COGNITIVE PREDICTORS OF TREATMENT OUTCOMES IN INDIVIDUALS WITH METHAMPHETAMINE USE DISORDER

By

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LIST OF ABBREVIATIONS

CBT	Cognitive Behavioural Therapy
CES-D	Center for Epidemiologic Studies Depression Scale
CPT-II	Continuous Performance Test – Second Edition
DDT	Delay Discounting Task
EEfRT	The Effort Expenditure for Rewards Task
GC-MS	Gas Chromatography-Mass Spectrometry
MA	Methamphetamine
MUD	Methamphetamine use disorder
QoL	Quality of life
SCID	Structured Clinical Interview for the DSM-IV
SDS	Severity of Dependence Scale
TLFB	Timeline Followback
WASI-II	Wechsler Abbreviated Scale of Intelligence – Second Edition
WHOQOL-BREF	World Health Organization Quality of Life Scale – Brief Version

ABSTRACT

Rates of problematic methamphetamine use are increasing worldwide and are accompanied by significant social and economic harms. On an individual level, methamphetamine use disorder is associated with high rates of relapse, poor quality of life and low treatment motivation. Identifying predictors of these poor outcomes may help to improve treatment programs and to identify vulnerable individuals. Research in other stimulants has established a link between substance induced cognitive deficits and poor treatment and daily functioning outcomes – however this has not been explored in the methamphetamine use disorder population.

The primary aims of this thesis were (i) to examine the longitudinal predictive value of working memory and impulsivity (and their interaction) on levels of methamphetamine use during early treatment, (ii) to identify the relative contributions of delay discounting and impulsive action on change in quality of life during early treatment, and (iii) to identify the predictive value of sustained attention and effort-based decision-making on change in treatment motivation in early treatment. Study 1 (Chapter 3) addressed the first aim, Study 2 (Chapter 4) the second aim, and Study 3 (Chapter 5) the third aim.

Participants with methamphetamine dependence were recruited from residential rehabilitation (n = 60), detoxification (n = 30), and outpatient counselling (n = 16) settings in Melbourne, Australia from April 2015 to December 2016. The study was approved by the Eastern Health Human Research Ethics Committee (E52/1213).

Participants completed a baseline assessment session within three weeks of commencing treatment, and a follow-up session six weeks later. For study one (n = 108) participants were tested on the Delay Discounting Task (impulsivity) and Longest Digit Span Sequencing (working memory) at baseline, and a 1cm. sample of hair was taken at follow-up to measure methamphetamine use. For study two (n = 108), participants were tested on the Delay Discounting Task (impulsivity) and the Continuous Performance Test-II (impulsivity) at baseline, while quality of life was recorded using the World Health Organization Quality of Life measure (brief version) at baseline and follow-up. For the third study (n = 72), participants were tested with the Continuous Performance Test-II (attention) and the Worth the Effort Task (effort-based decision-making) at baseline, and the Contemplation Ladder (treatment motivation) at baseline and follow-up. Multiple regression analyses were used in each study to examine the predictive value of cognitive predictors on outcome variables.

Working memory significantly predicted methamphetamine use, and this was moderated by impulsivity. Impulsivity significantly predicted change in social and psychological quality of life but did not predict physical or environmental domains. Sustained attention but not effort-based decision-making significantly predicted change in treatment motivation in early treatment. These findings suggest that methamphetamine-induced cognitive deficits are predictive of a range of treatment outcomes. Cognitive deficits have an impact on the frequency of drug use, the ability to engage socially, psychological wellbeing and maintaining motivation in treatment. These findings may be incorporated into methamphetamine use disorder treatment, by which cognitive deficits may be accommodated or rehabilitated.

THESIS INCLUDING PUBLISHED WORKS DECLARATION

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Masters' regulations, the following declarations are made: This thesis contains no material which has been accepted for an award of any other degree or diploma at any university or equivalent institution, and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of this thesis.

This thesis contains two original journal articles, published in peer-reviewed journals and one unpublished publication. The core theme of this thesis is the predictive value of cognitive function on treatment outcomes in methamphetamine-dependent individuals. The ideas, development and writing up of all the papers in this thesis were the principal responsibility of myself, the candidate, working within the School of Psychological Sciences under the supervision of Associate Professor Antonio Verdejo-Garcia and Professor Dan Lubman.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

For Chapters 3, 4, and 5 my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
Three	Working memory predicts methamphetamine hair concentration over the course of treatment: Moderating effect of impulsivity and implications for dual-systems model	Published: *Addiction Biology* doi: 10.1111/adb.12575	70% contribution by candidate, including conceptualisation, design, data collection/analysis, interpretation of results and manuscript preparation	R. Fitzpatrick (conceptualisation, data collection, manuscript preparation – 10%),	Yes
				D. Lubman (conceptualisation, design, manuscript preparation – 10%),	No
				A. Verdejo-Garcia (conceptualisation, design, interpretation of results and manuscript preparation – 10%)	No
Four	Impulsivity predicts poorer improvement in quality of life during early treatment for people with methamphetamine dependence	Published: *Addiction* doi: 10.1111/add.14058	70% contribution by candidate, including conceptualisation, design, data collection/analysis, interpretation of results and manuscript preparation	R. Fitzpatrick (conceptualisation, data collection, manuscript preparation – 10%),	Yes
				D. Lubman (conceptualisation, design, manuscript preparation – 10%),	No
				A. Verdejo-Garcia (conceptualisation, design, interpretation of results and manuscript preparation – 10%)	No
Five	Sustained attention but not effort-based decision-making is significantly predictive of early	Under Review: *Journal of Substance Abuse Treatment*	70% contribution by candidate, including conceptualisation, design, data collection/analysis,	R. Fitzpatrick (conceptualisation, data collection, manuscript preparation – 10%),	Yes

change in treatment motivation	interpretation of results and manuscript preparation	D. Lubman (conceptualisation, design, manuscript preparation – 10%),	No
		A. Verdejo-Garcia (conceptualisation, design, interpretation of results and manuscript preparation – 10%)	No

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: [redacted] **Date:** 23/4/18

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author, I have consulted with the responsible author to agree on the respective contributions of authors.

Main supervisor signature: [redacted] **Date: 23/4/18**

PREFACE

This thesis by publication reports findings from three studies examining the predictive value of cognition on treatment outcomes in individuals with methamphetamine use disorder, using behavioural measures of cognition and self-report and biological outcome measures. The thesis consists of two published articles and one journal article that has been submitted for publication. The findings suggest that cognitive function when entering treatment can impact social and psychological recovery, treatment motivation, and the intensity of drug use in early treatment. These findings can be applied to the treatment setting. Pre-treatment cognitive testing may identify vulnerable individuals that may require adjustment to treatment or may benefit from rehabilitation of cognitive deficits.

This thesis comprises six chapters. Chapter One is an introduction and literature review, describing the nature of methamphetamine use in Australia, and the cognitive consequences as observed in animal and human studies. The first chapter also reviews the literature in which cognitive function predicts treatment and functional outcomes in stimulant users and states the aims and hypotheses of the thesis. Chapter Two is an expanded methodology section, elaborating on the methods described in Chapters Three, Four and Five. This includes a more detailed description of the measures and procedures than is possible within each publication. Chapter Three details the first study: 'Working memory predicts methamphetamine hair concentration over the course of treatment: Moderating effect of impulsivity and implications for dual-systems model.' This study aimed to describe how working

memory and impulsivity (reflecting the 'dual systems' model) predict levels of methamphetamine use in early treatment. Chapter Four consists of the second study: 'Impulsivity predicts poorer improvement in quality of life during early treatment for people with methamphetamine dependence.' This study measured impulsivity multi-dimensionally and aimed to examine the relative contribution of delay discounting and impulsive action in predicting change in domains of quality of life (social, psychological, physical, environmental) in early treatment for methamphetamine use disorder. Chapter Five consists of the third study: 'Sustained attention but not effort-based decision-making is significantly predictive of early change in treatment motivation in methamphetamine use disorder.' This study aimed to determine whether measures of sustained attention and effort-based decision-making significantly predict change in treatment motivation over early treatment for methamphetamine use disorder. Chapter Six consists of a general discussion that reflects on the findings of the three studies included in the thesis and explores overall limitations and clinical implications.

CHAPTER ONE: INTRODUCTION

1.1 The methamphetamine problem in Australia

Methamphetamine use disorder (MUD) is a growing problem worldwide. Global seizures of methamphetamine (MA) increased by 21% from 2015 to 2016 (UNODC, 2016), while greater purity and reduced cost (Scott, Caulkins, Ritter, Quinn, & Dietze, 2015) in Australia has resulted in higher rates of problematic use, greater help-seeking (McKetin et al., 2017) and substantial social and psychological consequences on an individual level. This chapter characterises the MA problem in Australia from a social and individual perspective, before focusing specifically on the cognitive consequences of MA exposure in animals and humans.

The chapter begins with an explanation of the epidemiology of MA in Australia, different forms of MA and typical routes of administration, pharmacokinetics, mechanism of action, and physiological response. This is followed by the individual and social consequences of MA use and an explanation of MUD in the context of the dual-systems theory. Following this is greater detail around the cognitive domains impaired by long-term MA exposure in experimental animal models and observational human studies. This chapter also includes a review of studies that examine the predictive value of cognitive function on substance dependence outcomes in humans. These outcomes include abstinence, retention, and level of engagement with treatment. The broader implications of MUD are also discussed, specifically areas of daily functioning that may be impaired by cognitive deficits. This chapter concludes with a discussion of how the limitations of past findings have informed the aims and hypotheses of the current research.

1.1.1 Epidemiology of methamphetamine in Australia

In Australia, the proportion of regular MA users has increased from 0.74% (2009-10) to 2.09% (2013-14), while rates of MUD have increased from 0.47% to 1.24% over the same period (Degenhardt et al., 2016). Wastewater analysis from 2009-15 illustrated a fivefold increase in MA use in urban areas and a threefold increase in rural areas (Lai, O'Brien, Thair, Hall, & Mueller, 2016), while border detections have increased from less than 200kg per year (2009-10) to over 1400kg (2012-13; Degenhardt et al., 2017). In Australia, the prevalence of the crystalline form has recently increased. Of those who use MA, the proportion using the crystalline form rose from 22% in 2010 to 57% in 2016 (Australian Institute of Health and Welfare, 2016). Among dependent users, 59% primarily use the crystalline form, 31% base and 9% powder (McKetin et al., 2017). Furthermore, rates of dependence are higher in those that typically use the crystalline form (66%), compared to powder (56%; Quinn, Stoove, Papanastasiou, & Dietze, 2013). The purity of crystalline MA has also increased (<10% to >70% in the same period) and has been accompanied by increases in treatment-seeking, hospital admissions, and rates of psychosis (Degenhardt et al., 2017; Ross, Adams, & Beovich, 2017).

1.1.2 Typical purchasing patterns

MA is usually purchased in units of one 'point' (one tenth of a gram), half-gram, or gram (Nguyen, Dietze, & Lloyd, 2013). A typical dose ranges from 0.05 to 0.35 grams (Dean, Groman, Morales, & London, 2013). Dependent users typically consume around half a gram daily (Montoya et al., 2016), using on 1-5 occasions per day (Dean et al., 2013). In 2013 in Australia, the cost of powder MA was approximately $252 per

gram (purity of 37%), while crystal MA was $795 per gram (purity of 64%; Scott et al., 2015). However, purchases are often in smaller quantities; one 'point' costs approximately $50 (range $14-$200) for MA powder and $100 (range $60-$200) for crystal MA (Nguyen et al., 2013). An average purchase (in injecting MA users) was $111 for MA powder and $140 for crystal MA (Scott, Caulkins, & Dietze, 2016).

1.1.3 Forms of methamphetamine, routes of administration, pharmacokinetics

MA in Australia is typically purchased in three forms: a low-purity powder (white or off-white in colour), an oily, waxy 'base' form (white to brown in colour), and a higher purity crystalline form ('ice'; clear in colour; McKetin, McLaren & Kelly, 2005). The crystalline form exhibits the highest rates of purity and can be smoked, hastening the brain's absorption of the drug without the risks associated with injection (Kish, 2008). The route of administration significantly impacts the pharmacokinetics of MA, as illustrated in Table 1. Among dependent and non-dependent users, rates of smoking MA have approximately doubled from 2010 to 2013 (to ~40%), rates of intravenous use have remained at similar rates (~10%), while other forms of administration (e.g. insufflation, oral) reduced from ~70% to ~50% in the same period (Degenhardt et al., 2017). Rates of injection are generally higher in dependent users, a group in which 85% report having injected at some point (McKetin et al., 2017).

Table 1. Pharmacokinetic profiles of different routes of administration in methamphetamine users (adapted from Cruickshank & Dyer, 2009).

Route	Bioavailability	Plasma half-life (hours)	Minutes to peak effect
Intravenous	100%	9.1 ± 0.8	<15
Smoked	90.3 ± 10.4%, 67%	12 ± 1	18 ± 2
Oral	67 ± 3%	9.1	180
Insufflated	79%	11 ± 1	≤ 15

Cook et al., (1993); Harris et al., (2003); Newton et al., (2005); Shappell, Kearns, Valentine, Neri, & DeJohn, (1996).

1.2 Mechanism of action and physiological response

MA is a central nervous system stimulant that exerts influence on dopamine, serotonin and norepinephrine neurotransmitters. These neurotransmitters function by carrying signals from one nerve fibre to another. After transmission, the reuptake process returns excess neurotransmitters to the releasing nerve fibre. However, MA triggers release of large quantities of neurotransmitters and prevents their reuptake, resulting in an abnormally high concentration of neurotransmitters at the receiving synapse (Fleckenstein, Volz, Riddle, Gibb, & Hanson, 2007; Panenka et al., 2013). Heightened concentration of these neurotransmitters leads to increased physiological and psychological arousal. Short-term physiological symptoms include increased heart rate, blood pressure, reduced appetite, increased respiration/perspiration, while psychological symptoms can include a sense of euphoria, heightened attention, aggression, increased anxiety and paranoia (Cruickshank & Dyer, 2009). The specific function of each impacted neurotransmitter is described below.

1.2.1 Dopamine

This neurotransmitter is involved in motor control, arousal, motivation and reward and is associated with feelings of pleasure. Long-term excessive dopamine release due to MA leads to neuroadaptation and diminished dopamine release for natural rewards, resulting in reduced motivation, low mood and anhedonia (Cruickshank & Dyer, 2009; Kalechstein, Newton, & Green, 2003; Riddle, Fleckenstein, & Hanson, 2006).

1.2.2 Serotonin

Serotonin is central to regulating psychological constructs of mood and aggression, but also physiological drives of sleep, sexuality and appetite. Individuals with MUD exhibit diminished levels of serotonin in orbitofrontal and occipital cortices, and experience dysregulated sleep, mood and appetite following MA withdrawal (Kish et al., 2009; Scott et al., 2007).

1.2.3 Norepinephrine

This neurotransmitter regulates wakefulness and is highly activated in situations of stress ('fight or flight response'), increases arousal and alertness, promotes memory function but can also precipitate anxiety and restlessness (Logan, 2002). MA induces diminished levels of norepinephrine after long-term use, and can result in memory problems and increased levels of anxiety (Freye, 2009; Wang, Chou, Jeng, Morales, & Wang, 2000).

1.3 Consequences of methamphetamine dependence

1.3.1 Individual

Long-term exposure to MA is associated with structural and functional damage to the brain. Structural changes (observed by Magnetic Resonance Imaging; MRI) include reduced white matter integrity (Tobias et al., 2010), reduced grey matter and cortical thickness (Harle et al., 2015; Nakama et al., 2011), and diminished hippocampal (Thompson et al., 2004), ventromedial prefrontal cortex and insula (Mackey & Paulus, 2013) volumes, reduced corpus callosum integrity (Kim et al., 2009) but increased striatal volumes (Chang, Alicata, Ernst, & Volkow, 2007; Mackey & Paulus, 2013). Changes in metabolite levels in specific brain regions (observed by Magnetic Resonance Spectroscopy) have also been found in individuals with MUD (Nordahl et al., 2005; Salo et al., 2007) and can reflect loss of neuronal integrity (Panenka et al., 2013). Functional changes have been observed in individuals with MUD using 'functional MRI' and Positron Emission Tomography, where significantly higher levels of microglia binding (associated with neurodegeneration) have been observed in previous MA users (Sekine et al., 2008), while Chung et al. (2010) found significantly diminished cerebral blood flow to all areas of the brain.

Individuals with MUD also experience a range of physical complications. These include significantly higher rates of heart disease, hypertension, asthma, and arthritis when compared to a healthy sample (Herbeck, Brecht, & Lovinger, 2015). Individuals with MUD are also at risk of cardiac pathology, with significantly higher rates of coronary artery disease than healthy samples, and direct links between MA intoxication and acute events (i.e., acute coronary syndrome, acute myocardial

infarction, acute aortic dissection, and sudden cardiac death; Kaye, McKetin, Duflou, & Darke, 2007). This group also exhibits significantly lower Body Mass Index and higher blood pressure than healthy controls (Lv et al., 2016), substantial dental and skin problems, and higher rates of hepatitis and renal failure (Vearrier, Greenberg, Miller, Okaneku, & Haggerty, 2012).

Individuals with MUD also experience high rates of psychological distress. Eighty-four per cent of MA users entering treatment have experienced either a major depressive episode or substance-induced depression over the past year (McKetin, Lubman, Lee, Ross, & Slade, 2011). Around 30% of individuals with MUD report an anxiety disorder, and a similar proportion report a psychotic disorder (Salo et al., 2011). Indeed, there is a five-fold greater risk of psychotic symptoms emerging during active MA use when compared to periods of no use (McKetin, Lubman, Baker, Dawe, & Ali, 2013).

1.3.2 Social

Increasing rates of MUD result in a range of societal and economic consequences. In Australia, approximately 4% of those in paid employment have used MA over the past year, with 13.4% of users missing work due to MA use, and 32.9% going to work under the influence of the drug (Roche, Pidd, Bywood, & Freeman, 2008). Australian healthcare services are also burdened by MA use, which is associated with 30,000 to 80,000 psychiatric admissions and 30,000 to 151,000 emergency departments visits annually (McKetin et al., 2017). Furthermore, MA-related deaths in Australia approximately doubled from 2009 (n = 142) to 2015 (n = 280; Darke, Kaye, &

Duflou, 2017). Higher rates of criminal activity in this population are also associated with a substantial societal impact. Of those who had recently used the crystalline form of MA, 26% had committed property crime in the last month, significantly higher than the rate of 14% in other injecting drug users, while 16% reported criminal activity as their primary source of income in the past month, significantly higher than the 5% reported in other injecting drug users (Degenhardt et al., 2008). Furthermore, between 2009 and 2014, arrests for amphetamine possession increased by 1.8% per month, and arrests for amphetamine dealing increased by 2.1% per month in a similar period (Degenhardt et al., 2017). These statistics are supported by estimates that describe the annual financial impact on healthcare ($200 million), premature mortality ($2.36 billion) crime and policing ($3.2 billion), road accidents ($125 million) and in the workplace ($289 million; Whetton et al., 2016).

These findings suggest that in Australia, MA has an impact on an individual level (physical and psychological health) and at a broad societal level (productivity, healthcare and criminal activity). These consequences emphasise the importance of understanding potential drivers of MUD and factors in the recovery process.

1.4 Dual process models of addiction

The chronic nature of MUD can be partly understood through the dual systems model of addiction. This model proposes that two cognitive systems, the 'bottom-up' reward-driven system and the 'top-down' cognitive control system, interact when confronted with a stimulus that is immediately pleasurable but has detrimental long-term consequences (e.g., drug use; McClure & Bickel, 2014). More specifically, individuals with high levels of impulsivity are more likely to experience the urge to use a substance that provides an immediate reward, and are less able to regulate these urges due to an impaired cognitive control system.

The 'incentive sensitisation theory' suggests that over time, the 'bottom-up' system is increasingly triggered by drug-related cues (e.g., a setting in which the individual has used a substance frequently, a low mood state; Robinson & Berridge, 1993). Desire and anticipation for the effects of the drug ('wanting') increase while the pleasure experienced from the effects of the substance may diminish ('liking'; Noel, Brevers, & Bechara, 2013). Furthermore, heightened levels of impulsivity associated with prolonged drug use (Stevens et al., 2014) increase the likelihood of acting on these more frequent urges arising from the 'bottom-up' system (Khurana, Romer, Betancourt, & Hurt, 2017). The process that typically regulates these urges is known as the 'top-down' system, where executive functions integrate current stimuli/information with achieving long-term goals. This occurs via: maintaining and updating relevant information, inhibition of impulses, and shifting attention between tasks (Hofmann, Schmeichel, & Baddeley, 2012). These functions are integrated with emotional/bodily responses associated with memories, knowledge and cognition

(Noel et al., 2013), to evaluate the short and long-term benefits of a course of action. Prolonged MA use results in deficits in executive functions (Dean et al., 2013), and may therefore reduce the capacity of the 'top-down' system to integrate 'bottom-up' urges with their long-term consequences (Hofmann, Friese, & Strack, 2009). In summary, the dual-systems model suggests that substance dependence is associated with a greater desire to use substances, accompanied with a reduced capacity to control these urges. This process is perpetuated by a positive feedback loop of substance-induced cognitive deficits (i.e., further consumption results in higher impulsivity and diminished control; Volkow et al., 2010).

1.4.1 Neurobiological underpinnings

The consumption of MA leads to large releases of dopamine, serotonin and norepinephrine, and damages the systems that process these neurotransmitters (Bickel et al., 2007; Kish et al., 2009). Importantly for the dual-systems model, dopamine plays a substantial role in reward behaviour, and brain areas associated with this neurotransmitter are implicated in the 'bottom-up' reward system. High arousal of the amygdala (associated with emotional and motivational interpretation of sensory input) stimulates the reward system (striatum, nucleus accumbens (ventral striatum), ventral pallidum), leading to execution (and subsequent strengthening) of the rewarding behaviour (Noel et al., 2013). Specifically, the nucleus accumbens is associated with the direct and conditioned reinforcement of substance use, while the dorsal striatum is associated with the habit-forming/compulsive components of substance dependence (Everitt & Robbins, 2005).

The reflective component of the dual-systems model is purported to involve the frontal and parietal systems (Bechara, 2005). Specifically, the lateral prefrontal cortex (and its connection with the posterior parietal cortex) is associated with making decisions with a long-term benefit, forecasting future consequences and working towards a defined goal (Bickel et al., 2007; McClure & Bickel, 2014). Damage to the ventromedial prefrontal cortex can result in difficulty incorporating feedback into future behaviour and can result in behaviour that is reliant on input from other brain areas (such as the reward system; Bickel et al., 2007). In substance dependence, cognitive control involves inhibiting the prepotent response of drug use (short-term reward) in order to engage in activities associated with long-term benefit (Salo, Ursu, Buonocore, Leamon, & Carter, 2009).

In summary, neurobiological consequences of MUD include: diminished functioning and lower dopamine availability in the striatum (Chang et al., 2007; Panenka et al., 2013), reduced frontal cortex volume and diminished connectivity with the parietal cortex (Oh et al., 2005; Thompson et al., 2004; Tobias et al., 2010). Frontal cortex changes may compromise the function of the top-down system, while a reduction in available dopamine in the striatum may result in greater sensitisation to MA and related cues, exciting the 'bottom-up' system. In this way, these systems can have a cyclical and reinforcing relationship, in which larger amounts of MA use further compromise top-down function and increase bottom-up activity, leading to greater difficulty in resisting MA consumption.

1.5 Methamphetamine and cognitive function

Previous literature has established that MUD results in structural and functional changes to the brain, including damage to the ventromedial prefrontal cortex (Mackey & Paulus, 2013), medial temporal lobe (Thompson et al., 2004) and striatum (Panenka et al., 2013). These brain areas are primarily associated with executive functioning processes and impulsivity (Bickel et al., 2007; McClure & Bickel, 2014). According to the dual-systems model, damage in these areas should result in significant and reinforcing executive deficits, specifically in cognitive control and heightened impulsivity. Therefore, the following section explores the impact of MUD on cognition in domains associated with executive functioning directly (i.e., working memory, cognitive control, impulsivity), and those domains that utilise the strategic or sequential processing associated with executive functioning (i.e., learning and memory, attentional function; Woods et al., 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). These deficits are first examined in the context of animal models, which allow highly controlled and uniform exposure to MA, and followed by studies of human participants, which shows the impact of MA in a naturalistic setting in our population of interest. To provide a conceptual map of each cognitive domain, Table 2 shows the measures used to assess different components of cognition in animals and humans.

Table 2: Measures used in animal and human research to assess the impact of methamphetamine exposure on cognition

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	**Description of Task**	**Outcome measure(s)**	**Task Name**	**Description of Task**	**Outcome measure(s)**
Attention							
Sustained attention	Maintaining visual attention and focus on a stimulus over a sustained period while not attending to or responding to irrelevant stimuli.	Five-choice Serial Reaction Time (5-CSRT) task (also measures impulsive action)	Animals are presented with a brief visual stimulus and rewarded with a food pellet after locating the target stimulus with a nose-poke response.	Omissions (failure to respond in 5s.), premature (response before target stimulus), incorrect (response in adjacent hole).	Continuous Performance Test-II (also measures impulsive action)	Participants watch letters of the alphabet appear, one at a time, on a computer screen and are instructed to press the space bar whenever any letter, except for 'X,' appears.	Omission errors (failure to press the space bar when letters other than X appear) and commission errors (pressing the space bar when 'X' appears).
					Trail making Test- A/B	In part A, participants connect 25 numbers randomly arranged on a page in ascending order. In part B, participants connect 25 circled numbers and letters in alternating order.	Time taken to complete each section.
					Rapid Visual Information Processing	Digits from 2-9 appear in random order (100 digits/min.). Participants press a button when they observe a pre-determined sequence.	Latency (speed of response), false alarms, and sensitivity.

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	Description of Task	Outcome measure(s)	Task Name	Description of Task	Outcome measure(s)
Selective attention	The ability to voluntarily control and focus attentional process on specific stimuli while suppressing irrelevant information.		See cognitive flexibility/set-shifting tasks		Stroop Colour Word Test (also response inhibition)	Part 1: naming randomised colour names in black/white (Stroop-word). Part 2: naming colour names in non-matching coloured ink (Stroop-colour). Part 3: naming colours that words are printed in, ignoring the word (Stroop colour-word).	Reaction time, number of interference errors, number of correct responses in 45s.
					d2 Test of Attention	Page filled with 'd' and 'p' characters with one or two marks above/below each character, participants cross out any letter 'd' with two marks above or below it.	Total number of correctly marked 'd' letters minus the number of errors.
					Attentional Network Task	Participants indicate the direction of an arrow on a screen which has two arrows on either side. Surrounding arrows are either in the same (congruent) or a different (incongruent) direction.	Response time and error rate in alerting, orienting and executive domains.

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	Description of Task	Outcome measure(s)	Task Name	Description of Task	Outcome measure(s)
Impulsivity							
Decision-making	Decision-making ability in situations and conditions with uncertain outcome.	Gambling Test in the 8 Arm Radial Maze	Four choice arms: one low-risk/low-return, one high-risk/high-return, and two empty. Low-risk/low-return arm, 87.5% of the time results in one pleasant food pellet, 12.5% of the time leads to unpalatable pellet. High risk/high return: large reward (more pellets) with low probability.	Proportion of high/low risk arm selections.	Two-choice prediction task	Participants are shown a house on a computer screen with two people on either side and asked to predict on which side a car will pick up either person (with no predictive information). Participants select based on preceding responses and outcomes. After selecting, the participant is shown the correct side. Unknown to the participant, the car is presented in a pre-determined order.	Response biases (overall left versus right selections; switching versus staying on a particular side).

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	Description of Task	Outcome measure(s)	Task Name	Description of Task	Outcome measure(s)
Decision-making (cont.)	Decision-making ability in situations and conditions with uncertain outcome.				Iowa Gambling Task	Participants make 100 selections from four decks of cards (A, B, C and D). Each time a participant selects a card, they receive a reward. However, decks also result in losses – decks A and B provide large gains but large losses (overall loss), while decks C and D provide small gains but small losses (overall gain).	Proportion of selections from 'good decks', proportion of choices between 'good' and 'bad' decks.
					Balloon Analog Risk Task	Participants pump on-screen balloon (value increases $0.25 each pump) or cash out earnings. Pumping either increases balloon size or causes balloon to explode (current earnings lost).	Adjusted average number of pumps on unexploded balloons.

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	**Description of Task**	**Outcome measure(s)**	**Task Name**	**Description of Task**	**Outcome measure(s)**
Delay Discounting	The tendency to discount the value of a reward based on its delay in time		.		Delay Discounting	Participants make choices between an amount of money available immediately or a larger amount after a specific delay (7, 30, 90, 180, or 365 days).	*k* value: a number that indicates how steeply value degrades over time.
Effort-based decision making	The motivation and willingness to expend effort to obtain reward with varying probabilities of success.	Effort Discounting	In T-shaped mazes animals choose either: a 'high reward' condition; or a 'low reward' condition. Wooden blocks of 15-30 cm heights are used to impede access to the high reward arm.	Proportion of selections of each condition.	Effort-Expenditure for Rewards Task: EEfRT	Participants choose between two options: a low-effort choice (small reward) and a high-effort choice (larger reward). High effort-task: 100 button presses in 21 seconds; low-effort: 30 button presses in 7 seconds. 12.5%, 50% or 87.5% chance of being paid reward.	Proportion of easy/hard selections in low, medium and high probability conditions.
Learning and Memory							
Visuospatial memory	Visual perception and memory of	Novel Object/Place Recognition	Animals recall which of two objects they have	Time spent exploring novel object or	Brief Visuospatial Memory Test	6 simple visual designs presented in 3 learning trials.	Immediate recall, delayed recall, recognition memory.

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	**Description of Task**	**Outcome measure(s)**	**Task Name**	**Description of Task**	**Outcome measure(s)**
	relationships between objects/spaces.		previously been exposed to.	location.			
		Morris Water Maze	Animals in a circular pool find a platform that allows escape.	Time to escape, path length and cumulative distance.	Rey Complex Figure Test	Participants copy a complex (Rey-Osterrieth) figure by hand and draw from memory after 3 mins.	Recognition (copying) and recall (drawing from memory).
		Sequential Motor Learning	In Radial Arm Maze, animals are repeatedly presented with the same sequences of door openings for food retrieval and are tested on memory in experimental phase.	Time taken to follow sequence learned in training phase.	Paired Associates Learning Task	A computer screen shows 6-8 boxes which are opened one by one in a random sequence revealing the location of a pattern (to be remembered by the participant). The number of patterns increase (two, three, six, eight).	First trial memory score; total number of trials; total number of errors.
		Y Maze Spontaneous Alternation Test	A Y-shaped maze with three arms at a 120° angle from each other. Rodents explore arms.	Rate of alternation (entry to less recently visited arm) is measured.	Groton Maze Learning Test	On a grid of 100 squares (10 by 10), participants find a path from one corner to another with corrective	Number of errors (legal, perseverative, and 'rule-break')

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	Description of Task	Outcome measure(s)	Task Name	Description of Task	Outcome measure(s)
						feedback, then attempt to repeat the path, making as few errors as possible.	
Prospective Memory	The ability to retrieve and execute a planned action at an appropriate moment in the future.				Virtual Week prospective memory task	Each circuit of the computerised board represents a day, where lifelike activities must be remembered (e.g., take medication).	Four categories of responses: correct, little late, lot late, and missed.
					Memory for Intentions Screening Test	Four time-based and four event-based trials, where participant is engaged in a distractor task (e.g., word search).	Number of errors: no response, task substitution, loss of content, loss of time.
Visual learning	The ability to recall verbally and/or visually presented information immediately and after a short delay.	Visual Discrimination learning	Animals are shown two concurrently presented stimuli (one reward and the other punishment) and select with	Percentage of correctly performed trials.	Repeated Memory Test	25 words and 25 pictures are presented individually. After 10 minutes, participants recall items presented. Recognition phase:	Number of items recalled, number of items recognised.

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	Description of Task	Outcome measure(s)	Task Name	Description of Task	Outcome measure(s)
			nosepoke.			test words and pictures as well as 25 distractor words and pictures.	
					The Map Memory Test	Participants study 12 different maps for four minutes, then presented with a testing page (12 maps, some previously seen, some unseen).	Number of correct identifications (seen and unseen maps).
					Picture Number Test	Sheet with 21 common items, each paired with a two-digit number. Subsequently, participants complete a test sheet with items in a different order.	Number of correct picture-number identifications.
Verbal learning	The ability to recall orally presented information immediately and after a delay.				Hopkins Verbal Learning Test/International Shopping List Task	Participants are read 12 words. Afterwards, participants repeat as many words as possible. This is repeated twice.	Recall for each trial, total recall, recognition, delayed recall (25 min.).

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	Description of Task	Outcome measure(s)	Task Name	Description of Task	Outcome measure(s)
Verbal Learning (cont.)	The ability to recall orally presented information immediately and after a delay.				California Verbal Learning Test	Participants are read 16 words and repeat back as many words as possible. This is repeated four times. Afterwards, an interference list of 16 words is presented for one trial. Participants recall the original list.	Free recall, recall with cues, recognition (20 min. delay).
					Selective Reminding Test	Verbal presentation of a 12-word list over 12 trials (participant must recall after each trial). Words not recalled are re-presented on subsequent trials.	Total recall (12 trials), number words recalled on consecutive trials, number words remembered on non-consecutive trials, items not on list.
					Rey Auditory Verbal Learning Test	Participants read 15-word list (five trials) and must recall. After, a list of 15 unrelated words is read aloud; participant must repeat the original	Recall (each trial), unrelated words (errors), similar words (errors), total recall, learning rate, proactive interference, forgetting.

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	**Description of Task**	**Outcome measure(s)**	**Task Name**	**Description of Task**	**Outcome measure(s)**
						list (and after 30 mins).	
					Babcock Story Recall	Participants read a story (21-unit paragraph).	Immediate recall, delayed (20 mins.) recall.
Cognitive control							
Working memory	The capacity to temporarily hold and manipulate information.	Reference and Working Memory version of the Radial Arm Maze	All 8 arms of maze are baited, the sequence of arms entered is measured.	Number of re-entries when pellet already collected.	Tic-tac-toe	Participants shown Xs and Os in a grid, containing a low or high memory pattern. Participants indicate when the patterns in recognition phase matches patterns from presentation phase.	Number of correctly recognized patterns.
		Spatial Working Memory: Delayed Spatial Win-Shift (SWSh) task – Radial Arm Maze	Placement of the food pellet reward alternates between the training and test phases (moves to the opposite arm).	Number of re-entries to a non-reward arm in test phase.	Missing Digit Span	Participants are read a string of digits, followed by the same string that is one digit shorter. Participants identify missing digit from the second string.	Longest set size in which at least two sequences are correct.

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	**Description of Task**	**Outcome measure(s)**	**Task Name**	**Description of Task**	**Outcome measure(s)**
Working memory (cont.)	The capacity to temporarily hold and manipulate information.	Cincinnati Water Maze	A water maze with nine interconnected T-intersections that rodents must negotiate to escape.	Latency to escape, number of errors.	Digit Span/Letter Number Sequencing	Participants read string of digits and repeat in same order, reverse, or sequenced from lowest to highest. Letter number sequencing, digits from smallest to largest, then letters in alphabetical order.	Digit/Letter Number span forward, backward, sequencing (raw and scaled scores).
					Sentence Span	Sentences read aloud (4-10 words). Two to four sentences per trial. After last sentence in trial, participant recalls last word in each sentence.	Longest set in which participant remembered last word correctly on at least two trials.
					Paced Auditory Serial Addition Task	One digit read aloud every 3 seconds. Participant adds each new digit to the immediately preceding digit.	Proportion of correct answers.

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	Description of Task	Outcome measure(s)	Task Name	Description of Task	Outcome measure(s)
Working memory (cont.)	The capacity to temporarily hold and manipulate information.				Spatial working memory task	Four, six or eight boxes appear on screen, participants touch each box until the blue counter is revealed (the aim is to fill a column with blue counters).	Number of returns to a box already sampled.
					Delayed match to sample task	Participants must choose the correct stimulus from four that were presented 0, 4, or 12s previously.	Percent correct under each condition.
					Tower of London Task/Stockings of Cambridge	Configurations of different coloured beads on three pegs are presented (one configuration on each half). Participants transform the start state (left half) to the goal state (right half). Tasks must be solved in three to seven moves.	Total correct; total errors; total moves; time until first move; time from first move to completion.

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	Description of Task	Outcome measure(s)	Task Name	Description of Task	Outcome measure(s)
Working memory (cont.)	The capacity to temporarily hold and manipulate information.				Halstead Category Test	Participants select a number between 1 and 4 for each on-screen stimulus and receive corrective feedback. Participants must determine the concept or principle that connects the figures/numbers.	Number of errors.
					Global/Local figure task	Participants shown a cue of a small or large figure. 400ms later, a geometric figure is presented consisting of a global figure (square or rectangle) composed of smaller local figures (squares or rectangles). Participants indicate which shape is associated with the cue provided (global or local).	Median reaction time, percentage errors cue alternation, percentage errors cue repetition.

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	**Description of Task**	**Outcome measure(s)**	**Task Name**	**Description of Task**	**Outcome measure(s)**
Response inhibition/ Inhibitory control	Ability to voluntarily inhibit or control prepotent attentional or behavioural responses no longer required.	Discrimination reversal learning	Animals presented with two visual stimuli (one reward and one punishment). In reversal trials, reward and punishment contingencies are reversed.	Percentage of correct trials.	Hayling Sentence Completion Test-B	Participants must complete a sentence with a word missing at the end (section A: must be congruent, section B: must be incongruent).	Response latency, number of errors.
		Attentional set shifting tasks	Access to two bowls (one baited with food reward), four discovery trials, followed by learning discrimination phases: scent, reversal, intra-dimensional and extra-dimensional shifts.	Number trials to criterion, number of errors in reaching criterion.	Stop signal task	The participant is presented with a targeted stimulus, (e.g. letter "O" or "X") and must respond as fast as possible with button presses. If a 'stop signal' tone follows the target stimulus, participants inhibit their response. This signal occurs at a variable delay after the target stimulus.	Reaction time to go signal, reaction time to stop signal

Cognitive Domain	Operational Definition	Animal Research			Human research		
		Task Name	Description of Task	Outcome measure(s)	Task Name	Description of Task	Outcome measure(s)
Response inhibition/ Inhibitory control (cont.)	Ability to voluntarily inhibit or control prepotent attentional or behavioural responses no longer required.	Go/no-go procedure	Animals are trained to press a lever for a food reward in response to a 'Go' signal (a rapid flash of light) and to not press the lever in response to a 'No-Go' signal (slower light flash). Correct responses result in a food reward.	Commission errors, omission errors, number of correct go-trials, reaction time in go-trials.	Go/no-go task	Participants perform an action (e.g., button presses) when presented with certain stimuli (i.e., X and Y) that differ from the preceding stimulus (i.e., XY or YX) on the computer screen. Participants inhibit that action under a different set of stimuli (i.e., XX or YY).	Commission errors, omission errors, number of correct go-trials, reaction time in go-trials.

1.5.1 Animal studies

This review begins with studies of animals in which the level of drug exposure can be directly manipulated, resulting in uniform levels of exposure across animals and minimal variation in other characteristics that might influence cognition (e.g., history of MA use/exposure to other drugs, mental or physical illnesses). Animals are typically exposed to either a binge dose (a small number of large exposures) or an escalating dose (dosages increasing gradually over a longer period, either self or experimenter administered). These exposures are intended to mirror the different forms of use in humans. It is estimated that users typically take doses of between 0.60 and 3.5 mg/kg per administration (Dean et al., 2013), however a "binge and crash" pattern of use is common, where an escalating binge dose is used for a number of days (Cretzmeyer, Sarrazin, Huber, Block, & Hall, 2003). It is therefore difficult for animal studies to accurately model human usage patterns. However, the following collection of studies are examined in the context of volume and length of exposure, and time prior to cognitive testing, to determine how broadly each domain is impaired.

1.5.1.1 Learning and memory

Recognition memory appears to be significantly impaired in two domains, novel object and novel odour recognition. In novel object recognition, length of time spent exploring a non-familiar object was impaired in MA exposed rodents in thirteen studies (Belcher, Feinstein, O'Dell, & Marshall, 2008; Belcher, O'Dell & Marshall, 2005; Herring, Schaefer, Gudelsky, Vorhees, & Williams 2008; Janetsian, Linsenbadt, & Lapish, 2015; Kamei et al., 2006; Le Cozannet, Markou, & Kuczenski, 2013; Melo et al., 2012; North et al., 2013; Reichel, Ramsey, Schwendt, McGinty, & See, 2012; Reichel,

Schwendt, McGinty, Olive, and See, 2011; Rogers, De Santis & See, 2008; Siegel, Craytor & Raber, 2010; Thanos et al., 2016). Novel odour recognition is assessed by exploration of a bead containing an odour from an unfamiliar cage; in one study, exposed rats showed significantly lower preference to the novel odour when compared to controls (O'Dell, Feinberg, & Marshall, 2011). The majority of these studies utilised a binge regimen for periods of up to ten days and tested cognitive functions within the following week. However, deficits were also observed in rodents subjected to a longer binge regime (daily doses for 16 weeks; Thanos et al., 2016). In self-administration protocols, rodents had short access to MA (one to two hours) for 7-10 days, followed by 14 days of long access (6 hours), and exhibited significant deficits one to two weeks after cessation of MA access (Reichel et al., 2011; Rogers et al., 2008). However, significant deficits were not observed when a short access regime was maintained for the entire three weeks (Rogers et al., 2008), suggesting that when access to (and therefore quantity consumed) is restricted, fewer deficits may be observed.

Sequential motor learning (learning a sequence of movements to receive a food reward) was also significantly impaired in MA exposed rodents in two studies with identical protocols (10mg/kg every two hours for eight hours, tested three weeks later; Chapman, Hanson, Kesner, & Keefe, 2001; Daberkow, Kesner, & Keefe, 2005). Spatial memory (time/route taken in navigating a maze) was also significantly impaired in four studies (Bigdeli, Asia, Miladi-Gorji, & Fadaei, 2015; North et al., 2013; Simoes et al., 2007; Vorhees et al., 2009). This included a moderate dose (2 mg/kg daily for five days) that persisted after a 30-day withdrawal period (Bigdeli et al., 2015), while deficits persisted for over two months in Vorhees and colleagues' (2009) study. Spatial

memory was also significantly impaired in MA-exposed rodents following a single, very high dose (30 mg/kg), but not when exposed to an escalating dose (increasing from 5-30 mg/kg over one week; Simoes et al., 2007). However, the study included a very small sample (n = 4 in each group) and rodents were tested one day after their last exposure, which could result in some residual cognitive effects. These findings provide some evidence for persistent spatial learning deficits at a range of dosages, however, more studies (utilising larger samples) are required to reinforce these findings.

One study found significant impairment in long-term memory (time spent interacting with familiar objects after a delay; Janetsian et al., 2015; 5mg/kg every second day for two weeks). These deficits were observed acutely (1 day following cessation) and over a longer time period (30 days). A single study also identified significant deficits in visual discrimination learning in rodents (distinguishing images associated with reward/punishment using nose-poke; Ye, Pozos, Phillips, & Izquierdo, 2014). However, in a study of non-human primates, Kangas and Bergman (2016) found that although daily administration of MA slowed the development of discrimination learning, these deficits did not persist once administration was discontinued.

There is substantial evidence for the existence of impairment in recognition memory in early recovery, across a range of dosages, and binge and self-administration protocols. Furthermore, the preliminary evidence (four studies) regarding spatial learning is indicative of a deficit that persists for over one month, and that binge exposure to MA may confer a greater risk of deficits than an escalating dose, however

further well-controlled research is required. In other domains, evidence is limited. The two studies supporting sequential motor learning and the single studies supporting deficits in long-term memory and visual discrimination learning remain to be replicated and expanded, while one study of primates did not support a deficit in discrimination learning.

1.5.1.2 Attention and working memory

Five studies have examined whether rodents exposed to MA experience significant deficits in attention and working memory. One study found that sustained visual attention (responding to a stimulus to receive food) was significantly poorer in animals that self-administered MA when compared with animals that received saline (Dalley et al., 2007). Significant deficits in working memory have been observed in four studies of rodents (Braren, Drapala, Tulloch, & Serrano, 2014; Herring et al., 2008; Mizoguchi et al., 2011; Vorhees et al., 2009). Impairments were observed in the first two weeks (Mizoguchi et al., 2011), second two weeks (Herring et al., 2008), fifth week (Braren et al., 2014), and seven to eight weeks (Vorhees et al., 2009) post exposure. These studies included different levels of binge dosing: from 10 mg/kg (Herring et al., 2008; Vorhees et al., 2009) to 30 mg/kg (Braren et al., 2014). Different forms of administration were also explored within single studies. One study compared different levels of binge dosing (10 and 25 mg/kg) between groups and found both were significantly impaired when compared to the control group (Vorhees et al., 2009). A binge and consistent low dose were compared in another study (10mg/kg every two hours or 24 doses at 1.67 mg/kg every 15 minutes); both MA groups were significantly

impaired when compared to the control group but did not differ significantly from each other (Herring et al., 2008).

Evidence for impairment in attentional function requires further research. However, studies of working memory problems suggest deficits in early periods following the cessation of an MA binge dose, while there is evidence from one study that indicates similar impairments even when exposed to a low, consistent dose.

1.5.1.3 Cognitive control

Reversal learning in animals measures the ability to cease and reverse ongoing reward-related behaviour, and reflects cognitive control (Kehagia, Murray, & Robbins, 2010). Reversal learning is directly measured with lever-pressing or chamber selection for reward, and was significantly impaired in seven studies of MA exposed rodents (Cheng, Etchegaray, & Meck, 2007; Cox et al., 2016; Izquierdo et al., 2010; Kosheleff, Rodriguez, O'Dell, Marshall, & Izquierdo, 2012; Son, Kuhn, & Keefe, 2013; Stolyarova, O'Dell, Marshall, & Izquierdo, 2014; Ye et al., 2014) and one study of non-human primates (Groman et al., 2012). Similarly, set-shifting, the ability to adapt to changing reward contingencies, was significantly impaired in MA-exposed rodents in two studies (Izquierdo et al., 2010; Parsegian, Glen, Lavin, & See, 2011), however one study did not find a significant difference (Cox et al., 2016). Across these studies, deficits were observed shortly after exposure (Cheng et al., 2007), in early abstinence (3-5 days; Cox et al., 2016; Kosheleff et al., 2012; Stolyarova et al., 2014; Ye et al., 2014) and around three weeks after last exposure (Izquierdo et al., 2010; Son et al., 2013). Binge doses ranged from 2mg/kg (Izquierdo et al., 2010) to 10mg/kg (Son et al., 2013), while four studies utilised an escalating dose protocol (Cox et al, 2016; Kosheleff et al., 2012;

Stolyarova et al., 2014; Ye et al., 2014). When directly comparing escalating dose and binge protocols, one study found that both groups were significantly impaired when compared to the control group (Stolyarova et al., 2014), while another found significant deficits in a group exposed to a single large dose but not in the escalating dose group (Kosheleff et al., 2012). Although further research will more clearly elucidate precise differences in dosage, these findings provide evidence for cognitive control deficits across binge and escalating dose protocols that persist for at least three weeks.

1.5.1.4 Decision-making/impulsivity

Decision-making measures the evaluation of high and low risk options associated with food rewards and has been examined in five studies (Kosheleff et al., 2012; Mizoguchi et al., 2015; Richards, Sabol, & de Wit, 1999; Stolyarova, Thompson, Barrientos, & Izquierdo, 2015; Thompson et al., 2017). Rodents exposed to an extended binge dose of MA exhibit a significantly greater preference for high risk-high reward options when compared to controls (Mizoguchi et al., 2015), and show a greater tendency to select smaller rewards sooner rather than wait for a larger reward (Richards et al., 1999). When exposed to an escalating dose protocol, rodents do not show any change in proportion of high reward decisions, but do increase selection of moderate reward choices, with an accompanying decrease in low reward selections (Stolyarova et al., 2015). However, willingness to exert effort for a preferred reward significantly diminishes in both escalating dose (Thompson et al., 2017) and binge (Kosheleff et al., 2012) protocols. MA-exposed rodents also exhibit significantly greater difficulty inhibiting reward-related responses (impulsive action), showing significantly

higher rates of premature responding than controls (Dalley et al., 2007). Collectively, although further evidence is required for both escalating and binge dose protocols, MA-exposed rodents appear to show a preference for greater rewards, a reduced willingness to wait for rewards, and may have difficulty with the inhibition of impulsive behaviour.

Interim conclusion

Table 3 summarises the key findings of each study. Animal studies provide direct links between specific levels of substance exposure and cognitive outcomes due to the stringent control of extraneous variables. There is consistent evidence to support significant MA-related deficits in recognition memory, working memory (binge dose), cognitive control and impulsivity. Each of these domains is strongly influenced by executive dysfunction. Recognition memory involves strategic executive recall processes (Woods et al., 2005), while working memory, cognitive control and impulsivity are interlinked with executive process functions (McClure & Bickel, 2014). These findings suggest that cognitive deficits associated with MA exposure, even for short periods, can result in dysregulation of the executive system in animals. To elaborate on these findings, it is important to determine the nature of cognitive deficits in MA-dependent humans. The following section explores cognitive deficits in cross-sectional studies of MA-dependent human participants, compared with non-using controls.

Table 3. Summary of design, sample size and domains assessed in studies of methamphetamine exposure in animals

Authors	**Design (all compared to saline)**	**Sample size**	**Cognitive domains assessed**
Belcher et al., (2008)	Experiment 1: Escalating dose: .1mg/kg injections increasing every 3h up to 4 mg/kg. Binge: 4mg/kg Experiment 2: Binge: 1, 2, 3, or 4 mg/kg	E1: ED+Binge (*n* = 13) Saline+Binge (*n* = 12) Binge only (*n* = 14) Saline (*n* = 11) E2: 1mg/kg (*n* = 11) 2mg/kg (*n* = 14) 3mg/kg (*n* = 24) 4mg/kg (*n* = 27) Saline (*n* = 40)	E1: Novel object recognition* (Saline+Binge and Binge only groups) E2: Novel object recognition* (impaired in 2, 3, 4 mg/kg groups, dose-dependent)
Belcher et al., (2005)	4mg/kg x 4 injections/2h	MA (*n* = 15) Control (*n* = 13)	Novel object recognition*
Bigdeli et al., (2015)	2mg/kg daily, 5 days	Four groups: 2 x MA, 2 x Control (*n* = 9-10 each group)	Spatial memory*
Braren et al., (2014)	30mg/kg twice, one week apart	MA (*n* = 4) Control (*n* = 4)	Working memory*
Chapman et al., (2001)	5.0, 7.5, or 10 mg/kg /2h for 8h	MA 5.0 (*n* =10) MA 7.5 (*n* = 8) MA 10 (*n* = 10) Control (*n* = 10)	Sequential motor learning
Cheng et al., (2007)	3mg/kg x 4 injections/2h	MA (*n* = 8) Control (*n* = 7)	Reversal learning* Long-term memory*
Cox et al., (2016)	Self-admin: .06mg/kg 6h, 14 days	*n* = 19-23 per group	Visual discrimination recall Set-shifting Reversal learning*
Daberkow et al., (2005)	10mg/kg x 4 injections/2h	MA (*n* = 11)	Sequential motor learning*

Authors	Design (all compared to saline)	Sample size	Cognitive domains assessed
		Control (*n* = 6)	
Dalley et al., (2007)	Self-admin: (.02mg dose) – 1 hour access (days 1-7) 6 hours access (days 8-21)	MA (*n* = 10) Control (*n* = 9)	Impulsivity* Sustained visual attention*
Groman et al., (2012)	Escalating dose: .25-1.0 ml/kg over 31 days	MA (*n* = 7) Control (*n* = 7)	Reversal learning* (significantly impaired at week 3 of dosing, no difference five days after cessation of dosing)
Herring et al., (2008)	10mg/kg x 4 injections/2h or 1.67mg/kg x 24 injections/15min	MA (10mg/kg; *n* = 19) Control (*n* = 19) MA (1.67mg/kg; *n* = 20) Control (*n* = 20)	Novel object recognition* Path integration learning* Spatial learning
Izquierdo et al., (2010)	2mg/kg x 4 injections/2h	Experiment 1: MA (*n* = 7) Control (*n* = 5) Experiment 2: MA (*n* = 9) Control (*n* = 7)	E1: Reversal learning* E2: Set shifting*
Janetsian et al., (2015)	5mg/kg dose every second day for 14 days	MA (*n* = 20) Control (*n* = 17)	Object memory* (Day 1 abstinence) Novel object recognition* (Day 1 abstinence) Object memory* (Day 30 abstinence) Novel object recognition (Day 30 abstinence)
Kamei et al., (2006)	1mg/kg daily for seven days	MA (*n* = 24) Control (*n* = 24)	Novel object recognition*
Kangas & Bergman, (2016)	Self-admin.: .0032-.1 mg/kg 2h for 30 days	MA (*n* = 4) Control (*n* = 4)	Discrimination learning* Reversal learning
Kosheleff et al., (2012)	Single dose: 6mg/kg Escalating dose: 4 weeks, increasing by .3mg/kg daily	MA (*n* = 9) Control (*n* = 6)	Reversal learning*

Authors	Design (all compared to saline)	Sample size	Cognitive domains assessed
	(culminating in 6mg/kg)		
Le Cozannet et al., (2013)	Limited access: .05mg/kg 1h daily Extended access: .05mg/kg 1h/5 days, 3h 5 days, 12h 20 days. Two days rest between	MA limited access (n = 12) MA extended access (n = 15) Control (n = 20)	Novel object recognition* (extended access group impaired)
Melo et al., (2012)	5mg/kg every 2h for 6h. Daily for ten days	*n* = 44 in four groups, MA, MA age-matched, 12 months old, 20 months old	Novel object recognition*
Mizoguchi et al., (2011)	4mg/kg dose daily for seven days	MA (*n* = 11-14) Control (*n* = 11-14)	Spatial learning*
Mizoguchi et al., (2015)	4mg/kg dose daily for 30 days	MA (*n* = 3-4) Control (*n* = 3-4)	Impulsivity*
North et al., (2013)	24mg/kg dose daily for 14 days	MA (*n* = 8) Control (*n* = 8)	Novel object recognition Spatial recognition memory*
O'Dell et al., (2011)	4mg/kg x 4 injections/2h	MA (*n* = 20) Control (*n* = 20)	Novel odour recognition*
Parsegian et al., (2011)	Self-admin: (.02mg dose) – 1 hour access (days 1-7) 6 hours access (days 8-21)	*n* = ~130 (MA and control)	Set-shifting*
Reichel et al., (2012)	Experiment 1: 4x4mg/kg per 2h Experiment 2: self-admin: .02mg infusion, 7 days 1h daily, 14 days 6h daily	E1 *n* = 21 total E2 *n* = 24 total	Novel object recognition (both groups)*
Reichel et al., (2011)	Self-admin: (.02mg dose) – 1 hour access (days 1-7), 6 hours access (days 8-21)	MA (*n* = 21) Control (*n* = 21)	Novel object recognition*
Richards et al., (1999)	Acute: 0.5, 1, 2, 4mg/kg 30 mins	MA (*n* = 19) –	Impulsivity*

Authors	Design (all compared to saline)	Sample size	Cognitive domains assessed
	before testing Chronic: 4mg/kg daily for 14 days	counterbalanced order	
Rogers et al., (2008)	Self-admin.: (.02mg dose) – Group 1: 1 hours of access (24 days). Group 2: 2 hours access (24 days). Group 3: 1-2 hours of access (days 1-10) followed by 14 days of 6-hour access	Group 1: *n* = 6, Group 2: *n* = 8, Group 3: *n* = 11, Control: *n* = 6	Novel object recognition* (Group 3)
Siegel et al., (2010)	5mg/kg injection daily for 10 days	MA (*n* = 44) Control (*n* = 40)	Novel object recognition * Novel location recognition* (female mice)
Simoes et al., (2007)	7 days of increasing doses in mg/kg (10, 15, 15, 20, 20, 25, 30) compared to single dose (30mg/kg)	MA escalating (*n* = 4), MA single dose (*n* = 4), Control (*n* = 4)	Spatial memory* (single dose)
Son et al., (2013)	10mg/kg x 4 injections/2h	MA (*n* = 16) Control (*n* = 17)	Impulsivity* - perseverative
Stolyarova et al., (2014)	All subjects: 1ml/kg 5 times per week for 4 weeks Group 1: .3mg/kg increments daily, culminating in 6mg/kg Group 2: single dose of 6mg/kg on last day treatment Group 3: Saline	Group 1 (*n* = 9) Group 2 (*n* = 6) Group 3 (*n* = 6)	Reversal learning*
Stolyarova et al., (2015)	.3mg/kg increments, culminating in 6mg/kg, once daily, 5 times per week for 4 weeks	MA (*n* = 6) Control (*n* = 6)	Impulsivity*
Thanos et al., (2016)	Injections daily for 16 weeks. High dose: 8mg/kg	High dose (*n* = 14) Low dose (*n* = 16)	Novel object recognition* (High dose compared to control)

Authors	Design (all compared to saline)	Sample size	Cognitive domains assessed
Thompson et al., (2017)	Low dose: 4mg/kg .1mg/kg increments, culminating in 4mg/kg x 3 daily injections for 14 days	Control (*n* = 14) MA (*n* = 16) Control (*n* = 16)	Impulsivity*
Vorhees et al., (2009)	10mg/kg x 4 injections/2h compared to 25mg/kg x 4 injections/2h or saline – three different times (postnatal days 1-10, 6-15, 11-20)	1-10 (Control *n* = 42, MA10 *n* = 40, MA25 *n* = 25), 6-15 (Control *n* = 41, MA10 *n* = 40, MA25 *n* = 60), 11-20 (Control *n* = 38, MA10 *n* = 38, MA25 *n* = 61)	Reversal learning* (all MA groups) Path integration learning* (6-15, 11-20)
Ye et al., (2014)	.3mg/kg increments for 10 days (ultimately 3mg/kg)	MA (*n* = 10) Control (*n* = 8)	Visual discrimination learning* Reversal learning*

Note: * denotes a significant difference between MA exposed and control groups

1.5.2 Human studies

While it is not possible to stringently control drug exposure conditions in human studies, the following studies provide insight into MUD in a naturalistic setting over an extended period of time. This section critically analyses the evidence for the impact of MUD on cognition, describing the volume of evidence and factors that might contribute to the level of deficit observed (e.g., length of abstinence). Findings for each domain are described and collectively integrated with the dual-systems model, providing a summary of direct and theoretical evidence that links MUD and cognitive deficits.

1.5.2.1 Learning & Memory

There is strong evidence for deficits in verbal memory in six studies of individuals with MUD (Cherner et al., 2010; Gonzalez et al., 2004; Hoffman et al., 2006; Johanson et al., 2006; Kalechstein et al., 2003; Woods et al., 2005). These deficits are observed in samples with short (5-14 days; Kalechstein et al., 2003), or long and highly variable periods of abstinence (three months to 18 years; Johanson et al., 2006). The evidence for deficits in visuospatial memory is less conclusive. Four studies found partial support for such a deficit (Morgan et al., 2012; Simon et al., 2000; Van Wyk & Stuart, 2012; Zhong et al., 2016), though differences may be partly explained by methodological shortcomings, such as differences in education/psychological wellbeing between controls and the MUD group (Zhong et al., 2016) and the inclusion of individuals currently using high levels of MA in addition to those who had ceased use (Van Wyk & Stuart, 2012). Other studies identified no significant difference in visuospatial memory between control participants and individuals with MUD

(Hoffman et al., 2006; Johanson et al., 2006; Simon, Dean, Cordova, Monterosso, & London, 2010), even in very early stages of abstinence (Kalechstein et al., 2003). Significant deficits in prospective memory, remembering to perform a planned action in future, have been observed in two studies (Iudicello et al., 2011; Rendell, Mazur, & Henry, 2009), however, cognitive deficits might have been exaggerated by a high proportion (50%) of participants with an HIV diagnosis (Iudicello et al., 2011) or a high average severity of MA use in a small sample (Rendell et al., 2009). These findings suggest that verbal memory is impaired in individuals with MUD, however evidence for visuospatial and prospective memory deficits is mixed; further well-controlled studies are required to elucidate these relationships.

1.5.2.2 Attentional function

Studies of individuals with MUD have examined performance in two forms of attention. Maintaining a similar level of attention to a stimulus over time (sustained attention) and attending to one stimulus while ignoring others (selective attention). Three studies have found significantly poorer sustained attention performance in individuals with MUD when compared to controls (Hosak et al., 2011; Johanson et al., 2006; Morgan et al., 2014), including community (Johanson et al., 2006; Morgan et al., 2014) and inpatient (Hosak et al., 2011) samples, and abstinence times averaging 2 months (Morgan et al, 2014) to one year (Johanson et al., 2006). However, these differences may be partly explained by the cognitive influence of high rates of HIV infection in one study (Morgan et al., 2014) and significant differences in level of education between control participants and individuals with MUD (Hosak et al., 2011). Furthermore, four studies did not find significant differences between individuals with

MUD and controls (Cherner et al., 2010; Hoffman et al., 2006; Kalechstein et al., 2003; Simon et al., 2000). However, some cognitive deficits may have been masked by a high proportion of individuals using MA on the day of testing (Simon et al., 2000) or an under-powered sample size (Kalechstein et al., 2003).

Three studies found significant deficits in selective attention when individuals with MUD were compared to controls (Hoffman et al., 2006; Salo et al., 2011; Simon et al., 2010), including mean abstinence of six months (Hoffman et al., 2006) to over a year (Salo et al., 2011). However, two studies did not support such a deficit (Kalechstein et al., 2003; Simon et al., 2000), but again might have been masked by limitations previously discussed. Although some studies have established deficits in sustained and selective attention, there is a similar proportion of conflicting findings, suggesting that better controlled studies are required to better understand these potential deficits.

1.5.2.3 Working memory and cognitive control

Cognitive control is a component of executive functioning that allows the moment-to-moment adaptive and deliberative processing of information that changes flexibly with changing goals (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). This function is underpinned by working memory, the ability to manage incoming stimuli and temporarily access and store information (Baddeley, 2012). Working memory is critical to the flexibility associated with cognitive control, and indeed, deficits in working memory are associated with poorer cognitive control (Brooks,

2016). Due to the integrated nature of these constructs in human cognition, they have been grouped together in this and following sections.

Significant deficits in working memory have been supported by four well-controlled studies with a range of periods of abstinence (Cherner et al., 2010; Rendell et al., 2009; Van der Plas, Crone, van den Wildenberg, Tranel, & Bechara, 2009; Zhong et al., 2016) and partially supported by one study (Van Wyk & Stuart, 2012). However, four studies did not identify a significant difference between individuals with MUD and controls in tests of working memory (Johanson et al., 2006; Kalechstein et al., 2003; Simon et al., 2010; Simon et al., 2000). However, limitations of these studies might have reduced the observability of working memory deficits, including testing during very early recovery (when acute effects may still influence results; Johanson et al., 2006), a small sample size (Kalechstein et al., 2003) or a high proportion of participants with MUD using on the day of testing (Simon et al., 2000). In summary, there is some evidence to suggest that individuals with MUD experience significant working memory deficits after cessation of use, but the inconsistency of evidence suggests that further research may be required.

Ten studies found significant deficits in all measures of cognitive control assessed in individuals with MUD (Cherner et al., 2010; Chung et al., 2007; Farhadian, Akbarfahimi, Abharian, Hosseini, & Shokri, 2017; Henry, Mazur, & Rendell, 2009; Hosak et al., 2012; Kim et al., 2006; Kim et al., 2009; Rendell et al., 2009; Salo et al., 2007; Simon et al., 2000). Deficits are significantly reduced in individuals with longer periods of abstinence (> 6 months) when compared to those with less than 6 months

of abstinence (Kim et al., 2006), and even short periods of abstinence (greater than two weeks) when compared to current users (Farhadian et al., 2017). Deficits were observed in early treatment (the first few weeks of abstinence; Kim et al., 2009) and in those with an average abstinence period of over one year (Salo et al., 2007). Additionally, six studies provided partial support for a deficit in cognitive control, where significant impairment was observed in some measures (Johanson et al., 2006; Kalechstein et al., 2003; Salo et al., 2009; Salo, Fassbender, Buonocore, & Ursu, 2013; Van der Plas et al., 2009; Zhong et al., 2016). However, two studies did not find a significant difference between individuals with MUD and control participants (Hoffman et al., 2006; Simon et al., 2010). Hoffman and colleagues (2006) did find slightly poorer performance in individuals with MUD, however this did not reach statistical significance, while a lack of significance in Simon and colleagues' (2010) findings may be partly explained by an underpowered sample. Overall, there is a strong volume of evidence in support of significant deficits in cognitive control in individuals with MUD.

1.5.2.4 Impulsivity

Impulsivity is characterised by acting without deliberation or consideration of consequences (Stevens et al., 2014) and can be understood as comprised of three components (Verdejo-Garcia, Lawrence, & Clark, 2008): inhibition (impulsive action), defined as suppression of an automatic response (Stevens et al., 2014); delay discounting, a preference for smaller, sooner rewards rather than larger delayed rewards (Perry & Carroll, 2008); and decision-making, the ability to objectively evaluate information in relation to complex tasks (Verdejo-Garcia et al., 2008). This

section evaluates these three domains of impulsivity in the context of individuals with MUD.

Impulsive action has been widely studied in individuals with MUD. Seven studies found significantly poorer performance in participants with MUD when compared to controls (Chung et al., 2007; Farhadian et al., 2017; Hosak et al., 2012; Kim et al., 2006; Kim et al., 2009; Nestor, Ghahremani, Monterosso, & London, 2011; Salo et al., 2013) and two found partial support (Cherner et al., 2010; Hosak et al., 2011). Deficits were observed in current users, those who recently ceased use (Farhadian et al., 2017), and those abstinent for an average of 2.5 years (Chung et al., 2007). A greater length of abstinence diminished the severity of deficits (Kim et al., 2006). However, five studies found no significant difference in inhibition between individuals with MUD and controls (Hoffman et al., 2006; Kalechstein et al., 2003; Morgan et al., 2014; Simon et al., 2010; Van der Plas et al., 2009). However, the lack of significant findings might have been influenced by a lack of power (Kalechstein et al., 2003; Simon et al., 2010) or masked by a high rate of HIV diagnoses in both MUD and control groups (Morgan et al., 2014). Collectively, previous findings support higher rates of inhibition in individuals with MUD, though this may be better characterised by further well-controlled studies with larger sample sizes.

Four studies have examined delay discounting, and all have found significantly poorer performance in individuals with MUD when compared to controls (Ellis et al., 2016; Hoffman et al., 2006; Hoffman et al., 2008; Monterosso et al., 2007). All studies included participants in the early stages of abstinence, from under two months

(Hoffman et al., 2008; Monterosso et al., 2007) to around six months (Ellis et al., 2016; Hoffman et al., 2006). Although the generalisability of two of these studies is limited by a small sample size (Hoffman et al., 2008; Monterosso et al., 2007), collectively, these findings suggest impairment in delay discounting in individuals with MUD when compared to controls.

Finally, decision-making has been explored in three studies (Kohno, Morales, Ghahremani, Hellemann, & London, 2014; Van der Plas et al., 2009; Wang et al., 2013), each of which found significantly poorer performance in participants with MUD when compared to controls. These studies primarily included individuals in early abstinence (around the first two weeks; Kohno et al., 2014; Van der Plas et al., 2009), however, Wang and colleagues' (2013) study included six groups (6 days, 14 days, 1 month, 3 months, 6 months, 1 year). Those in very early recovery (6 days, 14 days) showed significantly poorer decision-making than healthy controls, while decision-making improved as length of abstinence increased (performance at 12 months was significantly better than at 6 days). In one study, age and education differed significantly between individuals with MUD and controls (Van der Plas et al., 2009), however this was controlled for statistically. Overall, the current studies are well-controlled and explore a range of recovery periods. Although a greater number of studies is required to reinforce these findings, they provide strong preliminary evidence for a decision-making deficit in individuals with MUD.

Interim Conclusion

A summary of each study reviewed above is provided in Table 4. There is strong evidence of deficits in verbal memory, cognitive control and impulsivity (impulsive action, delay discounting, decision-making) and inconsistent evidence for attentional and working memory deficits. These findings are largely consistent with damage to the areas underpinning the dual-systems model, by which the 'top-down' system of cognitive control is significantly compromised, while the 'bottom-up' system (impulsivity) becomes sensitised. Although findings regarding deficits in attentional function and working memory were not as conclusive, this may be indicative of the interactive nature of executive functioning, whereby deficits in attention and working memory contribute to broader executive dysfunction (Willcutt et al., 2005; Logue & Gould, 2014). There was also strong evidence for impairment in verbal memory, which is not directly related to the dual-systems model, but is likely to be influenced by dysfunction in the executive system and impairments in strategic encoding and recall (Woods et al., 2005).

There is evidence that cognitive deficits in individuals with MUD are characterised by deficits in executive functioning, specifically in a lack of cognitive control and heightened levels of impulsivity. These areas of cognition are particularly relevant when making decisions relating to drug use (Khurana et al., 2017); it is therefore important to explore the functional consequences of these deficits. The following section explores whether cognitive deficits are predictive of treatment outcomes (including drug use and treatment retention and engagement).

Table 4. Sample size, instruments used and main findings of each human study of MUD and cognition

Authors	Sample size	Instruments	Main findings
Cherner et al., (2010)	MUD history (*n* = 54), Controls (*n* = 46)	Brief Visuospatial Memory Test-Revised (BVMT-R); Figure Memory Test; Halstead Category Test (HCT); Hopkins Verbal Learning Test-Revised (HVLT-R); Letter and category fluency tests; Paced Auditory Serial Addition Test (PASAT); Story Memory Test; Stroop Color-Word Incongruent; Trail Making Test-A/B; Wechsler Adult Intelligence Scale-III (WAIS-III); Wisconsin Card Sorting Test (WCST)	Verbal memory* Sustained attention Working memory* Cognitive control* Impulsive action*
Chung et al., (2007)	MUD history (*n* = 32), Controls (*n* = 30)	WCST	Cognitive control* Impulsive action*
Ellis et al., (2016)	MUD (*n* = 30), Controls (*n* = 24)	Delay Discounting Task (DDT)	Delay discounting*
Farhadian et al., (2017)	MUD (*n* = 41), MUD history (*n* = 60), Controls (*n* = 60)	WCST; Stroop Color Naming Test; Tower of London task	Cognitive control* Impulsive action*
Gonzalez et al., (2004)	MA abuse/dependence history (*n* = 26), MA and marijuana abuse/dependence history (*n* = 27), Controls (*n* = 41)	BVMT-R; Controlled Oral Word Association Test (COWAT); Figure Memory Test; HCT; HVLT-R; Letter and Category Fluency Test; PASAT; Story memory Test; Trail-Making Test B; WAIS-III	Verbal memory*

Authors	Sample size	Instruments	Main findings
Henry et al., (2009)	MUD history (*n* = 20), Controls (*n* = 20)	Rey Auditory Verbal Learning Test (RAVLT); Hayling Sentence Completion Test (HSCT); Controlled Oral Fluency	Cognitive control*
Hoffman et al., (2006)	MUD history (*n* = 41), Controls (*n* = 41)	Rey-Osterrieth Complex Figure Test; Babcock Story Recall (BSR); RAVLT; Trailmaking Test (TMT); Stroop Color Naming Test; WCST; DDT	Verbal memory* Visuospatial memory Sustained attention Selective attention* Cognitive control Impulsive action Delay discounting*
Hoffman et al., (2008)	MUD history (*n* = 20), Controls (*n* = 22)	DDT	Delay discounting*
Hosak et al., (2012)	MUD (*n* = 43), Controls (*n* = 52)	WCST	Cognitive control* Impulsive action*
Hosak et al., (2011)	MUD (*n* = 45), Controls (*n* = 118)	CPT	Sustained attention* Impulsive action*
Iudicello et al., (2011)	MUD (*n* = 39), Controls (*n* = 26)	Memory for Intentions Screening Test	Prospective memory*
Johanson et al., (2006)	MUD history (*n* = 16), Controls (*n* = 18)	California Verbal Learning Test (CVLT); Paired Associates Learning Task; Digit Symbol Substitution Test; Cambridge Automated Neuropsych Assessment Battery (CANTAB); WCST (CANTAB); Spatial Working	Verbal memory* Visuospatial memory Sustained attention* Working memory Cognitive control*

Authors	Sample size	Instruments	Main findings
		Memory Test (CANTAB); Delayed Match to Sample (CANTAB); Rapid Visual Information Processing (CANTAB); Stockings of Cambridge (CANTAB); Controlled Oral Fluency	
Kalechstein et al., (2003)	MUD (*n* = 27), Controls (*n* = 18)	Controlled Oral Fluency; Rey Complex Figure Test; Stroop Color-Word Task; Symbol Digit Modalities Test; Trail Making Test A/B; Wechsler Memory Scale-III; RAVLT	Verbal memory* Sustained attention Selective attention Working memory Cognitive control* Impulsive action
Kim et al., (2009)	MUD history (*n* = 24), Controls (*n* = 21)	WCST	Cognitive control* Impulsive action*
Kim et al., (2006)	MUD short-term abstinence (<6 mo.) (*n* = 11), MUD long-term abstinence (>6 mo.) (*n* = 18), Controls (*n* = 20)	WCST	Cognitive control* Impulsive action*
Kohno et al., (2014)	MUD (*n* = 25), Controls (*n* = 27)	Balloon Analogue Risk Task (BART)	Decision-making*
Monterosso et al., (2007)	MUD (*n* = 12), Controls (*n* = 17)	DDT	Impulsive action*
Morgan et al., (2014)	MUD (*n* = 35), Controls (*n* = 55)	Conners' Continuous Performance Test, Second Edition (CPT-II)	Sustained attention* Impulsive action

Authors	Sample size	Instruments	Main findings
Morgan et al., (2012)	MUD (*n* = 114), Controls (*n* = 110)	Brief Visuospatial Memory Test – Revised (BVMT)	Visuospatial memory*
Nestor et al., (2011)	MUD (*n* = 10), Controls (*n* = 18)	Stroop Color-Word Interference Task	Impulsive action*
Rendell et al., (2009)	MUD history (*n* = 20), Controls (*n* = 20)	Virtual Week Prospective Memory Task	Prospective memory* Working memory* Cognitive control*
Salo et al., (2013)	MUD history (*n* = 30), Controls (*n* = 30)	Stroop Color-Word Interference Task	Cognitive control* Impulsive action*
Salo et al., (2011)	MUD history (*n* = 30), Controls (*n* = 22)	Attentional Network Task	Selective attention*
Salo et al., (2009)	MUD recent abstinence (3 weeks to 6 months; *n* = 38), MUD long-term abstinence (> 1 year; *n* = 27), Controls (*n* = 33)	Stroop Attention Task	Cognitive control*
Salo et al., (2007)	MUD (*n* = 36), Controls (*n* = 16)	Stroop Attention Task	Cognitive control*

Authors	Sample size	Instruments	Main findings
Simon et al., (2010)	MUD (*n* = 27), Controls (*n* = 28)	TMT; Stroop Attention Task; Digit Span; Sentence Span; Reading Span; Missing Digit Span; Selective Reminding Test; Repeated Memory Test; WCST	Visuospatial memory Selective attention* Working memory Cognitive control Impulsive action
Simon et al., (2000)	MA abuse/dependence (*n* = 65), Controls (*n* = 80)	Repeated Memory Test; Stroop Color-Word Test; Trail Making Test A/B; Verbal Fluency Test; WAIS-Revised; WCST	Visuospatial memory* Sustained attention Selective attention Working memory Cognitive control*
Van der Plas et al., (2009)	MUD (*n* = 38), Controls (*n* = 36)	Global/Local Cognitive Flexibility Task; Iowa Gambling Task (IGT); Tic Tac Toe task; WCST; Stop Signal Task	Working memory* Cognitive control* Impulsive action Decision-making*
Van Wyk & Stuart, (2012)	MUD (*n* = 14), MUD history (*n* = 17), Controls (*n* = 18)	The Map Memory Test; Picture-Number Test (PNT); Auditory Number Span Test	Visuospatial memory*
Wang et al., (2013)	MUD (*n* = 183), Controls (*n* = 39)	IGT	Decision-making*
Woods et al., (2005)	MUD (*n* = 87), Controls (*n* = 71)	HVLT	Verbal memory*
Zhong et al., (2016)	MUD (*n* = 54), Controls (*n* = 58)	CogState Battery: International Shopping List Task	Visuospatial memory* Working memory* Cognitive control*

Note: * denotes a significant difference between MUD and control groups

1.6 Cognitive deficits and clinical outcomes

Poorer treatment outcomes are a major consequence of cognitive dysfunction in substance dependence (Stevens et al., 2014). Indeed, the dual-systems model implies that cognitive deficits are likely to result in greater substance use, where the cognitive control system is unable to exert control over impulses to use substances (Khurana et al., 2017). Higher impulsivity and diminished control may also impact the ability to engage with treatment (difficulty maintaining focus; Carroll et al., 2011) and remain in treatment (difficulty evaluating long-term benefits; Washio et al., 2011). The importance of understanding these links is reinforced by high vulnerability to relapse and disengagement among individuals with MUD in the first two months of treatment (Brecht & Herbeck, 2014). This section examines the longitudinal, predictive link between cognitive function in early treatment and subsequent treatment outcomes. As there are relatively few studies that directly examine MUD, this section also discusses stimulants that are associated with similar difficulties in treatment, such as high rates of relapse and poor engagement (e.g., cocaine; Penberthy, Ait-Daoud, Vaughan, & Fanning, 2010; nicotine; Zhou et al., 2009). Participants were tested in early treatment and then followed up to confirm abstinence/completion of a treatment program or their level of engagement. Studies examined whether differences between groups (e.g., completers vs. non-completers) were significant or whether cognitive values at baseline were predictive of longitudinal treatment outcomes.

1.6.1 Learning and Memory

Although MUD samples have not been assessed, five studies have examined the link between learning/memory and cocaine-dependence outcomes (Aharonovich,

Nunes, & Hasin, 2003; Aharonovich et al., 2006; Fagan et al., 2015; Fox, Jackson, & Sinha, 2009; Turner, LaRowe, Horner, Herron, & Malcolm, 2009). Deficits in visual and verbal memory were significantly greater in those who dropped out of treatment when compared to individuals completing the program (Aharonovich et al., 2006), while declarative, recognition and auditory memory have been significantly associated with higher levels of cocaine use after inpatient treatment (Fox et al., 2009). However, three studies did not find any support for the role of verbal learning and memory in either treatment abstinence and retention (Aharonovich et al., 2003; Turner et al., 2009) or appointment attendance/medication adherence (Fagan et al., 2015). However, the role of learning and memory might have been masked by small sample size (Aharonovich et al., 2003) and samples that may not fully reflect the cocaine-dependent population (e.g., comorbid bipolar disorder; Fagan et al., 2015; taking pharmacological medication; Turner et al., 2009). In summary, although there is some evidence to suggest a link between learning and memory and treatment outcomes in stimulant users, conflicting findings suggest that further well-controlled research is required to clearly establish this relationship.

1.6.2 Attentional function

There is strong support for the role of attentional function in predicting treatment outcomes. Five studies found significant support for this link (Aharonovich et al., 2003; Aharonovich et al., 2006; Fagan et al., 2015; Harris et al., 2014; Streeter et al., 2008), while two found partial support (Carroll et al., 2011; Chen, Chen, & Wang, 2015). Sustained or selective attention predicted attendance or number of sessions completed in psychologically-based (e.g., Cognitive Behavioural Therapy; CBT)

programs of substance dependence in six of these studies (Aharonovich et al., 2003; Aharonovich et al., 2006; Carroll et al., 2011; Fagan et al., 2015; Harris et al., 2014; Streeter et al., 2008). One study found that attention was predictive of relapse but not dropout in a sample of individuals with MUD (Chen et al., 2015), while another study found that sustained attention predicted the number of psychological treatment modules completed and days in treatment, but not abstinence (Carroll et al., 2011).

Although these findings primarily relate to cocaine (Aharonovich et al., 2003; Aharonovich et al., 2006; Carroll et al., 2011; Fagan et al., 2015; Streeter et al., 2008) or nicotine (Harris et al., 2014), all available research reported either complete or partial support for a link between attentional function and psychologically-based treatment outcomes and suggests a consistent link between the variables. The association between attentional function and drug use/relapse is less conclusive, with one study finding a significant relationship (Chen et al., 2015) and another finding no relationship (Carroll et al., 2011), and suggests that further well-controlled research is required.

1.6.3 Working memory and cognitive control

Two studies have directly examined the predictive value of working memory on substance dependence outcomes (Dean et al., 2009; Patterson et al., 2010). In a MUD sample, working memory performance significantly predicted completion of a 12-week treatment program, though this relationship was no longer significant after adjusting for baseline MA use (Dean et al., 2009). Poorer working memory performance (slower reaction time under highest working memory load) was also significantly negatively

associated with days to nicotine relapse (Patterson et al., 2010). Other measures of cognitive control have significantly predicted stimulant treatment outcomes in eight studies, including relapse (Adinoff et al., 2016; Carroll et al., 2011; Powell, Dawkins, West, Powell, & Pickering, 2010), treatment retention/completion (Aharonovich et al., 2003; Aharonovich et al., 2006; Streeter et al., 2008; Turner et al., 2009) and adherence to a treatment program (Fagan et al., 2015). However, three of these studies found only partial support for the relationship, where not all measures of cognitive control were significantly predictive (Aharonovich et al., 2006), abstinence was predicted at only one of three time points (Powell et al., 2010) or cognitive control did not predict other treatment-related outcomes (treatment sessions completed; Carroll et al., 2011). Furthermore, two studies found no significant relationship between cognitive control and treatment outcomes (Chen et al., 2015; Harris et al., 2014), however relationships may have been masked by liberal inclusion criteria (i.e., participants who met criteria for MA abuse rather than dependence; Chen et al., 2015) or a small sample size (Harris et al., 2014).

Overall, the available evidence supports a relationship between working memory/cognitive control and a range of treatment outcomes (relapse, treatment completion and adherence). However, there are some conflicting findings, and further evidence is required specifically examining MUD samples.

1.6.4 Impulsivity

All three forms of impulsivity have been explored in the context of treatment outcomes. Delay discounting significantly predicted treatment retention (Stevens et

al., 2014) and abstinence (Sheffer et al., 2012; Washio et al., 2011) in primarily stimulant dependent individuals. However, Harris and colleagues (2014) found that delay discounting was not a significant predictor of reduction in nicotine use, but may be partly explained by the young age of the sample (adolescents) and the tendency for delay-discounting to be higher and less-variable in younger individuals and therefore less useful as a predictor.

Two studies have supported a link between impulsive action and treatment outcomes, predicting nicotine abstinence at 1 week, 1 month, and 3 months (Powell et al., 2010) and relapse in cocaine-dependent individuals, but not days in treatment or sessions completed (Carroll et al., 2011).

Decision-making has been examined in stimulant-dependent individuals in five studies, and has predicted relapse at 3 months (Verdejo-Garcia et al., 2014), proportion of positive drug tests (Nejtek, Kaiser, Zhang, & Djokovic, 2013), dropout from treatment for MUD (Chen et al., 2015) and psychological sessions/modules completed and days of abstinence (Carroll et al., 2011). However, other studies found that decision-making did not predict days in treatment (Carroll et al., 2011) or relapse (Adinoff et al., 2016; Chen et al., 2015).

Overall, these findings are mixed, and suggest that while there is evidence that delay discounting and impulsive action frequently predict relapse, it is unclear what role these constructs play in predicting retention and adherence to treatment. Furthermore, decision-making shows a relationship with treatment outcomes broadly

but does not show a consistent pattern (i.e., there is conflicting evidence for relapse and treatment retention, while one study supports a link with treatment engagement). Additional well-controlled studies are needed in this domain.

Interim Conclusion

There is strong evidence of some specific domains of cognition predicting specific treatment outcomes in individuals with MUD. While evidence for the role of learning and memory was inconclusive for all treatment outcomes, there is strong evidence linking attentional function with outcomes in psychologically-focused treatment (e.g., CBT), but not relapse or drug use. Findings relating to cognitive control and working memory suggest an association with relapse and retention, and while delay discounting and impulsive action tended to predict relapse, decision-making was predictive of both relapse and treatment retention or engagement but only in a small number of studies. These findings collectively suggest that deficits in executive functioning are predictive of treatment outcomes in a range of domains.. Deficits in these systems may mean that individuals cannot effectively inhibit impulses to leave therapy, to begin using again or may make engagement with therapy difficult. However, it appears that these relationships are complex, where different components of the executive system impair different treatment outcomes, which highlights the importance of a nuanced approach of the key contributors to each outcome. Indeed, current cognitive and behavioural interventions show relatively consistent outcomes across modality (i.e., CBT, Motivational Interviewing, Contingency Management) and substance (Dutra et al., 2008), while pharmacological interventions provide limited adjunctive benefit (Hill & Sofuoglu, 2007). Therefore,

identifying individual factors such as cognitive function, that may enhance the effectiveness of psychological interventions is an area worthy of further exploration.

The treatment outcomes discussed in this section incorporate important indices of recovery (cessation of drug use, treatment retention/engagement/motivation), however cognitive deficits are also likely to have a broader impact on substance dependent individuals, and impair day-to-day functioning. Therefore, the following section reviews research which explores associations between cognitive deficits and daily functioning in substance dependent individuals and interprets these findings in the context of the dual-systems model.

1.7 Stimulant dependence related cognitive deficits and quality of life/daily functioning outcomes

Cognitive deficits have an impact on different elements of daily functioning. Impaired areas include practical tasks such as household chores and medication adherence, but also more complex functions such as social interactions, employment, and the ability to self-reflect or manage emotional distress (Schmitter-Edgecombe, Woo, & Greeley, 2009). Deficits in these areas impact an individual broadly and can be conceptualised as reflecting a diminished level of quality of life (Land, Michalos, & Sirgy, 2012; QoL). QoL is a person's subjective consideration of their position in life in the context of goals and expectations associated with their culture and values (World Health Organization, 1998), and incorporates physical, psychological, social and environmental domains. Individuals with MUD exhibit significantly lower levels of QoL when compared to a normative sample (Gonzales et al., 2011), while those entering treatment are typically concerned with improving their lives in a range of areas associated with QoL (Laudet, Becker, & White, 2009). QoL is an important outcome measure that can have an almost bidirectional relationship with treatment outcomes (Gonzales et al., 2009), but also effectively integrates abstinence and improvement in other domains of life (Laudet, 2011). The importance of QoL has been reflected in the recommendation that it be incorporated as a primary outcome measure of substance dependence treatment in a recent consensus paper (Tiffany, Friedman, Greenfield, Hasin, & Jackson, 2012). The following section reviews the literature linking cognitive deficits with functional outcomes and QoL in individuals dependent on MA or similar stimulants.

1.7.1 Learning and Memory

Two studies have found evidence that learning and memory abilities significantly predict functional outcomes in individuals with MUD. Spatial and delayed memory predicted poorer emotional state and higher depression ratings (Herbeck & Brecht, 2013), while verbal and visual learning predicted unemployment in another study (Weber et al., 2012). Both of these studies had long periods of abstinence (average 5 months; Weber et al., 2012; nearly 50% abstinent for over 5 years; Herbeck & Brecht, 2013), which suggests persistent links between these variables, however conclusions around longitudinal relationships cannot be drawn due to the cross-sectional design of each study.

1.7.2 Attentional function

One study has examined the role of sustained attention in functional outcomes among individuals with MUD (Morgan et al., 2014). Sustained attention significantly predicted deficits in performing daily tasks associated with independent community functioning (e.g., communication, transportation, comprehension/social planning) and cognitive difficulties in everyday life (e.g. cognitive functions associated with employment, language, memory). However, sustained attention did not predict instrumental activities of daily living or driving violations in a car simulator. Although very limited conclusions can be drawn from a single study, results in this study suggest that sustained attention deficits tended to impact daily tasks requiring higher complexity, leaving simpler tasks (Activities of Daily Living) less affected.

1.7.3 Working memory and cognitive control

Five studies have found that cognitive control (Casaletto et al., 2015; Cattie et al., 2012; Henry, Minassian, & Perry, 2010; Herbeck & Brecht, 2013; Weber et al., 2012) and working memory (Casaletto et al., 2015; Weber et al., 2012) significantly predict daily functioning outcomes. Two studies suggested generalised deficits in which cognitive control significantly predicted decline in a range of routine daily tasks (e.g., employment, financial management, food preparation, housekeeping; Cattie et al., 2012; Henry et al., 2010). In more specific deficits, unemployment (Weber et al., 2012), and lower mood and poorer emotional state (Herbeck & Brecht, 2013) have also been identified as consequences of cognitive control deficits. Furthermore, deficient cognitive control is also predictive of overestimation of memory skills (poorer metamemory; Casaletto et al., 2015), which is likely to exacerbate problems with daily functioning. In one study, cognitive control did not significantly predict social functioning (Cunha, Bechara, de Andrade, & Nicastri, 2011), however, this study had a small sample, and may not have been large enough to detect the cognitive control deficits that might predict social dysfunction. Despite limitations in some of the previously mentioned studies (e.g., small sample size; Henry et al., 2010; sample that may not represent dependent users; Cattie et al., 2012), these findings provide evidence for the impact of cognitive control on broad and specific domains of daily functioning.

1.7.4 Impulsivity

Five studies have examined the role of impulsive action and delay discounting on everyday function. Three studies found that impulsive action is significantly

predictive of cognitive difficulties in daily life and problems with routine daily tasks (Cattie et al., 2012; Morgan et al., 2014) and QoL and social dysfunction (Albein-Urios, Pilatti, Lozano, Martínez-González, & Verdejo-García, 2014). Although these samples exhibited relatively high rates of Hepatitis C (Cattie et al., 2012), HIV infection (Morgan et al., 2014) and personality disorders (Albein-Urios et al., 2014), high rates of these conditions are reflective of the MUD population (Darke, Kaye, McKetin, & Duflou, 2008; Gonzales, Marinelli-Casey, Shoptaw, Ang, & Rawson, 2006; Lubman et al., 2016), and do not substantially detract from the findings. One well-controlled study found significantly higher delay-discounting in individuals with MUD, that was accompanied by subjective deficits in daily functioning (e.g. planning and organisation of tasks, emotional control, self-monitoring behaviour; Ellis et al., 2016), while another found deficits in monitoring time in cocaine-dependent individuals (Wittman, Leland, Churan, & Paulus, 2007). Overall, these findings suggest a relationship between impulsivity and broad measures of daily functioning and social interactions, that warrant further examination.

Interim Conclusion

Overall, although there were studies that supported the link between learning, memory and attention with daily functioning/QoL, these findings are too few to draw definite conclusions, and further research may be warranted to better understand potential relationships. There was stronger support for cognitive control/working memory (five studies) and impulsivity (five studies). These findings are consistent with the dual-systems model, and suggest that poor cognitive control not only impacts drug use and treatment outcomes, but can have a broad impact on daily functioning

activities that range in complexity (e.g., social planning/interaction, organising transport). Poorer cognitive control and higher impulsivity may contribute to disruption of communication and planning and result in engaging with activities that provide short-term pleasure but distress over the long-term. These findings provide evidence of a general relationship between cognitive control/working memory and impulsivity with QoL outcomes, however an understanding of direct relationships between areas of cognition and specific domains of QoL will increase the utility and applicability of this link in a clinical setting.

1.8 Conclusions and ways forward

What we know

This review has described the neurobiological and chemical function of MA, the epidemiology of MA in the Australian context, and explored the social consequences of MUD. This review has also described the cognitive impact of MA exposure in animals and humans and the consequences for treatment outcomes and daily functioning/QoL. There is evidence of cognitive deficits in animals and humans that are consistent with executive dysfunction associated with the compromise of cognitive control and sensitisation of impulsive urges (the dual-systems model). This is also consistent with the structural and functional changes that have been observed in neuroimaging of individuals with MUD. These changes and deficits have broad consequences, and include a greater likelihood of relapse, disengagement from treatment, and deficits in day-to-day functioning (e.g., social interaction, arranging transport). The upcoming section integrates the findings of this review with outcomes that are characteristically poor in individuals with MUD (e.g., high rates of relapse; Brecht & Herbeck, 2014; poor treatment motivation; Fiorentine, Nakashima, & Anglin, 1999; low levels of QoL; Gonzales et al., 2011) to formulate the research questions addressed in this thesis.

What we don't know

Results linking drug use with cognitive control, working memory and impulsivity are consistent with the dual-systems model, by which heightened impulsivity and diminished cognitive control result in a greater likelihood of drug use (Adinoff et al., 2016; Carroll et al., 2011; Patterson et al., 2010; Powell et al., 2010).

However, it is also important to consider the interactional nature of the dual-systems model (i.e., the positive feedback loop between deficits in cognitive control and increased impulsivity). This has been demonstrated in research showing that working memory improvements result in significantly improved delay discounting in stimulant users (Bickel, Yi, Landes, Hill, & Baxter, 2011; Brooks et al., 2017), while those with significant working memory deficits have difficulty regulating impulsive urges (Houben, Wiers, & Jansen, 2011). These findings suggest that although working memory and impulsivity may both independently predict stimulant use, impulsivity may moderate the relationship between working memory and use.

The relationship between cognition and motivation/engagement with psychologically-based treatment is also complex. There is strong evidence to support the role of attentional function in this process (Aharonovich et al., 2003; Aharonovich et al., 2006; Carroll et al., 2011; Fagan et al., 2015; Harris et al., 2014; Streeter et al., 2008), and indeed, the cognitive and behavioural components of psychological therapy do require the ability to maintain attention over time (Sofuoglu, DeVito, Waters, & Carroll, 2013). However, while attention is important for focusing on treatment content, decision-making is also likely to play an important role in evaluating the costs and benefits of continued engagement. There is some empirical support for the importance of decision-making in treatment outcomes (Carroll et al., 2011; Chen et al., 2015), however, from a theoretical perspective, effort-based decision-making (a sub-component of decision-making) is strongly linked to motivation/engagement. Effort-based decision-making measures motivational elements of decision-making, where individuals expend energy for an uncertain

reward (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009). Effort-based decision-making may be analogous to the treatment process, where a 'decisional balance', evaluating the costs and benefits of treatment involvement is engaged in by participants (Le Berre et al., 2012). Overall, although it appears that the factors driving treatment motivation are complex, there is empirical and theoretical support for the involvement of attentional function and effort-based decision-making that warrants further exploration.

Furthermore, there is strong evidence for the role of cognitive control/working memory and impulsivity in daily functioning and QoL outcomes (Albein-Urios et al., 2014; Cattie et al., 2012; Herbeck & Brecht, 2013; Morgan et al., 2014). Although this evidence suggests a significant generalised effect of both cognitive control and impulsivity on QoL, specific relationships between these constructs and separate domains of QoL have not been explored. Specifically, different forms of impulsivity (action, delay discounting) appear to impact QoL differentially (Stevens et al., 2014). However, previous findings have examined domains of impulsivity separately in the context of a general measure of QoL (e.g., Albein-Urios et al., 2014) or examined a single domain of QoL (e.g., Herbeck & Brecht, 2013). This relationship is likely to be better understood with a systematic exploration of the predictive value of both types of impulsivity on each domain of QoL.

Cognitive function has shown utility in longitudinally predicting treatment outcomes in individuals with MUD (Chen et al., 2015), and can be accommodated and rehabilitated in treatment (Sofuoglu, DeVito, Waters, & Carroll, 2016). However

previous studies have exhibited a range of limitations that will be addressed in this thesis. MUD individuals are particularly vulnerable to poor outcomes in early treatment (the first six to eight weeks; Brecht & Herbeck, 2014), however many previous studies have utilised a cross-sectional (e.g., Herbeck & Brecht, 2013; Morgan et al., 2014) or moderate to long-term (>3 months; e.g., Aharonovich et al., 2006; Fox et al., 2009) follow up period. The prospective design of the current study will provide insight into longitudinal predictors of treatment outcomes, while incorporating a period of particularly high vulnerability by utilising a six-week follow-up. Past studies have also frequently utilised small sample sizes (e.g., Aharonovich et al., 2003; Harris et al., 2014), limiting the power to detect meaningful differences between groups or the predictive value of specific measures. In this thesis, our sample size will be determined *a priori* and based on effect sizes observed in similar previous studies (e.g., Morgan et al., 2014). Furthermore, our recruitment strategy will reflect a balance of control and representativeness, by including a range of recruitment sites (i.e., residential rehabilitation, outpatient therapy, detoxification), excluding participants with low prevalence psychological or physical conditions that are likely to influence cognition (e.g., intellectual disability, bipolar or psychotic disorders) and including but statistically controlling for conditions that are commonly observed in the MUD population (e.g., depressive symptoms, marijuana use/dependence, alcohol use/dependence; Lubman et al., 2016; Luan et al., 2017).

As such, this thesis will use a stringently recruited sample to examine the predictive value of cognitive variables (identified in the current review) on relapse, and change in treatment motivation and QoL. The overarching goal of this thesis is to

address the methodological limitations of previous research and integrate links between cognitive function and a range of treatment outcomes into a cohesive narrative underpinned by the dual-systems model.

1.8.1 Aims and Hypotheses

This section summarises the aims and hypotheses developed after a review of the literature in preceding sections. This thesis has three aims, which were addressed with three studies.

Aim 1: To examine the longitudinal predictive value of cognitive measures of the dual-systems model (cognitive control and impulsivity) and their interaction on levels of MA use during early treatment in individuals with MUD.

Hypothesis 1 (Study 1): We hypothesised that poorer performance in working memory tasks and higher levels of impulsivity would each significantly predict higher levels of MA use.

Hypothesis 2 (Study 1): We hypothesised that impulsivity would moderate the relationship between working memory and MA use, according to the dual-systems model.

Aim 2: To identify how elements of impulsivity are predictive of different components of quality of life. Specifically, identifying the relative contributions of delay discounting and impulsive action to change in quality of life in early treatment.

Hypothesis (Study 2): We hypothesised that higher levels of delay discounting and impulsive action would significantly predict less change in social, psychological and physical aspects of quality of life in early recovery from MUD.

Aim 3: To identify the predictive value of cognitive measures of sustained attention and effort-based decision-making on change in treatment motivation in early treatment for MUD.

Hypothesis (Study 3): We hypothesised that lower levels of sustained attention and poorer effort-based decision-making would predict a lower change in early treatment motivation.

CHAPTER TWO: EXPANDED METHODOLOGY

2 Introduction

This chapter provides an overview of the general methodology of the studies that comprise this thesis, a more detailed description than can be provided in each individual manuscript. This section includes the nuisance and demographic variables that were recorded, predictor and outcome variables, a detailed procedures section, and a table that describes the design, participants and statistical analysis of the four studies.

2.1 Participants

The overall sample consisted of 108 adults (Age M = 31.1, SD = 7.2, 81 males). This sample size was determined *a priori* with 80% power, α = .05, a moderate effect size and multiple regression analysis with a maximum of ten predictors, performed across all outcomes (based on similar previous studies; e.g., drug use: Nejtek et al., 2013; treatment engagement: Carroll et al., 2011; QoL: Morgan et al., 2014). The study allowed for an attrition rate of 30%, based on studies of individuals with MUD over a similar follow-up period (Simon et al., 2010). Eighty participants were followed up, there were no significant differences on background or cognitive characteristics between those who completed the study and those who dropped out (t_{max} = -1.24 p_{min} = .219).

Participants were recruited through private and public inpatient and outpatient drug treatment services in Melbourne, Australia. These services provided detoxification, rehabilitation and/or counselling programs. Services that assisted with recruitment included Malvern Private Hospital, Wellington House (Eastern Health),

South Eastern Alcohol and Drug Service (SEADS), CoHealth and the Stepping Up Consortium. Additionally, all participants but one entered treatment voluntarily, ensuring a sample that is reflective of the wider treatment-seeking population.

2.2 Background measures

Centre for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977*):* This 20-item self-report measure assesses depressive affect and mood. Scores range from 0-60, with each question assigned a rating from 0-3, based on the frequency of symptoms (e.g. 'My sleep was restless' from 'Rarely – less than one day per week' to 'Most or all of the time – 5-7 days per week'), where a higher rating indicates a greater number of symptoms. Four reverse-worded items are also included (e.g. 'I felt I was just as good as other people'), these are reverse-scored. This measure is not diagnostic, however, a score of 16 or more is indicative of an individual who may be at risk of clinical depression (Radloff, 1977). This measure has been validated in a drug-using sample (Golub et al., 2004), and shows internal consistency reliability from .63-.93 in healthy and clinical groups, test-retest reliability of .61 (Devins et al., 1988), and high convergent validity (Radloff, 1977). The current study used the CES-D as a continuous measure to allow for the statistical control of low mood. Depressive symptoms are commonly observed in early recovery from MUD (Luan et al., 2017).

Severity of Dependence Scale (SDS): This five-item self-report questionnaire measures psychological dependence on drugs or alcohol (loss of control, concern about use, difficulty ceasing use; Gossop et al., 1995). All items load heavily on one item (Cronbach's *alpha* = .81 to .90), which is strongly correlated with the total score and

levels of use (Gossop et al., 1995). A cut-off of four or greater shows 71% sensitivity and 77% specificity in individuals with MUD (McKetin, McLaren, Lubman, & Hides, 2006). In the current research, the SDS was used a continuous measure that allowed statistical control of level of dependence on MA, cannabis and alcohol.

Structured Clinical Interview for the DSM-IV (SCID; First, Spitzer, Gibbon & Williams, 1996): This is an interview schedule that screens for disorders described in the DSM-IV, and shows strong reliability and validity for detecting substance dependence (Hasin, Hatzenbuehler, Keyes, & Ogburn, 2006). It was used in the current research to determine whether participants met criteria for a Major Depressive Episode and MUD. Participants were also screened for dependence on drugs other than MA, which resulted in exclusion from the study (except for those dependent on alcohol or cannabis).

Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II): This is a brief measure of cognitive functioning and is comprised of four tasks measuring performance IQ (visuospatial abilities) and verbal IQ (language comprehension and expression). The WASI-II has demonstrated high reliability and validity (Wechsler & Hsiao-pin, 2011) and has previously been used in estimating cognitive function in individuals with MUD (Cuzen, Koopowitz, Ferrett, Stein, & Yurgelen-Todd, 2015). In the current research, this measure was used to screen individuals with intellectual disability (IQ < 70), who were excluded from the study.

2.3 Cognitive measures

Continuous Performance Test-2 (CPT-2): This 14-minute, computer-based task is a measure of sustained attention and impulsivity (Conners, 2004). Participants are asked to press the space-bar in response to white letters of the Latin alphabet appearing on a black screen, except for the letter 'X'. Letters are presented for 250ms each, and new stimuli appear at varying intervals of 1, 2, or 4s. This test shows good levels of internal consistency reliability (Cronbach's *alpha* = .66 to .95), and moderate convergent and construct validity (Strauss, Sherman, & Spreen, 2006). The predictor variables used in the current study were commission errors (motor disinhibition) and detectability (cognitive disinhibition) in Chapter Four, and hit reaction time standard error (sustained attention) in Chapter Five.

Delay Discounting Task (DDT; Kirby, Petry, & Bickel, 1999*):* This task measures the tendency to discount the value of a reward as it becomes temporally distant. In this 27-item self-report measure, participants are presented with hypothetical money options: an amount to be received immediately or a larger amount to be received after a delay (e.g. 'Would you prefer $31 today or $85 in 7 days?'). This measure shows good predictive validity (Kirby et al., 1999), internal consistency reliability (Richards, Zhang, Mitchell, & De Wit, 1999) and test-retest reliability (Beck & Triplett, 2009). The predictor variable used in Chapters Three and Four was the *k* value – a number that indicates the rate at which monetary value is degraded for each participant, where larger values indicate higher levels of impulsivity.

Digit Span (Wechsler, 2008): This task measures working memory (the ability to hold multiple pieces of information in mind for a brief period). An examiner reads out numbers at a rate of one second per number. After the examiner has finished, the participant repeats back these numbers. After the completion of each trial, the length of the number sequence increases by one number. Within each trial there are two items (number sequences of equal length); the task is discontinued when a participant responds incorrectly to both items within a trial. There are three components to the task: forwards repetition, backwards repetition, and sequencing (rearranging numbers in order from lowest to highest). This task is a subtest of the Wechsler Adult Intelligence Scale-Fourth Edition and exhibits strong psychometric properties (Wechsler, 2008). The value for longest digit span sequencing was used as a predictor variable in Chapter Three.

Worth the Effort Task (EEfRT; Treadway et al., 2009): This measure assesses effort-based decision-making (the willingness to expend energy for an uncertain reward). Participants press a button on a computer keyboard repeatedly to receive a reward. Participants select either the easy task ($1 reward) or the hard task (a reward ranging between $1.24 and $4.30). To complete the easy task, participants make 30 button presses with their dominant index finger in seven seconds. To complete the hard task, participants make 100 button presses in 20 seconds with their non-dominant little finger. Rewards are not guaranteed to be paid; prior to selecting their task, the screen displays the reward amount and the probability of being paid at three levels (12%, 50%, 88%). This measure has shown good external and concurrent validity (Horan et al., 2015), and test-retest reliability (Reddy et al., 2015). In Chapter Five, the proportion

of selections of the hard task in the medium (50%) probability conditions was used as a predictor variable.

2.4 Outcome Measures

Contemplation Ladder (Biener & Abrams, 1991): This measure assesses treatment readiness and motivation and consists of ten statements relating to recovery and motivation towards treatment (i.e. the bottom 'rung' is the statement "No thought about quitting. I cannot live without drugs", the top 'rung' is the statement, "I have changed my drug use and will never go back to the way I used drugs before.") The Contemplation Ladder has shown good convergent and concurrent validity (Amodei & Lamb, 2004; Hogue, Dauber, & Morgenstern, 2010) and discriminant and predictive validity (Hogue et al., 2010). In Chapter Five, the dependent variable was change from in Contemplation Ladder score from baseline to follow-up session (Contemplation Ladder^{T2} – Contemplation Ladder^{T1}).

Methamphetamine Concentration in Hair: A 1cm. strand of hair was taken from each participant at their follow-up testing session. This length is the approximate rate of hair growth in one month. The hair was analysed using gas chromatography-mass spectrometry (GC-MS) to determine the level of MA metabolites present, measured in ng/mg (Meng et al., 2009). This metric provides and objective and continuous measure of MA use and has been recommended in consensus guidelines as the most appropriate technique for assessing an extended period of drug use (Donovan et al., 2012). Level of use in the month before follow-up session was used as the outcome measure in Chapter Three.

The Timeline Followback (*TLFB*; Sobell & Sobell, 1996): This self-report measure records the number of days an individual has used drugs or alcohol in the past month. The TLFB consists of a calendar of the past year on which participants mark their days of use with the *ü* symbol. The TLFB has shown convergent, discriminant, test-retest validity and high levels of agreement with informants and objective measures of drug use (Fals-Stewart, O'Farrell, Freitas, McFarlin, & Rutigliano, 2000). The TLFB has also previously been used with MUD samples (Hides et al., 2015; Winhusen et al., 2013). In the current research, this measure was combined with hair sample data to confirm drug use frequency.

World Health Organisation Quality of Life Scale – Brief Version (WHOQOL-BREF): This 26-item self-report scale measures an individual's subjective assessment of their position in life in the context of their culture and values, and consists of four domains: physical, psychological, social and environmental quality of life (World Health Organisation, 1998). Each item is measured from 1-5 on a Likert scale (e.g., 'How satisfied are you with your health?' from 1 – 'Very poor' to 5 – 'Very good'). The WHOQOL-BREF is a valid tool in substance dependent samples (Chang, Wang, Tang, Cheng, & Lin, 2014; Da Silva Lima, Fleck, Pechansky, De Boni, & Sukop, 2005), and has shown excellent internal consistency reliability, discriminant and construct validity (Skevington, Lofty, & O'Connell, 2004). Social, psychological, physical and environmental domain change scores were used as outcome measures in Chapter Four.

2.5 Procedures

The study was approved by the Eastern Health Human Research Ethics Committee (E52/1213). Participants were introduced to the study by a clinician involved in their care, and were subsequently screened and consented by a researcher. The first testing session occurred within 3 weeks of last use of MA, while the follow-up session took place six weeks after the baseline session. In both sessions, participants were tested on cognitive predictor measures. QoL and treatment motivation were also measured at both time points so that change scores could be calculated. A hair sample (1 cm. length) was taken at the follow-up session to test for MA use over the preceding month. Follow-up was arranged by contacting participants by telephone or email or facilitated by their treating clinician. Participants received a $AUD40 gift card after completing both assessment sessions. Testing was conducted by the first two authors, who have post-graduate training in clinical assessment methods.

Table 1: Design, number of participants, cognitive tasks, outcome measures and analytical technique used in each study.

Study (Chapter)	Design	Participants	Cognitive Tasks	Outcome measure	Analytical Technique
1 (4)	Longitudinal, observational cohort study	One hundred and eight adults (75% male; age *M* = 31.1; years of use *M* = 6.9; days use past month *M* = 23.4). Eighty at follow-up.	Delay Discounting Task (DDT); Digit Span Sequencing (DSS)	1cm. length of hair. Gas-Chromatography Mass-Spectrometry (GC-MS) used to analyse level of methamphetamine use over past month (ng./mg.)	Multiple regression to examine the predictive value of DDT and DSS on methamphetamine use after controlling for nuisance variables. Moderation analysis to determine if relationship between DSS and methamphetamine use moderated by DDT.
2 (5)	Longitudinal, observational cohort study	One hundred and eight adults (75% male; age *M* = 31.1; years of use *M* = 6.9; days use past month *M* = 23.4). Eighty at follow-up.	CPT-2; DDT	World Health Organization Quality of Life measure Brief Version (WHOQoL-BREF), social, psychological, physical, environmental domains (change score)	Four multiple regression analyses to determine predictive value of two CPT-2 measures and one DDT measure on four domains of quality of life, after controlling for nuisance variables.
3 (6)	Longitudinal, observational cohort study	Seventy-two adults (70% male; age *M* = 31.1; years of use *M* = 7.2; days use past month *M* = 23.4). Fifty at follow-up.	CPT-2; Effort expenditure for rewards task (EEfRT)	Contemplation Ladder (change score)	Multiple regression; predictive value of one level of the EEfRT and one CPT-2 variable on change in treatment motivation, after controlling for nuisance variables.

CHAPTER THREE: WORKING MEMORY PREDICTS METHAMPHETAMINE HAIR CONCENTRATION OVER THE COURSE OF TREATMENT: MODERATING EFFECT OF IMPULSIVITY AND IMPLICATIONS FOR DUAL-SYSTEMS MODEL

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Working memory predicts methamphetamine hair concentration over the course of treatment: moderating effect of impulsivity and implications for dual-systems model

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ABSTRACT

High impulsivity and poor executive function are characteristic of methamphetamine use disorder. High arousal in the impulsive system has been proposed to compromise the executive system's regulating ability (i.e. the dual-systems model). While interaction between these variables may partly explain poor treatment outcomes associated with methamphetamine use disorder, previous research has tended to examine each factor separately. We investigated whether high impulsivity (measured with an impulsive choice task) and poor executive function (measured with a working memory task) predict methamphetamine use (determined by hair sample) in the 6 weeks following treatment commencement. We also investigated whether impulsive choice moderates the relationship between working memory and methamphetamine use. One hundred and eight individuals with methamphetamine use disorder (75 percent male) were tested within 3 weeks of commencing treatment; 80 (74 percent) were followed up 6 weeks following baseline testing. Cognitive measures significantly predicted drug use after controlling for nuisance variables. Working memory was a significant predictor, while impulsive choice was not. The interaction model included working memory as a predictor and impulsive choice as a moderator. This model was significant, as was the interaction term. Working memory significantly predicted levels of methamphetamine use in early treatment, and impulsive choice moderated this relationship. Those with working memory deficits are particularly vulnerable to using greater amounts of methamphetamine. As working memory increased methamphetamine use decreased among individuals with low/medium delay discounting. Pre-treatment cognitive testing may identify patients at high risk, while remediation of working memory function may be a treatment target for reducing methamphetamine use.

Keywords dual systems, executive function, impulsivity, methamphetamine use disorder, working memory.

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INTRODUCTION

Methamphetamine is a highly addictive stimulant, used by an estimated 24 million people worldwide (United Nations Office on Drugs and Crime, 2016). Methamphetamine use disorder (MUD) is placing an increasing burden on health care services globally (Courtney & Ray 2014; Lubman *et al.* 2016; McKetin *et al.* in press). Psychosocial approaches are the predominant treatment for individuals with MUD; however, treatment engagement is often poor with frequent periods of relapse (McKetin *et al.* 2012). Furthermore, current predictors of relapse cannot be measured at treatment commencement (length of treatment/engagement post-treatment; Brecht & Herbeck 2014) or are unfeasible in clinical practice (neuroimaging measurements of brain activity; Gowin *et al.* 2015). Nevertheless, objective measures of cognitive function have shown excellent predictive value in relation to treatment outcomes for individuals with MUD (Chen, Chen, & Wang 2015). Additionally, cognitive deficits can be simultaneously accommodated (e.g. developing strategies to adapt to patient-specific strengths and weaknesses) and rehabilitated (e.g. group-based cognitive remediation; Sofuoglu *et al.* 2016) in treatment.

The role of cognitive dysfunction in MUD can be partly understood through the dual-systems model, in which the top-down cognitive control system is compromised, while the bottom-up reward-driven system is sensitized (McClure & Bickel 2014). These systems are underpinned by the cognitive constructs of impulsivity (reward-driven behaviour) and executive function (cognitive control; Bickel *et al.* 2012). Impulsivity refers to a preference for short-term rewards and engaging in behaviour without adequate foresight (Stevens *et al.* 2014). This reward-driven behaviour is characterized by impulsive choice (the preference for smaller immediate rewards over larger, delayed rewards), which is analogous to the decisions made regarding drug use (Khurana *et al.* 2017). The top-down system of cognitive control is underpinned by working memory, the ability to temporarily store, access and manipulate a limited amount of information and to manage incoming stimuli (Baddeley 2012). Deficits are reflected in diminished cognitive control in substance-dependent individuals (Brooks 2016). Here, working memory fails to exert control over distracting, arousing stimuli (Okon-Singer *et al.* 2015), such as impulsive urges to use substances (Khurana *et al.* 2017). Therefore, high levels of reward-driven behaviour to use substances, combined with deficiencies in the ability to inhibit these impulses can 'hardwire' drug use and potentially explain the high levels of relapse among individuals with substance use disorders.

Both impulsivity and working memory are individually predictive of substance use and are consistently impaired in individuals with MUD (Ellis *et al.* 2016; Zhong *et al.* 2016). There is a strong theoretical rationale for the link between impulsivity, working memory and drug use in individuals with MUD; however, past research has been limited. Nejtek *et al.* (2013) studied methamphetamine-dependent and cocaine-dependent individuals in treatment. Impulsive choice at baseline predicted the number of positive urine screens over the 20-week study period. More recently, Chen *et al.* (2015) found that impulsive choice significantly predicted dropout in individuals with MUD in a 12-week psychologically based relapse prevention programme.

Similarly, few studies have directly addressed the link between working memory and MUD outcomes; however, this is emerging as a highly relevant area for understanding recovery trajectories (Bickel *et al.* 2011). In individuals with MUD, Dean *et al.* (2009) found distinct working memory performance in those who completed psychological and pharmacological treatment and those who did not. Working memory also predicted treatment outcomes among users of other stimulants. For example, cognitive (Patterson *et al.* 2010) and neuroimaging (Loughead *et al.* 2015) measures of working memory were significantly predictive of nicotine relapse during a counselling intervention. In cocaine-dependent individuals, neuroimaging measures of cognitive control significantly predicted self-reported days of use at 3-month follow-up (Marhe, van de Wetering, & Franken 2013) and number of positive urine samples across 16 weeks of psychological and pharmacological treatment (Moeller *et al.* 2010).

Both elements of the dual-systems model (impulsivity and working memory) are individually predictive of stimulant relapse (Moeller *et al.* 2010; Nejtek *et al.* 2013). However, previous studies have not examined their interactive effect (Bickel *et al.* 2012). Consistent with the interactional nature of the dual-systems model, improvements in working memory reduce the level of impulsive choice in stimulant users (Bickel *et al.* 2011), while individuals with MUD have exhibited significantly reduced impulsivity following working memory improvements (Brooks *et al.* 2017). These findings suggest that greater cognitive control (working memory) enhances the ability to manage incoming impulsive urges. Furthermore, those with compromised working memory are likely to have problems regulating impulsive urges, with greater difficulty as levels of impulsivity increase (Houben, Wiers, & Jansen 2011). In addition, previous studies have not examined cognitive predictors in relation to the intensity of stimulant use during treatment. This is critical, as previous research has found a dose–response relationship between methamphetamine use and poorer outcomes (Lappin *et al.* 2016; McKetin *et al.* 2016).

This study aimed to examine the longitudinal association between performance in cognitive measures of working memory and impulsivity (reflecting the function of the top-down system and the bottom-up system, respectively) and levels of methamphetamine use among people with MUD during early treatment. Cognitive measures were conducted within the first 3 weeks of treatment, and levels of methamphetamine use over a 6-week follow-up period were quantified with hair toxicology. We hypothesized that poorer working memory and heightened impulsivity would longitudinally predict levels of methamphetamine use. Furthermore, we predicted that impulsivity would moderate the relationship between working memory and methamphetamine use, according to the dual-systems model.

MATERIALS AND METHODS

Design

We conducted a longitudinal cohort study. Participants with MUD underwent a cognitive battery within the first 3 weeks of commencing treatment and provided a hair sample in a follow-up session 6 weeks later. We examined the longitudinal link between baseline cognitive functioning and levels of methamphetamine use at the 6-week follow-up.

Participants

The sample comprised 108 adults meeting criteria for MUD (age, M = 31.1, SD = 7.2, 81 male participants) recruited through public and private inpatient and outpatient detoxification, counselling and rehabilitation facilities in Melbourne, Australia. The sample size was determined a priori, with 80 percent power and $\alpha = 0.05$, assuming a moderate effect size and allowing for 30 percent attrition, based on the findings of similar longitudinal studies conducted in people with methamphetamine use disorder (e.g. Simon *et al.* 2010).

The selection criteria for participants were defined as follows: aged between 18 and 55 years, meeting DSM-IV criteria for MUD measured with the Structured Clinical Interview for the DSM-IV (First et al., 1996) and being abstinent for at least 2 days and a maximum of 3 weeks indicated by self-report and confirmed by clinicians, to minimize between-subjects variability on cognitive performance due to abstinence duration. Participants were excluded if they reported a loss of consciousness for more than 30 min, a history of major depression, bipolar disorder, psychotic disorder, intellectual disability or dependence on substances other than methamphetamine, alcohol or cannabis (as determined by the Structured Clinical Interview for the DSM-IV).

Procedures

The Eastern Health Human Research Ethics Committee approved the study (E52/1213). Recruitment was conducted between April 2015 and December 2016. People with MUD commencing treatment were introduced to the study by one of their primary clinicians, prior to screening and consenting by one of the researchers. In the baseline session, participants were tested on measures of impulsivity and working memory. Experimenters took a hair sample at the follow-up session 6 weeks later. Seventy-nine participants (73 percent of the sample) provided the hair sample at the follow-up session. The remaining 29 participants were unreachable (n = 28) or refused to provide a sample (n = 1). After completing both sessions, participants were provided with a $AUD40 gift card and a report of their cognitive performance. The first two authors, who have postgraduate training in clinical assessment methods, conducted all assessments.

Measures

Background measures

Wechsler Abbreviated Scale of Intelligence—Second Edition (WASI-II): This measure briefly assesses general cognitive functioning and consists of four tasks. These tasks incorporate performance IQ (visuospatial abilities) and verbal IQ (language comprehension and expression). Our study used a two-task estimate of IQ, using Vocabulary and Matrix Reasoning tasks. This measure is highly valid and reliable (Wechsler & Hsiao-pin 2011).

Severity of Dependence Scale (SDS): This 5-item self-report measure provides an indication of an individual's level of dependence on a substance. Questions are rated on a 4-point scale (e.g. 'Did you wish you could stop?' from 'Never/almost never' to 'Always/nearly always'). The SDS is valid and reliable in drug-dependent populations (Gossop *et al.* 1995). Our study used the methamphetamine, cannabis and alcohol versions of the SDS. The cannabis score was used as a nuisance variable because a substantial proportion of individuals with MUD also use cannabis (Lubman *et al.* 2016).

Centre for Epidemiological Studies Depression Scale (CES-D): This scale is a 20-item self-report measure of physical and emotional correlates of low mood. Questions are rated on a 4-point scale, based on the frequency of symptom occurrence (e.g. 'I talked less than usual' from 'Rarely or none of the time—less than 1 day' to 'Most or all of the time—5 to 7 days'). Ratings are assigned a number from 0 to 3 (items 4, 8, 12 and 16 are reverse scored); higher scores are indicative of greater symptomatology. The CES-D shows high validity and reliability (Orme, Reis, & Herz 1986). This measure was used as a nuisance variable to account for low mood.

Socio-economic Indexes for Areas (Australian Bureau of Statistics 2011): These data rank postal-coded areas in Australia according to socio-economic status (considering income, employment and education). Each postal code is categorized into a decile from 1 to 10 (from most disadvantaged to most advantaged).

Cognitive measures

Impulsive choice

Delay Discounting Task (DDT): The DDT measures the tendency to discount the value of a reward as it becomes temporally distant. This was measured by the 27-item questionnaire developed by Kirby, Petry, & Bickel (1999). Participants are presented with hypothetical monetary options—an amount to be received immediately and a larger amount to be received after a delay. This measure has been found to be highly reliable and valid (Kirby *et al.* 1999). The main performance index is the k value, a number that indicates how rapidly monetary value is degraded for each participant—larger values indicate greater impulsivity.

Working memory

Digit Span Sequencing (Wechsler & Hsiao-pin 2011): This task measures the ability to hold multiple pieces of information in mind for a brief period. An examiner reads out a sequence of unrelated numbers at a rate of 1 second per item (e.g. 1, 4, 3 and 7). After the examiner has finished the sequence, the participant repeats back the numbers in the same order. The length of numbers to be

repeated becomes longer as the task continues. Each sequence is considered one item, and a trial consists of two items. The task ends when a participant's response is incorrect for both items within a trial. There are three components of the task—forwards repetition, backwards repetition and sequencing (rearranging the numbers in order from lowest to highest). We chose this task over more complex and longer measures of working memory to increase the feasibility of the assessment in the clinical setting, while maintaining excellent reliability and validity (Wechsler & Hsiao-pin 2011). The main performance index in our study was the longest digit span sequence achieved. In factor analysis, this index loads on both attentional and executive functioning domains and exhibits greater validity to measure working memory than forward or backward variants that load on attentional function alone (Vogel *et al.* 2015).

Outcome measures

Methamphetamine concentration in hair: A single strand of 1 cm from the root (approximate length of hair growth in 1 month) from each participant was analysed using gas chromatography–mass spectrometry (Meng et al., 2009). Gas chromatography–mass spectrometry provides a quantitative measure of methamphetamine concentration in hair, expressed in ng/mg. This metric provides an objective, continuous measure of the intensity of methamphetamine use over the first month of treatment (i.e. period between baseline and follow-up) and has been recommended by expert consensus guidelines as the most appropriate technique to measure long periods of drug use in addiction treatment research (Donovan *et al.* 2012).
Timeline Followback (Sobell & Sobell 1996): This self-report measure of drug use consists of a calendar on which a participant marks a *u* on each day that they used the relevant substance. We used it to obtain a baseline measure of methamphetamine use in the last month before treatment and to cross-validate methamphetamine hair concentration values at follow-up.

Statistical analysis

We used IBM SPSS (version 21.0) to compute statistical analysis. Data were initially explored for missing data and outliers, as well as data distribution. There were no outliers in the predictor variables. Pairwise deletion was used for three missing data values in the *k* parameter (Enders 2010). Most variables met assumptions for linear multiple regression, but levels of methamphetamine use (ng/mg) were log-transformed to fit an appropriate distribution of errors.

We conducted a hierarchical regression analysis to determine whether impulsivity and working memory predict levels of methamphetamine use after controlling for nuisance variables (age, gender, IQ estimate, socio-economic status decile, CES-D depression scores, SDS methamphetamine use severity score and SDS cannabis use severity score). The nuisance variables were entered in the first block, followed by impulsivity (DDT *k* value) and working memory (longest digit span sequencing score) in a second block. The statistics of interest were the change in F and P values after entry of impulsivity and working memory predictors and the *Beta* values of individual predictors in the final model.

We subsequently conducted a moderation analysis to determine if the relationship between working memory and methamphetamine use was moderated by impulsivity. This analysis was conducted using Hayes' PROCESS macro for SPSS (Hayes 2012). This macro uses a path analysis approach with ordinary least squares regression to estimate continuous outcomes (i.e. methamphetamine use), in which predictor variables are mean-centred before analysis. The interaction term is the product of the predictor and moderator terms—its significance is tested in the regression model. 'Simple slopes' analysis graphically represents the extent to which two cases that differ by one unit on the predictor (i.e. working memory) will differ on the outcome (i.e. methamphetamine use) at low, medium and high levels of the moderator (i.e. delay discounting).

RESULTS

Preliminary analyses

Demographic and clinical characteristics of the sample are shown in Table 1. The majority of the sample was male and unemployed, and the average daily dose was 0.75 g.

Preliminary analyses were conducted to account for the potential influence of drug use patterns on cognitive predictors. Time since last use of methamphetamine at baseline testing and methamphetamine use characteristics (route of administration, average daily usage and days used in month prior to testing) were not significantly correlated with cognitive predictors ($r_{max} = -0.17$, all $P > 0.05$).

A bivariate correlation was conducted to assess the consistency between methamphetamine concentration in hair and self-reported methamphetamine use indicated by the Timeline Followback at follow-up. Results showed a significant correlation ($r = 0.46$, $P < 0.001$), supporting the reliability of the quantitative hair measure.

Link between cognition and longitudinal methamphetamine use

Table 2 shows the results of the regression model. The nuisance variables (age, gender, IQ, socio-economic status decile, depression score, methamphetamine dependence severity score and cannabis dependence severity score) explained 3.6 percent of the variance in methamphetamine use at follow-up, $F(7, 68) = 1.40$, $P = 0.220$. The addition of DDT *k* value and longest digit

Table 1 Demographic and clinical characteristic of the MUD sample ($N = 108$).

	Mean/n (percent)	*SD*
Age	31.1	7.2
Sex (M/F)	81.0 (75.0)	
Years of education	13.0	2.4
IQ estimate	96.1	11.0
Unemployed	77.0 (71.3)	
Smokers	87.0 (80.6)	
Cigarettes per month	414.4	260.0
Daily level of MA use (g)	0.75	0.62
Days of MA use in month prior to treatment	22.1	9.3
Years of MA use prior to treatment	6.9	4.9
Age commenced MA use	23.8	8.1
MA route of administration		
Smoking	76.0 (70.4)	
Intravenous	25.0 (23.1)	
Multiple routes	7.0 (6.5)	
Ever used MA intravenously	45.0 (41.7)	
MA SDS	11.1	3.1
Cannabis use	54.0 (50.0)	
Cannabis use disorder	27.0 (25.0)	
Cannabis SDS	2.7	4.3
Alcohol use	59.0 (54.6)	
Alcohol use disorder	9.0 (8.3)	
Alcohol SDS	1.7	3.3
CES-D score	28.3	12.3
Clinical measures	*Mean*	*SD*
Delay discounting *k* value	0.06	0.07
DS longest digit span sequencing	5.57	1.18
Concentration of methamphetamine in hair (ng/mg)	6.06	14.20

Note: CES-D = Centre for Epidemiologic Studies Depression Scale; DS = digit span; MA = methamphetamine; SDS = Severity of Dependence Scale.

Table 2 Hierarchical multiple regression examining the predictive value of impulsivity and working memory on methamphetamine use.

Outcome	*Methamphetamine concentration in hair*		
	FΔ	*β*	*Sig.*
Block 1	1.40		0.220
Age		0.19	0.103
Gender		0.01	0.919
IQ estimate		−0.02	0.855
SES decile		−0.04	0.719
CES-D		−0.01	0.912
SDS methamphetamine		−0.14	0.258
SDS cannabis		−0.25	0.033
Block 2	4.20		0.019
Age		0.16	0.145
Gender		−0.04	0.705
IQ estimate		0.12	0.416
SES decile		−0.06	0.650
CES-D		−0.02	0.839
SDS methamphetamine		−0.10	0.379
SDS cannabis		−0.23	0.040
DDT *k* value		−0.06	0.594
LDSS		−0.35	0.007

Note: CES-D = Centre for Epidemiologic Studies Depression Scale; DDT = Delay Discounting Task; LDSS = longest digit span sequencing; SES = socio-economic status decile, Socio-economic Indexes for Areas; SDS = Severity of Dependence Scale.

span sequencing significantly improved the predictive value of the model $F\Delta(2, 66) = 4.20$, $P = 0.019$, and resulted in a significant model $F(9, 66) = 2.12$, $P = 0.040$. Cognitive variables explained an additional 8.3 percent of the variance in the dependent variable. DDT *k* value ($\beta = -0.06$, $P = 0.594$) was not a significant predictor, however longest digit span sequencing ($\beta = -0.35$, $P = 0.007$) emerged as significant.

Moderation analysis

The interaction model included longest digit span sequencing as the predictor, DDT *k* value as the moderator and cannabis dependence severity as a covariate, as this was the only nuisance variable that was a significant predictor in the regression model. The interaction model was statistically significant $F(4, 71) = 6.37$, $P < 0.001$, as was the interaction term, $t(71) = 2.22$, $P = 0.029$. Longest digit span sequencing was a significant predictor, $t(71) = -2.57$, $P = 0.012$; DDT *k* value was not, $t(71) = -0.93$, $P = 0.357$. Figure 1 shows the simple slopes analysis of methamphetamine use—predicted by working memory and delay discounting at low or high levels. The relationship between working memory and methamphetamine use changed as a function of delay discounting rates. As working memory increased, methamphetamine use significantly decreased among individuals with low and medium delay discounting groups, but this relationship was not significant among individuals with high discounting. As illustrated in Table 3, in the low delay discounting group, every unit increase in working memory performance predicted a 0.62-unit decrease in methamphetamine use; in the medium group, there was a decrease of 0.38 units.

Discussion

This study examined if cognitive performance in tests of working memory and impulsivity at treatment commencement predicted levels of methamphetamine use over the following 6 weeks of treatment. We found that working memory performance significantly

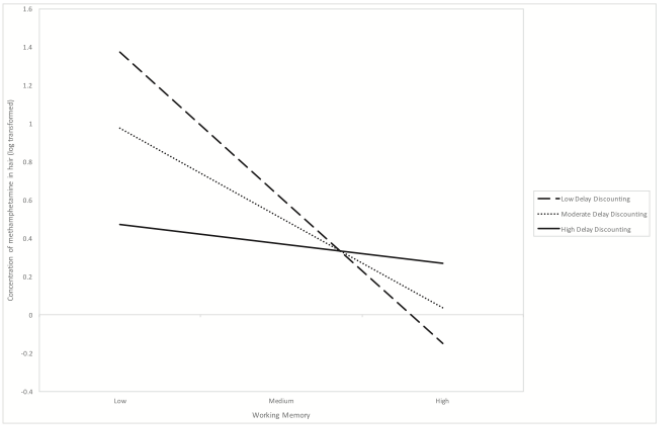

Figure 1 The interaction between different levels of delay discounting and working memory performance on concentration of methamphetamine in hair. NB: High delay discounting reflects more impulsivity.

Table 3 The moderating effect of impulsivity on working memory and methamphetamine concentration in hair relationship.

Delay discounting group	*β*	*Sig.*
Low	−0.62	$P = 0.002$
Average	−0.38	$P = 0.012$
High	−0.08	$P = 0.677$

predicted levels of methamphetamine use measured by hair toxicology. Although impulsivity did not directly predict methamphetamine use, it moderated the relationship between working memory and methamphetamine levels (i.e. among users with low to moderate levels of impulsivity, better working memory was associated with less methamphetamine use).

Findings regarding working memory are consistent with previous research linking such deficits with increased stimulant use (Moeller *et al.* 2010; Marhe *et al.* 2013). We found that this link generalizes to methamphetamine use in early recovery. These findings can be understood in the context of working memory's role in broader executive functioning, which includes involvement in representation of self-regulatory goals, control of attention towards goal-relevant stimuli and regulation of desires and cravings (Hofmann, Schmeichel, & Baddeley 2012). Those with significant working memory dysfunction may have difficulty in regulating habits and impulses (even of mild intensity) to engage in drug use. Previous research has suggested that a high load on working memory results in greater vulnerability to decisions providing short-term benefit, such as drug use (Fridberg, Gerst, & Finn 2013). Those with poorer working memory functioning may more readily experience a substantial cognitive load that interferes with self-regulatory goals, such as maintaining abstinence.

Results were not consistent with previous work that associated impulsivity and methamphetamine use (Nejtek *et al.* 2013; Chen *et al.* 2015). However, these studies utilized measures of impulsive decision-making (Iowa Gambling Task; Nejtek *et al.* 2013) and self-reported impulsivity (Barratt Impulsiveness Scale; Chen *et al.* 2015) rather than delay discounting. Indeed, scores on these same measures differed significantly among cocaine-dependent individuals according to hair-indexed changes in use over a 1-year period, while delay discounting did not (Hulka *et al.* 2015). Furthermore, findings that directly link delay discounting with prognosis have measured length of abstinence/treatment retention rather than drug use intensity (Stevens *et al.* 2015). From a theoretical perspective, our findings are partly consistent with the dual-systems approach (McClure & Bickel 2014). Impairment in top-down cognitive control (working memory) significantly predicted higher levels of drug use in early recovery. However, this relationship was not moderated by high levels of delay discounting, which were used as a proxy of the reward-impulsive system. High rates of delay discounting may significantly impact the initial decision to leave a treatment setting and recommence drug use (Stevens *et al.* 2015), but it has not been consistently associated with measures of drug relapse (Dominguez-Salas *et al.* 2016). In the current study, low and medium levels of delay discounting significantly moderated the relationship between working memory and methamphetamine use. Participants with lower levels of delay discounting showed a significant reduction in drug use as working memory performance increased. Individuals with MUD

who place greater value on long-term outcomes may remain engaged in treatment, while a greater working memory capacity may allow the management of a greater cognitive load and focus on long-term goals such as abstinence (Hofmann *et al.* 2012).

Our findings need to be considered in the context of a number of limitations. There were a small number of participants that reported cannabis and/or alcohol use disorder or met criteria for a major depressive episode at the time of testing. However, the inclusion of these participants allowed for a sample that is representative of treatment-seeking individuals with MUD (Lubman *et al.* 2016), and the impact of these variables was controlled in statistical analysis. Although rates of smoking methamphetamine (~70 percent) were higher in the current sample than in the most recently available Australian data (~40 percent; Australian Institute of Health and Welfare, 2013), this likely reflects the increasing prevalence of the crystal form of the drug in the Australian population, which is typically smoked (Degenhardt *et al.* 2016). The impact of route of administration was also controlled for statistically. The study's follow-up period was also brief at 6 weeks, and while an extended follow-up would allow for examination of longer-term predictors of relapse, the current study incorporates the period of the greatest relapse vulnerability (Brecht & Herbeck 2014).

Despite these limitations, our findings have important clinical implications. Individuals with MUD entering treatment with working memory deficits appear to be particularly vulnerable to relapse and higher levels of use. Additionally, those with low to moderate levels of impulsive choice and intact working memory are likely to use less methamphetamine following treatment. Pre-treatment cognitive testing may help categorize patients that require additional support and those at lower risk. Furthermore, individuals with impaired working memory are likely to benefit from learning specific strategies to manage a reduced cognitive capacity (e.g. list making and taking notes on a mobile phone), which may allow more considered decision making in relation to methamphetamine use, in combination with behavioural strategies (e.g. leaving a situation where drugs may be present). Furthermore, the cognitive domain of working memory has been specifically identified as a candidate for rehabilitation in substance dependence due to its broad impact on functioning and relapse (Bickel *et al.* 2011). Working memory training has been effective in improving decision making in individuals with MUD (Brooks *et al.* 2017) and reducing consumption in alcohol-dependent individuals (Houben *et al.* 2011). From a neurobiological perspective, impulsivity and working memory are associated with lower levels of dopamine availability in the basal ganglia in people with MUD (Dobbs, Lemos, & Alvarez 2017). However, when such individuals receive working memory training, reduced levels of impulsivity are accompanied by increased bilateral basal ganglia volume (Brooks *et al.* 2016). These findings reflect potential neurobiological drivers of the behavioural outcomes observed in the current study.

Our study demonstrates that working memory, and its interaction with impulsivity, predicts levels of methamphetamine use during early treatment. These findings support the trialling of adjunctive cognitive remediation interventions focused on working memory for treatment-seeking individuals with MUD.

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Disclosure/Conflict of Interest

All authors declare no competing interests.

Authors Contribution

All authors were responsible for the study concept and design. AVG and DL facilitated recruitment of participants. AR and RF were responsible for recruitment and data collection. AR and AVG were responsible for data analysis and interpretation of results. AR drafted the manuscript; AVG and DL provided intellectual input. All authors critically analysed the manuscript prior to submission.

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CHAPTER FOUR: IMPULSIVITY PREDICTS POORER IMPROVEMENT IN QUALITY OF LIFE DURING EARLY TREATMENT FOR PEOPLE WITH METHAMPHETAMINE DEPENDENCE

ADDICTION
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Impulsivity predicts poorer improvement in quality of life during early treatment for people with methamphetamine dependence

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ABSTRACT

Background and aims Methamphetamine dependence is associated with heightened impulsivity and diminished quality of life, but the link between impulsivity and changes in quality of life during treatment has not been examined. We aimed to investigate how different elements of impulsivity predict change in quality of life in the 6 weeks after engaging in treatment. **Design** Longitudinal, observational cohort study. **Setting** Public and private detoxification and rehabilitation facilities in metropolitan Melbourne, Australia. **Participants** One hundred and eight individuals with methamphetamine dependence (81 male) tested within 3 weeks of commencing treatment; 80 (74%) were followed-up at 6 weeks. **Measurements** The Continuous Performance Test-2 measured impulsive action (cognitive and motor impulsivity); the Delay Discounting Task measured impulsive choice. Quality of life was measured with the World Health Organization Quality of Life Scale—Brief, which includes social, psychological, physical and environment domains. Control variables included age, gender, estimated IQ, depression severity score, methamphetamine dependence severity score, cannabis dependence severity score and treatment modality. **Findings** We found that all three forms of impulsivity were significant predictors of change in the social domain: motor impulsivity ($\beta = -0.54$, $P = 0.013$), cognitive impulsivity ($\beta = -0.46$, $P = 0.029$) and impulsive choice ($\beta = -0.26$, $P = 0.019$). Change in the psychological domain was predicted significantly by motor impulsivity ($\beta = -0.45$, $P = 0.046$). Control variables of age and depression were associated significantly with changes in the physical domain. **Conclusions** In Australian methamphetamine-dependent individuals, elevated impulsivity predicts lower improvement of social and psychological quality of life in the first 6–9 weeks of treatment.

Keywords Cognitive tests, impulsive action, impulsive choice, impulsivity, methamphetamine dependence, quality of life.

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INTRODUCTION

Methamphetamine dependence (MD) is associated consistently with poor physical and mental health and high levels of family and social conflict [1,2], impacting upon an individual's wellbeing and overall quality of life (QOL [3]). QOL, the perception of one's position in life, comprises physical (energy, pain, and difficulties engaging with activities of daily living and work), psychological (affect, self-perception, perceived cognition), social (personal relationships, social and sexual activity) and environmental (financial/accommodation stability and access to services/information) domains [4]. Previous research has identified that MD is associated with poorer QOL in at least three of these domains: physical (physical and medical impairment [3]), psychological (diminished emotional control [5], high rates of anxiety, depression and psychosis [6]) and social (high interpersonal conflict and lower social support [7]). Improvement in such domains is a key focus for treatment, with QOL and wellbeing identified as key indicators of addiction recovery and treatment success [8,9].

Heightened levels of impulsivity (acting without sufficient deliberation) have also been linked to poorer QOL in people with stimulant dependence [10,11]. Indeed, a latent class study based on impulsivity indices identified that people with cocaine dependence and high impulsivity

levels report lower overall subjective wellbeing, greater psychological complaints and higher social dysfunction compared to those with low levels of impulsivity [12]. However, previous studies have not separated two aspects of impulsivity that can impact QOL differentially; impulsive action and impulsive choice [13]. Impulsive action is acting without deliberation to make an object or event more pleasant or less unpleasant [14]. Impulsive action has two components: motor disinhibition (difficulty inhibiting a prepotent action pattern [13]) and cognitive disinhibition (difficulty focusing on relevant versus irrelevant aspects of a task [15]). Impulsive choice reflects an increased preference for smaller short-term rewards compared to delayed rewards of greater magnitude [16]. In social settings, impulsive action is significantly predictive of language difficulties and problems with planning recreational activities [17]. Psychological aspects of QOL are also impacted; diminished emotional self-control has been observed in MD individuals with heightened impulsive choice and action [5]. Impulsive action is also associated with deficits in managing transportation and finances [10], medication management, completing chores around the home [18] and reduced activities of daily living performance [17].

Collectively, current findings suggest a link between heightened impulsivity and social, psychological and physical domains of QOL, based on cross-sectional designs. However, we lack longitudinal evidence on how separate aspects of impulsivity predict QOL during the course of MD treatment. As such, this study takes a multi-dimensional approach to impulsivity assessment (measuring impulsive action and impulsive choice) and links impulsivity indices with longitudinal measures of QOL in people with MD who are seeking treatment. Specifically, the study aims to identify the relative contributions of impulsive choice and action to change in QOL during the first 6–9 weeks of MD treatment. QOL was assessed as a multi-dimensional construct comprising social, psychological, physical and environmental domains [4]. Based on prior, cross-sectional evidence [5,10,17,18], we hypothesized that higher levels of impulsive choice and action (including motor and cognitive disinhibition) would be significantly predictive of less change in social, psychological and physical aspects of QOL in treatment during the short term.

METHODS

Design

Participants with MD were assessed with a cognitive battery and a measure of QOL at two time-points: within 3 weeks of commencing treatment and at a follow-up session 6 weeks later. This early recovery phase represents a period of significant vulnerability for people with MD [19], but also a time in which significant changes in QOL have been observed [20]. We examined the association between baseline cognitive status and changes in QOL between baseline and follow-up.

Participants

The sample comprised 108 participants with MD [age, mean = 31.1, standard deviation (SD) = 7.2, 81 males]. Sample size was determined a priori using a power analysis for multiple regression in G*Power, based on a medium effect size [17], 80% power and alpha < 0.05, and factoring in an anticipated attrition rate of 30% [21]. Participants were recruited from public and private treatment facilities across Melbourne, Australia from April 2015 to December 2016. Treatment modalities included three categories: residential rehabilitation ($n = 60$), detoxification only ($n = 30$) and out-patient counselling ($n = 16$). Residential rehabilitation consisted of individual and group-based psychological and behavioural interventions within a hospital setting for 4–6 weeks. Detoxification involved medically supported residential withdrawal for approximately 10 days followed by discharge into the community. Out-patient counselling involved community-delivered weekly or fortnightly individual or group therapy utilizing cognitive, motivational and behavioural interventions. All participants took part in their treatment voluntarily.

Participants were excluded if they reported a loss of consciousness for more than 30 minutes, a history of bipolar or psychotic disorder or intellectual disability. Participants were also excluded if they reported dependence upon a substance that was not methamphetamine (or similar stimulants), alcohol or cannabis, as determined by the Structured Clinical Interview for the DSM-IV [22]. Participants were required to have been abstinent from methamphetamine, alcohol and other drugs for at least 2 days (and no more than 21 days) before their first assessment. Abstinence was confirmed by self-report and clinician report.

Eighty participants (74% of the sample) completed the follow-up assessment at 6 weeks (mean days = 45.3, SD = 6.1). The remaining 28 participants were either unreachable or declined to participate.

Procedures

The study was approved by the Eastern Health Human Research Ethics Committee (E52/1213). Participants were introduced to the study by a clinician involved in their care, and were subsequently screened and consented by a researcher. In both sessions, participants were tested on measures of impulsivity and QOL. Follow-up was arranged by contacting participants by telephone or e-mail or facilitated by their treating clinician. Participants received a

$AUD40 gift card after completing both assessment sessions. Testing was conducted by the first two authors, who have postgraduate training in clinical assessment methods.

Measures

Background measures

Structured Clinical Interview for the DSM-IV [22]. A structured assessment was conducted to determine whether an individual met criteria for DSM-IV amphetamine dependence (methamphetamine) and dependence on other substances.

Severity of Dependence Scale (SDS). This five-item self-report measure indicates an individual's level of dependence on a substance [23]. We used the methamphetamine, cannabis and alcohol versions of the scale. The SDS score for methamphetamine was used as a dimensional estimate of severity of use at baseline. SDS scores for cannabis and alcohol were used as control variables. SDS scales exhibit high validity and reliability in drug-dependent populations [23,24].

Wechsler Abbreviated Scale of Intelligence—second edition (WASI-II). This brief measure of IQ comprises four tasks measuring performance IQ (visuospatial abilities) and verbal IQ (comprehension/expression of language). We used the two-task estimate of IQ (vocabulary and matrix reasoning). This measure has high levels of reliability and validity [25] and has been used previously in individuals with MD [26].

Centre for Epidemiological Studies Depression Scale (CES-D). This 20-item self-report assesses depressive symptoms. Each rating is assigned a number from 0 to 3, with higher scores indicating a higher level of symptoms. This scale has high internal validity [27] and reliability [28], and was used as a control variable to account for mood.

Impulsivity measures

Impulsive action

Continuous Performance Test—II (CPT-2). The CPT-2 is a 14-minute computer-based task of attention and impulsivity that shows high levels of validity and reliability [29]. During the test, letters flash on the screen and participants must press the space bar after each letter, except for the X. Letters are presented for 250 msec and a new stimulus appears after either 1, 2 or 4 sec. MD individuals exhibit significant deficits in the CPT-2 domains of sustained attention and impulsivity [30].

CPT-2 produces indices including commission errors (frequency of hitting the space bar when the X appears) and detectability (distinguishing between target and non-target stimuli). The main performance indices were commission errors (motor disinhibition) and detectability (cognitive disinhibition).

Impulsive choice

Delay Discounting Task (DDT). This self-report, 27-item task measures the tendency to discount the value of a reward as it becomes temporally distant (impulsive choice). The DDT presents hypothetical monetary options—participants choose between an amount received immediately or a larger amount received after a delay [31]. This measure is highly reliable and valid in substance-using populations [31,32]. The main performance index is the k value, a number that indicates how steeply delay degrades value for the participant.

Outcome measure

World Health Organization Quality of Life Scale—Brief Version (WHO QOL-BREF). This 26-item scale is a measure of an individual's subjective assessment of their QOL [33]. It is measured across social, psychological, physical and environmental domains. Each item is measured from 1 to 5 on a Likert scale. The WHO QOL-BREF has sound psychometric properties throughout a broad range of cultures and groups in large samples [34] and a good level of validity and reliability in the substance-dependent population [35]. The dependent variable was the 'change score', in which baseline raw scores were subtracted from scores at 6-week follow-up for each domain (change score = WHO QOL-BREF raw score^{T2} – WHO QOL-BREF raw score^{T1}).

Statistical analyses

Statistical analyses were conducted using IBM SPSS version 21.0. Data were explored initially to identify missing data and outliers. There was one outlier in the CPT-2 distribution (Z-score > 3.29); this score was changed to 1 unit larger than the next most extreme score that was not an outlier [36]. Pairwise deletion was used to address missing data, including losses to attrition [37]. In those who were followed-up, missing data were fewer than 5% for all variables (DDT: three participants, WHO QOL-BREF: two participants), and therefore did not require imputation [36].

We conducted four separate linear regression analyses to examine the predictive value of the three measures of

impulsivity on change in QOL domains, after controlling for age, gender, IQ, depressive symptoms, severity of methamphetamine dependence, severity of cannabis dependence and treatment modality. The cannabis, but not alcohol severity, score was included in the final analyses due to the low rate of alcohol dependence (< 10%) in our sample. In each regression analysis, we entered the control variables in the first block [age, gender, WASI IQ, CES-D, SDS methamphetamine scores, SDS cannabis scores, and treatment modality (effect coded)], and the impulsivity measures in the second block (CPT-2 commission errors and detectability and DDT *k*-value). We found adequate levels of collinearity between predictors in tolerance analyses (range = 0.87–0.93). The outcome measures were the change scores of the four domains of QOL. The key statistics were the change in the *F*, R^2 and *P*-values associated with the block of impulsivity measures, which indicates if impulsivity measures significantly increase the prediction achieved by the control variables, and the Beta values of each of the individual predictors in the full model, which indicates the predictive power of each predictor.

We also conducted sensitivity analyses to test the influence of other potential confounders. These included methamphetamine use patterns (days of use in month before treatment, years of use, daily dosage, route of administration) and change scores throughout treatment (T2–T1). Change scores included change in severity of dependence for methamphetamine, cannabis and alcohol (baseline and change) and change in impulsivity variables (CPT-2 commission errors and detectability and DDT *k*-value). We first ran bivariate correlation analyses between each of these variables and outcomes. For those variables showing significant correlations, we re-ran the multiple regression models including such variables.

RESULTS

Preliminary analyses

The demographic characteristics of the sample, and the scores on impulsivity and QOL measures at baseline and follow-up, are shown in Table 1. Most participants were unemployed, male, smoked methamphetamine and had used on most days prior to commencing treatment (Table 1). A number of participants were currently dependent upon a drug other than methamphetamine (34%, n = 37), mainly cannabis (25%, n = 27). Differences between baseline and follow-up measures of QOL were significant in all domains (all $P < 0.001$).

Preliminary analyses were also conducted to rule out the potential influence of drug use patterns on the impulsivity predictors. Time since last use of methamphetamine at the time of testing and methamphetamine use characteristics (route of administration, length of use, typical daily usage) were not correlated significantly with any of the predictors (all $r < 0.17$).

Table 1 Demographic and clinical statistics for the sample.

	Mean/n (%)	*SD*
Age	31.1	7.2
Sex (M/F)	81 (75.0%)	
Years of education	13.0	2.4
IQ estimate	96.1	11.0
Unemployed	77 (71.3%)	
Smokers	87 (80.6%)	
Cigarettes per month	414.4	260.0
Daily level of use (g)	0.75	0.62
Days of use in month prior to treatment	22.1	9.2
Years use prior to treatment	9.3	4.9
Age commenced use	23.8	8.1
Route of administration		
Smoking	76 (70.4%)	
Intravenous	25 (23.1%)	
Multiple routes	7 (6.5%)	
Ever used intravenously	45 (41.7%)	
Methamphetamine SDS	11.1	3.1
Cannabis use	54 (50.0%)	
Cannabis use disorder only	24 (22.2%)	
Cannabis SDS	2.7	4.3
Alcohol use	59 (54.6%)	
Alcohol use disorder only	6 (5.6%)	
Alcohol SDS	1.7	3.3
Alcohol and cannabis use disorder	3 (2.8%)	
Cocaine use disorder	2 (1.9%)	
CES-D score	28.3	12.3
Clinical measures	*Mean*	*SD*
CPT-2 motor impulsivity	16.98	7.76
CPT-2 cognitive impulsivity	0.57	0.43
Delay discounting *k*-value	0.06	0.07
WHO QOL-BREF		
Social baseline	7.39	2.71
Social follow-up	8.86	2.89
Psychological baseline	15.33	4.08
Psychological follow-up	19.31	4.73
Physical baseline	21.33	4.55
Physical follow-up	25.05	5.54
Environment baseline	23.93	5.42
Environment follow-up	27.69	6.03

SD = Standard Deviation; SDS = Severity of Dependence Scale; CPT-2 = Continuous Performance Test-2; CES-D = Centre for Epidemiological Studies Depression Scale; WHO QOL-BREF = World Health Organization Quality of Life Scale—Brief.

Link between impulsivity and changes in QOL

Detailed results of the four regression models are shown in Table 2.

Social QOL change

Impulsivity measures (commission errors, detectability and *k*-value) improved the predictive value of the model significantly, including the control variables (adjusted $R^2\Delta = 0.11$, $P = 0.010$). Higher rates of commission errors

Table 2 The predictive value of impulsivity on four domains of quality of life (QOL).

	Social QOL				*Psychological QOL*				*Physical QOL*				*Environmental QOL*			
Outcome	*Adj.* R^2	*β*	*Sig.*	*95% CI*	*Adj.* R^2	*β*	*Sig.*	*95% CI*	*Adj.* R^2	*β*	*Sig.*	*95% CI*	*Adj.* R^2	*β*	*Sig.*	*95% CI*
Control variables	0.129		0.022		0.102		0.050		0.212		0.002		0.085		0.076	
Age		−0.21	0.061	(−0.43, 0.01)		−0.14	0.222	(−0.36, 0.09)		−0.28	0.009	(−0.49, −0.07)		−0.15	0.180	(−0.38, 0.07)
Gender		−0.08	0.483	(−0.29, 0.14)		0.06	0.612	(−0.17, 0.28)		0.07	0.490	(−0.13, 0.28)		−0.13	0.240	(−0.36, 0.09)
IQ		0.29	0.012	(0.07, 0.52)		0.19	0.112	(−0.04, 0.42)		0.25	0.022	(0.04, 0.46)		0.20	0.091	(−0.03, 0.43)
CIS-D		0.25	0.041	(0.01, 0.49)		0.28	0.025	(0.04, 0.53)		0.23	0.047	(0.00, 0.46)		0.24	0.059	(−0.01, 0.49)
SDS-meth		0.12	0.298	(−0.11, 0.35)		0.22	0.068	(−0.02, 0.46)		0.15	0.171	(−0.07, 0.37)		0.14	0.231	(−0.09, 0.38)
SDS-cannabis		0.19	0.096	(−0.03, 0.41)		0.13	0.270	(−0.10, 0.35)		0.13	0.211	(−0.08, 0.34)		0.15	0.181	(−0.07, 0.38)
Rehabilitation			Ref				Ref				Ref				Ref	
Detoxification		−0.25	0.041	(−0.49, −0.01)		−0.10	0.401	(−0.35, 0.14)		−0.19	0.093	(−0.42, 0.03)		−0.18	0.148	(−0.43, 0.07)
Out-patient		−0.11	0.346	(−0.35, 0.12)		−0.06	0.602	(−0.30, 0.18)		−0.24	0.039	(−0.46, −0.01)		−0.17	0.171	(−0.42, 0.07)
Full model	0.234, Δ = 0.105		0.002		0.152, Δ = 0.05		0.023		0.220, Δ = 0.008		0.003		0.092, Δ = 0.007		0.094	
Age (years)		−0.20	0.051	(−0.41, 0.00)		−0.14	0.204	(−0.36, 0.08)		−0.28	0.010	(−0.48, −0.07)		−0.15	0.174	(−0.38, 0.07)
Gender		−0.09	0.363	(−0.30, 0.11)		0.05	0.668	(−0.17, 0.26)		0.06	0.564	(−0.15, 0.27)		−0.15	0.189	(−0.37, 0.08)
IQ		0.17	0.146	(−0.06, 0.40)		0.13	0.285	(−0.11, 0.37)		0.19	0.103	(−0.04, 0.42)		0.18	0.146	(−0.07, 0.43)
CIS-D		0.25	0.034	(0.02, 0.47)		0.26	0.031	(0.03, 0.50)		0.23	0.048	(0.00, 0.46)		0.23	0.065	(−0.02, 0.48)
SDS-meth		0.10	0.378	(−0.12, 0.32)		0.19	0.105	(−0.04, 0.42)		0.14	0.211	(−0.08, 0.36)		0.13	0.295	(−0.11, 0.37)
SDS-cannabis		0.25	0.022	(0.04, 0.46)		0.17	0.137	(−0.06, 0.39)		0.17	0.126	(−0.05, 0.38)		0.18	0.123	(−0.05, 0.41)
Rehabilitation			Ref				Ref				Ref				Ref	
Detoxification		−0.26	0.021	(−0.49, −0.04)		−0.13	0.294	(−0.36, 0.11)		−0.20	0.079	(−0.43, 0.02)		−0.19	0.121	(−0.44, 0.05)
Out-patient		−0.09	0.417	(−0.32, 0.14)		−0.02	0.843	(−0.26, 0.22)		−0.22	0.062	(−0.45, 0.01)		−0.12	0.347	(−0.37, 0.13)
DDT *k*-score		−0.26	0.019	(−0.47, −0.05)		0.06	0.604	(−0.17, 0.29)		−0.13	0.245	(−0.34, 0.09)		0.07	0.569	(−0.17, 0.30)
CPT-2 Commissions		−0.54	0.013	(−0.96, −0.12)		−0.45	0.046	(−0.90, −0.01)		−0.32	0.134	(−0.74, 0.10)		−0.41	0.082	(−0.87, 0.05)
CPT-2 Detectability		−0.46	0.029	(−0.87, −0.05)		−0.20	0.359	(−0.63, 0.23)		−0.29	0.160	(−0.71, 0.12)		−0.32	0.161	(−0.77, 0.13)

β = standardized regression coefficient; Adj. R^2 = adjusted *R*-squared value; SDS = Severity of Dependence Scale; Meth = methamphetamine; CIS-D = Centre for Epidemiological Studies Depression Scale; DDT = Delayed Discounting Task; CPT = Continuous Performance Test-2; CI = confidence interval.

(β = −0.54), more interference when distinguishing between stimuli (β = −0.46) and decisions favouring short-term benefits (β = −0.26) predicted less improvement in social QOL. Beta coefficients indicate that all impulsivity variables were equal or superior to the control predictors ($\beta_{max} = -0.26$).

Psychological QOL change

Although impulsivity measures did not improve the predictive value of the model with the control variables significantly (adjusted $R^2\Delta = 0.05$, $P = 0.082$), the model was only significant after inclusion of the impulsivity predictors ($P = 0.023$). Higher rates of commission errors (β = −0.45) predicted less improvement in psychological QOL, and Beta coefficients indicated that it was the strongest predictor in the model. The other impulsivity predictors were not significant.

Physical QOL change

Control variables predicted physical QOL change significantly (adjusted $R^2 = 0.21$, $P = 0.002$), and the addition of impulsivity measures did not improve the predictive value of the model significantly. Age and depression were significant predictors in the full model.

Environmental QOL change

Control variables did not predict significantly the environmental QOL change, and the addition of impulsivity measures did not significantly improve the predictive value of the model.

Sensitivity analysis

Change in methamphetamine use during the follow-up period was associated significantly with environmental ($r = -0.33$, $P = 0.003$) and physical ($r = -0.30$, $P = 0.008$) QOL change, but no other outcome variables. When entered into the regression model, change in methamphetamine use was not a significant predictor. With regard to other substances, only change in cannabis SDS was associated significantly with change in physical ($r = -0.27$, $P = 0020$) and social ($r = -0.25$, $P = 0.034$) QOL, but was not significant when entered into the multiple regression models together with impulsivity predictors.

DISCUSSION

This study examined if impulsive choice and action at treatment commencement predict changes in QOL during the first 6 weeks of treatment among people with MD. We found that higher levels of impulsivity throughout domains (action and choice) predicted significantly less change in social QOL. We found partial support for the hypothesis that impulsivity measures would be significant predictors of less change in psychological QOL; impulsive action (motor disinhibition) emerged as a significant negative predictor; however, impulsive choice and cognitive disinhibition did not. No elements of impulsivity were predictive of change in physical or environmental QOL.

Findings concerning social QOL are consistent with previous research showing that high impulsivity can disrupt communication, language and planning in people with MD [10,17]. We found that these deficits generalize broadly across the areas that define social QOL (personal relationships, social support and sexual activity). The broad impact of impulsivity can be interpreted through the constructs of impulsive choice and action. Individuals may prioritize other activities above social engagements (impulsive choice), show disinhibited or aggressive behaviour in social settings and have difficulty understanding the perspective of others (impulsive action [38,39]). Social QOL findings are also consistent with the process of addiction treatment. Treatment programmes emphasize reducing contact with drug-using peers and strengthening social connections with non-drug-using groups [40]. This renegotiation, engagement and discontinuation of relationships occurs typically during the early period of recovery [41]. Individuals with lower levels of impulsivity may take a more considered approach when trying to distance themselves from drug-using peers, and may find it easier to develop new relationships among non-drug-using networks. Furthermore, because individuals often define themselves by their social relationships [40,42], the inability to regain 'conventional' societal roles (which is more difficult for those with higher levels of impulsivity) can compromise long-term recovery by maintaining problematic social environments [42].

Findings linking impulsivity and psychological wellbeing are particularly relevant in people with MD, as poor mental health can often precipitate and reinforce drug use [43]. Our findings support previous work linking motor disinhibition to reduced emotional self-awareness in individuals with MD [44]. Acting on the spur of the moment can involve engaging with activities that provide short-term pleasure followed by distress (e.g. drug use, risky behaviours), and can have a broad impact upon the areas that comprise psychological QOL (affective state, bodily image, self-esteem, perceived cognitive function). Engagement with these activities may be particularly prominent in the early periods of recovery, where certain behaviours may increase in compensation for the cessation of methamphetamine use, but may hinder the psychological recovery process. In populations with drug dependence, impulsive action is strongly predictive of psychological distress and externalizing behaviour [45],

while heightened impulsivity has been associated directly with anxiety in people with MD [46]. Other elements of impulsivity were not predictive of change in psychological QOL. Cognitive impulsivity reflects difficulty in focusing attention on tasks and is therefore more likely to impact upon functioning in complex tasks (such as social interactions), rather than leading directly to psychological distress. Furthermore, impulsive choice also differs from motor impulsivity, in that it involves conscious reflection on options prior to making a choice, and may involve important decisions that provide short-term pleasure but negative consequences that may not be experienced until much later, beyond the follow-up period of the current study (e.g. taking out a loan that cannot be repaid, leaving employment abruptly).

Findings regarding physical QOL suggest that the impact of ceasing methamphetamine use and demographic and clinical factors (i.e. age, depressive symptoms) have stronger predictive value than cognitive factors. Indeed, some of the facets that comprise physical QOL (i.e. fatigue, pain and discomfort and sleep difficulties) are common symptoms during the first 3 weeks after methamphetamine cessation, but improve as part of the natural trajectory of recovery [47], while older age is associated with lower levels of physical QOL in drug-dependent samples [48]. Additionally, the non-significant relationship between impulsivity and environmental QOL may be explained partly by the substantial environmental changes that take place when entering either in-patient (a controlled, drug-free, safe environment) or out-patient (e.g. more linkages with health-care services) settings. Change in environmental QOL was correlated significantly with reduction in methamphetamine use; this may reflect the process of remaining in treatment-related environments rather than cognitive factors.

Our findings need to be considered in the context of a number of limitations. Although the proportion of QOL variance explained by predictive models was only 15–23%, this result is consistent with studies examining similar predictors and outcomes [17,18]. The study was also subject to a short follow-up period of 6 weeks. Although QOL in people with MD has been shown to change within the first 3 weeks of treatment [20], a longer period of stabilization may clarify further relationships between impulsivity and psychological and physical domains of QOL. Furthermore, the composition of the sample included a high proportion of polysubstance users (particularly individuals dependent upon cannabis) and those with clinically significant levels of depression. The inclusion of these participants ensured a large, representative sample of individuals with MD in treatment settings [49], and their impact was controlled for in statistical analyses. Additionally, participants self-reported their abstinence at baseline testing. Although not as accurate as biological measures, procedures were put in place to maximize the accuracy of this self-reported data (i.e. assurance of confidentiality, use of recall cues, collection from multiple sources, consistent and clear instructions [50]). Finally, although the rate of attrition (26%) must be considered as a factor limiting generalizability of the study, this outcome is comparable to similar longitudinal research with this population [21,51].

Notwithstanding these limitations, our findings have important implications for clinical practice. People with MD presenting to treatment with heightened impulsivity of all forms may benefit from additional support during and following treatment, but also the development of specific skills in recovery (e.g. delay/evaluation of actions, social skills training) to improve their functioning in the community. Similarly, individuals entering treatment with high levels of motor disinhibition may benefit from psychological support with a focus on behavioural interventions (rather than strictly cognitive). These strategies might allow an individual to pause prior to engaging in a behaviour that might be immediately reinforcing, but detrimental in the long term. Heightened impulsivity has been identified consistently as a deficit in individuals with MD, and has an impact upon social and psychological QOL change in early treatment. Future research may explore these relationships during a longer time-period, and test the efficacy of cognitive remediation strategies to buffer the impact of impulsivity on QOL [52,53]. Treatment settings may benefit from tailoring MD treatment programmes based on impulsivity profiles [54].

Declaration of interests

None.

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CHAPTER FIVE: SUSTAINED ATTENTION BUT NOT EFFORT-BASED DECISION-MAKING IS SIGNIFICANTLY PREDICTS TREATMENT MOTIVATION CHANGE IN METHAMPHETAMINE USE DISORDER

Abstract

Background: Early treatment motivation is a meaningful predictor of clinical outcomes in the context of methamphetamine use disorder (MUD). Cognitive deficits associated with MUD can have a significant impact on motivational fluctuations during early treatment. We specifically examined if sustained attention and effort-based decision-making predict early treatment motivation change in individuals with MUD. We hypothesised that both variables would be significant predictors of individual differences in treatment motivation change.

Methods: We conducted a longitudinal, observational, cohort study on individuals with MUD (N = 72, Age, M = 31.1, SD = 7.3, 29% female). Participants were assessed with cognitive tests of sustained attention (continuous performance test) and effort-based decision-making (effort expenditure for rewards task) within three weeks of entering treatment and rated their treatment motivation at baseline and at follow up six weeks later (n = 50). Multiple regression was used to examine the predictive value of cognitive variables after controlling for nuisance variables.

Results: Cognitive measures significantly predicted change in treatment motivation after accounting for nuisance variables, $F(5,43) = 2.89$, $p = .025$. Analysis of individual predictors showed that sustained attention, but not decision-making, was a significant predictor of less improvement in treatment motivation ($\beta = -.34$, $p = .015$).

Conclusions: Poorer sustained attention predicts lesser improvement in motivation during early treatment. These findings help to characterise cognitive predictors of treatment motivation and suggest directions for tailored treatment programs. Individuals entering treatment with attentional deficits may benefit from adjustments to therapy and/or cognitive remediation.

1. Introduction

Treatment motivation represents a drive to engage with the requirements of a treatment program and thus achieve therapeutic goals (Drieschner, Lammers, & van der Staak, 2004; O'Donohue, James, & Snipes, 2017). This construct is critical to successful recovery from addiction and predicts treatment completion (Ball, Carroll, Canning-Ball, & Rounsaville, 2006) and long-term abstinence (Myers, van der Westhuizen, Naledi, Stein, & Sorsdahl, 2016). Individuals with methamphetamine use disorder (MUD) are particularly vulnerable to low levels of motivation following cessation of use (Fiorentine et al., 1999), and exhibit very poor rates of long-term abstinence (Herbeck & Brecht, 2013; Zorick et al., 2010). Early treatment, specifically the first two months, is associated with very high variability in treatment motivation (Baker et al., 2005), and is a period of high vulnerability to relapse in individuals with MUD (Brecht & Herbeck, 2014). Despite the importance of this period, previous research has not examined the factors underlying early changes in treatment motivation in the context of MUD. Individuals with MUD have cognitive deficits in the domains of attention, memory and cognitive control or impulsivity (Dean, Groman, Morales, & London, 2013). Moreover, these deficits are associated with clinical problems in areas related to change in treatment motivation: engagement with treatment sessions (Aharonovich, Amrhein, Bisaga, Nunes, & Hasin, 2008), exploration of different perspectives and learning new behaviours (Katz et al., 2005), and interpersonal engagement (Henry, Mazur, & Rendell, 2009). Therefore, cognitive function may be an important predictor of changes in treatment motivation among individuals with MUD.

Attentional function is a component of cognition that is particularly important in the context of treatment motivation. Sustained attention is the ability to maintain a similar level of attention to a stimulus over time, as is required in cognitive and behavioural components of individual counselling in drug treatment (Sofuoglu, DeVito, Waters, & Carroll, 2013). Poorer sustained attention in individuals with MUD is significantly associated with diminished performance in daily functioning and greater cognitive complaints, including deficits in communication and comprehension (Morgan et al., 2014). Such deficits are likely to reduce the ability to effectively engage in the treatment process. However, despite this theoretical link between sustained attention and change in treatment motivation, previous literature is limited to stimulants other than methamphetamine. In cocaine users, Carroll et al., (2011) found that poorer sustained attention was significantly predictive of reduced engagement and motivation (fewer sessions and tasks completed) in a psychological treatment program. In another stimulant (nicotine), better performance in a task of sustained attention significantly predicted membership in a therapeutic group defined by more engagement with a treatment program and reduced nicotine use (Harris et al., 2014).

Decision-making similarly plays an important role in change in treatment motivation. Individuals with MUD report more impulsive decision-making than healthy controls, accompanied by greater difficulty in day-to-day measures of cognitive functioning (e.g., inhibition, emotional control, self-monitoring; Ellis et al., 2016). This cognitive profile may represent a short-term focus in which the long-term benefits of treatment may be difficult to access/comprehend (Washio et al., 2011). Indeed, impulsive decision-making also significantly predicted disengagement with a

12-week psychologically-focused treatment program for individuals with MUD (Chen, Chen, & Wang, 2015). In a criminal justice sample of individuals with MUD, self-reported short-term focused decision-making significantly predicted a 6-9 month longitudinal measure of change in treatment motivation (including satisfaction, rapport, participation and support; Joe, Rowan-Szal, Greener, Simpson, & Vance, 2010). These findings suggest that a short-term focus underpins the link between decision-making and changes in treatment motivation. This short-term focus may be related to specific components of decision-making: placing greater value on immediate rewards, and a reluctance to exert effort for future, uncertain rewards. Both of these components can be assessed with effort-based decision-making tasks, which require a prolonged effort for a reward that is not guaranteed, and specifically addresses motivational elements of decision-making (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009). The effort-based decision-making process may be analogous to the treatment process, where participants engage in an ongoing 'decisional balance' of evaluating the benefits and limitations of applying effort to a treatment program with an uncertain outcome (Le Berre et al., 2012). Therefore, effort-based decision-making may measure the ability to maintain motivation over time despite uncertain, delayed rewards.

In summary, previous research has shown that poorer attention and decision-making are generally linked to lower treatment motivation in the context of stimulant addiction. However, in people with MUD, motivation fluctuates significantly throughout the early months of treatment (Baker et al., 2005) and this is a key indicator of long-term treatment outcomes (Ball et al., 2006; Myers et al., 2016; Tuliao

& Liwag, 2011). Although previous studies have not examined the cognitive factors that contribute to the stability or variability of treatment motivation during MUD treatment, sustained attention and effort-based decision-making are conceptually relevant domains. Patients with MUD typically show lower levels of sustained attention compared with healthy controls (Hosak et al., 2011) and, anecdotally, these deficits seem to be reflected in treatment performance (e.g., Morgan et al., 2014). Although there is no research on effort-based decision-making in people with MUD, rodent research has shown that methamphetamine exposure is linked to steeper discounting of the value of rewards when they require significant effort (Thompson et al., 2017). Therefore, patients with MUD with poorer effort-based decision-making may experience loss of motivation during the course of treatment (i.e., discounting of the reward value of treatment as a function of perceived effort required to complete it).

We aimed to examine the extent to which performance in objective cognitive measures of sustained attention and effort-based decision-making are longitudinally predictive of change in treatment motivation over the first six weeks of treatment for MUD. Cognitive measures were administered within the first three weeks of treatment (the baseline session), and a measure of treatment motivation was recorded at the baseline session and at a follow-up six weeks after the baseline session. We hypothesized that lower levels of sustained attention and effort-based decision-making would predict a lower change in early treatment motivation.

2. Material and Methods

2.1 Design

Participants with MUD were assessed with a cognitive battery including the specific measures of sustained attention and effort-based decision-making within the first three weeks after commencing treatment (baseline), and a measure of treatment motivation at two time points: at baseline and at a follow up session six weeks after their first session.

2.2 Participants

Our sample comprised 72 participants with MUD at baseline testing (Age, M = 31.1, SD = 7.3, 21 females), recruited through private and public detoxification and rehabilitation facilities, and community-based counselling organisations in suburban Melbourne, Australia from April 2015 to December 2016. Participants were engaged in three forms of treatment: residential rehabilitation (n = 37), detoxification only (n = 21), and outpatient counselling (n = 14). Residential rehabilitation consisted of psychological (e.g., cognitive behavioural therapy, relapse prevention) and behavioural interventions (e.g., exercise, art therapy) in group and individual contexts, in a hospital setting for 4-6 weeks. Detoxification involved medically supervised detoxification for seven to 10 days prior to discharge into the community. Outpatient counselling involved weekly or fortnightly individual or group therapy utilising cognitive, behavioural and motivational components, while remaining in the community.

The sample size was determined *a priori* using the G*Power program: 80% power, alpha level = 0.05 and a moderate effect size (Morgan et al., 2014). The study assumed a 30% attrition rate, based on similar longitudinal studies of individuals with MUD (e.g., Simon Dean, Cordova, Monterosso, & London, 2010).

The selection criteria included the following requirements: aged 18-55 years, meet DSM-IV criteria for MUD determined by the Structured Clinical Interview for the DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1996), abstinent for at least two days and no more than three weeks (self-report and clinician confirmed). Participants were excluded if they reported: loss of consciousness >30 minutes, a history of bipolar disorder, schizophrenia, psychotic disorders, or dependence on substances other than methamphetamine, alcohol, or cannabis (measured by the SCID). Participants with an intellectual disability (IQ <70 as determined by the Wechsler Abbreviated Scale of Intelligence 2) were also excluded.

2.3 Measures

2.3.1 Background measures

2.3.1.1 Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-2): This is a brief measure of general cognitive functioning with four tasks, assessing performance IQ (visuospatial abilities) and verbal IQ (understanding and use of language). Our study used a two-task IQ estimate, using Vocabulary and Matrix Reasoning tasks. The WASI-2 is valid and reliable in non-clinical (Wechsler & Hsiao-pin, 2011) and MUD populations (King Alicata, Cloak, & Chang, 2010).

2.3.1.2 Severity of Dependence Scale (SDS): The SDS is a 5-item self-report measure of level of dependence on a substance, with high validity and reliability in substance-dependent populations (Gossop et al., 1995). Questions are rated on a four-point scale (e.g., 'how difficult would you find it to stop or go without (drug)?' from 'Not difficult at all' to 'Impossible'). Our study used the methamphetamine, cannabis and alcohol versions of the scale. The baseline SDS scores were considered as potential control variables; higher scores appear to be associated with motivation at baseline (McKetin et al., 2012).

2.3.1.3 Timeline Followback (Sobell & Sobell, 1996): This self-report measure of drug use consists of a blank calendar on which a participant marks each day of use. We used this measure to obtain a baseline record of methamphetamine use in the month before treatment, and the month before the participant's follow-up assessment as a potential control variable.

2.3.1.4 Centre for Epidemiological Studies Depression Scale (CES-D): This scale is a 20-item, self-report measure of low mood, with high validity and reliability (Orme, Reis, & Herz, 1986). Each question is rated on a four-point scale, based on symptom frequency (e.g., I felt lonely, from 'Rarely or none of the time' to 'Most or all of the time'). Ratings for each question are assigned a number from 0-3. A higher total score indicates a higher level of depressive symptomatology, and was used as a potential control variable to account for low mood, a high prevalence symptom in early recovery from MUD (Luan et al., 2017).

2.3.2 Cognitive Measures

2.3.2.1 The Effort Expenditure for Rewards Task (EEfRT; Treadway et al., 2009*):* This computer-based task measures the willingness to expend effort for an uncertain monetary reward. In each trial, participants select an easy task ($1 reward) or hard task ($1.24-$4.30 reward). The tasks involves pushing a computer key either 20 times in seven seconds with the dominant index finger (easy task) or 100 times in 20 seconds with the non-dominant little finger (hard task). The probability of receiving the associated reward after completing the task varies (12%, 50% or 88%). EEfRT shows high levels of validity and reliability in populations with cognitive deficits (Horan et al., 2015; Reddy et al., 2015). To maintain adequate power, the current study used only the proportion of hard task selection at 50% probability of reward as a predictor, as this reflects decision-making in a situation of high uncertainty, while the 12% and 88% conditions tend to exhibit low and high selections of hard tasks respectively in healthy populations (Treadway et al., 2009), and therefore the proportion of selections in these conditions may not be reflective of cognitive changes due to methamphetamine use.

2.3.2.2 Continuous Performance Test – Second Edition (CPT-2)

The CPT-2 is a computer-based task of attention that takes 14 minutes to complete and shows good levels of validity and reliability (Conners, 2004). During the test, letters of the Latin alphabet flash in white on a black screen and participants press the space bar after each letter except for X. Letters are presented for 250ms, after which a new stimulus appears after either 1, 2 or 4s. The variable used in the current study is 'Hit Reaction Time standard error'. This variable indicates reaction time consistency

over the course of the task, which reflects the sustained attention construct (Egeland & Kovalik-Gran, 2010a; Egeland & Kovalik-Gran, 2010b).

2.3.2 Outcome Measure

2.3.2.1 Contemplation Ladder (Biener & Abrams, 1991): This measure comprises 10 statements relating to recovery and motivation towards ceasing drug use. A rating of zero corresponds with 'No thought about quitting. I cannot live without drugs.', while a rating of ten corresponds with the statement 'I have changed my drug use and will never go back to the way I used drugs before.' This measure has shown excellent psychometric properties in substance dependent individuals as a measure of treatment motivation (Amodei & Lamb, 2004; Hogue, Dauber, & Morgenstern, 2010). We were specifically interested in the fluctuation of motivation over time and therefore the dependent variable was the 'change in motivation score.' Baseline scores were subtracted from scores at the follow-up session (change in motivation score = Contemplation Ladder^{T2} – Contemplation Ladder^{T1}).

2.4 Procedures

The Eastern Health Human Research Ethics Committee approved the study (E52/1213). Individuals with MUD commencing treatment were introduced to the study by one of their primary clinicians, before screening and consenting by a researcher.

Fifty participants (71% of the sample) completed the follow-up assessment (M = 44.7 days, SD = 5.8); the remaining 22 participants were unreachable or refused to participate further. There were no significant differences on background or cognitive

characteristics between completers and dropouts (t_{max} = -1.99 p_{min} = .051). After completing both sessions, participants received a $AUD40 gift card. The first two authors, who have post-graduate training in clinical assessment methods, conducted all assessments.

2.5 Statistical Analysis

We performed all analyses in the IBM SPSS (Version 21.0) statistical package. Data were assessed for missing data, outliers, and distribution. There were no univariate or multivariate outliers in the data. Pairwise deletion was used for the two participants with missing data for the EEfRT task. The proportion of missing data was less than 5% and therefore did not require imputation (Tabachnick & Fidell, 2013).

We conducted a multiple regression analysis to examine the predictive value of effort-based decision-making and sustained attention on treatment motivation change. We conducted preliminary analyses to determine which demographic and clinical variables (i.e., age, gender, IQ, treatment modality, severity of dependence scores for alcohol, cannabis and methamphetamine, level of depressive symptoms, days of methamphetamine use over past month) were associated with the outcome measure. Treatment modality (r = .16), severity of dependence score for alcohol (r = -.12) and depressive symptoms (r = .11) showed the highest correlations with treatment motivation change (all other variables r < .10) and were therefore added as nuisance variables to the regression model. In the analysis, nuisance variables were entered in the first block, and cognitive variables of sustained attention ('hit reaction time' standard error) and the effort-based decision-making variable (proportion of hard

selections at 50% probability of being paid the reward) in the second block. The key statistics were the change in the *F* and *p* values associated with the predictor variables and the *Beta* values of individual predictors in the full model.

There is a tendency for motivation to change (and often improve) in early treatment in the absence of an intervention (~12-25% of participants in a similar sample; Hughes, Keely, Fagerstrom, & Callas, 2005). Therefore, we conducted sensitivity analyses to ensure independent relationships between cognitive variables and baseline motivation/change in motivation.

3. Results

3.1 Background characteristics

Participants' demographic and clinical characteristics are illustrated in Table 1. The majority of the sample was male, most participants were unemployed and smoked methamphetamine as their primary route of administration, while more than half of participants had used intravenously at some point (54.3%).

3.2 Change in motivation

Contemplation Ladder score at baseline did not differ significantly between completers and non-completers ($t = 1.87$, $p = .067$). On average, participants expressed a high level of motivation at the start of treatment, which increased slightly at the follow-up session. Change in motivation ($M = .51$) exhibited a relatively wide standard deviation ($SD = 1.54$) as originally expected. Group changes and inter-individual variability on treatment motivation are displayed for illustrative purposes in Figure 1.

3.3 Link between baseline cognitive function and change in treatment motivation

Table 2 shows the results of the regression model. Nuisance variables (treatment modality, severity of dependence score for alcohol, level of depressive symptoms) non-significantly predicted change in early treatment motivation, $F(3,45) = 1.58$, $p = .208$. The addition of effort-based decision-making and sustained attention predictors significantly improved the predictive value of the model $F\Delta(2,43) = 4.48$, $p = .017$, and explained an additional 12.9% of variability in change in Contemplation Ladder scores, and resulted in a significant model, $F(5,43) = 2.89$, $p = .025$. 'Hit reaction time' standard error emerged as a significant predictor ($\beta = -.34$, $p = .015$), however EEfRT medium ($\beta = .18$, $p = .189$) did not. For each unit increase in sustained attention (indicating higher variability) there was a decrease of 0.34 units in change in motivation.

3.4. Sensitivity analysis

To ensure that the longitudinal results were not driven by cross-sectional relationships between the cognitive predictors and treatment motivation, we re-ran the model using baseline treatment motivation as the outcome variable. Neither of the cognitive variables were significant predictors of baseline treatment motivation ($\beta_{max} = -0.22$, $p_{min} = .072$).

4. Discussion

Our study examined whether performance in tests of effort-based decision-making and sustained attention at the start of treatment predicted change in

motivation over the following six weeks among individuals with MUD. Poorer sustained attention, indicated by a measure of attentional fluctuation, predicted lesser improvement in treatment motivation. Effort-based decision-making and other demographic and clinical variables did not predict change in treatment motivation.

This is the first study that links sustained attention and treatment motivation in MUD, but is consistent with past literature in the context of cocaine (Carroll et al., 2011) and nicotine dependence (Harris et al., 2014). This finding may be partly understood by the relationship between poorer sustained attention and difficulty absorbing content during treatment sessions (Medalia & Choi, 2009), lower levels of skill acquisition (Kurtz, Seltzer, Fujimoto, Shagan, & Wexler, 2009) and poorer social engagement (Kurtz, 2011) as observed in other populations with similar cognitive deficits. During psychological treatment sessions, substance dependent individuals with impaired sustained attention show a reduced ability to focus on therapeutic content (Zulauf, Sprich, Safren, & Wilens, 2014) and explore more complex concepts and perspectives (Aharonovich et al., 2008). The combination of these factors may underpin the link between attentional dysfunction and diminished motivation.

Effort-based decision-making did not predict change in treatment motivation in our results. A previous study found decision-making significantly predicted change in treatment motivation outcomes, however, this study examined self-reported decision-making (Joe et al., 2010) rather than an objective 'effort-based' task. Another study examined decision-making in the context of a psychologically-based treatment program, but measured dropout rather than treatment motivation (Chen et al., 2015).

These previous findings may reflect a tendency to make ill-considered decisions rather than less willingness to expend effort for an uncertain outcome. In contrast to expectations, changes in treatment motivation may be related to discrete moments of inopportune decision-making (e.g. an outburst in session, deciding to leave therapy against advice) rather than consideration of the 'big picture' and whether a long-term sacrifice is worthwhile. Furthermore, the worth the effort task involves only a very brief period of testing (e.g. maximal effort is required for 20 seconds at most) and may not model the long-term process of treatment.

Our findings need to be considered in the context of limitations. In the current study, 22 participants (31%) were lost to attrition. Participants who experienced lower levels of motivation are less likely to have completed the study, and as a result, motivation scores at follow-up may have been inflated, which may partly explain high rates of motivation at baseline and follow-up. Additionally, the follow-up period in the study was brief at six weeks. However, MUD treatment episodes are typically short (around two months; McKetin et al., 2017), and therefore the current study leads to a greater understanding of the drivers of treatment motivation prior to discharge or withdrawal. Finally, the sample included a small number of participants with cannabis and alcohol use or dependence. Although these substances can impair cognition, the inclusion of these participants ensured a representative sample (Lubman et al., 2016), and the impact of these variables was controlled in statistical analyses.

4.1 Conclusions

Notwithstanding these limitations, our study has meaningful clinical

implications. Individuals with MUD entering treatment with deficits in sustained attention may benefit from adjustments to therapy such as those implemented in other groups with attentional problems (consolidation of recently-learned skills, regular reviews of key content; Ramsay, 2017). These patients may also benefit from cognitive remediation therapy, which has been particularly effective in improving sustained attention in other populations with cognitive impairment (Kurtz, 2011). In one variation of cognitive remediation, a combination of Motivational Interviewing and chess significantly improved attentional functioning in the first month of treatment for stimulant users (Goncalves et al., 2014). These interventions enhance the ability to maintain attention over time and to retain in-session content, which are critical skills in individual and group treatment settings (Sofuoglu et al., 2013) and play a key role in the ability to remain engaged and motivated in the treatment process (Aharonovich et al., 2008). Future research may explore the effectiveness of the combination of tailored treatment programs and cognitive remediation for individuals with MUD with attentional deficits.

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Table 1. Demographic and clinical characteristics of the sample

	Mean/N(%)	SD
Age	31.1	7.4
Sex (M/F)	49 (70.0%)	
Years of Education	13.1	2.6
IQ estimate	97.0	11.3
Unemployed	50 (71.4%)	
Smokers	57 (81%)	
Cigarettes per month	405.5	274.3
Daily level of use (grams)	.81	.69
Days of use in month prior to treatment	23.4	9.3
Years use prior to treatment	7.2	5.3
Age commenced use	23.7	8.3
Route of administration		
Smoking	43 (61.4%)	
Intravenous	22 (31.4%)	
Multiple routes	5 (7.1%)	
Ever used intravenously	38 (54.3%)	
Methamphetamine SDS	10.4	3.5
Cannabis use	31 (44.3%)	
Cannabis dependence	18 (25.7%)	
Cannabis SDS	2.7	4.3
Alcohol use	35 (50.0%)	
Alcohol dependence	6 (8.6%)	
Alcohol SDS	2.0	3.5
CES-D score	28.1	12.6
Clinical measures	Mean	SD
Contemplation ladder baseline	8.47	1.35
Contemplation ladder follow-up	8.75	1.23
Contemplation ladder change	.51	1.54
CPT-2 Reaction Time Standard Error (T-score)	59.53	15.19
EEfRT proportion hard selections (medium)	.53	.21

Note: SDS, Severity of Dependence Scale; CES-D, Centre for Epidemiological Studies Depression Scale; CPT-2, Continuous Performance Test-2; EEfRT, The Effort Expenditure for Rewards Task. Mean of Contemplation ladder baseline score derived from complete sample (n = 72).

Table 2. Findings from the multiple regression examining the predictive value of effort-based decision-making and sustained attention on change in treatment motivation.

Outcome	Change in Contemplation Ladder score			
	F Δ	*Adj.* R^2 Δ	*β* [95% CI]	*Sig.*
Block 1	1.58	.035		.208
SDS alcohol			-.18 [-.47, .11]	.215
CES-D			.24 [-.07, .54]	.128
Treatment modality (residential)			.21 [-.09, .52]	.166
Block 2	4.48	.129		.017
SDS alcohol			-.13 [-.41, .14]	.332
CES-D			.28 [-.01, .57]	.055
Treatment modality (residential)			.22 [-.06, .50]	.126
CPT-2 Reaction Time Standard Error (T-Score)			-.34 [-.62, -.07]	.015
EEfRT medium			.18 [-.09, .45]	.189

Note: SDS, Severity of Dependence Scale; CES-D, Centre for Epidemiological Studies Depression Scale; CPT-2, Continuous Performance Test-2; EEfRT, The Effort Expenditure for Rewards Task.

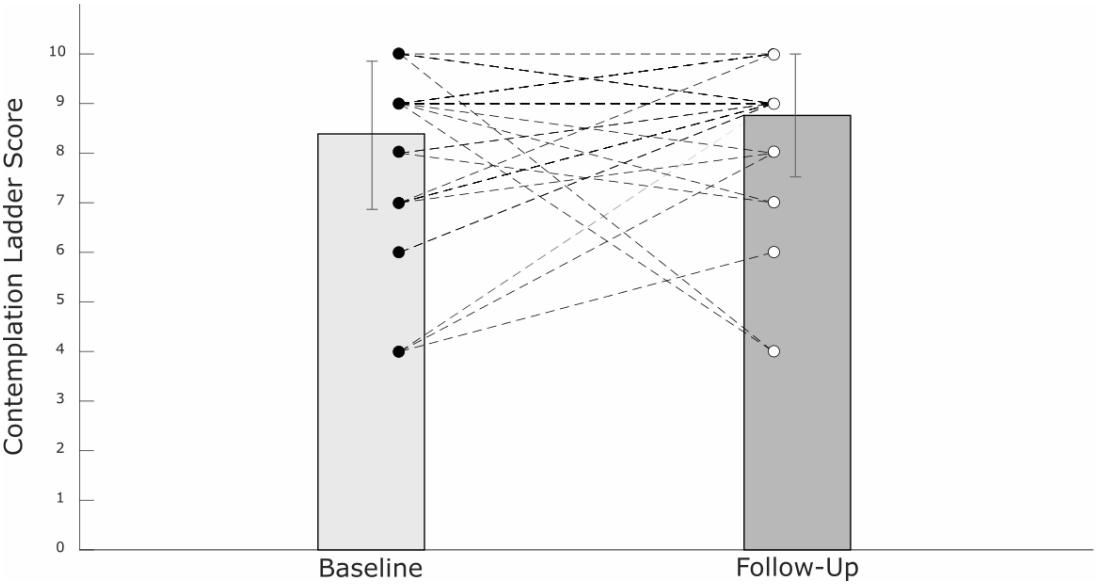

Figure 1: Mean level of motivation at baseline and follow-up, and individual motivation trajectories for each participant.

CHAPTER SIX: GENERAL DISCUSSION

6 Discussion

This chapter examines the key findings of the thesis in the context of the original research aims and past research in cognitive deficits and treatment outcomes in MA and stimulant dependent individuals. Subsequently, clinical implications, overall strengths and weaknesses, and suggestions for future research are discussed, followed by concluding remarks.

6.1 Key Findings

This section summarises the major findings of the thesis. We had three main aims, namely, to determine: (i) the predictive value of cognitive measures of the dual-systems model (cognitive control and impulsivity) on levels of MA use during early treatment; (ii) how elements of impulsivity are predictive of different components of quality of life, specifically, identifying the relative contributions of delay discounting and impulsive action to change in quality of life in early treatment; and (iii) the predictive value of cognitive measures of sustained attention and effort-based decision-making on change in treatment motivation in early treatment. All aims were explored in the first 6-9 weeks of treatment, in which individuals with MUD are highly vulnerable to relapse and disengagement (Brecht & Herbeck, 2014).

In Manuscript One we reported that working memory but not delay discounting was a significant predictor of MA use during early treatment. However, delay discounting moderated this relationship: those with low and moderate levels of delay discounting are likely to use less MA in this period. These findings have implications for the dual-systems model. As expected, poorer 'top-down' function

(cognitive control) was associated with higher rates of drug use. Additionally, low and moderate levels of delay discounting ('bottom-up' function), when combined with better 'top down' performance, were associated with less drug use. However, contrary to expectations and previous findings (Khurana et al., 2017), higher delay discounting did not predict drug use. Delay discounting may not represent the sensitisation of the reward-system as described in the dual-systems model, and may instead reflect a cognitive process of comparing values of short and long-term rewards (Da Matta, Goncalves, & Bizarro, 2012). Indeed, delay discounting is not consistently associated with relapse (Dominguez-Salas, Diaz-Batanero, Lozano-Rojas, & Verdejo-Garcia, 2016), and may instead influence the decision to leave treatment (Stevens, Verdejo-Garcia, Roeyers, Goudriaan, & Vanderplasschen, 2015; i.e., the short-term rewards of leaving treatment may exceed the perceived value of long-term sobriety). Furthermore, if decisions around the frequency and intensity of day-to-day drug use are highly influenced by contextual triggers and sensitisation (Noel et al., 2013), this may reflect a process of cognitive disinhibition (impulsive action) rather than delay discounting. Indeed, impulsive action has been previously directly associated with relapse (Carroll et al., 2011). Overall, these findings partially support the dual-systems model but are indicative of more complex interactions between top-down and bottom-up systems, which may involve multiple forms of impulsivity.

In Manuscript Two, we examined delay discounting and impulsive action in the context of quality of life (QoL). Both were significant predictors of change in the social domain, while impulsive action alone was also a significant predictor of change in the psychological domain. No domains of impulsivity were significantly predictive of

environmental or physical domains. Heightened delay discounting might be reflected in prioritisation of other activities over social events (e.g., staying at home playing video games rather than attending a birthday celebration). This directly reflects deficits in conscious and deliberative 'top-down' function, which is involved with integrating current possibilities with long-term consequences (i.e., the immediate satisfaction of playing video games outweighs potential long-term loneliness and isolation). Impulsive action was significantly predictive of less improvement in both psychological and social domains, suggesting that individuals with MUD and poor inhibition (diminished 'top-down' cognitive control) have difficulty in these settings. This may include engaging in activities that provide short-term pleasure but psychological distress over longer periods (e.g. risky activities such as dangerous driving, or spending money recklessly), and in behaviour that is not socially acceptable (e.g., aggression, lack of conversational turn-taking, difficulties taking the perspective of others). Overall, deficient inhibition demonstrated in these findings reflects a lack of cognitive control over impulsive urges. This is consistent with the dual-systems model and suggests that compromised executive functioning due to MUD may impair day-to-day functioning and decision-making.

Manuscript Three found that sustained attention but not effort-based decision-making significantly predicted less change in treatment motivation. These findings are consistent with previous work linking sustained attention and treatment motivation in stimulant users (Carroll et al., 2011, Harris et al., 2014). Poorer sustained attention may also be linked to diminished comprehension of content in session (Kurtz, Seltzer, Fujimoto, Shagan, & Wexler, 2009; Medalia & Choi, 2009), and poorer quality of

interpersonal interactions (Kurtz, 2011). These functional consequences of sustained attention fluctuations are likely to be underpinned by executive dysfunction, since sustained attention involves the control of attention, managed by the 'top-down' system. Furthermore, previous links between decision-making and treatment motivation may reflect a tendency to make ill-considered decisions (e.g., outbursts in session, leaving therapy against advice) rather than a rational evaluation of the value of expending effort for an uncertain outcome (Chen et al., 2015; Joe, Rowan-Szal, Greener, Simpson, & Vance, 2010). These actions are also likely to be driven by executive dysfunction and the inability of the 'top-down' system to regulate impulsive urges. Overall, we found that sustained attention significantly predicts treatment motivation, however there may be other related components of the 'bottom-up' system (i.e., impulsive action) that may help to better characterise the potentially interactive nature of the relationship.

Collectively, this thesis suggests that executive function in individuals with MUD is significantly predictive of early treatment outcomes (MA use, change in QoL and change in treatment motivation). The cognitive variables that emerged as significant are important components of executive functions (impulsivity, working memory, attention; Miyake & Friedman, 2012) and underpin the dual-systems model of addiction. Different components of the 'top-down' and 'bottom-up' systems are variably related with different outcomes (e.g., working memory predicts drug use, sustained attention predicts treatment motivation etc.), but generally support the overarching theory and its relevance for addiction treatment. It is important to note that the dual-systems concept encompasses a wide range of theories (e.g., incentive

sensitisation; Noel et al., 2013; I-RISA model; Goldstein & Volkow, 2002; opponent processes; Koob & Le Moal, 2005) and is linked to a range of state-related drivers (e.g., 'hot' and 'cold' emotions; Metcalfe & Mischel, 1999; situation specific cost-benefit analyses; Kahneman, 2003; hedonic processes; Kalivas & Volkow, 2005). Despite variation in the precise descriptions of the model, different iterations consistently endorse the dysregulation of cognitive control systems and heightened activity in impulsive systems; therefore our findings are interpreted in this broad context. While we established the role of cognitive control and impulsivity in predicting MA use, we were also better able to characterise the 'bottom-up' system with regards to QoL outcomes (i.e., differential effects of different forms of impulsivity). Furthermore, we determined that in the context of treatment motivation, fluctuations in sustained attention may most clearly reflect 'top-down' dysfunction, however, precise variables underpinning 'bottom-up' sensitivity require further examination. These findings support a complex version of the dual-systems model in the context of addiction treatment, in which different domains of cognition are predictive of specific outcomes in the context of overall executive dysfunction. Although not assessed in this thesis, a foundation of general executive dysfunction may make an individual susceptible to a combination of deleterious outcomes (e.g., higher drug use, less improvement in QoL/treatment motivation) and increase the complexity of treatment required.

6.2 Clinical Implications

The findings from this thesis have important clinical implications for inpatient and outpatient treatment settings and the broader wellbeing of individuals with MUD entering treatment. Changes in treatment approaches may lead to improvement in the

currently low rates of long-term abstinence and engagement (Brecht & Herbeck, 2014), and poor QoL and functioning in the community (Ellis et al., 2016; Gonzales et al., 2011). Such changes may also contribute to ameliorating the substantial social and economic costs of MUD (McKetin et al., 2017; Moore, 2007).

All studies in this thesis found that diminished cognitive performance is predictive of higher rates of problematic outcomes or less improvement in markers of treatment success. Treatment programs that accommodate for cognitive deficits may reduce their negative consequences (Dutra et al., 2008; Ramsay, 2017). Initially, pre-treatment cognitive testing/screening may help to categorise individuals in need of greater support or those at higher risk. Subsequently, a range of strategies can be used to accommodate for deficits.

High levels of impulsivity can be managed with cognitive and behavioural strategies. Delay discounting can be addressed with the development of skills around decision-making (e.g., methodically exploring positive/negative consequences in the short and long-term). Impulsive action may be better addressed with behavioural interventions (e.g., pausing or delaying a gratifying activity, distraction with other behaviour such as exercise). These strategies are likely to be applicable to drug use and daily functioning. Individuals with poorer working memory performance may benefit from learning strategies to manage a diminished cognitive capacity (e.g., list-making, reminders, the use of a diary). Such strategies may allow for the reduction of cognitive load and therefore more considered decisions in relation to MA use. Finally, individuals with deficits in sustained attention may benefit from changes to the

structure of treatment sessions (e.g., consolidation of recently learned skills and regular reviews of key content; Ramsay, 2017), to enhance treatment engagement and motivation. Collectively, these skills facilitate completing tasks associated with treatment, but may also generalise to drug use, and social and professional settings in the community.

In addition to accommodating deficits, there is increasing evidence that the rehabilitation of cognitive dysfunction can be an efficacious adjunct to traditional treatment (Sofuoglu et al., 2016; Verdejo-Garcia, 2016). Cognitive remediation can take place in group or individual settings, in direct contact with a clinician or with the use of a computer-based program (Medalia & Bowie, 2016). Cognitive remediation often addresses areas of executive dysfunction to enhance control over 'bottom-up' impulses (e.g., strategy-based learning in a group setting, computer tasks such as the 'N-back'; Marceau, Berry, Lunn, Kelly, & Solowij, 2017; Sofuoglu et al., 2016). Specifically, cognitive remediation has been successful in improving performance in domains of impulsivity (Bickel et al., 2011; Marceau et al., 2017), working memory (Brooks et al., 2017; Houben et al., 2011) and attentional function (Kurtz, 2011) in substance dependent and cognitively impaired populations. Furthermore, rehabilitation of cognitive function is often accompanied by improved treatment or daily functioning outcomes. For example, working memory training is associated with improved self-regulation and self-control (Brooks et al., 2017) and reduced alcohol consumption (Houben et al., 2011); sustained attention training has led to improved daily life skills (Kurtz, Wexler, Fujimoto, Shagan, & Seltzer, 2008; Kurtz et al., 2009); and remediation

of both working memory and impulsivity has been accompanied by improvement in QoL (Marceau et al., 2017).

The timing of integrating these practical strategies can also be adapted in consideration of the findings of this thesis. Early in treatment, individuals are particularly prone to relapse (Brecht & Herbeck, 2014). Therefore, in a controlled inpatient setting, gradual rehabilitation of working memory and impulsivity may be an ongoing component of therapy from the time of admission until discharge. However, in community treatment, in which an individual is likely to encounter risky/drug-related situations more frequently (Passetti et al., 2011), a greater focus on compensatory strategies from very early treatment may be more appropriate. Strategies relating to treatment motivation are best integrated into each psychological treatment session according to the judgement of the clinician, as fluctuation of motivation and commitment is variable within and between sessions (Aharonovich, Amrhein, Bisaga, Nunes, & Hasin, 2008). Cognitive functions that influence QoL outcomes may also be integrated flexibly by the clinician. The role of delay discounting and impulsive action in social situations may be integrated with psychoeducation or intervention sessions that directly address social skills (Homer et al., 2008). Similarly, individual psychological sessions may also integrate impulsivity interventions with tasks related to cognitive and behavioural processes (Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2007). These social and psychological strategies may be incorporated into broader 'transition' or 'day programs' that assist clients to return to environments of higher vulnerability following discharge from an inpatient setting.

In summary, individuals with MUD entering treatment are likely to benefit from a comprehensive and tailored program that includes (i) cognitive assessment and profiling to identify deficits, (ii) additional support/adjustments to treatment programs to accommodate dysfunction, and (iii) rehabilitation of cognitive deficits.

6.3 Thesis Strengths

Previous research has established cognitive deficits (Dean et al., 2013), poor QoL (Gonzales et al., 2011), high rates of relapse (Brecht & Herbeck, 2014) and low treatment motivation (Fiorentine et al., 1999) in MUD. This research provides novel insights into the longitudinal association between executive function and these outcomes in MUD individuals, emphasising the critical importance of addressing and managing cognitive deficits soon after treatment commencement. When compared to previous studies with comprehensive assessment batteries (e.g., Chen et al., 2015; Henry et al., 2010), this thesis includes a larger sample (one of the largest in the MUD literature), recruitment from a broader range of treatment settings (i.e., inpatient, outpatient, community therapy), the exclusion of participants with low prevalence conditions likely to influence cognition, and statistical control of conditions frequently observed in the MUD population. Participant characteristics are therefore more likely to be representative of the broader Australian MUD population, while a larger sample allowed greater specificity in statistical analyses. Findings are further reinforced by the comprehensive and systematic approach to measuring treatment outcomes. Our study took a multimodal and objective perspective that is consistent with recommendations from recent consensus papers (Donovan et al., 2012; Tiffany et al., 2012).

Furthermore, these findings not only extend the theoretical understanding of the dual-systems model but also illustrate the direct applicability of this theory in the context of MUD treatment. Indeed, our findings reinforce the interactional nature of the model in drug use, more clearly characterise 'bottom-up' components contributing to specific areas of QoL, and the 'top-down' process in treatment motivation.

6.4 Thesis Limitations

The findings of this thesis need to be considered in the context of limitations. In the interests of maintaining a large sample size, participants with a diagnosis of depressive disorder, alcohol dependence, or cannabis dependence were not excluded from the study. Although these diagnoses are significantly associated with cognitive deficits (McDermott & Ebmeier, 2009; Stavro, Pelletier, & Potvin, 2013), the inclusion of these participants allowed for a representative sample of individuals with MUD in the community (Lubman et al., 2016). Furthermore, these diagnoses were recorded and quantified during testing and controlled when statistical analyses were conducted (i.e., inclusion as a nuisance variable or explored in sensitivity analyses).

Results must also be appraised in the context of the characteristics of our sample. The sample was restricted to individuals with MUD, which limits generalisability to other populations using other substances, however these findings do provide conceptual support for research in stimulants with similar treatment programs/difficulties with relapse/engagement (e.g., cocaine; Penberthy et al., 2010). Furthermore, the current study tested only treatment-seeking individuals. Indeed,

non-treatment seeking individuals with MUD have a significantly longer history of use, higher rates of intravenous use, are older, report lower motivation, fewer past treatment episodes and higher rates of depression (McKetin et al., 2012). These characteristics may influence relationships between cognition and drug use intensity, QoL and motivation, and highlights the importance of replication in other groups within the MUD population. Furthermore, as the current sample was recruited from a single Australian state, caution is required in interpreting these findings in other settings, where treatment approaches may differ (Babor, Stenius, & Romelsjo, 2008).

Additionally, the study had a short follow-up period (six weeks), which is likely to have improved retention rates in the sample. A longer follow-up period might have allowed for a clearer characterisation of change in some outcome variables (e.g., predictors of physical and environmental QoL) and offered greater prognostic specificity. However, the time-period chosen for this thesis (early recovery; 6-8 weeks) often involves substantial changes to QoL (Bagheri, Mokri, Khosravi, & Kabir, 2015), high rates of relapse (Brecht & Herbeck, 2014), and high variability in treatment motivation (Baker et al., 2005). Furthermore, this time-period captures the typical length of an MUD treatment episode of around two months (McKetin et al., 2012). Therefore, these findings characterise treatment outcomes across a period in which clients maintain a higher level of contact with treatment services, and clinicians may have more frequent opportunities for intervention.

6.5 Future Research Directions

This thesis presents novel findings in relation to the dual-systems model that warrant replication and further examination. To further validate these findings and their generalisability, replication studies may include a multi-site approach, utilising the same protocol in international settings. Expansion would also allow for more sophisticated predictive modelling with a larger number of variables (e.g., machine learning with multiple predictors and outcome definitions). Future studies may also include a comparison group of non-treatment seeking individuals to understand whether relationships between cognition and outcome variables differ between groups. Furthermore, multiple assessment points across a longer time period (e.g., 3 months, 6 months, 1 year), would more clearly characterise relationships between cognition and outcomes beyond initial periods of vulnerability.

Other studies may also expand on the conceptual findings in this thesis, by examining cognitive domains that may add to the predictive value of those already identified. More specifically, identifying 'bottom-up' predictors of drug use and treatment motivation (e.g., impulsive action) and 'top-down' predictors of QoL (e.g., measures of working memory or cognitive control that predict specific, rather than generalised, domains of QoL). Neuroimaging studies may also help to further characterise the role of the dual-systems model in treatment outcomes. Imaging of the reward (striatum, amygdala) and reflective (prefrontal and posterior parietal cortices) systems at treatment commencement may illustrate whether (dys)function in these systems is associated with behaviourally measured cognitive deficits and longitudinal treatment outcomes.

Our findings may also inform intervention studies. Cognitive functions identified as predictive of treatment outcomes in this thesis (i.e., working memory, impulsivity, sustained attention) are candidates for rehabilitation in future studies. Indeed, cognitive remediation has significantly improved functioning in these domains in similar populations (e.g., Brooks et al., 2017). Specifically, future studies may utilise a randomised controlled trial design comparing a cognitive remediation intervention (tailored to the treatment outcome of interest; e.g., working memory for intensity of substance use) with treatment as usual and non-treatment groups. Such interventions may contribute to further development of evidence-based, tailored treatment programs for individuals with MUD.

6.6 Concluding Remarks

This thesis has demonstrated the predictive utility of executive functions on treatment outcomes in individuals with MUD. Poorer working memory was predictive of greater MA use, and delay discounting moderated this relationship. Delay discounting and impulsive action predicted less improvement in social QoL, while impulsive action alone predicted less improvement in psychological QoL. Sustained attention significantly predicted less improvement in treatment motivation.

The key findings summarised above contribute to the growing evidence that executive dysfunction in people with stimulant use disorders predicts not only relapse, but broader elements of recovery such as intensity of drug use, QoL, and treatment motivation. Furthermore, these findings support the applicability of dual-systems models to addiction treatment, though replication and expansion studies are required

to more clearly characterise these relationships. This study also has implications for treatment settings and may inform the development of approaches in which the accommodation and rehabilitation of specific cognitive deficits is integrated into evidence-based recovery programs.

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