means are graphically illustrated in *Figures 41 - 43* below.

Predictions for these outcome measures were as follows:

1. Directions Errors on Stop and Go Trials: MA participants would make more errors on (where the wrong button was pressed, i.e. the incorrect direction was chosen) than NC participants.
2. Proportion of Successful Stops: MA participants would not be able to successfully stop as often as NC participants and therefore have fewer successful stops.
3. Median Correct Reaction Time on Go Trials: MA participants would show slower reaction times compared to NC participants.
4. Stop Signal Delay: MA participants would have a shorter stop signal delay. This is due to the fact that this group often responds before the stop signal is deployed, thereby resulting in more errors. Their stop signal is therefore shortened in order to minimize errors. Furthermore, NC participants were predicted to have a longer stop signal delay.

5. Stop Signal Reaction Time: MA participants would show slower SSRTs than NC control participants.

*Table 28*. Descriptive Statistics for the Stop Signal Task

| | Group 1: MA+ (***n*** **= 19)** | | Group 2: MA- (***n*** **= 16)** | | Group 3: NC (***n*** **= 18)** | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Directions errors on stop/go trials*** | 0 – 32 | 7.79 (9.25) | 0 – 11 | 3.31 (3.2) | 0 – 7 | 1.72 (2.02) |
| **Proportion of successful stops** | 0.15 – 0.8 | 0.46 (0.14) | 0.35 – 0.9 | 0.53 (0.14) | 0.28 – 0.82 | 0.5 (0.16) |
| **Median correct RT on go trials** | 319 – 825 | 564.63 (147.48) | 365.5 – 953 | 589.47 (167.7) | 394.5 – 897 | 552.89 (142.32) |
| **SSD (last half)** | -186.22–548.25 | 283.81 (231.19) | 72.1 – 708.2 | 366.97 (174.84) | 150.62 – 738.82 | 341.87 (147.28) |
| **SSRT (last half)** | 113.48 – 588.98 | 280.82 (134.31) | 102.62 – 403.72 | 222.47 (75.41) | 139.92 – 291.92 | 211.02 (44.43) |

*Note: * indicates significance at p < .05; ** indicates significance at p < .001*

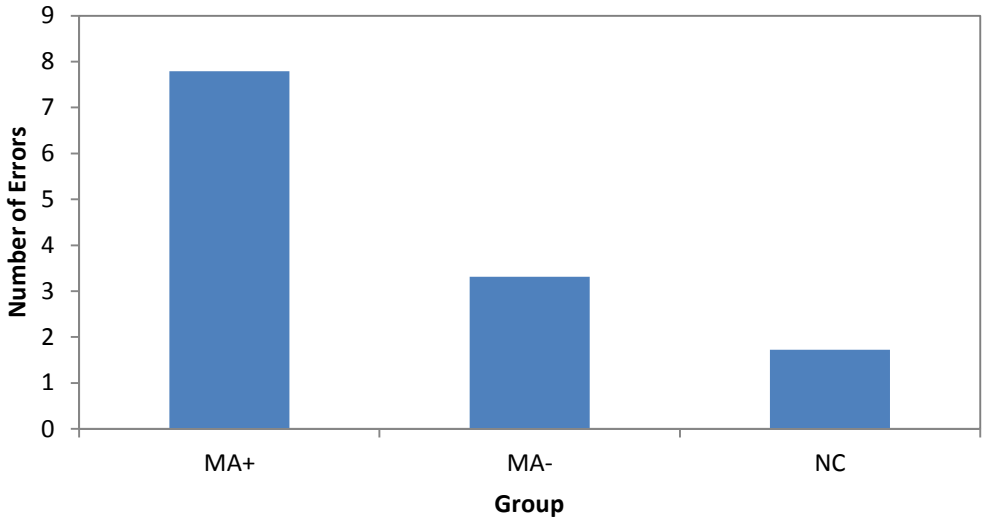


*Figure 41*. Mean Direction Errors on Stop and Go Trials

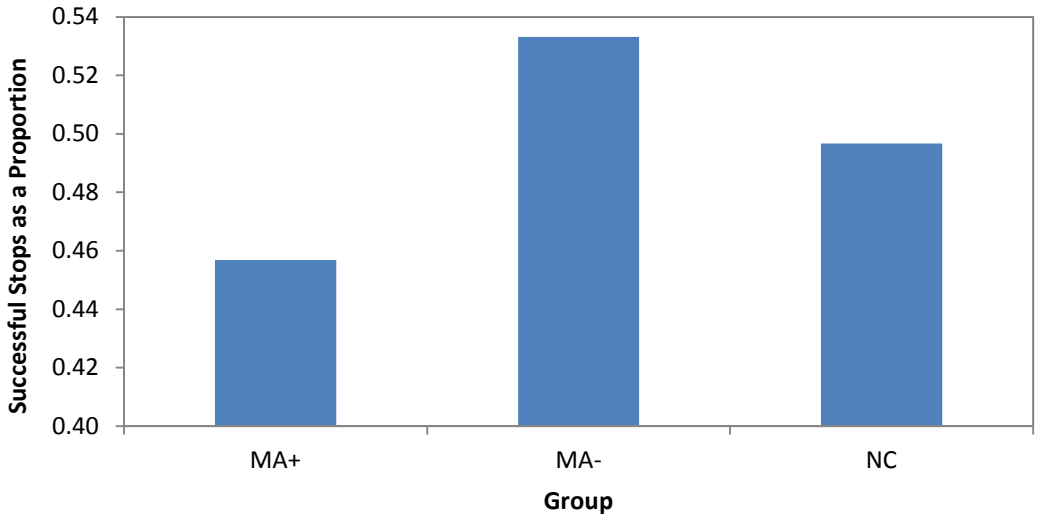


*Figure 42.* Proportion of Successful Stops (last half)

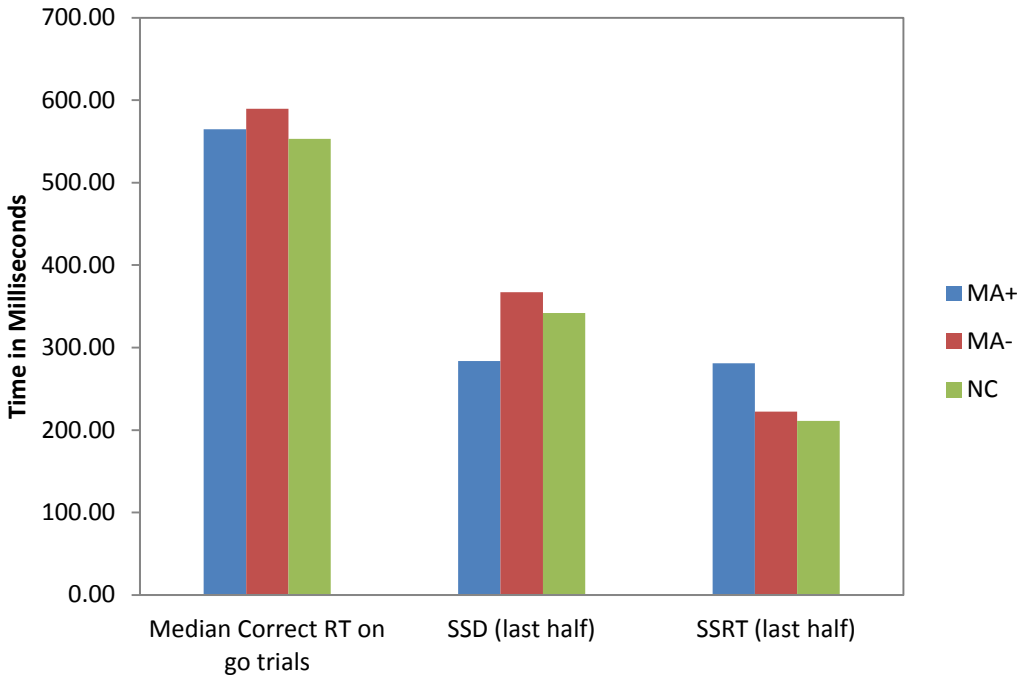


*Figure 43*. Bar chart illustrating outcome measures of the SST relating to time

One-way ANOVAs were conducted on the data in order to establish between-group differences. The ANOVA results summary is presented in *Table 29* below.

*Table 29*. ANOVA Results Summary for the SST

| | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| **Directions errors on stop/go trials** | | | | | |
| **Between groups** | 366.246 | 2 | 183.123 | 4.762 | .016 |
| **Within groups** | 1764.207 | 50 | 35.284 | | |
| **Total** | 2130.453 | 52 | | | |
| **Proportion of successful stops** | | | | | |
| **Between groups** | .051 | 2 | .025 | 1.171 | .318 |
| **Within groups** | 1.085 | 50 | .022 | | |
| **Total** | 1.136 | 52 | | | |
| **Median correct RT on go trials** | | | | | |
| **Between groups** | 11699.255 | 2 | 5849.628 | .253 | .778 |
| **Within groups** | 1157725.933 | 50 | 23154.519 | | |
| **Total** | 1169425.189 | 52 | | | |
| **SSD (last half)** | | | | | |
| **Between groups** | 64835.257 | 2 | 32417.629 | .906 | .411 |
| **Within groups** | 1789363.438 | 50 | 35787.269 | | |
| **Total** | 1854198.695 | 52 | | | |
| **SSRT (last half)** | | | | | |
| **Between groups** | 51678.856 | 2 | 25839.428 | 2.820 | .069 |
| **Within groups** | 458221.075 | 50 | 9164.422 | | |
| **Total** | 509899.931 | 52 | | | |

Directions Errors on Stop/Go Trials was the only outcome measure to yield a statistically significant result, Welch's $F(2, 50) = 4.762$, $p = .016$. The Games-Howell calculation of multiple comparisons was used to shed further light on the data. Statistically significant differences were found between the MA+ and NC groups ($p = .029$). No statistically significant differences were found between the MA+ and MA- groups ($p = .077$), nor the MA- and NC groups ($p = .717$). Tukey's HSD homogenous subsets analysis separated the MA+ and MA- groups on the one hand, and the MA- and NC groups on the other.

No other outcome measures of this task yielded statistically significant results, however, between-group differences on SSRT were marginally significant, $p = .069$. This indicates a non-significant trend in the predicted direction indicating that MA+ participants performed slower than MA- and NC groups, MA- participants performed quicker than MA+ participants, but slower than NC participants, and NC participants performed more quickly than the other two groups. This indicates that the MA+ group was the most impaired on this outcome measure.

## The Stroop Task

The Stroop Task yielded a number of outcome measures per participant. There were a total of 4 trials and for each trial there were three outcome measures; Total Time, Non Corrected Errors, and Self Corrected Errors. Results largely confirmed predictions for this task. Descriptive statistics are presented in *Table 30* below and are graphically illustrated in *Figure 44* below.

The prediction for the Total Time over the 4 trials across the 3 comparison groups was that there would be significant differences between groups across all four trials as they increase in difficulty. Our predictions were largely confirmed by our results.

*Table 30.* Descriptive Statistics for the Stroop Task

| | Group 1: MA+ **(*n* = 19)** | | Group 2: MA- **(*n* = 19)** | | Group 3: NC **(*n* = 20)** | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| Trial 1: | | | | | | |
| **Total time** | 21 – 43 | 33.00 (9.17) | 18 – 42 | 26.26 (6.61) | 15 – 31 | 22.60 (3.91) |
| **Errors** | 0 – 4 | 0.74 (1.15) | 0 – 3 | 0.26 (0.81) | 0 – 1 | 0.1 (0.31) |
| **Self corrected** | 0 – 4 | 1.47 (1.39) | 0 – 3 | 0.79 (1.08) | 0 – 1 | 0.1 (0.31) |
| Trial 2: | | | | | | |
| **Total time** | 31 – 79 | 53.00 (13.96) | 21 – 58 | 37.16 (11.07) | 21 – 53 | 31.10 (6.8) |
| **Errors** | 0 – 6 | 1.53 (1.9) | 0 – 3 | 0.37 (0.83) | 0 – 3 | 0.15 (0.67) |
| **Self corrected** | 0 – 5 | 2.16 (1.30) | 0 – 5 | 1.58 (1.43) | 0 – 3 | 0.7 (0.92) |
| Trial 3: | | | | | | |
| **Total time** | 49 – 122 | 81.89 (21.12) | 44 – 105 | 68.84 (16.98) | 37 – 69 | 52.5 (9.53) |
| **Errors** | 0 – 16 | 3.11( 4.16) | 0 – 5 | 0.84 (1.3) | 0 – 5 | 0.3 (1.13) |
| **Self corrected** | 1 – 13 | 4.42 (3.02) | 0 – 6 | 3.16 (1.86) | 0 – 7 | 1.45 (1.82) |
| Trial 4: | | | | | | |
| **Total time** | 40 – 230 | 103.68 (57.65) | 47 – 150 | 79.21 (25.41) | 43 – 104 | 59.85 (14.73) |
| **Errors** | 0 – 21 | 3.58 (6.14) | 0 – 5 | 1.00 (1.33) | 0 – 6 | 0.8 (1.77) |
| **Self corrected** | 0 – 18 | 4.42 (4.54) | 0 – 7 | 2.42 (1.77) | 0 – 5 | 0.9 (1.33) |

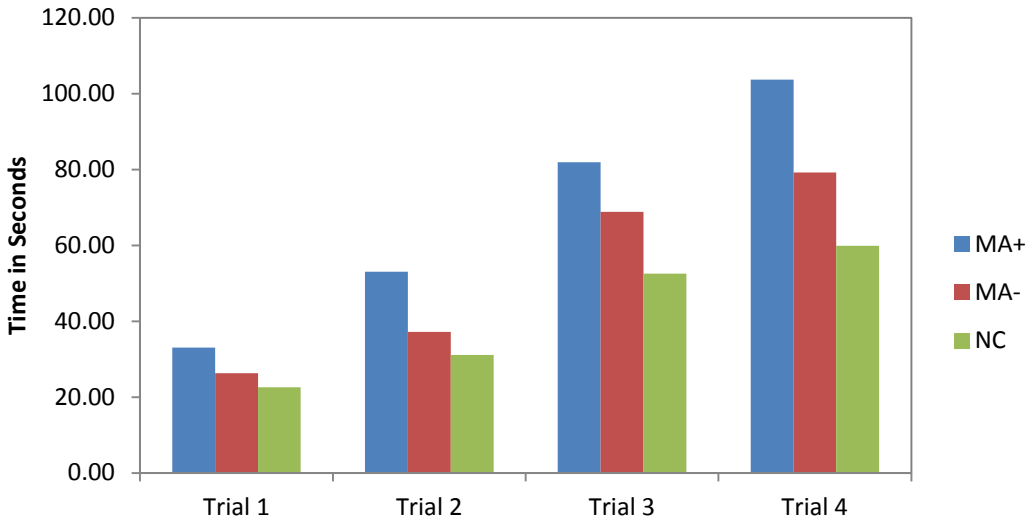


*Figure 44.* Mean Times Taken per Trial for the Stroop Task

A repeated-measures ANOVA was conducted on the data. Mauchly's test was significant, $\chi^2(5) = 0.107$, $p < .001$; therefore the assumption of sphericity was violated. Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = .453$). There was a statistically significant main effect of Trials on Total Time to complete the trial when testing within-subjects effects, $F(1.358, 74.708) = 112.13$, $p < .001$. The Trials x Group interaction was also statistically significant, $F(2.717, 74.708) = 3.218$, $p = .032$; and there was a statistically significant main effect of Group, $F(2, 55) = 15.546$, $p = < .001$. Pairwise comparisons indicated statistically significant differences across all four trials. The Games-Howell calculation of multiple comparisons revealed statistically significant differences between the MA+ and MA- groups, $p = .034$; between the MA- and NC groups, $p = .004$; and between the MA+ and NC groups, $p < .001$.

The predictions for the Errors (Non Corrected) over the 4 trials across the 3 comparison groups were that there would be significant differences between groups across all four trials as they increase in difficulty. Our predictions were largely confirmed by our results, as illustrated by *Figure 45* below.

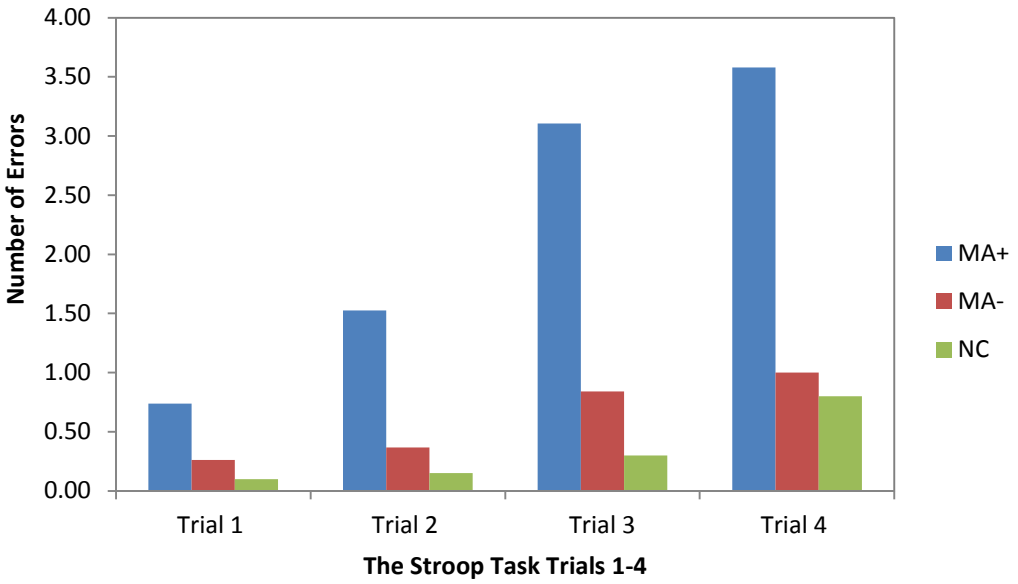


*Figure 45*. Mean Number of Non Corrected Errors on the Stroop Task

A repeated-measures ANOVA was conducted on the data. Mauchly's test was significant, $\chi^2(5) = 0.274$, $p < .001$; therefore the assumption of sphericity was violated. Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = .605$). There was a statistically significant main effect of Trials on Non Corrected Errors when testing within-subjects effects, $F(1.814, 99.783) = 6.479$, $p = .003$. The Trials x Group interaction was not statistically significant, $F(3.628, 74.708) = 1.783$, $p = .144$. There was however a statistically significant main effect of Group, $F(2, 55) = 7.114$, $p = .002$. Pairwise comparisons revealed few significant differences across trials. Statistically significant between-trials differences were observed between trials 1 and 3 ($p = .034$), trials 1 and 4 ($p = .037$) and trials 2 and 4 ($p = .049$). The Games-Howell calculation of multiple comparisons revealed statistically significant differences between the MA+ and NC groups, $p = .022$. None of the other between-group comparisons were statistically significant.

The predictions for the Self Corrected Errors over the over the 4 trials across the 3 comparison groups was that there would be significant differences between groups across all four trials as they increase in difficulty. Our predictions were largely confirmed by our results, as illustrated by *Figure 46* below.

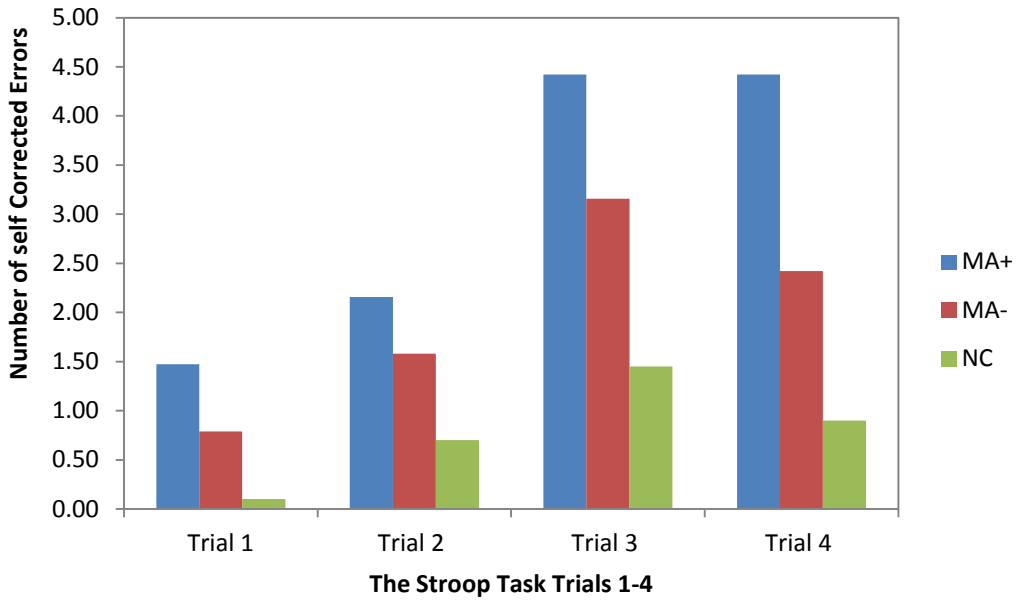


*Figure 46*. Mean Number of Self Corrected Errors on the Stroop Task

A repeated-measures ANOVA was conducted on the data. Mauchly's test was significant, $\chi^2(5) = 0.446$, $p < .001$; therefore the assumption of sphericity was violated. Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = .710$). There was a statistically significant main effect of Trials on Self Corrected Errors when testing within-subjects effects, $F(2.130, 117.148) = 20.491$, $p < .001$. The Trials x Group interaction was not statistically significant, $F(4.260, 117.148) = 2.038$, $p = .089$. There was however a statistically significant main effect of Group, $F(2, 55) = 14.180$, $p < .001$. Pairwise comparisons indicated significant differences across all trials, excluding trials 3 and 4. Results indicate similar number of Self Corrected Errors for these trials. The Games-Howell post-hoc calculation of multiple comparisons revealed statistically significant differences between the MA+ and NC groups, $p < .001$; between the MA- and NC groups, $p = .002$; but no statistically significant difference was observed between the MA+ and MA- groups.

## The Wisconsin Card Sorting Task (WCST)

The WCST yielded a total of 5 outcome measures, namely, Trials administered, Total Correct, Total Errors, Perseverative Responses, and Perseverative Errors. Less data were collected for this task due to a technical error that occurred during data collection and required fixing. The task could therefore not be administered to a number of participants during the data collection process. While a large number of participants returned in order for testing to take place, a number of others chose not to return. Predictions were that the MA participants would perform worse than the NC participants on this task. Descriptive statistics are presented in *Table 31* below and are graphically illustrated in *Figures 47 - 48* below.

The prediction for the outcome measure "Trials Administered" was that more trials would be administered to MA participants than NC participants, due to the fact that they would make more Perseverative Responses and therefore more Perseverative Errors than NC participants. It was also predicted that NC participants would score a higher number of Total Correct choices, and therefore make fewer Total Errors than MA participants. Predictions were largely confirmed as illustrated graphically in *Figure 47* below.

*Table 31.* Descriptive Statistics for the Wisconsin Card Sorting Task

| | Group 1: MA+ **(*n* = 17)** | | Group 2: MA- **(*n* = 12)** | | Group 3: NC **(*n* = 13)** | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Trials Administered** | 76 - 128 | 115.41(19.31) | 75 - 128 | 105.08 (21.86) | 70 - 128 | 96.69 (21.52) |
| **Total correct** | 44 – 95 | 67.53 (15.09) | 58 – 86 | 74.50 (10.47) | 42 – 83 | 64.23 (11.6) |
| **Total errors** | 12 – 84 | 47.88 (25.68) | 11 – 70 | 30.58 (18.43) | 8 – 86 | 32.46 (28.91) |
| **Perseverative responses*** | 5 – 77 | 33.00 (22.32) | 5 – 33 | 15.00 (8.91) | 4 – 66 | 19.54 (20.19) |
| **Perseverative errors*** | 5 – 66 | 28.29 (18.52) | 5 – 29 | 13.67 (7.67) | 4 - 53 | 16.77 (16.22) |

*Note: * indicates significance at p < .05; ** indicates significance at p < .001*

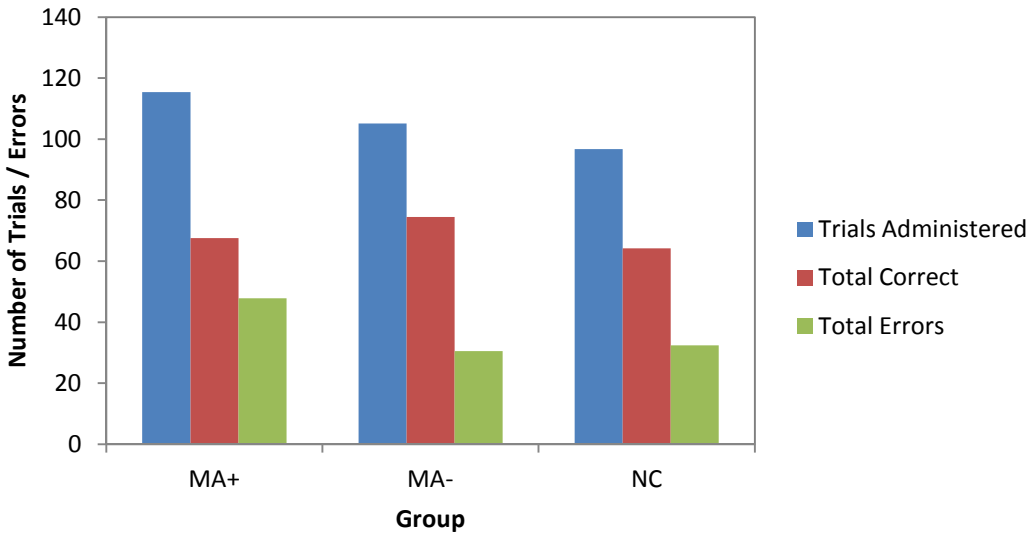


*Figure 47*. Mean Number of Trials administered per Group; Mean Number of Total Correct Choices per Group; and Mean Total Errors per Group

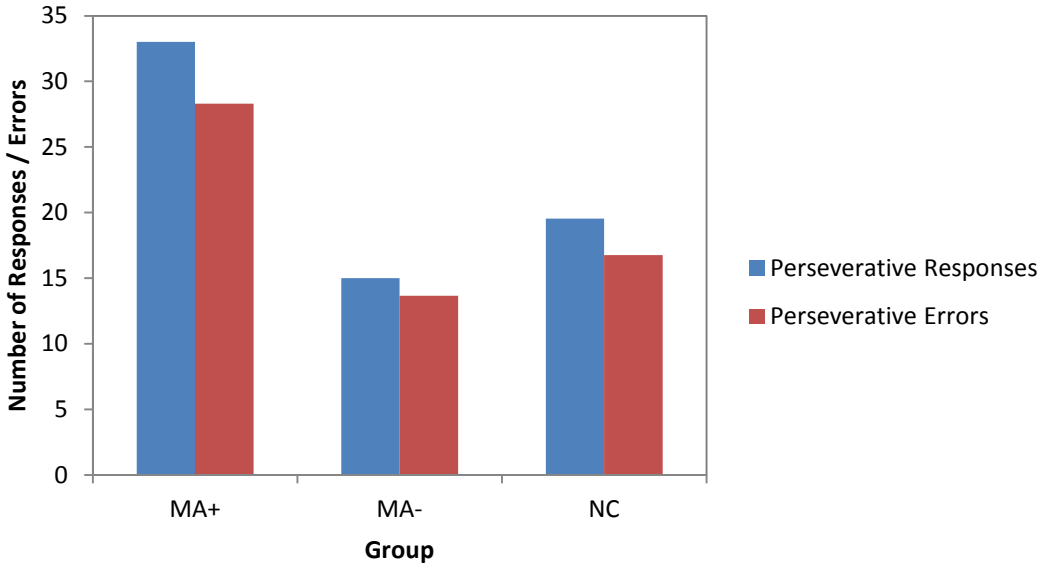


*Figure 48*. Mean Number of Perseverative Responses per Group; and Mean Number of Perseverative Errors per Group

One-way ANOVAs were conducted on the data in order to compare means across the three participant groups. Levene's statistics are presented in *Table 32*below. Where Levene's test was found to be significant, an adjusted (Welch's) *F* is reported.

*Table 32*. ANOVA Results Summary for the WCST

| | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| **Trials Administered** | | | | | |
| **Between groups** | 2623.530 | 2 | 1311.765 | 3.049 | .059 |
| **Within groups** | 16779.804 | 39 | 430.251 | | |
| **Total** | 19403.333 | 41 | | | |
| **Total correct** | | | | | |
| **Between groups** | 648.957 | 2 | 342.479 | 2.067 | .140 |
| **Within groups** | 6461.543 | 39 | 165.681 | | |
| **Total** | 7146.500 | 41 | | | |
| **Total errors** | | | | | |
| **Between groups** | 2717.921 | 2 | 1358.961 | 2.180 | .127 |
| **Within groups** | 24315.912 | 39 | 623.485 | | |
| **Total** | 27033.833 | 41 | | | |
| **Perseverative responses** | | | | | |
| **Between groups** | 2603.745 | 2 | 1301.873 | 4.404 | .024 |
| **Within groups** | 13737.231 | 39 | 352.237 | | |
| **Total** | 16340.976 | 41 | | | |
| **Perseverative errors** | | | | | |
| **Between groups** | 1773.901 | 2 | 886.950 | 4.153 | .028 |
| **Within groups** | 9290.504 | 39 | 238.218 | | |
| **Total** | 11064.405 | 41 | | | |

Results from the number of Trials Administered were marginally significant, $p = 0.59$. This indicates a non-significant trend in the direction predicted. Therefore MA participants were administered more trials than NC participants.

Statistically significant between-group differences were observed on Perseverative Responses, Welch's $F(2, 39) = 4.404$, $p = .024$. The Games-Howell calculation of multiple comparisons was used to shed further light on the data. Statistically significant differences were observed between the MA+ and MA- groups ($p = .017$). No other statistically significant between-group differences were observed. Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ and NC groups and Group 2 included the MA+ and MA- groups.

Statistically significant between-group differences were also observed on Perseverative Errors, Welch's $F(2, 39) = 4.153$, $p = .028$. The Games-Howell calculation of multiple comparisons was used to shed further light on the data. Statistically significant differences were observed between the MA+ and MA- groups ($p = .020$). No statistically significant between-group differences were observed between the MA+ and NC groups ($p = .184$), or between the MA- and NC groups ($p = .812$). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ and NC groups and Group 2 included the MA+ and MA- groups.

# DISCUSSION

Our hypothesis predicted that Response Inhibition would be impaired in methamphetamine dependence. Particularly, it was predicted that the MA+ group would perform worse than the control group; indicated by the following: MA+ > MA- > NC. This prediction was largely confirmed.

Our results indicate that, in general, Response Inhibition is impaired in methamphetamine dependence. Specifically, the AGN task indicated that MA participants performed more slowly and made more errors than control participants. The MA+ group performed the slowest out of the three groups. Statistically significant results were observed between the MA+ and control groups and between the MA- and control groups. However, no differences were observed between the MA+ and MA- groups, indicating that these groups performed similarly. The MA+ group scored the highest number of both positive and negative omissions. Statistically significant differences were observed between the MA+ and control groups regarding positive omissions. While there were differences observed between all three participant groups, in the direction predicted, none of the other between-group differences were statistically significant. Consistent with our predictions, statistically significant differences were observed between all three participant groups regarding negative omissions. These findings are consistent with previous research (Kim et al., 2006; Lelands et al., 2008; Monterosso, Aron, Cordova, Xu & London, 2005; Scott et al., 2007; Salo et al., 2002). Although Leland et al. (2008) observed improved response inhibition in MA Dependence when the Go/No Go task was cued, the authors still observed impairment on that task, when compared to controls.

The SS Task only produced one significant result. The MA+ group scored more Direction Errors than the control group. No other statistically significant between-group differences were observed. Monterosso et al. (2005) found somewhat different results when investigating performance on the SST in MA abusers. Their results indicated that MA abusers performed worse than controls on the SSRT outcome measure. No other statistically significant differences were observed on the other outcome measures of the SST. Our results are similar in the sense that we observed a trend towards significance on the SSRT outcome measure. This indicates that, in our sample, the latency to inhibit an initiated motor response was slightly longer for the MA+ group; however this difference did not

reach statistical significance. Our results are also similar to those of Monterosso et al. (2005) in the sense that few outcome measures of this task yielded significant results.

The Stroop Task indicated that MA participants performed more slowly across all four trials and made more Non Corrected Errors and more Self Corrected Errors than controls. Statistically significant differences were observed between all three groups regarding Time. The MA+ group made significantly more Non –Corrected Errors than the control group. The MA+ and MA- groups made significantly more Self-Corrected Errors than the control group. No statistically significant difference was observed between the MA+ and MA- groups, indicating that they performed similarly. These results are contrary to previous findings indicating that MA participants perform similarly to controls (Chang et al., 2002; Kim et al., 2006). However, our results are consistent with relatively recent research indicating a significant difference between MA participants and controls on Stroop RT (Salo et al., 2009). Our results are also consistent with results from Scott et al.'s (2007) meta-analysis indicating that response inhibition on the Stroop is particularly impaired in MA.

The WCST was used to measure cognitive control in our sample. We observed statistically significant results on Perseverative Responses and Perseverative Errors. Results indicated that the MA+ group made significantly more Perseverative Responses and Perseverative Errors than the MA- group. Neither of these groups differed significantly from the control group. This was contrary to our prediction and to previous findings that suggest a significant difference between MA- participants and control participants on the WCST Errors (Kim, S. J. et al., 2006; Kim, Y. T. et al., 2009). Kim, S. J. et al. (2006) found a significant difference between all error measures on the WCST, including Errors, Perseverative Errors, and Non-Perseverative Errors. Moreover, Kim, Y. T. et al. (2009) observed that the MA dependent participants in their study completed fewer categories and made more Perseverative Errors and Total Errors than control participants on the WCST.

Although there was not a statistically significant difference between our groups on number of trials administered, there was a trend towards significance in the predicted direction. This indicates that the most number of trials were administered to the MA+ group and the least number of trials were administered to the control group, indicating that the control group was able to task-switch with relative ease and therefore able to move onto the next set of trials, resulting in fewer total number

of trials administered. We therefore suggest that a larger sample size would magnify our group differences and produce significant results.

In summary, we found that the MA+ group had the most severe impairments on tests of response inhibition and set-shifting compared to the MA- and NC groups, with MA- participants considerably slower to respond on the majority of tasks compared to controls. There is a strong attentional component in most of these tasks, and the results from our Attention and Working Memory tasks will now be presented and discussed.

# CHAPTER SEVEN: ATTENTION AND WORKING MEMORY

Attention and Working Memory were assessed using the following five tasks: Task Switching, Reaction Time, the Attention Network Task, Spatial Working Memory and Spatial Span. The outcome measures for each of these tasks, as explained in the methods section, will be analysed below. Descriptive statistics for each outcome measure for each task are presented in tables and figures below. One-way ANOVAs were conducted in order to establish between-group differences. The data were generally normally distributed (see Appendix D) and Levene's test of homogeneity of variance was generally upheld. Where this assumption was violated, an adjusted (Welch's) *F* is reported. Our groups were largely equal in size.

## Task Switching

Task Switching yielded two dependent variables or outcome measures, namely, Errors, and Reaction Time. Results indicate that in general, MA participants made more errors and performed more slowly than NC participants. Descriptive statistics are presented in *Table 33* below and are graphically illustrated in *Figures 49 - 50* below.

*Table 33.* Descriptive Statistics for the Task Switching Task

| | Group 1: MA+ (***n*** **= 20)** | | Group 2: MA- (***n*** **= 19)** | | Group 3: NC (***n*** **= 20)** | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Errors**** | 9 – 111 | 61.90 (32.87) | 1 – 264 | 52.84 (63.74) | 1 – 93 | 20.85 (25.36) |
| **Reaction Time** | 655.88 - 1976.61 | 1220.5 (409.65) | 571 - 1761 | 1104.02 (258.79) | 601.41 – 2255.03 | 1121.32 (467.39) |

*Note: * indicates significance at p < .05; ** indicates significance at p < .001*

The prediction for the outcome measure Errors was that MA participants would make more Errors than NC participants. It was further predicted that MA participants would exhibit slower Reaction Times than NC participants. Predictions were largely confirmed as illustrated graphically in *Figures 49 - 50* below.

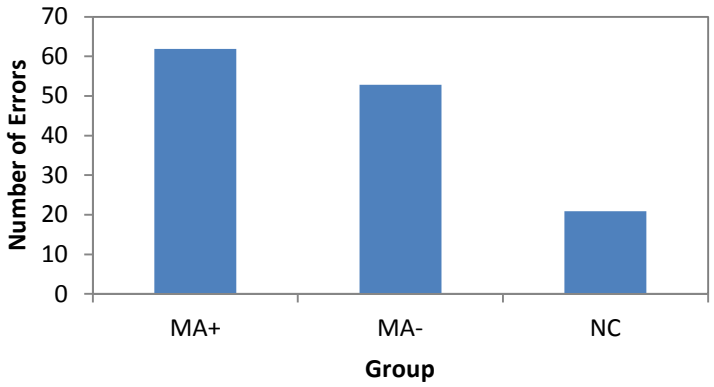


*Figure 49*. Mean Number of Errors per Group for the Task Switching Task

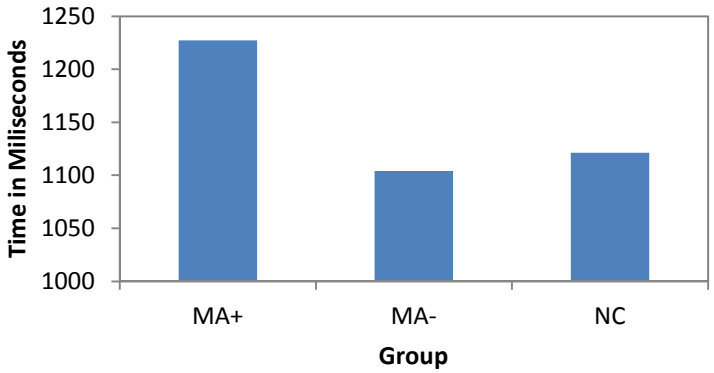


*Figure 50.* Mean Reaction Times per Group for the Task Switching Task

A one-way ANOVA was conducted on the group means in order to establish significant differences between the three participant groups on Errors. Levene's test was significant $F(2, 56) = 5.307$, $p = .008$; therefore the assumption of homogeneity of variance was violated, and an adjusted $F$ is reported here. A statistically significant between-group difference was observed, Welch's $F(2, 56) = 10.172$, $p < .001$. The Games-Howell post-hoc calculation of multiple comparisons was used to shed

further light on the data. Statistically significant differences were found between the MA+ and NC groups, $p < .001$. No statistically significant between-group differences were observed between the MA- and NC groups ($p = .064$), or between the MA+ and MA- groups ($p = .846$). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ and MA- groups and group 2 included the MA- and NC groups.

Levene's test for Average Reaction Time was significant $F(2, 56) = 3.453$, $p = .039$; therefore the assumption of homogeneity of variance was violated, and an adjusted $F$ is reported here. No statistically significant between-group differences were observed, Welch's $F(2, 56) = 0.617$, $p = .545$.

## Reaction Time Task

The Reaction Time Task has two outcome measures, namely, Five Choice Movement Time, and Five Choice Reaction Time. Results indicate that in general, MA participants performed more slowly than NC participants on both outcome measures, however, only negligibly. Descriptive statistics are presented in *Table 34* below and are graphically illustrated in *Figure 51* below.

The predictions for both outcome measures were that the MA participants would perform more slowly than NC participants. This prediction was largely confirmed, however, the results were not statistically significant.

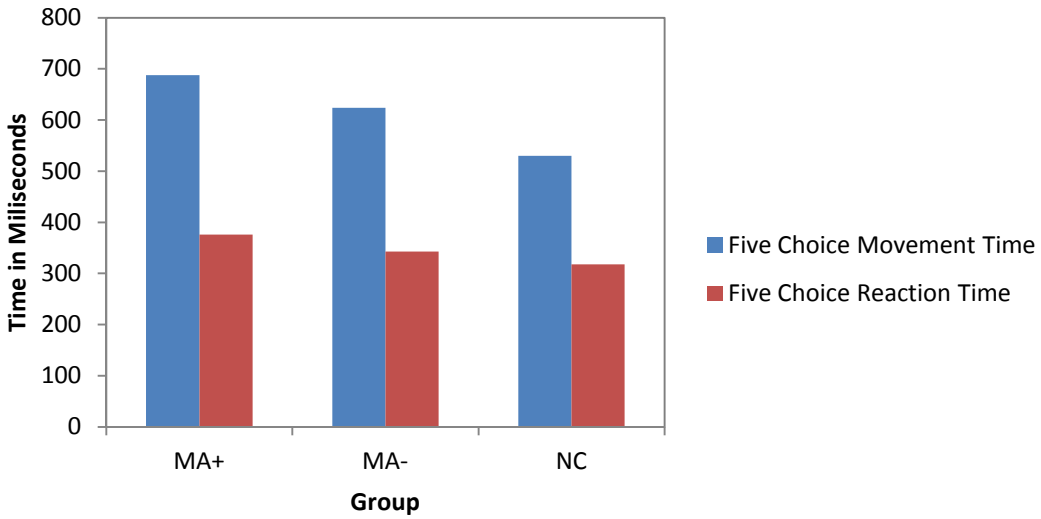


*Figure 51.* Mean Reaction Times for Two Conditions of the Reaction Time Task

*Table 34*. Descriptive Statistics for the Reaction Time Task

| | Group 1: MA+ (***n*** = **19**) | | Group 2: MA- (***n*** = **14**) | | Group 3: NC (***n*** = **18**) | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Five Choice Movement Time** | 493.25 – 1267.71 | 687.44 (190.37) | 399.29 – 1538.5 | 623.29 (285.11) | 309.62 – 688.25 | 530.09 (113.46) |
| **Five Choice Reaction Time** | 299.12 - 680 | 375.90 (100.52) | 264.5 – 549.25 | 342.62 (82.49) | 257.88 – 387.75 | 317.73 (38.09) |

*Note: * indicates significance at p < .05; ** indicates significance at p < .001*

A one-way ANOVA was conducted on the group means in order to establish significant differences between the three participant groups on Five Choice Movement Time and Five Choice Reaction Time. Levene's test was not significant for the Five Choice Movement Time outcome measure, $F(2, 48) = 1.480$, $p = .238$; therefore the assumption of homogeneity of variance was upheld. Results from this outcome measure indicated marginally significant between-group differences, $F(2, 48) = 2.869$, $p = .067$. This indicates a non-significant trend in the predicted direction. MA+ participants therefore performed more slowly than the MA+ and NC groups. The NC group performed faster than the two MA groups.

Levene's test was significant for the Five Choice Reaction Time outcome measure, $F(2, 48) = 4.367$, $p = .018$; therefore the assumption of homogeneity of variance was violated, and an adjusted $F$ is reported here. Results from this outcome measure indicated marginally significant between-group differences, Welch's $F(2, 48) = 2.951$, $p = .071$. This indicates a non-significant trend in the predicted direction. MA+ participants performed more slowly than the MA- and NC groups. The NC group performed faster than the two MA groups.

## The Attention Network Task (ANT)

The ANT yielded 6 outcome measures; three measures across two conditions. Accuracy is measured across Congruent Trials, Incongruent Trials and Neutral Trials; and Reaction Time is measured across Congruent Trials, Incongruent Trials and Neutral Trials. Results indicate in that in general, NC participants performed better on this task than MA participants. Descriptive statistics are presented in *Table 35* below and are graphically illustrated in *Figures 52 - 53* below.

The prediction for these outcome measures was that MA groups would score lower on Accuracy than the NC group and would also perform slower than the NC group. These predictions were largely confirmed as illustrated by *Figure 52* below.

*Table 35*. Descriptive Statistics for the Attention Network Task

| | Group 1: MA+ (***n*** = **20**) | | Group 2: MA- (***n*** = **19**) | | Group 3: NC (***n*** = **20**) | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| Accuracy: | | | | | | |
| **Neutral Trials*** | 33.33 – 100 | 87.28 (17.55) | 85.42 – 100 | 97.02 (4.19) | 95.83 – 100 | 99.06 (1.26) |
| **Congruent Trials*** | 33.33 – 100 | 87.61 (17.48) | 89.58 – 100 | 97.59 (3.63) | 93.75 – 100 | 99.17 (1.57) |
| **Incongruent Trials*** | 10.42 – 100 | 71.42 (29.97) | 68.75 – 100 | 91.56 (7.43) | 87.5 – 100 | 94.89 (3.35) |
| Reaction Time: | | | | | | |
| **Neutral Trials*** | 432 – 1019 | 649.65 (138.20) | 462 – 803 | 567.74 (93.02) | 425 – 752 | 547.65 (92.37) |
| **Congruent Trials*** | 416 – 1037 | 633.35 (135.61) | 420 – 805 | 573.21 (105.63) | 414 – 760 | 543 (88.96) |
| **Incongruent Trials** | 485 – 1030 | 703.25 (138.28) | 528 - 1046 | 671.21 (137.71) | 492 - 795 | 620.2 (80.22) |

*Note: * indicates significance at p < .05; ** indicates significance at p < .001*

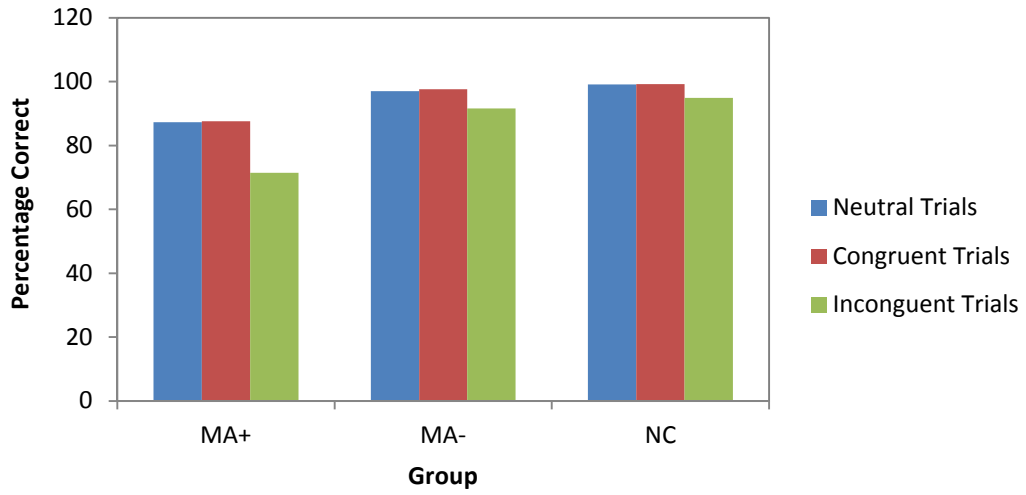


*Figure 52.* Accuracy on the Attention Network Task

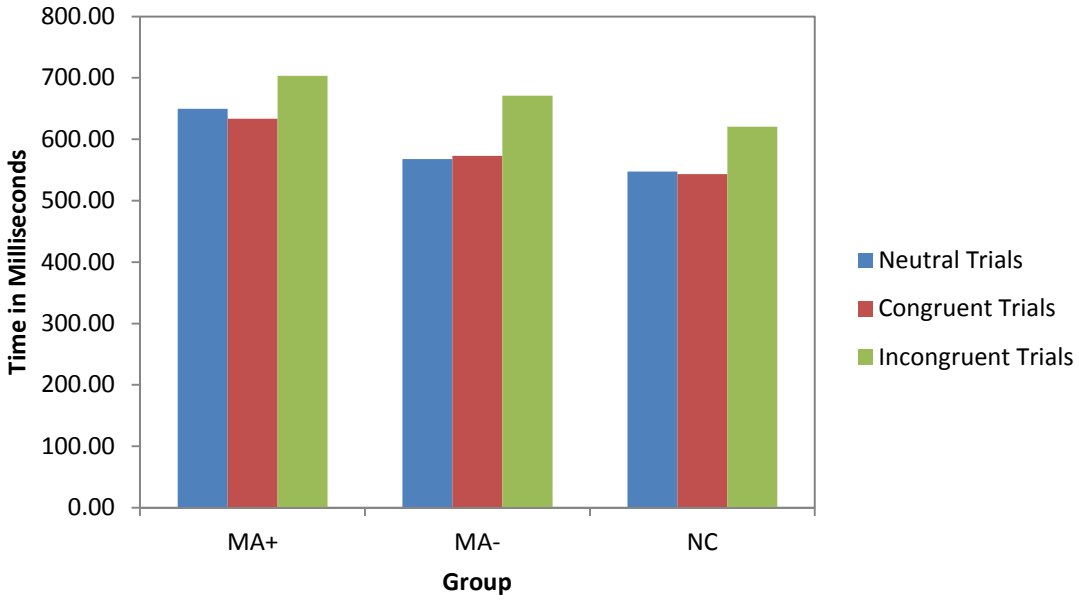


*Figure 53*. Reaction Time on the Attention Network Task

One-way ANOVAs were conducted on the group means in order to establish significant differences between the three participant groups on Accuracy and Reaction Time (see *Table 36*). Statistically significant between-group differences were observed on all outcome measures except Reaction Time for Incongruent Trials. Post hoc calculations of multiple comparisons were conducted in order to shed further light on the data.

*Table 36*. ANOVA Results Summary for the ANT

| | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| **Accuracy:** | | | | | |
| **Neutral Trials** | | | | | |
| **Between groups** | 1579.474 | 2 | 789.737 | 6.294 | .006 |
| **Within groups** | 6199.319 | 56 | 110.702 | | |
| **Total** | 7778.793 | 58 | | | |
| **Congruent Trials** | | | | | |
| **Between groups** | 1564.376 | 2 | 782.188 | 5.569 | .009 |
| **Within groups** | 6086.566 | 56 | 108.689 | | |
| **Total** | 7650.942 | 58 | | | |
| **Incongruent Trials** | | | | | |
| **Between groups** | 6421.478 | 2 | 3210.739 | 7.237 | .003 |
| **Within groups** | 18274.499 | 56 | 326.330 | | |
| **Total** | 24695.976 | 58 | | | |
| **Reaction Time:** | | | | | |
| **Neutral Trials** | | | | | |
| **Between groups** | 116349.724 | 2 | 58174.862 | 9.839 | .012 |
| **Within groups** | 680742.782 | 56 | 12156.121 | | |
| **Total** | 797092.508 | 58 | | | |
| **Congruent Trials** | | | | | |
| **Between groups** | 84515.818 | 2 | 42257.909 | 4.786 | .041 |
| **Within groups** | 700627.708 | 56 | 12511.209 | | |
| **Total** | 785143.525 | 58 | | | |
| **Incongruent Trials** | | | | | |
| **Between groups** | 70132.028 | 2 | 35066.014 | 3.378 | .102 |
| **Within groups** | 826940.108 | 56 | 14766.788 | | |
| **Total** | 897072.136 | 58 | | | |

The Games-Howell post-hoc calculation of multiple comparisons was used to shed further light on the Neutral Trials data. Statistically significant differences were found between the MA+ and NC groups, $p$ = .019. No statistically significant between-group differences were observed between the MA+ and MA- groups ($p$ = .062), or between the MA- and NC groups ($p$ = .127). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ group and Group 2 included the MA- and NC groups.

The Games-Howell post-hoc calculation of multiple comparisons was used to shed further light on the Congruent Trials. Statistically significant differences were found between the MA+ and NC groups, $p$ = .021. No statistically significant between-group differences were observed between the

MA+ and MA- groups ($p$ = .053), or between the MA- and NC groups ($p$ = .208). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ group and group 2 included the MA- and NC groups.

The Games-Howell calculation of multiple comparisons was used to shed further light on the Incongruent Trials. Statistically significant differences were found between the MA+ and NC groups, $p$ = .007; and between the MA+ and MA- groups, $p$ = .021. No statistically significant between-group difference was observed between the MA- and NC groups ($p$ = .193). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ group and group 2 included the MA- and NC groups.

The following post hoc comparisons were conducted on Reaction Time. Tukey's HSD multiple comparisons were conducted on Neutral Trials and revealed a statistically significant difference between the MA+ and NC groups, $p$ = .014. No statistically significant between-group differences were observed between the MA+ and MA- groups (p = .061), or between the MA- and NC groups ($p$ = .837). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ and MA- groups and group 2 included the MA- and NC groups.

Tukey's HSD multiple comparisons were conducted on Congruent Trials and revealed a statistically significant difference between the MA+ and NC groups, $p$ = .035. No statistically significant between-group differences were observed between the MA+ and MA- groups ($p$ = .222), or between the MA- and NC groups ($p$ = .678). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ and MA- groups and group 2 included the MA- and NC groups.

## Spatial Working Memory

Spatial Working Memory yielded two dependent variables or outcome measures, namely, Between Errors and Strategy. Results indicate that in general, MA participants scored more errors and showed

poorer strategy when compared to NC participants. Descriptive statistics are presented in *Table 37* below and are graphically illustrated in *Figure 54* below.

*Table 37.* Descriptive Statistics for Spatial Working Memory

| | Group 1: MA+ **(*n* = 20)** | | Group 2: MA- **(*n* = 15)** | | Group 3: NC **(*n* = 20)** | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Between Errors*** | 8 – 75 | 43.70 (20.32) | 1 – 73 | 35.87 (21.78) | 0 – 52 | 20.85 (15.27) |
| **Strategy*** | 30 - 44 | 37.75 (3.71) | 24 - 41 | 34.01 (5.68) | 22 - 43 | 32.1 (6.01) |

*Note: * indicates significance at p < .05; ** indicates significance at p < .001*

The predictions for these outcome variables were that MA participants would make more errors and show a poorer strategy than NC participants. This would be indicated by high scores on both of these outcome measures for MA participants and low scores on both of these measures for NC participants. These predictions were confirmed as illustrated in Figure 54 below. One-way ANOVAs were conducted on the data in order to establish between-group differences.

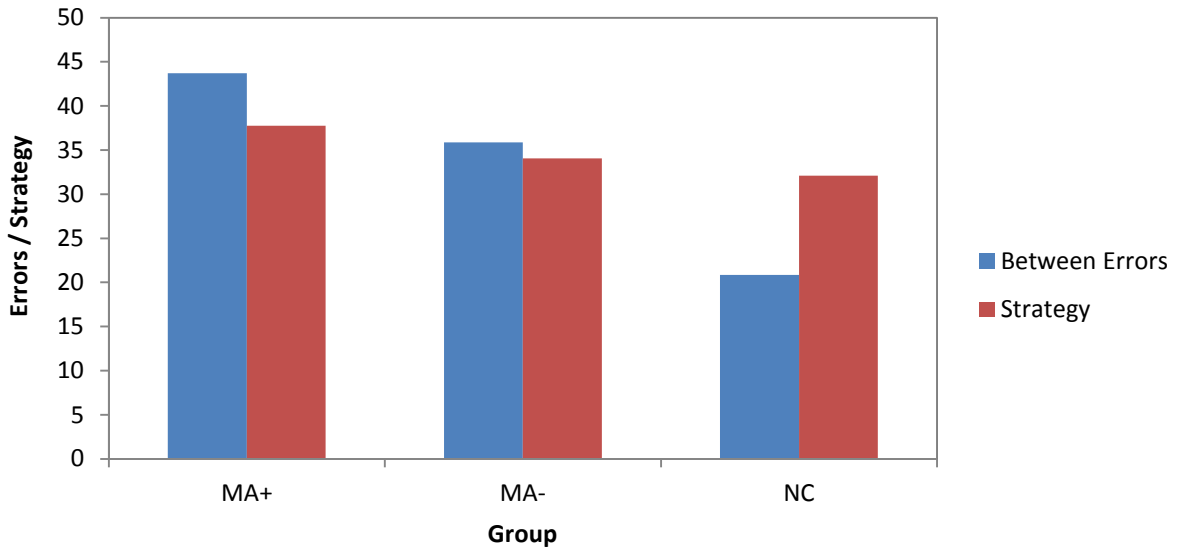


*Figure 54*. Mean Error and Strategy Scores for the Spatial Working Memory Task

The outcome measure Between Errors revealed a non-significant Levene's test, $F(2, 52) = 1.641$, $p = .204$; therefore the assumption of homogeneity of variance was upheld. Statistically significant between-group differences were observed, $F(2, 52) = 7.370$, $p = .002$. Tukey's HSD multiple comparisons revealed a statistically significant difference between the MA+ and NC groups, $p = .001$. No statistically significant between-group differences were observed between the MA+ and MA- groups ($p = .457$), or between the MA- and NC groups ($p = .064$). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ and MA- groups and group 2 included the MA- and NC groups.

The outcome measure Strategy revealed a non-significant Levene's test, $F(2, 52) = 1.800$, $p = .175$; therefore the assumption of homogeneity of variance was upheld. Statistically significant between-group differences were observed, $F(2, 52) = 6.084$, $p = .004$. Tukey's HSD multiple comparisons revealed a statistically significant difference between the MA+ and NC groups, $p = .003$. No statistically significant between-group differences were observed between the MA+ and MA- groups ($p = .104$), or between the MA- and NC groups ($p = .512$). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ and MA- groups and group 2 included the MA- and NC groups.

## Spatial Span

Spatial Span yielded only one dependent variable or outcome measure, namely, Span Length. Results indicate that in general MA participants had a shorter Span Length than NC participants. Descriptive statistics are presented in *Table 38* below and are graphically illustrated in *Figure 55* below.

*Table 38*. Descriptive Statistics for Spatial Span

| | Group 1: MA+ (***n*** **= 20)** | | Group 2: MA- (***n*** **= 15)** | | Group 3: NC (***n*** **= 20)** | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Span length*** | 2 - 8 | 5.00 (1.49) | 3 - 8 | 5.53 (1.36) | 3 - 9 | 6.05 (1.54) |

*Note: * indicates significance at p < .05; ** indicates significance at p < .001*

The prediction for this outcome measure, Span Length, was that MA participants would have a shorter Spatial Span than NC participants. It was further predicted that NC participants would have a longer Spatial Span than MA participants, as indicated by the following: MA+ < MA- < NC. This prediction was largely confirmed as illustrated by *Figure 55* below. However, results were not statistically significant.

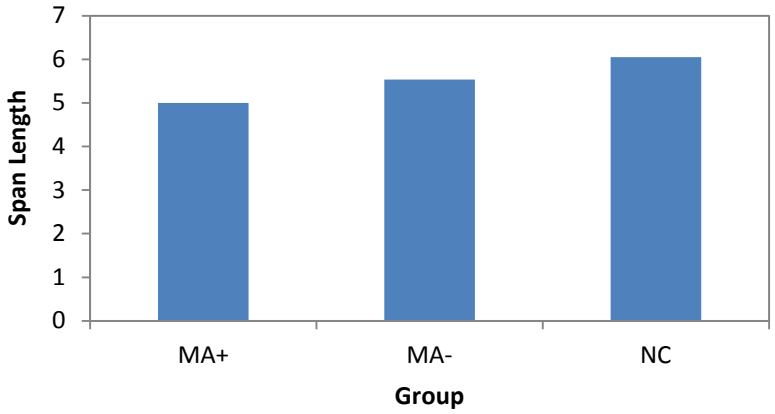


Figure 55. Mean Span Length per Group

A One-way ANOVA was conducted on the group means in order to establish significant differences between the three participant groups on Strategy. Levene's test was not significant, $F(2, 52) = 0.217$, $p = .805$; therefore the assumption of homogeneity of variance was upheld. Results from this outcome measure indicated marginally significant between-group differences w, $F(2, 52) = 2.544$, $p = .088$. This indicates a non-significant trend in the predicted direction indicating that the MA groups had shorter Spatial Spans than the NC group.

# DISCUSSION

Our hypothesis predicted that Attention and Working Memory would be impaired in methamphetamine dependence. Particularly, it was predicted that MA+ participants would perform worse than the control group; indicated by the following: MA+ > MA- > NC. This prediction was largely confirmed.

Our results indicate that, in general, attention and working memory are impaired in MA. The Task Switching Task measures the individual's ability to switch between cognitive tasks and places high demands on their working memory processes. Results from this task indicated that MA participants scored a larger number of errors than control participants. Particularly, a statistically significant difference was observed between the MA+ and the control groups. No statistically significant differences were observed between the MA- group and the other two groups. Statistically significant differences were also not observed on the Reaction Time outcome measure for this task. This task places high demands on working memory processes, as the participant needs to keep a number of rules in mind during the task. A larger number of errors on this task therefore indicate that MA+ participants were not able to hold these rules in mind as well as control participants, indicating impairment in working memory.

Our results are consistent with research indicating such an association (Scott et al., 2007). For example, Chang et al. (2002) observed in their study that MA participants performed similarly to controls on simple tasks. However, on more complex tasks, where high demand was placed on working memory processes, MA participants performed worse than controls. This result is also confirmed by Gonzalez et al (2007) who also observed working memory deficits in their sample of MA abusers.

No statistically significant results were observed on the Reaction Time task. This result is consistent with previous research that indicated no significant differences between MA participants and controls regarding psychomotor speed (Chang et al., 2002).

The ANT indicated that the MA+ group generally performed worse than the control group on both conditions of this task: Accuracy and Reaction Time. The MA+ group performed significantly worse than the control group on the Accuracy trials. This task requires a high level of attention in order to complete the trials accurately, therefore our MA+ group showed a high degree of inattention on this task. Our results are consistent with previous research indicating attentional difficulties in MA (Gonzalez, Bechara and Martin, 2007; Chang et al., 2002).

Reaction Times across the three conditions produced similar results. Statistically significant differences were observed between the MA+ and control groups on the Neutral and Congruent Trials; however the incongruent trials yielded no significant results. This last result is consistent with results from the Chang et al. (2002) study mentioned above, that indicated no significant differences between MA participants and controls regarding psychomotor speed.

The SWM task yielded similar results to those from the Task Switching Task. Statistically significant differences were observed between the MA+ and control groups on both outcome measures (Between Errors and Strategy). No significant results were observed regarding the MA- group. This task assesses the participants' ability to retain spatial information and to manipulate remembered items in working memory. It is a self-ordered task which also tests heuristic strategy. MA+ participants scored more Between Errors than controls, indicating that they revisited boxes in which a token had already been found. They therefore seemed to struggle with keeping this information in mind during the task. In addition, they also scored higher on Strategy then controls. A high score indicates poor strategy on this task, indicating that MA+ participants did not apply a predetermined sequence, but rather approached the task in a haphazard manner. This outcome measure may apply more to planning behaviour and indicates that MA+ participants showed poor planning skills on this task. These results are consistent with previous research using a similar task. Van Der Plaas et al. (2009) used a Tic Tac Toe working memory task where participants were presented with a spatial array of X's and O's and these had to be kept in mind by the participant in order to identify the pattern seconds later. Results from their study indicated that MA participants performed more poorly than control participants. MA participants performed more slowly and made more errors than controls, indicating impairment in working memory.

The SSP task yielded slight differences between the groups; however, these were not statistically significant. Span Length was found to be similar between the groups. This result is similar to those of Simon et al. (2000) who used a backward digit span task to assess working memory in MA participants compared to controls. The authors did not find a significant difference between their groups.

In summary, our results indicate that MA+ participants show impairment on tasks of Attention and Working Memory, indicating that they have trouble holding items in memory for short periods of time. This is consistent with previous research indicating an association between attention and working memory deficits and MA (Chang et al., 2002; Gonzalez et al., 2007; van der Plaas et al., 2009).

# CHAPTER EIGHT: VERBAL FLUENCY IMPAIRMENT IN METHAMPHETAMINE

Verbal Fluency was assessed using the D-KEFS Verbal Fluency subtests. Phonemic Fluency was assessed using FAS and Semantic Fluency was assessed using Category Fluency and Category Switching. Results indicate that in general, MA participants performed worse than NC participants on all tasks of Verbal Fluency. Descriptive statistics are presented in *Table 39* below and are graphically represented in *Figures 56 - 58* below.

The predictions for the all outcome measures were that MA participants would generate fewer items when compared to control participants. It was further predicted that control participants would generate more items when compared to the MA participants, as follows: MA+ > MA- > NC. This prediction was confirmed as illustrated by *Figures 56 - 58* below.

All results were analysed using one-way ANOVAs in order to establish between-group differences. ANOVAs results are presented in *Table 40* below.

*Table 39*. Descriptive Statistics for Tasks of Verbal Fluency

| | Group 1: MA+ **(*n* = 20)** | | Group 2: MA- **(*n* = 19)** | | Group 3: NC **(*n* = 20)** | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| Verbal Fluency | | | | | | |
| α = 0.92 | | | | | | |
| **Phonemic (letter) fluency** | | | | | | |
| **F*** | 5 – 22 | 9.58 (4.54) | 4 – 20 | 10.21 (4.72) | 6 – 24 | 14.05 (4.65) |
| **A*** | 4 – 14 | 6.42 (2.85) | 1 – 15 | 7.74 (4.0) | 1 – 26 | 11.4 (5.48) |
| **S**** | 4 – 17 | 8.79 (3.57) | 4 – 18 | 10.95 (4.39) | 3 – 25 | 15.35 (5.07) |
| **Total**** | 14 – 52 | 24.79 (9.46) | 13 – 47 | 28.74 (11.7) | 10 - 75 | 40.80 (13.9) |
| **Semantic (category) fluency** | | | | | | |
| **Animals**** | 6 – 21 | 13.00 (3.93) | 10 – 25 | 16.84 (4.19) | 12 – 29 | 19.45 (4.51) |
| **Boy's Names**** | 6 – 24 | 13.53 (4.22) | 8 – 27 | 16.58 (4.78) | 12 – 29 | 19.7 (4.87) |
| **Total**** | 12 – 44 | 26.68 (7.77) | 24 – 48 | 34.63 (7.3) | 27 – 58 | 39.15 (8.1) |
| **Category switching** | | | | | | |
| **Total correct responses*** | 6 - 18 | 11.11 (2.83) | 8 – 19 | 11.95 (2.84) | 10 – 18 | 13.7 (2.11) |

*Note: * indicates significance at p < .05; ** indicates significance at p < .001*

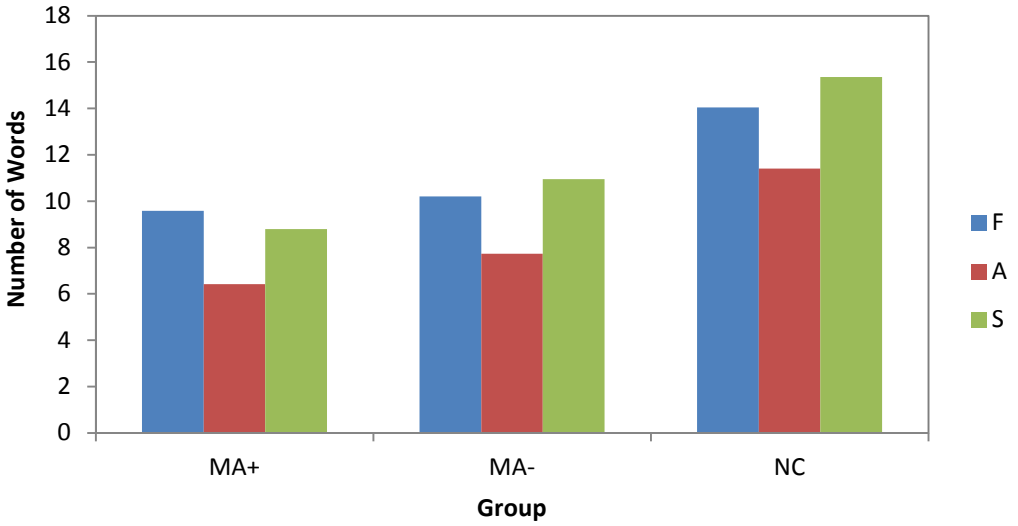


*Figure 56*. Mean Number of Words Generated per Group for F, A, and S

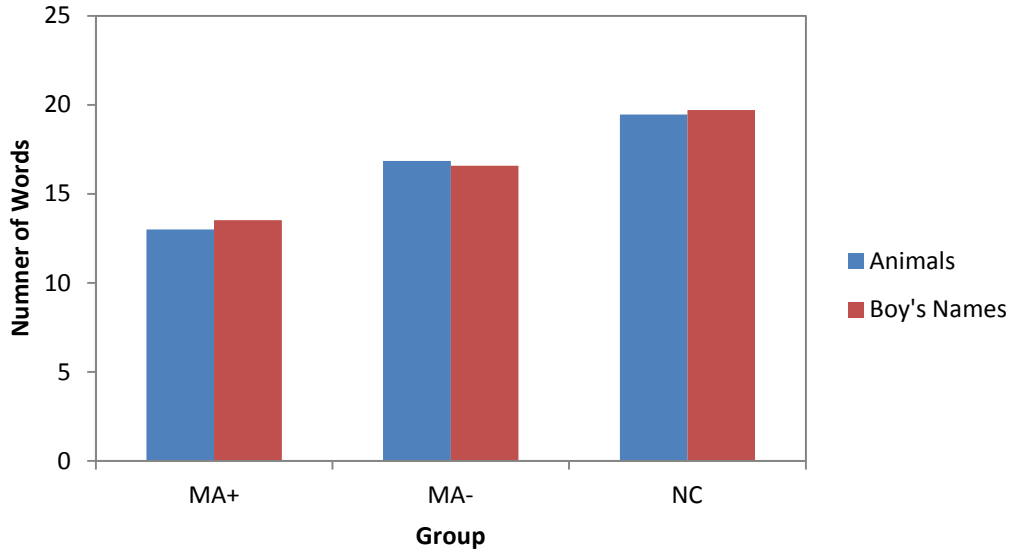


*Figure 57*. Mean Number of Words Generated per Group on Categories

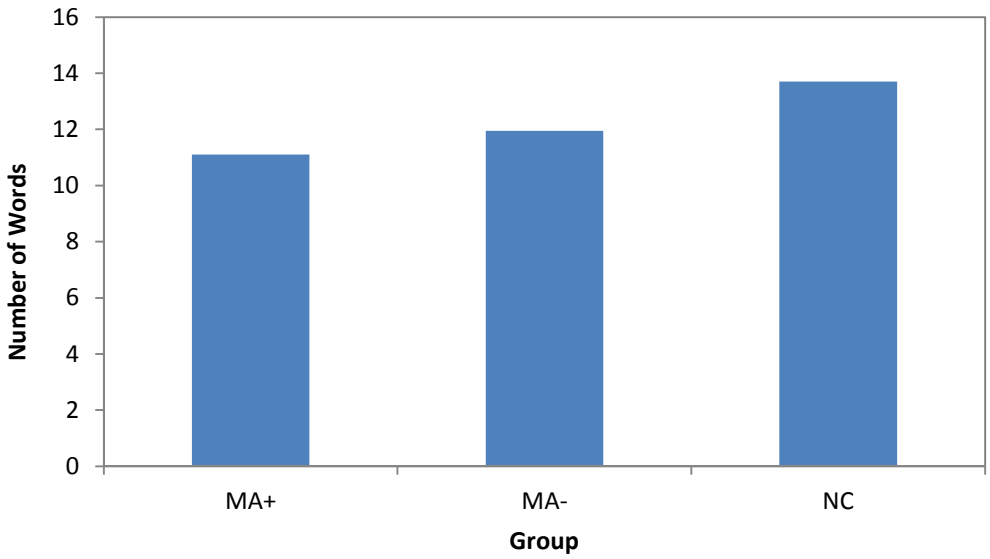


*Figure 58*. Mean Number of Words Generated per Group for Category Switching

*Table 40*. ANOVA Results Summary for Verbal Fluency

| | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| **F** | | | | | | |
| | **Between groups** | 230.036 | 2 | 115.018 | 5.349 | .008 |
| | **Within groups** | 1182.739 | 55 | 21.504 | | |
| | **Total** | 1412.77 | 57 | | | |
| **A** | | | | | | |
| | **Between groups** | 261.108 | 2 | 130.554 | 7.144 | .002 |
| | **Within groups** | 1005.116 | 55 | 18.275 | | |
| | **Total** | 1266.224 | 57 | | | |
| **S** | | | | | | |
| | **Between groups** | 437.965 | 2 | 218.983 | 11.313 | < .000 |
| | **Within groups** | 1064.655 | 55 | 19.357 | | |
| | **Total** | 1502.621 | 57 | | | |
| **Total** | | | | | | |
| | **Between groups** | 2729.837 | 2 | 1364.919 | 9.689 | < .000 |
| | **Within groups** | 7748.042 | 55 | 140.873 | | |
| | **Total** | 10477.879 | 57 | | | |
| **Animals** | | | | | | |
| | **Between groups** | 409.006 | 2 | 204.503 | 11.460 | < .000 |
| | **Within groups** | 981.476 | 55 | 17.845 | | |
| | **Total** | 1390.483 | 57 | | | |
| **Boy's Names** | | | | | | |
| | **Between groups** | 371.535 | 2 | 185.768 | 8.647 | .001 |
| | **Within groups** | 1181.568 | 55 | 21.483 | | |
| | **Total** | 1553.103 | 57 | | | |
| **Total** | | | | | | |
| | **Between groups** | 1544.993 | 2 | 772.496 | 12.902 | < .000 |
| | **Within groups** | 3293.076 | 55 | 59.874 | | |
| | **Total** | 4838.069 | 57 | | | |
| **Category Switching** | | | | | | |
| | **Between groups** | 68.649 | 2 | 34.325 | 5.062 | .010 |
| | **Within groups** | 372.937 | 55 | 6.781 | | |
| | **Total** | 441.586 | 57 | | | |

Statistically significant between-group differences were observed on all outcome measures of Verbal Fluency. Post hoc multiple comparisons were conducted in order to shed further light on the data.

Comparisons for F, A, and S yielded the same results as the combined total of FAS together. Therefore only FAS total (Phonemic Fluency) is reported here. Tukey's HSD multiple comparisons revealed a statistically significant difference between the MA+ and NC groups, $p < .001$, and between the MA- and NC groups, $p = .007$. No statistically significant differences were observed between the

MA+ and MA- groups ($p$ = .564). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ and MA- groups and group 2 included the NC group.

When Animals and Boy's Names were combined (Semantic Fluency), Tukey's HSD multiple comparisons revealed a statistically significant difference between the MA+ and NC groups, $p < .001$; and between the MA+ and MA- groups, $p$ = .007. No significant differences were observed between the MA- and NC groups ($p$ = .172). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ group and Group 2 included the MA- and NC groups.

Tukey's HSD multiple comparisons for Category Switching revealed a statistically significant difference between the MA+ and NC groups, $p$ = .008. No statistically significant between-group differences were observed between the MA- and NC groups ($p$ = .099) or the MA+ and MA- groups ($p$ = .582). Tukey's HSD homogenous subsets revealed two homogenous groups. Group 1 included the MA+ and MA- groups and Group 2 included the MA- and NC groups.

# DISCUSSION

Our hypothesis predicted that Verbal Fluency would be impaired in methamphetamine dependence. Particularly, it was predicted that MA+ participants would perform worse than controls; indicated by the following: MA+ > MA- > NC. This prediction was confirmed by our results.

The FAS condition, both individual letters and the total combined score, assessing phonemic fluency, yielded statistically significant results. Significant differences were observed between the MA+ and control groups as well as between the MA- and control groups. No statistically significant differences were observed between the two MA groups, indicating that they performed similarly.

Similar results were observed for semantic fluency. The Category Fluency condition yielded statistically significant results for the category “Animals” and “Boy’s Names”. Statistically significant differences were observed between the MA+ and control groups as well as between the MA+ and MA- groups for the “Animals” category. For the category “Boy’s Names” statistically significant differences were observed between the MA+ and control groups only. Combining these two categories also produced significant results. Statistically significant differences were observed between the MA+ and control groups and between the MA+ and MA- groups. Statistically significant differences were also observed between the MA+ and control groups on Category Switching. Thus, our methamphetamine dependent participants showed significant impairment on Verbal Fluency, both phonemic and semantic.

These findings are consistent with previous literature indicating moderate impairments in verbal fluency (Scott et al., 2007). Further studies, for example, Kalechstein et al. (2003) and Simon et al. (2007) also found significant verbal fluency deficits associated with MA.

In summary, our methamphetamine dependent groups were impaired on verbal fluency. Both groups performed similarly on phonemic fluency, however there were some differences on semantic fluency. The MA+ group were the most impaired on all three conditions of verbal fluency.

# CHAPTER NINE: THE CORRELATION BETWEEN EXECUTIVE FUNCTIONING AND CORTICAL THICKNESS IN METHAMPHETAMINE

The correlation between performance on tasks of executive functioning and cortical thickness of frontal brain regions was investigated by correlating neuropsychological data with structural MRI data. Specifically, we investigated which of the executive functioning domains that showed statistically significant differences between our groups correlated with left and/or right frontal hemisphere brain regions in terms of cortical thickness. The MRI data for our sample revealed cortical thickening in the MA-group and cortical thinning in the MA+ group. The prediction was therefore that impaired performance on tasks of executive functioning would be associated with decreased cortical thickness in the MA+ group and increased cortical thickness in the MA- group in the associated frontal brain regions. Specific hypotheses for each domain are presented under the corresponding sections below. Results indicate a number of significant correlations. Our predictions were therefore largely confirmed.

Structural MRI data were collected on 45 of the 58 participants used in this study. Demographic details for these 45 participants are presented in *Table 41* below.

*Table 41*. Demographic Characteristics for Participants in the Correlation Groups

| | **MA+ (n = 15)** | **MA- (n = 15)** | **NC (n = 15)** |
|---|---|---|---|
| **Age** | 24.13 (6.15) | 23.87 (3.82) | 24.6 (4.76) |
| **Gender (Male : Female)** | 12 : 3 | 13 : 2 | 11 : 4 |
| **Years of Education** | 9.73 (1.03) | 10.73 (2.28) | 12.2 (1.66) |
| **IQ (FSIQ)** | 73.8 (14.1) | 78.8 (18.6) | 89.9 (17) |

Our data were not normally distributed, as discussed under the methods section and therefore we report Spearman's Rho instead of Pearson's *r*. A series of Spearman's rank-order correlational analyses were conducted in order to determine if there were any relationships between performance on tasks of executive functioning, where significant between-group differences were observed, and frontal cortical thickness. Two-tailed tests of significance revealed a number of significant relationships. These are presented for each executive domain below.

## Decision Making and Impulsivity

The Decision-Making and Impulsivity domain yielded two statistically significant between-group differences in our ANOVA results, presented in Chapter 4 above. The Number of Discounts outcome measures from the Delay Discounting task and the Discrimination Errors on condition two of the Information Sampling Task yielded statistically significant between-group differences. We predicted that impairment on Decision Making and Impulsivity would be associated with thinner orbitofrontal cortex in the MA+ group and thicker orbitofrontal cortex in the MA-group.

Delay Discounting, i.e. Number of Discounts, was associated with decreased cortical thickness in a number of frontal regions. In the MA+ group the impairment on the DDT was associated with decreased cortical thickness of the left pars triangularis, $r(15) = -.583$, $p = .022$; the left precentral, $r(15) = -.801$, $p < .001$; the left frontal pole, $r(15) = -.634$, $p = .011$; and the left insula, $r(15) = -.690$, $p = .004$. This indicates that greater discounting, or impulsivity, is associated with cortical thinning of left frontal hemisphere regions.

There were also a number of significant correlations between Number of Discounts and areas in the right hemisphere in the MA+ group. Impairment on the DDT was associated with decreased cortical thickness of the right lateral orbitofrontal, $r(15) = -.721$, $p = .002$; the right paracentral, $r(15) = -.654$, $p = .008$; the right pars triangularis, $r(15) = -.600$, $p = .018$; the right precentral, $r(15) = -.541$, $p = .037$; and the right insula, $r(15) = -.649$, $p = .009$. This indicates that greater discounting, or impulsivity, is also associated with cortical thinning of the right frontal hemisphere regions in the MA+ group

The Information Sampling Task, particularly Discrimination Errors, was not found to be significantly correlated with cortical thickness in any frontal regions.

In summary, it was found that impulsivity was associated with cortical thinning of both left and right hemisphere frontal regions in MA+ participants.

## Response Inhibition and Set-Shifting

The Response Inhibition and Set-Shifting domain yielded a number of significant outcome measures. We predicted that impairment on these outcome measures would be associated with thinner anterior cingulate cortex (ACC) in the MA+ group and thicker ACC in the MA- group.

All four outcome measures of the Affective Go/No Go task yielded statistically significant between-group differences. Significant correlations were observed between these outcome measures and frontal cortical thickness.

In the MA- group, Mean Correct Latency for positive items ie slower reaction times were significantly associated with increased cortical thickness of the left caudal middle frontal, r(15) = .677, *p* = .006; the left paracentral, r(15) = .571, *p* = .026; the left pars opercularis, r(15) = .775, *p* = .001; the left pars triangularis, r(15) = .725, *p* = .002; the left precentral, r(15) = .611, *p* = .016; and the left superior frontal r(15) = .593, *p* = .020. Mean Correct Latency for negative items showed similar significant associations with increased cortical thickness of the left caudal middle frontal, r(15) = .735, *p* = .002; the left lateral orbitofrontal, r(15) = .586, p = .022; the left paracentral r(15) = .568, *p* = .027; the left pars opercularis, r(15) = .557, *p* = .031; the left precentral, r(15) = .536, *p* = .040; and the right rostral middle frontal, r(15) = .543, *p* = .037. This indicates a relationship between slower reaction times of the MA- participants and cortical thickening of left and right frontal hemisphere regions.

Total Omissions (positive) in the MA- group was significantly negatively correlated with cortical thickness of the right pars orbitalis, r(15) = -.540, *p* = .038. This indicates a moderate relationship between impaired response inhibition and cortical thinning of this right frontal hemisphere region. Total Omissions (negative) was not correlated with any frontal cortical areas.

However, in the MA+ group, Mean Correct Latency for negative items was significantly negatively correlated with cortical thickness of the left rostral middle frontal, r(15) = -.518, *p* = .048, and the right caudal middle frontal, r(15) = -.525, *p* = .044. This indicates a moderate relationship between slower reaction times and cortical thinning of left and right hemisphere frontal regions. Total Omissions, both positive and negative did not reveal any significant correlations in this group.

In the control group, decreased Mean Correct Latency, i.e. quicker response times, for negative items was associated with cortical thickness of the left rostral anterior cingulate, r(13) = -.610, *p* = .027; the left rostral middle frontal, r(13) = -.588, *p* = .035. Increased Total Omissions (positive) was associated with cortical thickness of the left rostral anterior cingulate, r(13) = .601, *p* = .030; the left frontal pole, r(13) = .573, *p* = .041; and the right caudal anterior cingulate, r(13) = .698, *p* = .008. Increased Total Omissions (negative) was associated with cortical thickness of the left lateral orbitofrontal, r(13) = .630, *p* = .021, and the medial orbitofrontal, r(13) = .610, *p* = .027. This indicates that increased errors are associated with cortical thickening of left hemisphere regions. However, faster reaction times were also associated with cortical thickening of left, and some right, hemisphere regions.

In summary, impairment on the AGN task in the MA+ group is associated with cortical thinning of frontal sub-region. However, impairment in the MA- group is associated with cortical thickening. This relationship was not observed for the SS task.

The Stop Signal task yielded one significant result, Direction Errors on Stop/Go Trials. In the MA- group, increased number of Directions Errors on Stop/Go Trials was associated with increased cortical thickness of the right caudal anterior cingulate, r(13) = .624, *p* = .023; and the right pars orbitalis, r(13) = .661, *p* = .014. This indicates a strong relationship between errors and cortical thickening of right hemisphere frontal regions.

In the MA+, increased Direction Errors on Stop/Go Trials was associated with increased cortical thickness of the left pars orbitalis, r(15) = .531, *p* = .042; the right pars orbitalis, r(15) = .564, *p* = .029; and the right pars triangularis, r(15) = .655, *p* = .008. This indicates moderate to strong relationships between errors and cortical thickening of left and right hemisphere frontal regions.

In the control group, Direction Errors on Stop/Go Trials was significantly positively correlated with the right paracentral, r(13) = .757, *p* = .003. This indicates a very strong relationship between errors and cortical thickening of this right hemisphere frontal region.

Evidently, increased number of errors is associated with cortical thickening in all three participant groups on the SS task. In addition, all three groups predominantly show cortical thickening in the right hemisphere.

The Stroop task yielded statistically significant between-group differences on all outcome measures; however, our correlational analyses will be focused on Time for Trials 3 and 4, as these are the inhibition trials. In the MA- group, increased Time taken for Trial 3 was associated with cortical thickening of the right lateral orbitofrontal, r(15) = .564, *p* = .029. This indicates a moderate relationship between increased time taken and cortical thickening of this right hemisphere frontal region in the MA- group. In the MA+ group Time taken for Trials 3 and 4 did yield any significant correlations.

However, in the control group, increased Time taken for Trial 3 was associated with cortical thinning of the left caudal middle frontal, r(15) = -.578, *p* = .024; the left rostral middle frontal, r(15) = -.517, p = .048; and the right caudal middle frontal, r(15) = -.524, *p* = .045. Increased Time taken on Trial 4 was associated with cortical thinning of the right caudal middle frontal, r(15) = -.633, *p* = .011. This result indicates a moderate relationship between increased time taken and cortical thinning of left and right hemisphere frontal regions.

In summary, the Stroop task showed a relationship between increased time taken and cortical thickening in the MA- group, but cortical thinning in the control group.

The WCST yielded two significant results; Perseverative Responses and Perseverative Errors. In the MA- group, increased Perseverative Responses was associated with cortical thinning of the left

frontal pole, r(10) = -.770, *p* = .009, and the right caudal middle frontal, r(10) = -.648, *p* = .043. Increased Perseverative Errors was also associated with cortical thinning of the left frontal pole, r(10) = -.760, *p* = .011, and the right caudal middle frontal, r(10) = -.663, *p* = .037. These results indicate a strong relationship between impairment on this task and cortical thinning in left and right hemisphere frontal regions in the MA- group. No significant correlations were observed in the MA+ group, or in the control group.

In summary, results from the response inhibition tasks provide inconsistent results. Some tasks indicate a relationship between impairment and cortical thinning in the MA+ group and thickening in the MA- group, however, other tasks indicate the opposite.

## Attention and Working Memory

The Attention and Working Memory domain yielded a number of significant between-group differences, except the Spatial Span and Reaction Time tasks. We predicted that working memory impairment would be associated with thinner dorsolateral prefrontal cortex in the MA+ group and thicker dorsolateral prefrontal cortex in the MA- group.

The Task Switching task yielded one significant result for the Errors outcome measure. In the MA- group, increased Errors was associated with cortical thinning of the left pars triangularis, r(15) = -.582, *p* = .023. This indicates that impairment on this task is associated with cortical thinning of this left hemisphere frontal region. In the MA+ and control groups, Errors did not yield any significant correlations.

The Attention Network Task produced six outcome measures and all of these except one yielded statistically significant between-group differences. Reaction Time on Incongruent trials was the only outcome measure that did not yield significant results.

In the MA- group, decreased Accuracy on congruent trials was associated with cortical thinning of the left rostral anterior cingulate, r(15) = .583, *p* = .023. Increased Reaction Time for all three conditions (Neutral, Congruent and Incongruent) was associated with cortical thinning of the left precentral, r(15) = -.639, *p* = .010; r(15) = -.629, *p* = .012; and r(15) = -.736, *p* = .002 respectively. Increased Reaction Time for all three conditions was also associated with cortical thinning of the right caudal middle frontal, r(15) = -.821, *p* < .001; r(15) = -.875, *p* < .001; and r(15) - .857, *p* < .001; as well as the right rostral middle frontal, r(15) = -.650, *p* = .009; r(15) = -.686, *p* = .005; r(15) = -.689, p = .004. In addition increased Reaction Time on Congruent trials was associated with cortical thinning of the right insula, r(15) = -.514, *p* = .050. This indicates that impaired attention is associated with cortical thinning of these left and right hemisphere frontal regions in the MA- group.

In the MA+ group, decreased Accuracy on the Neutral and Congruent trials was associated with cortical thinning of the left precentral, r(15) = .574, *p* = .025; r(15) = .563, *p* = .029 respectively. Decreased Accuracy on the Congruent trials was also associated with cortical thinning of the left frontal pole, r(15) = .529, *p* = .043. Decreased Accuracy on all three conditions was associated with cortical thinning of the right paracentral, r(15) = .590, *p* = .021; r(15) = .668, *p* = .007; r(15) = .560, *p* = .027. In addition, decreased Accuracy on the Neutral and Congruent trials was associated with cortical thinning of the right rostral middle frontal, r(15) = .598, *p* = .019; and r(15) = .543, *p* = .036 respectively as well as the right frontal pole, r(15) = .630, *p* = .012; and r(15) = .552, *p* = .033, respectively. Increased Reaction Time on Congruent trials was associated with cortical thinning of the right caudal anterior cingulate, r(15) = -646, *p* = .009. Again, this indicates that impaired attention is associated with cortical thinning of these left and right hemisphere frontal regions in the MA+ group.

In the control group, increased Accuracy on Incongruent trials was associated with cortical thickness of the left caudal anterior cingulate, r(15) = -.716, *p* = .003; and the left lateral orbitofrontal, r(15) = -.533, *p* = .041. Increased Accuracy on Congruent trials was associated with cortical thinning of the right lateral orbitofrontal, r(15) = -.695, *p* = .004. Increased Accuracy on Neutral trials was associated with cortical thinning of the right paracentral, r(15) = -.647, *p* = .009. Increased Accuracy on Incongruent trials was associated with cortical thinning of the right insula, r(15) = -.748, *p* = .001.

In summary, results from the ANT indicate that impaired attention in the two MA groups is associated with cortical thinning of the relevant frontal regions. However, with the control group, intact attention was, in general, associated with cortical thickening of the relevant frontal regions.

The Spatial Working Memory task yielded two statistically significant outcome measures, Between Errors and Strategy. In the MA- group, neither Between Errors nor Strategy was significantly correlated to cortical thickness of any frontal brain regions. In the MA+ group, increased Between Errors was associated with cortical thinning of the left lateral orbitofrontal, $r(15) = -.574$, $p = .025$. A high Strategy score (i.e. impaired strategy) was associated with cortical thinning of the right caudal anterior cingulate, $r(15) = -.536$, $p = .039$; and the right pars opercularis, $r(15) = -.551$, $p = .033$. In the control group, decreased Between Errors was associated with cortical thickness of the left caudal middle frontal, $r(15) = -.546$, $p = .035$; and the left precentral, $r(15) = -.678$, $p = .005$. A high Strategy score was associated with cortical thinning of the left precentral, $p(15) = -.585$, $p = .022$; and the left insula, $p (15) = -.549$, $p = .034$. These results indicate impaired working memory is associated with cortical thinning of left and right hemisphere frontal regions in the MA+ group. However, similar results were observed in the control group.

In summary, attention and working memory are associated with cortical thinning in both MA groups on the ANT. However, on the SWM task, impairment was associated with cortical thinning in the MA+ group, with similar results observed in the control group.

## Verbal Fluency

The Verbal Fluency domain yielded statistically significant results for all outcome measures of phonemic verbal fluency and semantic verbal fluency. We have therefore run correlational analyses on two outcome measures, one representing phonemic fluency (Total FAS score), and one representing semantic fluency (Total Category Fluency score). We predicted impaired verbal fluency would be associated with thinner anterior prefrontal and insula cortices in the MA+ group and thicker anterior prefrontal and insula cortices in the MA- group. In the MA- group, neither Phonemic Fluency nor Semantic Fluency were significantly correlated with any frontal brain regions.

In the MA+ group, a poor Semantic Fluency score was associated with cortical thinning of the left lateral orbitofrontal, p(15) = .762, p = .001; the left pars orbitalis, p(15) = .526, p = .044; the right lateral orbitofrontal, p(15) = .538, p = .039; and the right paracentral, p(15) = .698, p = .004. This indicates that impaired Semantic Fluency is associated with cortical thinning in left and right hemisphere frontal regions in the MA+ group.

In the control group, a high Semantic Fluency score was associated with cortical thinning of the left caudal anterior cingulate, p(15) = -.532, p = .041; the left pars orbitalis, p(15) = -.544, p = .036; the left rostral anterior cingulate, r(15) = -.517, p = .048; the left frontal pole, r(15) = -.539, p = .038; and the right frontal pole, p(15) = -.525, p = .044. This indicates that intact verbal fluency is associated with cortical thinning in these left and right hemisphere regions in the control group.

In summary, impaired semantic fluency is associated with cortical thinning in the MA+ group and intact impairment is associated with cortical thinning in the control group.

# DISCUSSION

Poor decision-making was observed in both the MA+ and MA- groups. These groups performed similarly on the Delay Discounting task and both of these groups performed significantly worse than the control group. Cortical thickening was observed in our MA- group; and cortical thinning was observed in our MA+ group. We therefore predicted that decision-making, in this case, number of discounts, would be associated with thinning of the orbitofrontal cortex in the MA+ group, and thickening in the MA- group. We also predicted an association with changes in thickness of the dorsolateral prefrontal cortex, given the association between decision-making and working memory (McClure et al., 2004). Specifically, we predicted thinning in the MA+ group and thickening in the MA- group. However, correlations between increased number of discounts and decreased cortical thickness were only significant in the MA+ group.

These significant correlations showed strong negative relationships between number of discounts and cortical thinning, indicating that the larger the number of discounts, the thinner the cortical area in the MA+ group, but not in the MA- group. These findings are consistent with greater structural damage and poorer decision-making in the MA+ group than the MA- group.

These results are also consistent with previous research which has associated delay discounting with orbitofrontal and dorsolateral prefrontal dysfunction (Paulus, et al., 2002). Our results are partially consistent with this finding as indicated by the strong relationship observed between delay discounting and thinning in the right lateral orbitofrontal cortex. We also observed significant correlations between delay discounting and thinning in the following cortical regions; left pars triagularis, precentral, and frontal pole, as well as the right paracentral, pars triangularis, and precentral. These brain regions are known to be involved in motor processes and are therefore suggested by McClure et al. (2004) to reflect non-specific aspects of task performance that may be engaged during the decision making process, but not necessarily directly related to immediate or delayed choices.

Impaired response inhibition was observed in both the MA+ and MA- groups. The composite z-score for the response inhibition domain revealed the MA- group as slightly more impaired than the MA+ group Significant correlations were observed within all three participant groups. First, impaired response inhibition was, in general, associated with cortical thickening of the DLPFC in the MA- group, and cortical thinning in the MA+ group. This is consistent with our prediction; however, this was not always the case. A few tasks showed the opposite result. On certain tasks of response inhibition, the MA- group showed greater impairment than the MA+ group. This may account for these inconsistent results. Where the MA+ group showed cortical thickening, it is suggested that this may be a compensatory response in order to preserve function. Similar results were observed by Chang et al. (2005) who found enlarged striatum, and intact neuropsychological functioning, in abstinent MA abusers. The association between response inhibition and cortical thickness of the DLPFC is consistent with previous research that found an association between response inhibition, the DLPFC (Gläscher et al., 2012). Second, in the control group there was a moderate to strong relationship between faster performance on the AGN and cortical thickening of the ACC as well as the OFC. Again, it can be argued that the cortical thickening preserves function and therefore this group was least impaired on this task.

The association between response inhibition and cortical thickness of the ACC is consistent with those of Aron et al. (2003; as cited in Chambers et al., 2009) who found an association between response inhibition and the inferior frontal gyrus. However, their findings were significant for the right hemisphere, and ours were significant for the left. Particularly, Aron et al. (2003; as cited in Chambers et al., 2009) suggested damage to the pars opercularis was associated with impairments in response inhibition. In our MA- group, a relationship between performance on the AGN and cortical thickening of the left pars opercularis was observed. Our findings are therefore consistent with previous research.

The SST confirmed this finding and revealed significant correlations between errors and cortical thickness in most of the regions of the inferior frontal gyrus. In the MA+ group, the expected associations between impaired SST and cortical thinning in the IFG were found. However, there were fewer such associations in MA- and control groups. This is most likely because the MA+ group is the most severely impaired group. In addition, it may be that a compensatory response occurred, resulting in cortical thickening.

The literature further suggests that poor performance on the Stroop task specifically has been associated with damage to the ACC (Gläscher et al., 2012; Bench et al. 1993, Pardo et al. 1990; as cited in Stuss & Levine, 2002) and the DLPFC (Gläscher et al. 2012; Stuss et al. 2001; as cited in Stuss & Levine, 2002). Our findings were not entirely consistent with these findings. We observed that an increase in time taken per trial was associated with cortical thickening in the right lateral orbitofrontal cortex in the MA- group. However, in the control group, reduced time taken was associated with cortical thickening of the middle frontal gyrus. The DLPFC lies in the middle frontal gyrus; therefore, this latter finding is what we would expect to find considering the suggested involvement of the DLPFC in the Stroop task (Gläscher et al. 2012; Stuss et al., 2001; as cited in Stuss & Levine, 2002). Again, the cortical thickening observed in the MA- group could be a compensatory mechanism in order to preserve function (Chang et al. 2005).

The WCST also confirmed these results. Performance on this task was associated with the middle frontal gyrus, i.e. the DLPFC in the MA- group. A strong relationship was observed between decreased errors and cortical thickening. The MA- group performed the least number of Perseverative Responses and Errors compared to both the MA+ and the NC group. This provides strong evidence for the hypothesis that cortical thickening provides a mechanism for the preservation of function. In addition, these results are consistent with previous research findings indicating an association between response inhibition on the WCST and the DLPFC (Kim, S. J. et al., 2006).

An association between preservation of function and cortical thickening was observed on tasks of attention and working memory as well. Attention and working memory were found to be impaired in our MA groups. Three tasks revealed statistically significant between-group differences; Task Switching, the Attention Network Task (ANT) and the Spatial Working Memory (SWM) task. Number of Errors on Task Switching was found to have no significant correlations with cortical thickness of any frontal regions.

In the MA- group, performance on the ANT was significantly correlated with the left rostral ACC. A relationship was observed between increased accuracy and increased cortical thickness. A

relationship was also observed between decreased reaction times and increased cortical thickness in the left precentral, right caudal middle frontal and right rostral middle frontal as well as the right insula. In the MA+ group, a relationship was observed between increased accuracy and increased cortical thickness in the left precentral, the left frontal pole, the right paracentral, the right rostral middle frontal, and the right frontal pole. These regions suggest DLPFC involvement here. A relationship was also observed between decreased reaction time and increased cortical thickness in the right caudal ACC. In the control group, a relationship was observed between increased accuracy and increased cortical thickness of the left caudal ACC, and the left lateral OFC. However increased accuracy was associated with decreased cortical thickness of the right lateral OFC, the right paracentral, and the right insula cortex. These results are consistent with literature suggesting an association between working memory and the DLPFC (Bechara et al., 2000), i.e.the middle frontal gyrus, as well as an association with the ACC (Lenartowicz & McIntosh, 2005).

The SWM task reflects a slightly different finding in that a relationship was observed between poor performance in the MA+ group and increased cortical thickness. The reasons for this finding are not entirely clear. These associations were found for the left lateral OFC, as well as the right caudal ACC and the right pars opercularis. The pars opercularis forms part of the inferior frontal gyrus which is adjacent to the middle frontal gyrus. In the control group, a relationship between poor performance and increased cortical thickness in the left caudal middle frontal, the left precentral, and the left insula was observed. Therefore more DLPFC involvement was observed in the control group than the MA+ group, which showed more OFC and ACC involvement. Our results are consistent with the results of Cazalis et al. (2011) who investigated traumatic brain injury and found that lower response accuracy on a spatial working memory task was associated with activity of the ACC, but only in their TBI participants and not controls. The authors also observed that performance on this task in the control participants was associated with the left sensorimotor cortex. Our results are similar to their findings.

Verbal fluency revealed statistically significant between-group differences for both phonemic and semantic verbal fluency. Literature suggests an association between the anterior PFC and insula and verbal fluency (Gläscher et al., 2012). While it has been suggested that semantic fluency requires intact executive functions (Lezak et al., 2004; as cited in Neill, Garvich & Rossell, 2013), phonemic fluency is significantly more reliant on executive functions (Spreen & Straus, 2008; as cited in Neill,

Garvich & Rossell, 2013). Our results did not indicate any significant correlations between phonemic fluency and frontal cortical thickness; however, a number of significant correlations were observed between semantic fluency and cortical thickness of frontal regions.

In the MA+ group, a relationship was observed between high scores on semantic fluency and cortical thickening of the left lateral OFC, the left pars triangularis, the right lateral OFC and the right paracentral. In the control group, however, a relationship was observed between high scores on semantic fluency and cortical thinning of the left caudal ACC, the left pars orbitalis, the left rostral ACC, and the left and right frontal poles. These results are consistent with those of Gläscher et al., (2012) who identified an association between verbal fluency and the anterior prefrontal cortex. However, it is not clear why cortical thinning was observed in the control group.

In summary, impairment on executive functioning domains was broadly associated with increased cortical thickness in the MA- group and decreased cortical thickness in the MA+ group in the predicted frontal sub-regions. Impaired decision-making was associated with decreased cortical thickness of the orbitofrontal cortex in the MA+ group, but not in the MA- group. Impaired response inhibition was associated with decreased cortical thickness of the anterior cingulate cortex as well as the dorsolateral prefrontal cortex in the MA+ group, but increased cortical thickness in these regions in the MA- group. This trend was not as clear for working memory impairment. Accuracy on a working memory tasks was associated with the increased thickness of the dorsolateral prefrontal cortex as well as the anterior cingulate cortex in the MA- group; however, slower response times were associated with increased cortical thickness in this group. Impairment on working memory tasks was associated with increased cortical thickness in the MA+ group. Verbal fluency was associated with decreased thickness of the anterior prefrontal cortex in the MA+ group, but not in the MA- group. In general, impaired performance was associated with cortical thinning in the MA+ group. In the MA- group, cortical thickening was associated with impairment. However, it is important to also examine which of these groups shows the most impairment. A pattern emerged, indicating that when the MA+ group is most impaired, cortical thinning occurs. However, in instances where the MA- group was most impaired, cortical thinning also occurred. This indicates that cortical thickening may be a compensatory response in order to preserve function.

CHAPTER TEN: THE CO-MORBIDITY OF ADHD SYMPTOMS IN METHAMPHETAMINE

Attention Deficit Hyperactivity Disorder was assessed using an ADHD self-report Questionnaire developed by Burke and Austin (2010). The outcome measures, as explained in the Methods section, will be analysed below. Descriptive statistics for each outcome measure for each task are presented in *Table 42* and *Figure 59* below One-way ANOVAs were conducted in order to establish between group differences. Spearman's rank order correlational analyses were conducted in order to investigate the relationship between executive domains and ADHD scores.

*Table 42*. ADHD Questionnaire Scores Across the 3 Participant Groups

| | **Group 1: MA+ (*n* = 20)** | | **Group 2: MA- (*n* = 19)** | | **Group 3: NC (*n* = 20)** | |
|---|---|---|---|---|---|---|
| | **Range** | **M (SD)** | **Range** | **M (SD)** | **Range** | **M (SD)** |
| **Childhood Score** | 3 – 132 | 47.65(46.21) | 0 – 115 | 51.21 (35.34) | 4 – 48 | 21.6 (13.32) |
| **Adulthood Score** | 0 – 252 | 70.8 (69.39) | 0 – 124 | 61.53 (32.74) | 6 – 72 | 42.35 (18.58) |
| **Total Score** | 4 – 372 | 118.5 (111.26) | 0 - 239 | 108.53 (62.33) | 11 - 106 | 63.9 (26.13) |

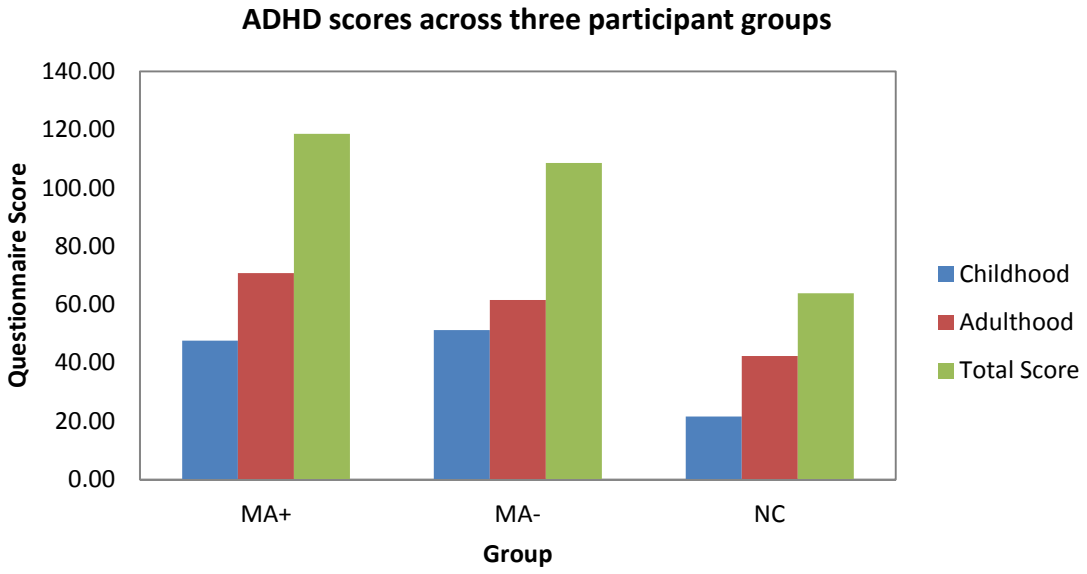


*Figure 59.* ADHD self-report questionnaire scores

The predictions for these outcome measures were that the MA groups would score higher on both the Childhood and Adulthood sections, and therefore score higher on the total score. This would indicate that MA participants show more symptoms of ADHD than controls. This trend can be seen in *Figure 59* above.

Results from the one-way ANOVAs are presented in *Table 43* below. Levene's test was found to be significant, therefore the assumption of homogeneity of variance was violated and an adjusted Welch's *F* is reported here.

*Table 43*. ANOVA Results Summary for ADHD Scores

| | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| **Childhood Score** | | | | | |
| **Between Groups** | 10329.424 | 2 | 5164.712 | 7.911 | .017 |
| **Within Groups** | 66428.508 | 56 | 1186.223 | | |
| **Total** | 76757.932 | 58 | | | |
| **Adulthood Score** | | | | | |
| **Between Groups** | 8409.818 | 2 | 4204.909 | 3.550 | .144 |
| **Within Groups** | 117344.487 | 56 | 2095.437 | | |
| **Total** | 125754.305 | 58 | | | |
| **Total Score** | | | | | |
| **Between Groups** | 33678.599 | 2 | 16839.299 | 5.833 | .060 |
| **Within Groups** | 318103.537 | 56 | 5680.420 | | |
| **Total** | 351782.136 | 58 | | | |

The only score to reveal a statistically significant between-group difference was the Childhood Score Welch's F (2, 56) = 7.911, $p$ = .017. The total score revealed a trend towards significance, Welch's *F* (2, 56) = 5.833, $p$ = .060; however, this result did not reach statistical significance.

The Games-Howell post-hoc calculation of multiple comparisons was used to shed further light on the data. The Childhood Score revealed statistically significant between-group differences between the MA- and control groups, $p$ = .006. A trend towards a significant difference was observed between the MA+ and control groups, $p$ = .060; however this difference did not reach statistical significance. No significant difference was observed between the MA+ and MA- groups, $p$ = .960, indicating that these two groups performed similarly.

No significant between-group differences were observed on the Adulthood Score or the Total Score for the ADHD questionnaire. This indicates that the executive functioning impairment found in our sample cannot be attributed to pre-existing impairment similar in nature to that associated with ADHD.

In order to further investigate this point, Spearman's rank order correlational analyses were conducted between our composite domains scores and the ADHD questionnaire scores. Interestingly, the only domain to show a significant correlation was Decision Making. This was the only domain that did not reveal the results that we expected. None of the other executive domains correlated with scores from the ADHD questionnaire, indicating no relationship between ADHD symptoms and performance on Response Inhibition, Working Memory or Verbal Fluency. The correlation matrix is presented in *Table 44* below.

*Table 44*. Correlation Matrix for the Executive Functioning Domains and the ADHD Scores

| | | | Decision Making | Response Inhibition | Working Memory | Verbal Fluency | Childhood Score | Adulthood Score | Total Score |
|---|---|---|---|---|---|---|---|---|---|
| **Spearman's rho** | Decision Making | Correlation Coefficient | 1.000 | -.042 | -.028 | .071 | -.305* | -.084 | -.197 |
| | | Sig. (2-tailed) | | .754 | .835 | .598 | .019 | .529 | .134 |
| | | N | 59 | 59 | 59 | 58 | 59 | 59 | 59 |
| | Response Inhibition | Correlation Coefficient | -.042 | 1.000 | .721** | .663** | -.225 | -.185 | -.194 |
| | | Sig. (2-tailed) | .754 | | .000 | .000 | .086 | .160 | .140 |
| | | N | 59 | 59 | 59 | 58 | 59 | 59 | 59 |
| | Working Memory | Correlation Coefficient | -.028 | .721** | 1.000 | .662** | -.061 | -.056 | -.020 |
| | | Sig. (2-tailed) | .835 | .000 | | .000 | .648 | .673 | .882 |
| | | N | 59 | 59 | 59 | 58 | 59 | 59 | 59 |
| | Verbal Fluency | Correlation Coefficient | .071 | .663** | .662** | 1.000 | -.186 | -.144 | -.155 |
| | | Sig. (2-tailed) | .598 | .000 | .000 | | .162 | .281 | .246 |
| | | N | 58 | 58 | 58 | 58 | 58 | 58 | 58 |
| | Childhood Score | Correlation Coefficient | -.305* | -.225 | -.061 | -.186 | 1.000 | .792** | .924** |
| | | Sig. (2-tailed) | .019 | .086 | .648 | .162 | | .000 | .000 |
| | | N | 59 | 59 | 59 | 58 | 59 | 59 | 59 |
| | Adulthood Score | Correlation Coefficient | -.084 | -.185 | -.056 | -.144 | .792** | 1.000 | .948** |
| | | Sig. (2-tailed) | .529 | .160 | .673 | .281 | .000 | | .000 |
| | | N | 59 | 59 | 59 | 58 | 59 | 59 | 59 |
| | Total Score | Correlation Coefficient | -.197 | -.194 | -.020 | -.155 | .924** | .948** | 1.000 |
| | | Sig. (2-tailed) | .134 | .140 | .882 | .246 | .000 | .000 | |
| | | N | 59 | 59 | 59 | 58 | 59 | 59 | 59 |

# DISCUSSION

We conducted a correlational analysis in order to investigate the relationship between performance on our executive domains and symptoms of ADHD. Only one significant correlation was observed. Decision-making was significantly correlated with the Childhood ADHD Score. None of the other executive domains revealed significant correlations. It is therefore unlikely that the executive dysfunction observed was due to a pre-existing condition of ADHD, but rather more likely due to the toxic effects of methamphetamine.

An inverse relationship was observed between decision-making and Childhood ADHD score, indicating that impaired decision making was associated with a higher score on Childhood ADHD. This result is consistent with previous research suggesting that poor decision making skills contribute towards the maintenance of substance use disorders (Wilson et al., 2005).

High rates of co-morbidity have been observed between MA Dependence and ADHD (Duarte, Woods, Rooney, Atkinson & Grant, 2011; Jaffe at al., 2005; Obermeit et al., 2013). While the current study did not employ measures to diagnose ADHD clinically, we rather investigated the symptoms associated with ADHD in order to assess the co-morbidity between these symptoms and MA dependence. We also wanted to investigate whether more severe symptoms i.e. higher scores, would be associated with MA+, given the fact that ADHD has been identified as a significant predictor of MA-induced psychosis (Fujii, 2002; Salo et al., 2013).

Our results did not indicate significant between-group differences on the Adulthood Score or the Total Score. Therefore, in our sample, symptoms associated with adult ADHD were not associated with MA. However, the Childhood Score did reveal a statistically significant between-group difference, indicating that childhood ADHD may be associated with later substance use, and in our case, this substance was MA. These results are consistent with research that indicates that childhood ADHD is a risk factor for substance use (Biederman et al., 1998; Matsumoto et al., 2005; Wilens et al., 1997).

# CHAPTER ELEVEN: SUMMARY AND CONCLUSIONS

## INTRODUCTION

The preceding chapters have attempted to address a number of aims and specific research questions that were stated at the outset of this thesis. Although in-depth discussions have been provided for the major findings in these chapters, I now summarise the major findings. This final chapter will firstly attempt to answer the original research questions formulated in the first chapter of this thesis and secondly provide conclusions. Lastly, limitations and suggestions for future research will be discussed.

## ANSWERING THE RESEARCH QUESTIONS

***Research Questions 1 and 2: Are executive functions impaired in MA? And if so which of the four domains shows the most severe impairment? Are these impairments more severe in MA Dependence with a history of psychosis compared to MA Dependence without a history of psychosis?***

Chapters 4 – 8 presented results attempting to address these questions. Previous studies were lacking in a comprehensive battery of tests measuring executive impairment (Scott et al. 2007). Our aim was to include a wide range of tests in order to assess a wide range of executive functions. This aim was achieved through the use of 14 tasks used across 4 different domains of executive functioning. When standardising these test scores and combining them to form one composite score of executive functioning, it was found that executive functions were impaired in MA. All three groups were significantly different from one another, indicating that, in general, the MA+ group showed the most severe impairments on tasks of executive functioning and control participants showed the least.

Moreover, we identified significant impairments in the domains of Response Inhibition and Set-Shifting, Attention and Working Memory, and Verbal Fluency (for a summary of these results refer to

Tables 45 – 47 below). We did not however observe significant impairment in Decision-Making and Impulsivity (for a summary of these results refer to Table 48 below). In our sample, very specific impairments regarding decision making were observed. For example we noted that MA participants were more impulsive than controls. However, both MA groups performed similarly on this domain. Significant impairments were observed on Response Inhibition and Set-Shifting tasks. It was shown that MA+ participants showed greater impairments than the other two participant groups. MA participants were also considerably slower to respond on the majority of tasks compared to NCs. Both MA groups also performed similarly on tasks of Attention and Working Memory and both of these groups performed poorly compared to normal controls. Both MA groups also performed similarly on phonemic fluency, however, on semantic fluency, the MA+ group performed worse than the MA- group. Both groups showed greater impairments on verbal fluency than controls. Hence, it is evident that MA dependence with a history of psychosis presents similarly to MA dependence without a history of psychosis in terms of executive functioning deficits, except with regards to response inhibition and set-shifting where the largest differences between these groups were observed.

*Table 45*. Summary of results for tasks of response inhibition and set-shifting

| | Between-Group Comparisons | | |
|---|---|---|---|
| | **MA+ > MA-** | **MA+ > NC** | **MA- > NC** |
| Affective Go/No Go task | | | |
| Mean correct latency (positive) | -- | ** | ** |
| Mean correct latency (negative) | -- | * | ** |
| Total omissions (positive) | -- | * | -- |
| Total omissions (negative) | * | ** | * |
| Stop signal task | | | |
| Directions errors on stop/go trials | -- | * | -- |
| Proportion of successful stops | -- | -- | -- |
| Median correct RT on go trials | -- | -- | -- |
| SSD (last half) | -- | -- | -- |
| SSRT (last half) | -- | -- | -- |
| Stroop task | | | |
| Total time | * | ** | * |
| Errors | -- | * | -- |
| Self corrected errors | -- | ** | * |
| Wisconsin card sorting task | | | |
| Total correct | -- | -- | -- |
| Total errors | -- | -- | -- |
| Perseverative responses | * | -- | -- |
| Perseverative errors | * | -- | -- |

*Table 46*. Summary of results for tasks of attention and working memory

| | Between-Group Comparisons | | |
|---|---|---|---|
| | **MA+ > MA-** | **MA+ > NC** | **MA- > NC** |
| Task switching | | | |
| Errors | -- | ** | -- |
| Average reaction time | -- | -- | -- |
| Reaction Time | | | |
| Five choice movement time | -- | -- | -- |
| Five choice reaction time | -- | -- | -- |
| Attention network task | | | |
| Accuracy: | | | |
| Neutral trials | -- | * | -- |
| Congruent trials | -- | * | -- |
| Incongruent trials | * | * | -- |
| Reaction time: | | | |
| Neutral trials | -- | * | -- |
| Congruent trials | -- | * | -- |
| Incongruent trials | -- | -- | -- |
| Spatial working memory | | | |
| Between errors | -- | ** | -- |
| Strategy | -- | * | -- |
| Spatial Span | | | |
| Span length | -- | -- | -- |

*Table 47.* Summary of results for tasks of verbal fluency

| | Between-Group Comparisons | | |
|---|---|---|---|
| | **MA+ > MA-** | **MA+ > NC** | **MA- > NC** |
| Phonemic (letter) fluency | | | |
| FAS total | * | ** | -- |
| Semantic (category) fluency | | | |
| Total Score | * | ** | -- |
| Category switching | | | |
| Total correct responses | -- | * | -- |

*Table 48.* Summary of results for tasks of decision-making and impulsivity

| | Between-Group Comparisons | | |
|---|---|---|---|
| | **MA+ > MA-** | **MA+ > NC** | **MA- > NC** |
| Delay Discounting Task | | | |
| Number of discounts | -- | ** | ** |
| Balloon Analogue Risk Taking Task | | | |
| Number of pumps | -- | -- | -- |
| Average number of pumps | -- | -- | -- |
| Maximum number of pumps | -- | -- | -- |
| Total points earned | -- | -- | -- |
| Information Sampling Task | | | |
| Win condition fixed | | | |
| Mean no. of boxes opened/trial | -- | -- | -- |
| Mean P (correct) | -- | -- | -- |
| Total correct | -- | -- | -- |
| Sampling errors | -- | -- | -- |
| Discrimination errors | -- | -- | -- |
| Mean box opening latency | -- | -- | -- |
| Win condition decreasing | | | |
| Mean no. of boxes opened/trial | -- | -- | -- |
| Mean P (correct) | -- | -- | -- |
| Total correct | -- | -- | -- |
| Sampling errors | -- | -- | -- |
| Discrimination errors | -- | * | -- |
| Mean box opening latency | -- | -- | -- |
| Cambridge Gambling Task | | | |
| Delay aversion | -- | -- | -- |
| Deliberation time | -- | -- | -- |
| Overall proportion bet | -- | -- | -- |
| Quality of decision making | -- | -- | -- |
| Risk adjustment | -- | * | -- |
| Risk taking | -- | -- | -- |

***Research Question 3: Were symptoms of ADHD found to be co-morbid in our MA groups and if so, was there a correlation between these symptoms and EFs?***

Chapter 10 dealt with this research question. Significant differences between our groups were only observed on childhood measures of ADHD rather than adulthood measures of ADHD. The MA groups performed similarly, but both groups were significantly different from controls. Therefore, both groups scored higher on symptoms of childhood ADHD than controls. The measure of adulthood symptoms of ADHD were also different across groups, however, this difference did not reach statistical significance. This indicates that the co-morbidity of symptoms of ADHD is more likely in

MA dependent populations. This then begs the question of whether the co-morbidity of ADHD symptoms in this population can account for the executive impairments observed. We ran correlational analyses to determine whether there was in fact a relationship between these two constructs. A relationship was observed between decision making and childhood symptoms of ADHD. The executive domain where we noted the least significant results was the only domain found to be associated with the childhood symptoms measured by the ADHD questionnaire. None of our other domains were found to relate to symptoms of ADHD. The executive dysfunction observed in methamphetamine dependence is therefore more likely a result of MA toxicity, rather than premorbid ADHD.

***Research Question 4: Is there a correlation between executive impairment and cortical thickness changes in our MA sample?***

Chapter 9 attempted to answer this research question. A relationship was observed between executive impairment and cortical thickness of frontal brain regions. Generally, these relationships were found in the expected regions. Decision-making was largely associated with cortical thickness of the OFC. Response inhibition was largely associated with cortical thickness of the ACC and the DLPFC. Working Memory was largely associated with cortical thickness of the DLPFC as well as the ACC. Verbal Fluency was largely correlated to the OFC and the ACC. We expected to find much overlap in our results given the overlap between these executive domains. This is exactly what we found.

# CONCLUSION

In concluding this thesis it is noted firstly that executive functions are impaired in methamphetamine dependence and particularly in methamphetamine psychosis. While response inhibition appears to be the most affected executive function in methamphetamine, working memory and verbal fluency impairments also exist. The domain that was least affected in our sample was decision-making. This may be due to the nature of the tests used; which may not be sensitive enough to measure such impairment in this population. Nonetheless, executive functions are significantly impaired in methamphetamine dependence, particularly methamphetamine psychosis. This not only has an impact on the course of the illness, but also on functional outcomes (Donaghue & Doody, 2012). "Cognitive impairment has been associated with poorer treatment outcomes in a range of studies" (Aharonovich et al., 2003; as cited in Scott et al., 2007, p. 287). Secondly, while childhood symptoms of ADHD were found particularly in our methamphetamine psychosis group, these scores did not appear to impact on executive functions in our sample, indicating that the executive dysfunction observed in our sample is likely due to the effects of MA toxicity. Thirdly, in general, increased cortical thickness was associated with impairment in our methamphetamine dependent group and decreased cortical thickness was associated with impairment in our methamphetamine psychosis group. Cortical thickening may be a compensatory response in order to maintain function in our sample. Executive functions were found to be correlated with regions of the frontal cortex.

# LIMITATIONS AND DIRECTIONS FOR FUTURE RESEARCH

The current study contains a number of limitations that should be addressed in future studies. Firstly, the relatively small sample size makes the generalisability of results challenging. Larger sample sizes are suggested for future studies. Small sample sizes may be attributed to the challenge of recruitment of MA dependent participants. This was due to various factors; namely, it is a time consuming process; the response rate is low; and the drop-out rate is high. In addition, the sample consisted of relatively pure MA users; such individuals are difficult to find, given that most drug users are poly-drug users. Secondly, our tasks of decision-making may have proved to be less sensitive to the construct being measured in this population. Future studies should explore alternative options when testing decision-making. For example, tasks where real rewards are offered may be more appealing to participants. In addition, gambling tasks where the participant believes they are playing against an opponent may result in more meaningful engagement in the task. Third, the wide range of abstinence among the sample may produce large amounts of variability in the data. Future studies should minimise the range of abstinence in order to reduce such variability. Fourth, differences between groups on level of education and IQ may impact on neuropsychological test results. Future studies should aim for equal levels of education and IQ scores across groups, as far as possible. Fifth, the focus of this thesis was executive functioning; therefore future studies should aim to assess other neuropsychological domains such as memory or language, but should do so comprehensively in order to gain a clearer understanding of neuropsychological functioning as a whole in methamphetamine.

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# APPENDICES

## APPENDIX A: PARTICIPANT SCREENING QUESTIONAIRE

**DATE: _____**

Personal Details:

Full Name: _____

Date of Birth: _____
Gender:_____

Contact Details:

Address:_____

_____
_____

Tel. number (home): _____

(mobile): _____

Email Address: _____

**Medical Details:** *Please circle*

1. Are you right-handed? Yes / No

2. Do you take any kind of medication on a regular basis? Yes / No
If yes, please specify what kind
_____

3. Have you ever had a head injury? Yes / No
If yes, describe most severe:
_____

4. Were you knocked unconscious? Yes / No
If yes, how long?
_____

5. Any surgery/hospitalisation as a result of your head injury? Yes / No
If yes, please specify:

_____

6. Have you ever had seizures or an epileptic fit? Yes / No

7. Has anyone in your immediate family (siblings, parents) ever been diagnosed with epilepsy? Yes / No
   If yes, please specify who:

_____

8. Have you ever been diagnosed with a psychiatric illness? Yes / No
   If yes, please specify:

_____

9. Have you ever had any neurological condition? Yes / No
   If yes, please specify:

_____

10. Do you have a metal object in your body (eg. aneurysm clip)? Yes / No
    If yes, please specify:

_____

11. Do you wear a metal prosthesis (eg. artificial leg)? Yes / No
    If yes, please specify:

_____

12. Do you have a pace-maker? Yes / No

13. Have you ever been diagnosed with asthma? Yes / No

14. Have you ever been diagnosed with chronic bronchitis, emphysema, or any other respiratory problems? Yes / No

15. Have you ever been diagnosed with a hepatic (liver) problem/ disorder? Yes / No

16. Have you ever been diagnosed with a renal (kidney) problem/ disorder? Yes / No

17. Have you ever been diagnosed with an endocrine (hormonal) problem/disorder? Yes / No

18. Have you ever had a seropositive test for HIV? Yes / No

29. If you are female, are you currently pregnant? Yes / No

Other notes:

_____

APPENDIX B: PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT:

Neural correlates of deficits in affect regulation in methamphetamine abusers with a history of psychosis

**REFERENCE NUMBER**: 340/2009

**PRINCIPAL INVESTIGATOR**: Dr Donald Wilson

**ADDRESS**: University of Cape Town, Dept of Psychiatry and Mental Health, Groote Schuur Hospital (J2), Anzio Road, Observatory 7925, Cape Town, South Africa

**CONTACT**: E-mail:d.wilson@uct.ac.za, Phone: +27-21-404-2182, Fax: +27-21-448-8158

Dear Volunteer

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is *entirely voluntary* and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the Faculty of Health Sciences Human Research Ethics Committee (FHS HREC) of the University of Cape Town, and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

This project is being run at the Department of Psychiatry, University of Cape Town. We aim to recruit a total of 60 participants over a period of 3 years.

What is this research study all about?

*Background:* The increasing use of methamphetamine (MA, also “tik” or “meth”) is a cause for concern for a number of reasons. On the personal level the chronic use of MA has been associated with brain damages resulting in potentially long-lasting mental health effects including confusion, impaired concentration and memory. Imaging studies have shown that MA use is associated with imbalances in the neurochemistry of the brain. Thus long-term abuse of “tik” or “meth” is associated with the development of paranoid, often violent psychotic states accompanied by auditory, visual and/or tactile hallucinations. MA abuse also has profound consequences on an interpersonal level, due to associated impairments in emotion regulation. For instance, aggression and hostility have been consistently identified in chronic users of MA and such emotional disturbances have been associated with abnormalities in functional and structural neuroanatomy.

*Methods:* Participants will have to complete questionnaires and a series of behavioural and cognitive tasks. Some of these will be used to determine whether MA abuse and MA-induced psychosis is associated with defects in social awareness and regulation of emotions. In addition, brain imaging techniques will be used to determine the effect of MA abuse, with and without a history of psychosis, on brain structure and function. Specifically, structural magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) will be employed to investigate how brain structure and metabolism change in MA abusers in comparison to healthy controls. DNA analyses of blood samples will be conducted to examine whether specific genes account for structural and functional brain abnormalities after methamphetamine abuse and for increased vulnerability to psychosis.

In addition, associations between "tik" abuse and the disability of controlling emotions will be assessed. Participants will therefore perform a simple task (Affective Labelling task) measuring emotional processing as part of the functional MRI scan. This task will be used to assess differences in brain activation corresponding to impairments in regulating behaviour.

Procedures

If you agree to take part in the study and if you meet all of the conditions required for entering the study (assessed in a screening interview), you will complete the following 3 phases and procedures:

At your first visit the study will be explained and written consent to take part will be obtained. Your study investigator will ask you some questions about your psychiatric and neurological history and you will have to fill out several questionnaires. If you are eligible and agree to participate in the study you will be asked to attend the second testing session at the Cape Universities Brain Imaging Centre (www.sun.ac.za/cubic).

During the second testing day, you will be asked to complete behavioural tasks. Following completion of these tasks the brain scanning session, Magnetic Resonance Imaging (MRI) and Spectroscopy (MRS), will take place.

During the third visit you will undergo neuropsychological testing including tasks about your memory, attention and risk taking behaviour.

It is estimated that none of the testing sessions should take more than 3-4 hours to complete.

The psychiatric interview will take place either at Valkenberg Hospital or in the Psychiatric department at Groote Schuur Hospital. Brain imaging will be conducted using a 3T Siemens Magnetom Allegra at CUBIC, Stellenbosch. Each scanning session will last approximately one hour. Structural and functional imaging data will be acquired. Stimuli for each cognitive-affective protocol will be computerized and displayed to you in the scanner via a screen display. The neuropsychological assessment, which will be computer based tests, will take place in the Psychiatric Department of Groote Schuur Hospital.

Urine screens will be performed on both days of testing to verify methamphetamine abstinence and to determine the degree of cannabis use, as well as for a pregnancy test (if you are female). You will have to pee in a cup for those tests. The results of those tests are not for legal medicine or police purpose, and will only be used for our study.

Blood samples will be collected for routine laboratory testing and for possible future gene and protein expression studies. Approximately 35ml (7 teaspoons) of blood will be drawn from your arm. We may need to contact you again to get another blood sample should we fail to get a DNA sample

from your blood. Candidate polymorphisms identified to be associated with drug dependency or psychosis and possibly playing a role in explaining variance in the MRI results will be investigated later on. This process will take place at the Division of Human Genetics at the University of Cape Town.

Magnetic Resonance Imaging

With an MRI you can obtain very detailed images of organs and tissues throughout the body, even of the brain, as in our study. MRS provides a tool to investigate metabolites in the living brain. Both MRI and MRS testing cause no pain and the magnetic fields produce no known tissue damage of any kind.

The MRI and MRS examination are performed in a special room that houses the MR system or "scanner". You will be escorted into the room by a staff member of the MRI facility and asked to lie down on a comfortably padded table that gently glides you into the scanner. This is typically a large, tunnel magnet that is open at both ends, so you won't be completely enclosed at any time.

As the scan is done in a relatively confined space, occasionally people feel closed-in or frightened. This does not happen often, and if you feel anxious, we will spend time allowing you to get used to the surroundings. Another side-effect might be a tingling feeling in your teeth if you have metal fillings.

The most important thing for you to do is to *relax and lie perfectly still* during the time the imaging takes place. For the functional imaging you will be asked to perform some simple tasks of emotional processing and attention, which will enable the investigators to determine your brain function. During the structural and diffusion tensor imaging you will be able to close your eyes and rest. Given that the testing session will take one hour to complete, you might get sleepy or uncomfortable after a while, but you are asked to stay awake and not to move throughout the scanning.

A radiologist will operate the scanner from behind a window, and will be able to see and hear you during the scan. You will be able to communicate with the radiologist or the study assistant at any time using an intercom system. You will also be given an alarm call button to hold during the scan, which you can press to get attention.

The MR scanner may produce loud tapping or knocking noises at times during the testing, which is normal and should not worry you. Especially when the magnet in the machine is switched on, it will make some loud banging noises, but you will be clearly warned when this will take place. You will feel nothing and the noise is not harmful to you in any way. To minimise the possible discomfort associated with this, we will give you some soft earplugs to put in.

MRI and MRS scans are commonly performed and a safe procedure if you have been screened correctly for the presence of any magnetic material on or inside you such as pace-makers, surgical clips and metal objects in the eyes. A formal screen for this will be done at the screening visit by a member of the study team.

Why have you been invited to participate?

Three groups of participants will be included in this study: methamphetamine (MA) abusers with a history of psychosis, MA abusers without a history of psychosis and non-substance-abusing healthy control subjects. Each of the groups will consist of 20 participants. You may fit into one of these categories as assessed during your initial screening.

What will your responsibilities be?

The study investigator will be required to ask you about medications that you may be taking currently or that you may have taken recently. Your study investigator will explain to you which medications need to be stopped during the entire length of the study and how soon before you take part in the study these medications must be stopped.

Your doctor will also advise you on which prescription or over-the-counter medications or any other remedies or foods that you will be required to either stop or restrict your consumption of during the entire length of the study. This will include a restriction on the amount of alcohol that can be consumed.

At each visit you may be asked to complete questionnaires or tasks to check the status of your symptoms. These will measure your mood, emotional responses, trust, sociability and emotional resilience.

*Please ensure that you are punctual at all times, as we are using specialized equipment during each of the sessions, for which costs are incurred. If for some reason you are unable to complete a visit on a particular day we may reschedule to complete the assessments at another time.*

Will you benefit from taking part in this research?

There are no direct benefits to you for participating in this study. However, you will be making an important contribution to this research that may benefit others in the future. We expect that the results of this study will help us understand the effects of methamphetamine on brain structure and function and how their abuse can lead to the development of psychosis.

Are there any risks involved in your taking part in this research?

There are no major risks involved in participation in this study. There will be several questionnaires, including some about past traumatic events that ask for information of a very personal and sensitive nature. This may cause some emotional discomfort.

Who will have access to your medical records?

Maintaining your confidentiality is important. Your personal information (for example your gender, age, the details of your medical conditions) and other information (the data collected by the investigators as part of the study) will be identified by a number (i.e. coded). Your name will not appear in any publications or reports produced from this study. The investigators will keep the information and the results collected about you in this study. This information about you will be kept in a secure place.

By agreeing to take part in this study, you will be allowing certain persons to see the information about you (both personal, including your name, and other information) held by the study doctor. You have the right to withdraw your consent to participate in this study at any time.

If you withdraw your consent to participate in this study no new information will be collected from you and added to existing data or to a database. Your information will be processed electronically (i.e. by a computer) or manually and analysed to determine the outcome of this study. Your information may/could be sent to regulatory authorities and to the Ethics Committees. You have the right to ask the study doctor about the data being collected on you for the study and about the

purpose of this data. You have the right to ask the study doctor to allow you to see your personal information and to have any necessary corrections made to it.

What will happen in the unlikely event of some form of injury occurring as a direct result of your taking part in this research study?

If you become ill or injured as a direct result of your participation in this clinical study, you will be referred for appropriate medical treatment. The University of Cape Town's insurance policy will cover the costs of such treatment. If you have any questions concerning the availability of compensation/medical care or if you think you have experienced a research-related illness or injury, contact details are below. Your legal right to claim compensation for injury where you can prove negligence is not affected.

If you have any questions about your rights as a research subject, you should contact the Faculty of Health Sciences Human Research Ethics Committee (FHS HREC), Tel: (021)4066492, Fax: (021)4066411.

If you have questions about this study you should first discuss them with your study doctor or the Faculty of Health Sciences Human Research Ethics Committee (FHS HREC), UCT.

Dr D. Wilson: (021)4042182

Dr H. Temmingh: (021)4403185

After you have consulted your doctor or the FHS HREC and if they have not provided you with answers to your satisfaction, you should write to the South African Medical Research Council at: Head Office Cape Town, Corporate Communications Office, Sarah Bok, PO Box 19070, Tygerberg, 7505, South Africa or Fax: (021)9380200.

Will you be paid to take part in this study and are there any costs involved?

All evaluations will be provided, hence there will be no costs involved for you or your medical aid, if you do take part in the study. You will be compensated for taking part in the study as your transport and meal costs will be covered with supermarket vouchers to exchange for food, amounting to R150.

Is there anything else that you should know or do?

You can contact the Committee for Human Research at (021)4066492 if you have any concerns or complaints that have not been adequately addressed by your study doctor.

You will receive a copy of this information and consent form for your own records.

Informed Consent Form for Study Participants

Title of the Research Project: *"Neural correlates of deficits in affect regulation in methamphetamine abusers with a history of psychosis."*

Declaration by participant

By signing below, I …….. agree to be interviewed and asked personal information as part of the above named study and that the information I give will be correct. Furthermore, I declare that:

I have read, or had read to me, the "Participant Information Leaflet and Consent Form" and it is written in a language with which I am fluent and comfortable.

I have had a chance to ask questions and all my questions have been adequately answered.

I understand that taking part in this study is voluntary and I have not been pressurised to take part.

I may choose to leave the study at any time and will not be penalised or prejudiced in any way.

I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) ..... on (*date*) …….. 20 .

Signature of participant

By signing below, I …….. agree to have my blood taken for the proposed genetic tests as described in the "Participant Information Leaflet and Consent Form".

Signed at (*place*) ..... on (*date*) …….. 20 .

Signature of participant

By signing below, I …….. agree to undergo brain scans (MRI/MRS) as described in the "Participant Information Leaflet and Consent Form".

Signed at (*place*) ..... on (*date*) …….. 20 .

Signature of participant

By signing below, I …….. agree to Neuropsychological testing as described in the "Participant Information Leaflet and Consent Form".

Signed at (*place*) ..... on (*date*) …….. 20 .

Signature of participant

Declaration by investigator

I *(name)* …… declare that:

I explained the information in this document to ……..

I encouraged him/her to ask questions and took adequate time to answer them.

I am satisfied that he/she adequately understands all aspects of the research, as discussed above.

Signed at (*place*) ..... on (*date*) …….. 20 .

Signature of investigator

APPENDIX C: SOCIO-DEMOGRAHIC QUESTIONNAIRE

**Study ID:** ----------

Rater:

Date of interview:

Subject's Address:

Telephone numbers: _____&_____

_____&_____

Collateral sources of information:

| Relationship with subject | Name | Contact numbers |
|---|---|---|
| | | |
| | | |

Subject's home language/ Mother tongue:

i) English ii) Afrikaans iii) Xhosa iv) Other

Language(s) that subject can communicate in fluently:

i) English ii) Afrikaans iii) Xhosa iv) Other

Section A: Demographic data

1. Gender : Male ..... Female .....

2. Age : .....

3. Race : i. Black
ii. White
iii. Coloured
iv. Asian other (specify).....

4. Religion.....

Would you describe yourself as a religious person? Yes..... No.....

5. Marital status: i. Single
ii. Married
iii. Co-habiting
iv. Widowed
v. Divorced
vi. Separated

6. Do you have children? Yes ..... No .....

If Yes, how many? .....

7. Who lives with you at home? (e.g Friend, Step-father, mother,etc).....

8. What is your highest level of education (highest grade completed)? .....

11. Employment status: i. Employed
ii. Unemployed
iii. Student

If employed, what kind of job do you do? .....

12. Monthly income .....

Section B: 'TiK' abuse history

13. What was your first drug of abuse? .....

Name the first 2 drugs in order of usage (i.....

(ii.....

14.a. How old were you when you first used Tik? .....

14.b. How old were you when you first used drug? .....

15.a. How long have you been using 'Tik' ? .....

15.b. When last did you use Tik? .....

16. How much do you spend on 'Tik' on a weekly basis? .....

17. What quantity of 'Tik' do you use on a weekly basis? .....

18. Have you had any previous treatment for 'Tik' abuse? Yes..... No.....

If Yes, which type: i. In-patient Rehab

ii. Out-patient Rehab

iii. Both in-patient and out-patient Rehab

19. How many attempts at rehabilitation have you had in the past? .....

20. What was your longest period of abstinence from 'Tik' as a consequence of treatment? .....

21. What was your longest period of voluntary abstinence from 'Tik', not as a consequence of treatment? .....

22. Why do (did) you use methamphetamine (tik) .....

_____

Section C: (Family and Personal history of Psychiatry illness)

23. Have you ever been diagnosed to have a psychiatric illness in the past? Yes.....

No.....

If Yes, when was the first time you had a psychiatric illness? (specify month and year)

.....

24. Has anyone in your family had a psychiatric illness not related to drug abuse?

Yes..... No.....

If Yes, who? (e.g. Father, Brother, Aunt, Cousin, etc) .....

Section D: General pattern of drug abuse

| Name of drug | Age started using | Date last used | Pattern of use in last 12 months | Average spend a month(R) | Period of heavy use | Quantity used per week |
|---|---|---|---|---|---|---|
| nicotine | | | | | | |
| meth(tik) | | | | | | |
| cannabis | | | | | | |
| alcohol | | | | | | |
| mandrax | | | | | | |
| opiods | | | | | | |
| cocaine | | | | | | |
| ecstasy | | | | | | |
| others | | | | | | |

Section E: Living condition

1. Do you have the following amenities at home?

| | | | |
|---|---|---|---|
| i. | Tap with running water | Yes | No |
| ii. | Electricity | Yes | No |
| iii. | Stove | Yes | No |
| iv. | Flush toilet in house | Yes | No |
| v. | TV | Yes | No |
| vi. | Fridge | Yes | No |
| vii. | Adequate clothing for child | Yes | No |
| viii. | Enough food to eat (at least 2 meals/day) | Yes | No |
| ix. | 2 people or less in bedroom. | Yes | No |
| x. | Do you read at least 1 newspaper/ magazine per week | Yes | No |

2. Type of dwelling: shack/ house/ flat / boarding house/ roofless/ refugee centre/ Skilled nursing facility.

3. Size of the dwelling where applicable (no. of bedrooms) ____

4. How many people live in the dwelling ? ___

5. Are your parents married / separated / divorced?

6. Do you share or do you have your own bedroom?_____

7. How often do you see your extended family? _____

8. Nationality: _____Age immigrated to SA (if applicable)

9. Parents' nationality_____

Section F: Treatment history of psychiatric disorder:

i. When was the first time you saw someone (like a social worker/psychologist/psychiatrist/counsellor) for emotional/psychiatric problems? _____

ii. What life changing event was associated with that 1st presentation (like divorce/death/new school/job loss)? _____

iii. Were you admitted or seen as an out- patient? And what diagnosis was given? _____

iv. Were you placed on medications? (If Yes, name them)
_____

Definite Diagnosis SCID-I summarized

Axis I:

Principle:

_____
_____
_____

Additional diagnosis

_____
_____
_____

Co morbid Diagnoses:

_____
_____
_____

Axis (GAF score) _____

APPENDIX D: BRIEF CHILDHOOD AND ADULTHOOD SCREENING QUESTIONNAIRE FOR ADHD

Biographical Information

Name (optional): _____

Age (in years & months): _____

Gender:

| | |
|---|---|
| Female | 1 |
| Male | 2 |

Highest Educational Level:

| | |
|---|---|
| Grade 7 or lower | 1 |
| Grade 8 - Grade 11 | 2 |
| Grade 12 | 3 |
| Post-matric certificate | 4 |
| Post-matric diploma | 5 |
| B-degree | 6 |
| Honours degree | 7 |
| Masters degree | 8 |
| Doctorate degree | 9 |
| Post-doctorate degree | 10 |

Has anybody in your childhood years mentioned that you may be suffering from ADHD?

| | |
|---|---|
| No | 0 |
| Yes | 1 |

Were you diagnosed with ADHD as a child by a Mental Health Professional (e.g. doctor, psychiatrist, psychologist, etc.)

| | |
|---|---|
| No | 0 |
| Yes | 1 |

Have you been diagnosed with ADHD as an adult by a Mental Health Professional (e.g. doctor, psychiatrist, psychologist, etc.)

| | |
|---|---|
| No | 0 |
| Yes | 1 |

INSTRUCTIONS

In the following part of the questionnaire you will find a list of thoughts, feelings and behaviours. For each item you must indicate whether or not you display or experience this thought, feeling or behaviour AND how often you display or experience it.

SECTION A: CHILDHOOD

Think back to your childhood years (5 – 17 years) and see if you can identify any of the following:

| Item | Occurrence | | | Frequency | | | |
|---|---|---|---|---|---|---|---|
| | Yes | No | Almost Never | Now and again | At least once a week | At least once a day | More than once per day |
| Failed to give close attention to details to schoolwork, work, or other activities | | | | | | | |
| Made careless mistakes in schoolwork | | | | | | | |
| Difficulty sustaining attention in tasks | | | | | | | |
| Adults and friends often complained that you did not seem to listen when spoken to directly | | | | | | | |
| In trouble for not finishing schoolwork, homework, chores or duties | | | | | | | |
| Compared to other children your schoolwork and other activities were disorganized | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| You avoided, disliked, or were reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework) | | | | | | | |
| Lost things that were necessary for tasks or activities (eg, toys, school assignments, pencils, books, or tools) | | | | | | | |
| Easily distracted by sounds | | | | | | | |
| Easily distracted by movements | | | | | | | |
| Forgetful in daily activities (e.g. forgot about homework assignments, or forgot to pack for your extra-mural activities) | | | | | | | |
| Fidgeted with hands or feet | | | | | | | |
| Had difficulty sitting still | | | | | | | |
| Left your seat in classroom or in other situations in which remaining seated was expected | | | | | | | |
| Compared to other children you ran around or climbed up things more than they did | | | | | | | |
| Others complained that you were noisy | | | | | | | |
| Compared to other children you were often more on the move than they were | | | | | | | |
| You had more energy than the other children around you | | | | | | | |
| Adults and friends complained that you talk too much | | | | | | | |
| Blurted out answers before questions had been completed | | | | | | | |
| Difficulty awaiting your turn | | | | | | | |
| Interrupted or intruded on others (e.g., butts into conversations or games) | | | | | | | |
| You had difficulty reading | | | | | | | |
| You disliked reading | | | | | | | |
| Your handwriting was not neat | | | | | | | |
| You disliked writing | | | | | | | |
| Mixed “b’s” and “d’s” or “6’s” and “9’s” | | | | | | | |
| You had difficulty with mathematics | | | | | | | |
| You disliked mathematics | | | | | | | |
| Had difficulty with “learning” subjects (e.g. History) | | | | | | | |
| Disliked “learning” subjects | | | | | | | |
| Told by teachers and parents that | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| you were lazy | | | | | | | |
| Told by teachers, parents and other adults that you were naughty | | | | | | | |
| You felt that you were not as clever as the other children | | | | | | | |
| Most other children disliked you | | | | | | | |
| You had the sense that most adults did not like you | | | | | | | |
| You were teased or got into trouble because you were clumsy | | | | | | | |

SECTION B: ADULTHOOD

In terms of your thoughts, which, and how often of the following do you experience?

| **Item** | **Occurrence** | | | **Frequency** | | | |
|---|---|---|---|---|---|---|---|
| | Yes | No | Almost Never | Now and again | At least once a week | At least once a day | More than once per day |
| Have difficulty falling asleep because my thoughts keep me awake | | | | | | | |
| I seem to be always thinking | | | | | | | |
| While listening to others my mind wanders | | | | | | | |
| While talking to others, I lose track of what I was going to say | | | | | | | |
| I have to consciously stop myself from blurting out my thoughts | | | | | | | |
| I have difficulty maintaining focus | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| I have difficulty relaxing because I'm constantly thinking | | | | | | | |
| I have difficulty organising my thoughts | | | | | | | |
| I replay situations in my mind | | | | | | | |
| I worry about becoming bored | | | | | | | |
| I have difficulty planning a task because my thoughts constantly wander | | | | | | | |
| Unrelated thoughts seems to pop into my head | | | | | | | |
| I am distracted by movement | | | | | | | |
| I am distracted by sounds | | | | | | | |
| Many possible outcomes to future scenarios run through my mind | | | | | | | |
| Once the challenge of a new task is over, I lose interest quickly | | | | | | | |
| Before I begin a complicated job/task, I fail to make careful plans | | | | | | | |
| Avoid, dislike, or am reluctant to engage in tasks that requires sustained mental effort | | | | | | | |
| Fail to give close attention to details | | | | | | | |
| Make careless mistakes in my work | | | | | | | |
| Have difficulty keeping your attention when you are doing boring or repetitive work | | | | | | | |

In my interactions with others:

| **Item** | **Occurrence** | | | **Frequency** | | | |
|---|---|---|---|---|---|---|---|
| | Yes | No | Almost Never | Now and again | At least once a week | At least once a day | More than once per day |
| Feel compelled to interrupt others during conversations | | | | | | | |
| Talk excessively | | | | | | | |
| Finish other people's sentences | | | | | | | |
| Have difficulty waiting my turn | | | | | | | |
| Difficulty concentrating on what people say to you, even when | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| they are speaking to you directly | | | | | | | |
| Prefer friends who are exciting and unpredictable | | | | | | | |
| Prefer a partner who is exciting and unpredictable | | | | | | | |
| Get bored with friends easily | | | | | | | |
| Constantly making new friends | | | | | | | |
| Get bored in intimate relationships | | | | | | | |
| My partner(s) often accuse me of a lack of commitment in our relationship | | | | | | | |
| I enjoy the thrill of a new intimate relationship, but lose interest when the thrill is gone | | | | | | | |
| People describe me as unreliable in my relationships | | | | | | | |

In terms of your behaviour, which, and how often of the following do you experience?

| **Item** | **Occurrence** | | | **Frequency** | | | |
|---|---|---|---|---|---|---|---|
| | Yes | No | Almost Never | Now and again | At least once a week | At least once a day | More than once per day |
| Fidget or squirm with your hands or feet when you have to sit down for a long time | | | | | | | |
| New and exciting experiences and sensations even if they are a little frightening | | | | | | | |
| Doing things just for the thrill of it | | | | | | | |
| Do things that others may describe as frightening | | | | | | | |
| Enjoy new and unpredictable situations | | | | | | | |
| Others describe me as being an impulsive person | | | | | | | |
| Begin a new job/task without much advance planning on how I will do it | | | | | | | |
| Do things on impulse | | | | | | | |
| Get so carried away by new and exciting things and ideas that I never think of possible | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| complication | | | | | | | |
| Tendency to change interests frequently | | | | | | | |
| Difficulty staying within the speed limit when I'm driving | | | | | | | |
| Others say that I take unnecessary risks when driving | | | | | | | |

In terms of your feelings, which, and how often of the following do you experience?

| **Item** | **Occurrence** | | | **Frequency** | | | |
|---|---|---|---|---|---|---|---|
| | Yes | No | Almost Never | Now and again | At least once a week | At least once a day | More than once per day |
| Lose temper | | | | | | | |
| Am touchy or easily annoyed by the others | | | | | | | |
| Am angry or resentful | | | | | | | |
| Get frustrated in traffic | | | | | | | |
| Get irritated when things are not done quickly enough to my liking | | | | | | | |

APPENDIX E: TESTS OF NORMALITY

**Tests of Normality: Shapiro-Wilk**

| Task | Outcome Measure | Group | Statistic | Sig. |
|---|---|---|---|---|
| DDT | NoDiscounts | MA+ | .896 | .069 |
| | | MA- | .922 | .407 |
| | | NC | .886 | .152 |
| BART | Pumps | MA+ | .866 | .024 |
| | | MA- | .841 | .060 |
| | | NC | .938 | .527 |
| | Avpumps | MA+ | .866 | .024 |
| | | MA- | .841 | .060 |
| | | NC | .938 | .527 |
| | Maxpumps | MA+ | .743 | .001 |
| | | MA- | .893 | .212 |
| | | NC | .895 | .195 |
| | Points | MA+ | .935 | .289 |
| | | MA- | .856 | .087 |
| | | NC | .926 | .406 |
| IST | Meanofboxesopenedpertrial | MA+ | .897 | .073 |
| | | MA- | .923 | .415 |
| | | NC | .911 | .285 |
| | MeanPcorrect | MA+ | .957 | .600 |
| | | MA- | .933 | .512 |
| | | NC | .938 | .533 |
| | TotalCorrect | MA+ | .853 | .015 |
| | | MA- | .863 | .102 |
| | | NC | .919 | .350 |
| | SamplingErrors | MA+ | .751 | .001 |
| | | MA- | .838 | .055 |
| | | NC | .819 | .025 |
| | DiscriminationErrors | MA+ | .749 | .001 |
| | | MA- | .844 | .065 |
| | | NC | .895 | .191 |
| | Meanboxopeninglatency | MA+ | .740 | .000 |
| | | MA- | .934 | .521 |
| | | NC | .963 | .818 |
| | Meanofboxesopenedpertrial | MA+ | .932 | .261 |
| | | MA- | .776 | .011 |
| | | NC | .964 | .834 |
| | MeanPcorrect | MA+ | .929 | .233 |
| | | MA- | .799 | .020 |
| | | NC | .863 | .083 |

| | | | | |
|---|---|---|---|---|
| | Totalcorrect | MA+ | .930 | .244 |
| | | MA- | .922 | .407 |
| | | NC | .920 | .359 |
| | SamplingErrors | MA+ | .930 | .241 |
| | | MA- | .844 | .065 |
| | | NC | .872 | .105 |
| | DiscriminationErrors | MA+ | .879 | .038 |
| | | MA- | .889 | .194 |
| | | NC | .802 | .015 |
| | Meanboxopeninglatency | MA+ | .703 | .000 |
| | | MA- | .943 | .611 |
| | | NC | .928 | .425 |
| CGT | DelayAversion | MA+ | .891 | .057 |
| | | MA- | .945 | .633 |
| | | NC | .971 | .903 |
| | DeliberationTime | MA+ | .894 | .065 |
| | | MA- | .924 | .426 |
| | | NC | .529 | .000 |
| | Overallproportionbet | MA+ | .943 | .387 |
| | | MA- | .962 | .820 |
| | | NC | .889 | .164 |
| | QualityofDecisionMaking | MA+ | .817 | .005 |
| | | MA- | .917 | .370 |
| | | NC | .928 | .432 |
| | RiskAdjustment | MA+ | .963 | .721 |
| | | MA- | .964 | .840 |
| | | NC | .896 | .196 |
| | RiskTaking | MA+ | .969 | .824 |
| | | MA- | .952 | .714 |
| | | NC | .928 | .432 |
| AGN | Meancorrectlatencypos | MA+ | .940 | .347 |
| | | MA- | .808 | .025 |
| | | NC | .937 | .519 |
| | Meancorrectlatencyneg | MA+ | .948 | .465 |
| | | MA- | .967 | .871 |
| | | NC | .967 | .861 |
| | TotalOmissionpos | MA+ | .892 | .061 |
| | | MA- | .926 | .447 |
| | | NC | .778 | .008 |
| | TotalOmissionsneg | MA+ | .919 | .165 |
| | | MA- | .964 | .840 |
| | | NC | .597 | .000 |
| SST | DirectionErrorsonstopandgotrials | MA+ | .815 | .004 |
| | | MA- | .883 | .169 |
| | | NC | .841 | .045 |
| | Proportionofsuccessfulstopslasthalf | MA+ | .968 | .813 |

| | | | | |
|---|---|---|---|---|
| | | MA- | .659 | .000 |
| | | NC | .939 | .546 |
| | MedianCorrectRTongotrials | MA+ | .949 | .478 |
| | | MA- | .848 | .071 |
| | | NC | .843 | .048 |
| | SSDlasthalf | MA+ | .913 | .128 |
| | | MA- | .917 | .371 |
| | | NC | .754 | .004 |
| | SSRTlasthalf | MA+ | .886 | .049 |
| | | MA- | .903 | .272 |
| | | NC | .970 | .894 |
| Stroop | Trial1 | MA+ | .900 | .079 |
| | | MA- | .962 | .817 |
| | | NC | .964 | .832 |
| | Errors | MA+ | .747 | .001 |
| | | MA- | .762 | .000 |
| | | NC | .366 | .000 |
| | SCerrors | MA+ | .883 | .043 |
| | | MA- | .713 | .002 |
| | | NC | .366 | .000 |
| | Trial2 | MA+ | .960 | .663 |
| | | MA- | .964 | .841 |
| | | NC | .828 | .032 |
| | Errors | MA+ | .803 | .003 |
| | | MA- | .531 | .000 |
| | | NC | .366 | .000 |
| | SCerrors | MA+ | .883 | .043 |
| | | MA- | .813 | .028 |
| | | NC | .603 | .000 |
| | Trial3 | MA+ | .946 | .430 |
| | | MA- | .880 | .157 |
| | | NC | .929 | .435 |
| | Errors | MA+ | .800 | .003 |
| | | MA- | .723 | .003 |
| | | NC | .366 | .000 |
| | SCerrors | MA+ | .903 | .090 |
| | | MA- | .898 | .242 |
| | | NC | .554 | .000 |
| | Trial4 | MA+ | .790 | .002 |
| | | MA- | .825 | .040 |
| | | NC | .865 | .086 |
| | Errors | MA+ | .696 | .000 |
| | | MA- | .710 | .002 |
| | | NC | .509 | .000 |
| | SCErrors | MA+ | .709 | .000 |
| | | MA- | .907 | .294 |

| | | | | |
|---|---|---|---|---|
| | | NC | .593 | .000 |
| WCST | Trialsadministered | MA+ | .649 | .000 |
| | | MA- | .788 | .015 |
| | | NC | .894 | .187 |
| | Totalcorrect | MA+ | .959 | .651 |
| | | MA- | .876 | .141 |
| | | NC | .933 | .476 |
| | Correct | MA+ | .891 | .059 |
| | | MA- | .907 | .295 |
| | | NC | .776 | .007 |
| | TotalErrors | MA+ | .898 | .075 |
| | | MA- | .909 | .310 |
| | | NC | .751 | .004 |
| | PerseverativeResponses | MA+ | .937 | .310 |
| | | MA- | .944 | .621 |
| | | NC | .737 | .002 |
| | PerseverativeErrors | MA+ | .938 | .326 |
| | | MA- | .934 | .525 |
| | | NC | .732 | .002 |
| | Failuretomaintainset | MA+ | .796 | .002 |
| | | MA- | .833 | .049 |
| | | NC | .594 | .000 |
| TS | Errors | MA+ | .954 | .557 |
| | | MA- | .847 | .070 |
| | | NC | .782 | .009 |
| | AvRT | MA+ | .952 | .517 |
| | | MA- | .961 | .807 |
| | | NC | .880 | .130 |
| RT | FiveChoiceMovementTime | MA+ | .820 | .005 |
| | | MA- | .964 | .835 |
| | | NC | .970 | .892 |
| | FiveChoiceReactionTime | MA+ | .718 | .000 |
| | | MA- | .755 | .006 |
| | | NC | .946 | .617 |
| ANT | FinalnACC | MA+ | .752 | .001 |
| | | MA- | .732 | .003 |
| | | NC | .731 | .002 |
| | FinalcACC | MA+ | .739 | .000 |
| | | MA- | .607 | .000 |
| | | NC | .500 | .000 |
| | FinaliACC | MA+ | .838 | .009 |
| | | MA- | .898 | .243 |
| | | NC | .892 | .179 |
| | FinalnRT | MA+ | .917 | .150 |
| | | MA- | .862 | .101 |
| | | NC | .930 | .451 |

| | | | | |
|---|---|---|---|---|
| | FinalcRT | MA+ | .875 | .033 |
| | | MA- | .871 | .126 |
| | | NC | .915 | .315 |
| | FinaliRT | MA+ | .957 | .614 |
| | | MA- | .666 | .001 |
| | | NC | .889 | .164 |
| SWM | BetweenErrors | MA+ | .934 | .282 |
| | | MA- | .961 | .808 |
| | | NC | .959 | .777 |
| | Strategy | MA+ | .962 | .695 |
| | | MA- | .929 | .473 |
| | | NC | .861 | .079 |
| SSP | SpanLength | MA+ | .961 | .680 |
| | | MA- | .971 | .906 |
| | | NC | .927 | .422 |
| FAS | F | MA+ | .871 | .029 |
| | | MA- | .868 | .118 |
| | | NC | .912 | .294 |
| | A | MA+ | .839 | .010 |
| | | MA- | .944 | .620 |
| | | NC | .966 | .849 |
| | S | MA+ | .901 | .084 |
| | | MA- | .914 | .344 |
| | | 3.0 | .897 | .202 |
| | TOTAL | MA+ | .883 | .043 |
| | | MA- | .914 | .343 |
| | | NC | .863 | .082 |
| | Animals | MA+ | .919 | .163 |
| | | MA- | .895 | .223 |
| | | NC | .920 | .360 |
| | BoysNames | MA+ | .976 | .922 |
| | | MA- | .945 | .641 |
| | | NC | .952 | .688 |
| | TOTAL | MA+ | .948 | .456 |
| | | MA- | .944 | .628 |
| | | NC | .933 | .481 |
| | FruitsFurnitire | MA+ | .958 | .633 |
| | | MA- | .910 | .313 |
| | | NC | .912 | .296 |
| ADHD Q | Childhood185 | MA+ | .796 | .002 |
| | | MA- | .921 | .397 |
| | | NC | .925 | .404 |
| | Adulthood255 | MA+ | .855 | .016 |
| | | MA- | .951 | .704 |
| | | NC | .973 | .915 |
| | Total440 | MA+ | .861 | .020 |

| | | | |
|---|---|---|---|
| | MA- | .931 | .493 |
| | NC | .955 | .722 |

# APPENDIX F: LEVENE'S STATISTICS

## CHAPTER FOUR

***Table 1.*** **Levene's statistic for all four composite executive domains**

| | Levene's Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|
| **Decision Making and Impulsivity** | 1.355 | 2 | 55 | .266 |
| **Response Inhibition and Set-shifting** | 4.515 | 2 | 55 | .015 |
| **Attention and Working Memory** | 21.491 | 2 | 55 | .000 |
| **Verbal Fluency** | 0.222 | 2 | 55 | .802 |

## CHAPTER FIVE

***Table 2.*** **Levene's statistic for the outcome measures of the BART**

| | Levene's Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|
| **Total pumps** | .702 | 2 | 56 | .500 |
| **Adjusted average** | .702 | 2 | 56 | .500 |
| **Maximum Pumps** | 2.329 | 2 | 56 | .107 |
| **Total Points** | .437 | 2 | 56 | .648 |

***Table 3.*** **Levene's statistics for the IST outcome measures**

| Outcome measure | Levene's Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|
| **Win Condition Fixed** | | | | |
| **Mean Number of boxes opened per trial** | 1.826 | 2 | 54 | .171 |
| **Mean P correct** | 1.038 | 2 | 54 | .361 |
| **Total Correct** | 1.326 | 2 | 54 | .274 |
| **Sampling errors** | 2.706 | 2 | 54 | .076 |
| **Discrimination errors** | 2.339 | 2 | 54 | .106 |
| **Mean box opening latency** | 1.022 | 2 | 54 | .367 |
| **Win Condition Decreasing** | | | | |
| **Mean Number of boxes opened per trial** | 2.275 | 2 | 54 | .113 |
| **Mean P correct** | 3.666 | 2 | 54 | .032* |
| **Total correct** | 2.719 | 2 | 54 | .075 |
| **Sampling errors** | 2.029 | 2 | 54 | .141 |
| **Discrimination errors** | 2.813 | 2 | 54 | .069 |
| **Mean box opening latency** | 4.463 | 2 | 54 | .016* |

***Table 4*****. Levene's statistics for the CGT outcome measures**

| Outcome measure | Levene's Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|
| **Delay aversion** | 3.791 | 2 | 55 | .029 |
| **Deliberation time** | .108 | 2 | 55 | .898 |
| **Overall proportion bet** | 1.568 | 2 | 55 | .218 |
| **Quality of decision making** | 3.167 | 2 | 55 | .050 |
| **Risk adjustment** | 2.886 | 2 | 55 | .064 |
| **Risk taking** | .634 | 2 | 55 | .534 |

***Table 5.*** **Levene's statistics for the IST outcome measures**

| Outcome measure | Levene's Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|
| **Win Condition Fixed** | | | | |
| **Mean Number of boxes opened per trial** | 1.826 | 2 | 54 | .171 |
| **Mean P correct** | 1.038 | 2 | 54 | .361 |
| **Total Correct** | 1.326 | 2 | 54 | .274 |
| **Sampling errors** | 2.706 | 2 | 54 | .076 |
| **Discrimination errors** | 2.339 | 2 | 54 | .106 |
| **Mean box opening latency** | 1.022 | 2 | 54 | .367 |
| **Win Condition Decreasing** | | | | |
| **Mean Number of boxes opened per trial** | 2.275 | 2 | 54 | .113 |
| **Mean P correct** | 3.666 | 2 | 54 | .032* |
| **Total correct** | 2.719 | 2 | 54 | .075 |
| **Sampling errors** | 2.029 | 2 | 54 | .141 |
| **Discrimination errors** | 2.813 | 2 | 54 | .069 |
| **Mean box opening latency** | 4.463 | 2 | 54 | .016* |

***Table 6.*** **Levene's statistics for the CGT outcome measures**

| Outcome measure | Levene's Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|
| **Delay aversion** | 3.791 | 2 | 55 | .029 |
| **Deliberation time** | .108 | 2 | 55 | .898 |
| **Overall proportion bet** | 1.568 | 2 | 55 | .218 |
| **Quality of decision making** | 3.167 | 2 | 55 | .050 |
| **Risk adjustment** | 2.886 | 2 | 55 | .064 |
| **Risk taking** | .634 | 2 | 55 | .534 |

## CHAPTER SIX

***Table 7*. Levene's statistics for the Stop Signal Task**

| Outcome measure | Levene's Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|
| **Directions errors on stop/go trials** | 12.330 | 2 | 50 | .000 |
| **Proportion of successful stops** | .178 | 2 | 50 | .838 |
| **Median correct RT on go trials** | .308 | 2 | 50 | .736 |
| **SSD (last half)** | 3.953 | 2 | 50 | .025 |
| **SSRT (last half)** | 5.583 | 2 | 50 | .006 |

***Table 8.* Levene's statistics for the WCST**

| Outcome measure | Levene's Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|
| **Trials Administered** | .601 | 2 | 39 | .553 |
| **Total correct** | 1.055 | 2 | 39 | .358 |
| **Total errors** | 1.725 | 2 | 39 | .192 |
| **Perseverative responses** | 4.775 | 2 | 39 | .014 |
| **Perseverative errors** | 5.160 | 2 | 39 | .010 |

## CHAPTER SEVEN

*Table 9*. Levene's Statistics for the ANT

| Outcome measure | Levene's Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|
| **Accuracy:** | | | | |
| **Neutral Trials** | 17.320 | 2 | 56 | .000 |
| **Congruent Trials** | 18.009 | 2 | 56 | .000 |
| **Incongruent Trials** | 25.607 | 2 | 56 | .000 |
| **Reaction Time:** | | | | |
| **Neutral Trials** | 1.456 | 2 | 56 | .242 |
| **Congruent Trials** | .669 | 2 | 56 | .516 |
| **Incongruent Trials** | 1.576 | 2 | 56 | .216 |

CHAPTER EIGHT

*Table 10.* Levene's Statistics for Verbal Fluency

| Outcome measure | Levene's Statistic | df1 | df2 | Sig. |
|---|---|---|---|---|
| **F** | .180 | 2 | 55 | .836 |
| **A** | 2.339 | 2 | 55 | .106 |
| **S** | 1.313 | 2 | 55 | .277 |
| **Total** | 1.210 | 2 | 55 | .306 |
| **Animals** | .140 | 2 | 55 | .870 |
| **Boy's Names** | .324 | 2 | 55 | .724 |
| **Total** | .018 | 2 | 55 | .982 |
| **Category Switching** | 1.001 | 2 | 55 | .374 |