Risky decision-making in the Context of Contingency Management for Methamphetamine Use Disorder

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COMPULSORY DECLARATION

This work has not been previously submitted in whole, or in part, for the award of any degree. It is my own work. Each significant contribution to, and quotation in, this dissertation from the work, or works, of other people has been attributed, and has been cited and referenced.

Signature: Signed by candidate Date: 29/01/2019

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Abbreviations

ANCOVA	Analysis of Covariance
BART	Balloon Analogue Risk Task
CBT	Cognitive Behavioural Therapy
CM	Contingency Manage
CTDCC	Cape Town Drug Counselling Center
GLMM	Generalized Linear Mixed-effects Model
HIV	Human Immunodeficiency Virus
IGT	Iowa Gambling Task
LMIC	Low-to middle-income country
LMM	Linear Mixed-effects Model
LMM-GC	Linear Mixed-effects Growth Curve Model
LR	Likelihood Ratio
MUD	Methamphetamine Use Disorder
PEBL	Psychology Experiment Building Language
RDM	Risky decision-making
SANCA	South African National Council on Alcoholism and Drug Dependence
SCID-5	Structured Clinical Interview for DSM-5
UPPS-P	Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale
vmPFC	Ventromedial Prefrontal Cortex
WASI	Wechsler Abbreviated Scale of Intelligence

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Abstract

Background: Risky decision-making is strongly implicated in adverse real-world risk-taking behaviour, and is associated with Substance Use Disorder, including Methamphetamine Use Disorder. Laboratory neurocognitive tasks typically utilized to assess risky decision-making have been able to distinguish participants with Substance Use Disorder from controls, although considerable heterogeneity is still evident *within* substance-using populations, which remains largely unexplained. Preliminary evidence has also tied risky decision-making to treatment outcomes, although no research has investigated risk-decision-making within Methamphetamine Use Disorder in the context of Contingency Management treatment.

Methods*:* This study aimed to investigate decision-making on the Iowa Gambling Task and the Balloon Analogue Risk at baseline as both a function and predictor of treatment response on an 8-week treatment of Contingency Management. Of 26 participants with Methamphetamine Use Disorder, 17 responded to Contingency Management treatment, whilst 9 were non-responders. Using various mixed-effect modelling techniques and ANCOVA, performance by non-responders were compared to responders, as well as a group of 19 healthy, nonsubstance-using control participants.

Results: Group differences between non-responders, responders and controls were exclusively obtained on the Iowa Gambling Task. A trend-level (p=.051), large effect size (g=-0.98*)* was observed in the effect of *reward magnitude* between non-responders and healthy controls. More specifically, non-responders tended to seek-out large short-term rewards in spite of long-term losses relative to controls, however, groups did not also differ in effect of short-term *loss magnitude*. Non-responders also appeared to demonstrate *poorer learning* than healthy controls,

although this finding was also at trend-level (p=.081*)* with a medium effect size (g =-0.63). In addition, results showed that responders and non-responders were differentially influenced by the *frequency* of outcomes, where responders demonstrated a greater preference for frequent rewards and infrequent losses relative to non-responders. This difference was at trend-level (p=.053) and the effect was moderately sized (g =-0.74). Impulsivity did not moderate group differences in decision-making, but did positively predict a greater likelihood of relapse at least once during Contingency Management (p =.035), although this effect was small (OR=1.10). Poor overall performance on the IGT appeared to predict a greater likelihood of *prolonged* relapse on Contingency Management following initial relapse, although this was at trend-level (p =.071) with a small effect size (OR=1.80).

Conclusion: Findings provide evidence for individual differences in risky decision-making *within* Methamphetamine User Disorder, suggesting that risky decision-making is unlikely to be a homogeneous characteristic of substance-using populations, as is typically treated in the literature. Risky decision-making may also act as a risk factor for poor treatment success on Contingency Management, which in turn suggests that assessing risky decision-making of individuals with Methamphetamine Use disorder *prior* to commencing Contingency Management treatment might assist in identifying those at high risk.

CHAPTER ONE: INTRODUCTION

Substance Use Disorder is strongly associated with deficits in decision-making. Some of these deficits have been specifically linked to excessive risk-taking, represented by a range of conducts, including criminality and risky sexual behaviour (Bechara & Damasio, 2002; Semple, Patterson & Grant, 2004; Watt et al., 2014). Methamphetamine is an example of an illicit substance associated with risky behaviours, and Methamphetamine Use Disorder (MUD) is prevalent amongst low-income communities in the Western Cape, South Africa (Plüddemann, Myers & Parry, 2008). The high prevalence of MUD and its strong connection to risky behaviours has in turn increased the public health burden in the region, and has propelled research efforts towards better understanding risky decision-making (RDM) within MUD, as well as the potential adverse implications RDM might have for treatment.

Risk-taking can be defined as the selection of actions or choices tied to probabilistic outcomes, where the outcomes can potentially result in harm or loss (Leigh, 1999). In this dissertation, risk-taking is encompassed within RDM. RDM is defined as the tendency to adopt maladaptive actions or choices about unknown probabilistic outcomes that are typically associated with direct loss or foregone gain, with limited learning of outcome probabilities across sequential choices (Pleskac, 2008). Moreover, RDM represents more than just maladaptive risk-taking behaviour, as it also subsumes neurocognitive and motivational processes (Bechara et al., 2001; Bechara & Damasio, 2002; Verdejo-Garcia, Perez-Garcia & Bechara, 2006).

Neurocognitive tasks such as the Iowa Gambling Task (IGT) have been utilized to assess RDM because of their ability to distinguish the performance of substance-using samples from non-substance-using samples, whilst also being able to partially attribute impaired performance to neurocognitive deficits in both the ventromedial prefrontal cortex (vmPFC) and amygdala

(Bechara et al., 2001; Bechara, Dolan & Hindes, 2002; Grant, Contoreggi & London, 2000). Poor performance by substance-using samples on neurocognitive gambling tasks has been strongly associated with real-world risk-taking behaviours including but not limited to sharing needle paraphernalia and engaging in unprotected sexual intercourse (Rajasingham et al., 2012; Semple et al., 2004). In particular, both of these behaviours are associated with increased risk of transmitting bodily fluid-borne diseases like the human immunodeficiency virus (HIV), whilst unprotected sex also exposes individuals to sexually transmitted diseases. Moreover, methamphetamine use has specifically been linked to an increased likelihood of exhibiting aggressive behaviour (Mcketin et al., 2014).

Whilst real-world risk-taking within Substance Use Disorder is associated with problematic behaviours, excessive risk-taking may also be tied to an increased likelihood of initiating substance use. Specifically, premorbid impulsivity and high risk-taking propensity can predispose one to risky behaviour, which can increase the prospect of initial engagement in drug use (Verdejo-Garcia, Lawrence & Clark, 2008). Moreover, once the development of the Substance Use Disorder is established, the risk of relapse is more likely, partly because decision-making is compromised by pervasive drug-seeking behaviour as the combined result of factors involved in substance dependence as well as premorbid impulsivity and risk-taking propensity (Koob & Le Moal, 2001).

In a large study drawing MUD participants from various treatment programs in Los Angeles, Brecht & Herbeck (2014) found that more than 50% of MUD individuals relapsed within 1-year following treatment. Nevertheless, Contingency Management (CM), a substance use treatment intervention designed to positively reinforce abstinence with monetary incentives, has proven to be particularly successful in reducing relapse and attrition rates in MUD samples,

as well as other substance types (Shoptaw et al., 2005; Prendergast, Podus, Finney, Greenwell & Roll, 2006). Although there is extensive literature demonstrating RDM differences between various substance-using and healthy control groups, less is known about how RDM profiles of patients with Substance Use Disorder may potentially relate to treatment success. Moreover, the specific RDM profiles amongst MUD individuals within the context of CM are even further unexplored.

This dissertation will specifically focus on RDM of MUD participants in the context of CM treatment. However, broader trait vulnerability and neurobiological models of substance-dependency will also be drawn upon in order to identify underlying RDM deficits relevant to MUD. Substance dependence and trait vulnerability models will be discussed in the order of incentive-sensitization theory, opponent process theory, impulsivity and risk-taking propensity. Moreover, this will be followed by discussion of underlying RDM deficits in MUD, including reward and loss sensitivity and their ties to reward and loss magnitude, reward and loss frequency, and learning: with examples provided from the Iowa Gambling Task (IGT) and Balloon Analogue Risk Task (BART).

CHAPTER TWO: LITERATURE REVIEW

Substance Dependence Theories of RDM

Incentive-sensitization theory. Robinson and Berridge (1993) introduced the incentive-sensitization theory to describe how substance usage can potentially lead to substance dependence and maintain maladaptive decision-making patterns, particularly in relation to Substance Use Disorder. The theory asserts that alterations in neurochemical processes within reward neural circuitry produced by prolonged substance use underlie RDM in individuals suffering from Substance Use Disorder. This occurs specifically by increasing the incentive salience of drug-related cues over prosocial reward cues. Sensitization is thought to emerge from reward circuits that encompass dopaminergic pathways through the striatum which become increasingly sensitized to drug stimuli and drug-related cues with prolonged substance use (Berridge, 2007). In extension, incentive-sensitization theory proposes that neurobiological sensitization leads substance users to continue using substances as a result of an emerged generalizable sensitivity to drug-related reward cues over and above the drug itself, in turn increasing the likelihood of relapse.

Everitt and Robbins (2016) argue that the mechanism by which sensitization through Substance Use Disorder develops is via a shift of dopaminergic activation from the ventral striatum, involved in generating *pleasurable* phenomenological states associated with recreational use, towards the dorsal striatum, involved in eliciting drug-seeking behaviours to avoid or diminish *aversive* phenomenological states as substance use becomes more regular. Furthermore, sensitization of reward-related circuitry has been tied to diminished learning capacity: where instrumental, goal-directed learning associated with ventral striatal functioning is substituted for habitual, compulsive behaviour linked to dorsal striatal activity with prolonged

substance use (Everitt & Robbins, 2016). This further supports the idea that decision-making becomes riskier with drug use, because actions are not adequately weighed up with potential consequences but are rather automatically driven. Such prepotent reward-seeking responses are likely to lead to the negative consequences associated with risky drug-related behaviour (Everitt & Robbins, 2016; Gowin, Mackey & Paulus, 2013).

Opponent process theory of motivation. Alternate theories of substance dependence, including the opponent process theory of motivation, have also been drawn upon to explain risky substance usage. First put forward by Solomon and Corbit (1978), the opponent process theory of motivation asserts that substance dependence results from neuroadaptations that disrupt the maintenance of homeostatic brain functioning. More specifically, the opponent process theory purports that there are two interconnected, functionally opposed systems, including: tolerance ("a-process") and withdrawal ("b-process") systems, which ordinarily operate together in order to maintain brain state equilibrium. However, prolonged substance usage can induce over-compensatory responses within these systems that maintain unregulated brain states, which in turn further engender future substance usage.

The "a-process" system is characterized by neuroadaptations to dopaminergic neural circuitry encompassed within the basal forebrain and ventral striatum, which are associated with producing a pleasurable phenomenological state following drug usage. More specifically, the neural system causes a diminished response with similar ingested magnitudes of a substance following repeated substance use: this underlies the development of tolerance (Koob, Moal, Le & Se, 2008). Tolerance refers to the gradual decline in pleasurable affective response elicited from equivalent amounts of an addictive substance, and is one way by which an unregulated brain state can be categorized (Solomon & Corbit., 1978). As such, the tolerance process

increases the likelihood of one engaging in more excessive drug use, namely with use of larger magnitudes of a substance, which further increases the likelihood of one experiencing adverse consequences associated with substance use (Mata, Hau, Papassotiropoulos & Hertwig, 2012). Combining "a-process" and incentive-sensitization theories allows one to explain the escalation and chronicity of substance use. The former is best explained by the "a-process", which drives one to seek out greater magnitudes of a substance to counteract the influence of tolerance, whilst the latter is explained by the incentive-sensitization theory, that heightens one's sensitivity to drug-related cues and further compounds the likelihood of engaging in future substance use.

Conversely, Koob et al. (2008) argue that the "b-process" system is located in the brain's stress response system involved in the release of corticotrophin–releasing factor, adrenalin and dynorphin. The release of these hormones generates an opposing, adverse withdrawal state during or following the removal of a pleasurable phenomenological state associated with the "a-process", where withdrawal is largely characterized as an aversive phenomenological state. Increased risky drug-taking is also more likely to take place during withdrawal states, given that these states increase the likelihood of drug-seeking as a form of negative reinforcement. More importantly, with prolonged use of an addictive substance, withdrawal states following drug use persist long after the initial consumption of the drug, increasing the likelihood of future drug use. Following from this, in the withdrawal state, additional non-drug-related losses that are experienced can be better endured. This is due to the fact that loss experienced over and above the current aversive withdrawal state has diminished impact on the state itself. This diminished subjective experience of loss can further increase the likelihood of drug-taking, as weighting of potential loss outcomes tied to drug-taking are discounted within the decision-making process.

Premorbid Vulnerabilities to Substance Use Disorder and RDM

Impulsivity. Ersche et al. (2005) argue that Substance Use Disorder could emerge from premorbid neurobiological vulnerabilities. In fact, a susceptibility to impulsive behavior has been strongly tied to increased predisposition to Substance Use Disorder (Ersche, Turton, Pradhan, Bullmore & Robbins, 2010). Any reference to vulnerability/susceptibility to impulsive behaviour in the dissertation will be merely referred to as "impulsivity." Impulsivity is regarded as a multidimensional construct, but there is a lack of consensus around its different facets, with definitions varying based on both proposed measure and associated conceptualization. In general, impulsivity is defined as any behavior characterized by a tendency to act rashly or "without-thinking" in response to rewarding stimuli (Leigh, 1999)

Impulsivity is argued to emerge from activity associated with the same subcortical neural structures implicated in incentive-sensitization theory, including the striatum and amygdala. In fact, Everitt (2014) argues that reward neurocircuitry are overly responsive to reward stimuli prior to *any* use of substances, biasing individuals to engage in drug use for its subjectively rewarding effects. With prolonged substance use, these neural circuits become "hijacked," where activation becomes particularly elevated in the presence of drug and drug-related stimuli. Interestingly, impulsivity is particularly associated with stimulant use (Ersche et al., 2010), but also increases the likelihood of demonstrating RDM.

In addition, impulsivity aligns strongly with "hot" over "cold" cognition, where the former refers to affective-driven processing, whilst the latter involves more deliberate, higher-order processing. Impulsivity is related to more deficient, affective-driven type behaviour, during which potential negative consequences associated with an action are not accounted for fully. In terms of methamphetamine use, Semple, Zians, Grant and Patterson (2005) found that highly

impulsive MUD participants displayed greater amounts of risky behaviour than less impulsive MUD individuals, where risky behaviour was defined by both the number of sexual partners and cases of unprotected sexual intercourse. A relatively greater incidence of risky behaviours amongst impulsive MUD participants is thought to reflect, in part, a diminished ability to account for potential negative consequences when making decisions. Furthermore, susceptibility to Substance Use Disorder and RDM may also partially emerge from premorbid trait-level decision-making factors.

Risk-taking propensity. Risk-taking propensity refers to the extent to which one will typically preference riskier choices/actions associated with greater outcome variability relative to safer choices/actions with less outcome variability (Schonberg, Fox, Poldrack, 2011). Methamphetamine users and other substance-using populations typically demonstrate greater risk-taking propensity relative to healthy controls, where riskier choices that are associated with greater potential reward but also greater potential loss are favoured over safer options with relatively more certain but smaller rewards and losses (Upton, Bishara, Ahn & Stout, 2011)

Like impulsivity, a high risk-taking propensity is, in part, thought to emerge from a neurobiological sensitivity to reward that precedes chronic substance use but can also be heightened as a result of chronic substance use (Aklin et al., 2009). Risky decisions can be made impulsively or "without thought," yet decisions can also be made consciously and deliberately, suggesting a partial overlap of neurobiological mechanisms underlying impulsivity *and* risk-taking propensity (Upton et al., 2011). MUD participants are also more likely to demonstrate both a greater risk-taking propensity as well as a predisposition to impulsive behaviour relative to healthy individuals (Mahoney et al., 2015). Finally, high risk-taking propensity is directly

related to RDM in that it underlies a general preference for riskier choices, increasing the likelihood of presenting RDM.

RDM Deficits in MUD

Reward sensitivity & loss insensitivity. Whilst substance dependency and premorbid vulnerability theories may explain the development of risky, prolonged substance use several authors have demonstrated that MUD participants are more likely to exhibit risky behaviour in areas other than substance use behaviour (Gonzalez, Bechara & Martin, 2007; van der Plas, Crone, van den Wildenberg, Tranel & Bechara, 2010). Both neurobiological vulnerabilities and alterations due to chronic use may enhance tendencies for RDM through altered reward and loss sensitivity (Bechara & Damasio, 2002). MUD participants demonstrate heightened reward sensitivity, where actions are biased towards reward stimuli (Ahn et al. 2014; Kohno, Morales, Ghahremani, Hellemann & London, 2014). Heightened reward sensitivity is in agreement with specific theories on susceptibility to impulsive behaviour, where quick action is taken in the presence of rewarding stimuli. Moreover, it closely aligns with incentive-sensitization and opponent process theory. Specifically, sensitization of drug and drug-related stimuli may explain increased sensitivity to drug-related reward stimuli, whilst unregulated emotional states in opponent process theory may explain the drive toward rewarding stimuli as a means to seek-out pleasurable phenomenological states (i.e. positive reinforcement) and/or counteract withdrawal (i.e. negative reinforcement).

Substance-using populations also demonstrate diminished loss reactivity, which refers to a relatively reduced subjective aversion to losses and diminishes the impact of loss in influencing decision-making (Verdejo-Garcia & Bechara, 2009). Moreover, a diminished loss reactivity may be explained by the same theories that explain increased reward sensitivity. In relation to the

incentive sensitization theory, neurobiological alterations prioritize the detection of reward over loss outcomes which may result in insufficient processing of loss outcomes. Diminished loss reactivity could also be underlined by opponent process theories, in which dysregulated states of tolerance and withdrawal can diminish processing prioritization of losses. This is because such dysregulated states strengthen the pre-potent drive towards rewarding stimuli as an attempt to adjust towards a homeostatic state. Furthermore, deficient reward and loss processing may specifically promote RDM via the presence of large reward and loss outcomes.

Reward and loss magnitude. RDM amongst MUD participants is more likely when rewards are larger, and this is apparent even in the presence of concurrent large losses (van der Plas et al., 2010). The sensitivity towards large rewards makes sense in relation to substance dependence theories, in that tolerance mechanisms combined with incentive sensitization processes can explain the sensitization towards *larger* over *smaller* rewards. Specifically, MUD participants may be continually driven to obtain larger-sized rewards to counteract tolerance processes that may blunt subjective experience of pleasure derived for smaller-sized rewards. Moreover, sensitization is demonstrated when choice options associated with large gains become favoured, and act as reward cues that increase the likelihood of future RDM.

Reward and loss frequency. Whilst the literature on gambling task performance within substance-using populations has largely focused on the influence of sensitivity to reward magnitude on decision-making, Horstmann, Villringer and Neumann (2012) argue that it is important to disentangle effects of frequency from magnitude, especially in gambling tasks with sequential choice and uncertain outcomes. In such tasks, one's choices may be influenced by one or a combination of preferences for the frequency *and* magnitude of a choice option. Research is lacking with respect to effects of reward and loss frequency relative to magnitude on RDM

amongst MUD participants. However, on a risk task in which obese, alcohol-using and methamphetamine-using groups chose between a sure and a risky choice on reward and loss outcomes, Voon et al. (2015) found that abstinent MUD participants demonstrated a greater preference for larger, infrequent rewards relative to smaller, frequent rewards. This suggests that RDM by MUD individuals may not just be influenced by effects of magnitude, but also effects of frequency. Moreover, MUD participants were found to avoid large, infrequent losses in place of smaller, frequent losses. This is contrary to other findings by Gowin, Stewart et al. (2013), who found that MUD participants were more likely to make risky choices following losses. This inconsistency in findings may have arisen because comparisons in the study by Voon et al. (2015) were not made in relation to a healthy control group, but rather other clinical populations who might also be expected to demonstrate RDM deficits.

Despite this, Voon et al. (2015) were the first to assess the potential impact of the combination of both outcome magnitude and frequency on RDM amongst MUD participants, using a risky choice task. This has not been fully investigated with regards to other gambling tasks such as the Iowa Gambling Task (IGT) and in relation to a healthy control group. Given the lack of research on sensitivity to outcome frequency amongst MUD individuals, it is still not clear to what extent effects of reward and loss frequency may be linked to neurobiological models of substance dependency and premorbid vulnerability. However, these models do account for compromised learning amongst methamphetamine-using populations.

Diminished risk learning. Heightened reward sensitivity and diminished loss reactivity can influence RDM through risk learning, which can be demonstrated by continuous poor performance over time by MUD participants relative to healthy controls on various gambling tasks that incorporate uncertain probabilistic outcomes, and which require learning of such

probabilities through experience (Kohno et al., 2014; Schonberg et al., 2011). Of the various gambling tasks employed to measure features of RDM under uncertainty, the IGT and the Balloon Analogue Risk Task (BART) represent two popular measures of real-world risk-taking.

IOWA Gambling Task (IGT). The IGT has been consistently able to differentiate performance between substance users and non-substance users (Bishara et al., 2009; Ashenhurst, Bujarski, Jentsch & Ray, 2014). Moreover, the IGT has also been able to confirm significant differences between specific substance-using populations, including MUD participants (Gonzalez et al., 2007). First developed by Bechara, Damasio, Damasio and Anderson (1994), a computerised version of the IGT involves the selection of cards from various decks, where cards from each deck consist of a reward value that is presented with every card selected from that particular deck, in addition to a simultaneous loss value that emerges probabilistically over time. Each deck is defined by a specific reward and loss magnitude, as well as a certain probability of loss. In turn, each deck is associated with a specific long-term pay-out, and the aim is to determine the long-term average pay-out associated with each deck, and select those decks that maximize long-term gains. Half of the decks are considered to be more advantageous with smaller immediate gains but greater long-term net gains. Conversely, the remaining decks are associated with larger short-term gains but are considered to be relatively disadvantageous, as selection for such decks result in a long-term net loss. On the IGT, the probabilities of "winning" and "losing" across decks is not made known to the participant and it is up to the participant to learn through experience to shift from risky, disadvantageous decks to more conservative, advantageous decks. In this way, given the uncertainty of outcomes, risk learning is obtained through experience on the first few deck selections.

Several studies have found that substance users typically do not learn to shift from disadvantageous decks to advantageous decks over time, leading to relatively poorer performances relative to healthy samples (Bishara et al., 2009; Bechara et al., 2002). However, given that a reward from a deck selection is experienced simultaneously with a loss, it is unclear to what extent RDM is driven by increased reward sensitivity or diminished loss sensitivity. Additionally, RDM on the IGT may be exacerbated by a tendency to act impulsively (Franken, van Strien, Nijs & Muris, 2008).

Balloon Analogue Risk Task (BART). Lejuez et al. (2002) developed the Balloon Analogue Risk Task (BART) as an alternative cognitive behavioural measure to self-report assessments of risk-taking. The BART involves inflating a virtual balloon to acquire monetary credit at the risk of potentially exploding the balloon and losing total accrued credit on that particular trial (Lejuez et al., 2002). Importantly, the explosion probability is not known by the participant and the explosion probability increases with each inflation (Fukunaga, Brown & Bogg, 2013). In this way, participants must use trial-by-trial experience to learn balloon explosion probabilities, in order to pump such as to maximize accrued monetary credit on the task.

Lejuez et al. (2002) have found riskier performance by smokers relative to healthy controls on BART, where smokers demonstrated both a higher pump average, in addition to a higher number of explosions. However, subsequent findings by Dean, Sugar, Hellemann and London (2011), have demonstrated reduced pumping of smokers relative to controls. Hellemann & London, 2011; Kohno et al., 2014). It is not entirely clear how these findings relate to MUD populations in particular, but Kohno et al. (2014) found that MUD participants did not significantly differ from healthy controls in average pumps.

RDM and Treatment Interventions for Substance Use Disorder

The strong relationship between RDM and MUD participants is particularly relevant when considering the adverse impact of RDM deficits on success in treatment (Chen, Chen & Wang, 2015). This is supported by Taymoori and Pashaei (2016), who demonstrated that higher RDM can adversely impact one's success on a matrix treatment programme for methamphetamine use, by increasing the likelihood of relapse. In particular, high risk-taking propensity at baseline, as traditionally scored on the BART, has been found to predict future relapse amongst methamphetamine users (Taymoori & Pashaei, 2016). However, limited research to date has investigated RDM by MUD individuals in the context of Contingency Management (CM).

CM is a substance use behavioral intervention that positively reinforces abstinence; it has been shown to be a promising treatment intervention for MUD. In a randomised control trial, Shoptaw et al. (2005) found that CM had a higher treatment efficacy than cognitive behavioural-based treatments (CBT) amongst gay and bisexual methamphetamine–using men, demonstrated by a greater number of methamphetamine-free urine samples, increased retention and fewer missed urine tests. A similar study comparing CBT and CM found that CM was more effective in treating MUD (Roll et al., 2006). Furthermore, CM treatment is particularly relevant to RDM amongst MUD participants, as CM treatment directly assesses real-world decision-making tied to drug use. This is because MUD participants make decisions regarding drug use that are underpinned by associated monetary rewards tied to abstinence and foregone monetary rewards (i.e. loss) linked to relapse.

In summary, several complementary neurobiological and trait models have been proposed to underlie RDM in Substance Use Disorder, suggesting that heterogeneous

mechanisms may give rise to various manifestations of reward and loss sensitivity deficits in RDM. Importantly, these models may account for both heightened reward and loss sensitivity in MUD populations compared to healthy controls, as well as variability *within* MUD populations. In fact, previous research has largely focused on only a few of these potential RDM manifestations, including biased action in relation to outcome magnitude, but less so on outcome frequency. Moreover, a limited number of studies have investigated these RDM features in the context of particular substance types, including methamphetamine. Further research is needed to identify the particular RDM profiles *within* MUD populations that may act as potential risk factors for poor treatment success, specifically in the context of CM treatment.

Research Aim and Hypotheses

This study had two broad aims. The first aim was to investigate whether RDM at baseline differed *within* the MUD group, namely between treatment responder and non-responder subgroups, as well as in relation to healthy controls. Non-responders were defined as those MUD participants who exhibited at least one methamphetamine-positive urine sample and/or missed sample throughout the duration of CM treatment, where a missed sample was considered drug positive, in line with previous CM literature (Correia & Benson, 2006; Petry et al., 2004; Rash, Alessi, & Petry, 2008). In contrast, responders were defined as those participants who attended all appointments and exclusively demonstrated methamphetamine-negative urine samples during CM treatment. RDM was assessed by several of its component features, including: effects of magnitude, effects of frequency, learning, and risk-taking propensity. This aim was further extended to investigate whether impulsivity moderates RDM.

The second aim of this study was to assess whether baseline RDM and impulsivity amongst MUD participants might potentially act as predictors of poor treatment success on CM.

My hypotheses were as follows:

1. **Group differences in baseline RDM and impulsivity at baseline**

a. MUD participants, treatment non-responders more so than responders, demonstrate greater RDM at baseline relative to healthy controls, where RDM is defined by several features, including: the effect of the magnitude of short-term reward and loss outcomes on decision-making (the magnitude effect), the effect of the frequency of reward and loss outcomes (the frequency effect), learning and risk-taking propensity.

b. Impulsivity positively moderates the relationship between MUD treatment response/healthy control groups and baseline RDM, but does not *entirely* account for potential group differences in RDM

2. **Baseline RDM and impulsivity as predictors of CM treatment outcomes amongst MUD participants**

a. Amongst MUD participants, greater RDM, alongside greater impulsivity, predicts relapse occurrence *and* relapse severity over the duration of CM treatment.

CHAPTER THREE: STUDY DESIGN, METHOD & MATERIALS

Design and Setting

This study formed part of a larger pilot project aimed at investigating the neural mechanisms underlying treatment success on CM for MUD. The current study utilized a between-groups, cross-sectional, matched case-control design; consisting of MUD and healthy control groups. MUD participants were administered test measures at the end of a 2-week baseline period, before beginning 8-weeks of CM treatment. The measures were also completed by a matched non-substance-using control group, who were included in the study design alongside MUD participants in order to describe the spectrum of RDM in a low-income setting, where decision-making by the MUD group would presumably differ from controls.

Participants

A sample size of 30 MUD and 30 healthy control participants was selected a priori as part of the broader pilot study, based on consideration of resource constraints and in line with the *pilot* nature of the study. Using the G*power statistical software program (Erdfelder, Faul & Buchner, 1996), a power calculation yielded a power of .80 to detect a large cohen's f effect size of .73 based on a 2-sided hypothesis test with an alpha of .05. All effect sizes were interpreted using Cohen's (1988) classifying convention, with a small effect represented by 0.20, medium as 0.50 and large as 0.80. An additional power analysis was conducted in order to establish sample size requirements for detecting potential group differences in gambling task performance. Given the absence of meta-analysis research on gambling task performance amongst MUD samples, a large pooled effect size of .99 was taken from Gonzalez et al. (2007) paper, which represents the difference in IGT performance between a MUD and healthy control group. In addition, the

significance level was set to .05, power was set to .80 and a two-sided hypothesis test was utilized. The power calculation inferred a recommendation of a total of 36 participants (18 within each group).

45 participants (17 female, aged 18-45) participated in the study, which surpassed the recommended power calculation. Of 269 methamphetamine-using candidates, 26 MUD participants represented the analytic sample of the MUD group in this study. Of 33 participants who were actually enrolled in CM treatment, 7 were excluded from the analyses due to the following: drop-out prior to completion of CM (2), cocaine use (1), meningitis (1), brain abnormality (1), education less than 7 years (1) and a methamphetamine-positive urine sample on the day of baseline task assessment (1). 148 candidates were not eligible for reasons including: psychiatric comorbidity, chronic medical illness, current use of psychoactive medication, MUD condition too severe for outpatient treatment, subthreshold MUD, HIV seropositive status, problematic use of certain drugs besides methamphetamine, primary drug of choice other than methamphetamine, not treatment-seeking or not committed to completing the entire CM treatment programme, under/over the age limit, subthreshold intellectual function, neurological illness or traumatic brain injury, left-handed, current pregnancy, claustrophobia, metal present within the body, or in recovery (i.e. not a current user of methamphetamine). A further 88 recruits were not eligible to partake in the study due to non-attendance of ≥4 scheduled meetings during the baseline period.

Of 149 control candidates screened, 19 matched non-substance users made up the complete analytical sample for the control group. Control group participants were matched against MUD participants using a frequency matching approach of characteristics, that aimed to acquire equal group distributions on relevant demographic characteristics such as age, gender,

years of education and broad intellectual function. 125 control candidates were not eligible for the following reasons: no corresponding match of a particular characteristic within the MUD group, psychiatric comorbidity, chronic medical illness, current use of psychoactive medication, use of substances other than occasional alcohol or cigarette smoking, left-handed, HIV seropositive, not interested in partaking in the study, subthreshold broad intellectual function, under/over the age limit, neurological illness or traumatic brain injury. 3 additional control candidates were not eligible due to non-attendance of ≥1 scheduled meeting. Of 24 healthy control participants who were initially enrolled in the study, 5 participants were removed from analysis due to (2) study drop-out, (1) suspected chronic illness, (1) missing data and (1) cannabis-positive test on the day of baseline task assessment.

Despite attempts to match MUD and healthy control groups, gender distribution was unbalanced both *within* the MUD group and *between* MUD and control groups. Males outnumbered females 2:1 within the MUD group, although this disproportion is somewhat representative of the gender distribution seen amongst treatment-seeking populations, where males typically represent a greater proportion (Myers, Louw & Pasche, 2011). In addition, MUD participants were not fully matched against the control group in relation to gender, given that the control group consisted of fewer total participants, with males in the MUD group (17) outnumbering those in the control group (11).

The majority of MUD participants were recruited from outpatient clinics (*n*=16), including: The Cape Town Drug Counselling centre (CTDCC) in Observatory, the South African Council of Alcoholism and Drug Dependence (SANCA) in Athlone and Sultan Bahu rehabilitation centres in Mitchell's Plain, Hanover park and Bonteheuwel. Both CTDCC and SANCA outpatient clinics offered motivational interviewing as their primary treatment for

substance use, whilst Sultan Bahu offered group therapy. In addition, newspaper advertisements were utilized to recruit the minority of both MUD participants (n=10) and control group participants (n=8). Snowball recruitment strategies were used to obtain the remaining control group participants (n = 11), where efforts were placed in recruiting non-substance-using and non-biological relatives, friends and colleagues of MUD participants.

Eligibility criteria.

(1) Individuals between 18-45 years of age were included in both the MUD and control group.

(2) MUD participants had to be both primary and chronic users of methamphetamine. (Discussed further under "Structured Clinical Interview for DSM-5 (SCID-5)" subsection under "Measures"). Secondary use of methaqualone (mandrax), cannabis and/or nicotine was accepted due to the high prevalence of concurrent use alongside methamphetamine, especially in South Africa (Peltzer, Ramlagan, Johnson & Phaswana-Mafuya, 2010). Problematic use of drugs besides methamphetamine, methaqualone, cannabis or nicotine that was either regular and/or required treatment (in past two years) was excluded for. In addition, MUD participants were eligible if they were current users (Discussed further under "Urine testing" subsection of "Measures"). Furthermore, verified abstinence (i.e. methamphetamine-negative test) had to be obtained on the day of the baseline task assessment, in order to prevent potential confounding acute effects of methamphetamine on gambling task performance (Stough et al., 2012).

(3) Conversely, control group individuals had to be non-substance users, given that the study sought to compare MUD participants against healthy controls. However, cigarette smoking

and occasional alcohol usage was accepted, given the high prevalence of use of these substances, especially within low-income populations in South Africa (Dada et al., 2017).

(4) MUD participants had to be seeking treatment for current methamphetamine usage and must have demonstrated intentions to maintain outpatient treatment in order to be eligible for the study. Individuals with MUD that was considered too severe for outpatient treatment were not eligible to participate in the study. Only those control participants that were interested in partaking in the study, and who were committed to attending all sessions, were eligible.

(5) Individuals with current comorbid psychiatric illnesses not induced by substance usage were excluded across MUD and control groups. People with substance-induced psychosis were additionally excluded, but those with Antisocial Personality Disorder were accepted within the MUD group (Discussed further in "Structured Clinical Interview for DSM-5 (SCID-5) subsection of "Measures").

(6) Amongst both MUD and control groups, use of psychoactive medication/s was exclusionary, given its potential impact on decision-making capabilities (Gendle & Golding, 2010).

(7) Both MUD and control groups had to meet threshold broad intellectual functioning (Discussed further under "Wechsler Abbreviated Scale of Intelligence (WASI)" subsection of "Measures"). In addition, MUD and control participants needed 7 or more years education (i.e. they needed to have completed at least primat school education).

(8) Amongst both MUD and control groups, participants with self-reported chronic physical illness, neurological illness/s and/or traumatic brain injury were excluded given their potential impact on cognitive functioning and brain structure, which could confound treatment

outcomes amongst MUD participants and/or decision-making capabilities amongst both MUD and control groups (Cotrena, Branco, Zimmermann, Cardoso & Grassi-oliveira, 2014; Fecteau et al., 2013). HIV seropositive status was excluded for across MUD and control group given the potential impact of HIV on task performance (Gonzalez, Wardle, Jacobus, Vassileva & Martin-Thormeyer, 2010).

(8) Related to objectives of the larger pilot study and requirements for the magnetic resonance imaging, presence of metal in the body, current pregnancy and/or claustrophobia was excluded for amongst MUD participants. MUD and control participants also had to be right-handed.

Measures

Screening measures.

Wechsler Abbreviated Scale of Intelligence (WASI). The WASI is a shortened version of the more comprehensive Weschler Adult Scale of Intelligence utilized for persons aged 6-89, and demonstrates comparable psychometric properties to the full-scale measure (Wymer, Rayls & Wagner, 2003). Moreover, the WASI has been found to demonstrate similar validity and reliability across both healthy and clinical populations (Wymer et al., 2003). The measure was administered to both MUD and control group participants in order to determine individuals' available cognitive capacity to understand and successfully complete computerised gambling tasks as well as other self-report measures. A cut-off score of 55 was chosen based on its applicability to a low- to middle-income country (LMIC) context, like South Africa's (Shuttleworth-Edwards & van der Merwe, 2016).

Considering that study participants predominantly consisted of *both* English and Afrikaans first-language speakers, both an English and validated Afrikaans-translated version of the questions were provided for the verbal scale of the WASI. Acceptable reliability, with Cronbach alpha values ranging from 0.73-0.84, has been demonstrated across the English and Afrikaans versions of the WASI in South Africa (Grieve & van Eeden, 2010).

Structured Clinical Interview for DSM-5 (SCID-5). The SCID-5, intended for use by researchers, was utilized as a screening tool to establish whether methamphetamine users met the criteria for current primary MUD, and is considered the gold standard for clinical interviewing and has demonstrated good reliability (Ventura, Liberman, Green, Shaner & Mintz 1998). Methamphetamine use was classified as current MUD, based on evidence of methamphetamine use over at least the past 12-month period, in addition to meeting several of the criteria laid-out in the SCID-5 (American Psychiatric Association, 2013). MUD was considered primary if one demonstrated a history of greater use and longer duration of use of methamphetamine relative to other substances. If one also demonstrated concurrent secondary use (and not primary use) of cannabis and/or methaqualone (mandrax), this was accepted.

The SCID-5 was also utilized to exclude for the presence of psychiatric comorbidities amongst MUD and control groups. By excluding psychiatric comorbidities, the study is better able to isolate unique effects of MUD on task performance and CM treatment success. Importantly, methamphetamine-induced psychosis was also excluded for, given its potential for confounding treatment outcomes amongst MUD participants and/or affecting cognitive capacities required for decision-making tasks amongst both MUD and control groups (Cotton, 2014). However, antisocial personality disorder was included given that rates of antisocial

tendencies are highly prevalent in LMIC countries such as South Africa (Waller, Gardner & Cluver, 2018).

Urine testing. In order to verify current use of methamphetamine, MUD participants underwent a 2-week baseline period, in which urine samples were drawn and tested three times per week, with a maximum of 2 days in between urine tests. This particular interval period is associated with optimal sensitivity to detect methamphetamine use (i.e. within 48 hours following drug use). Two urine tests were conducted at each visit, including tests for methamphetamine and d-amphetamine (a methamphetamine metabolite). Testing for d-amphetamine assisted in validating findings from tests of methamphetamine, in addition to extending the detection period from 2 to 3 days. Furthermore, MUD participants were randomly tested for 4 additional substances over several occasions, both during the baseline period and whilst partaking in CM treatment. These substances included cannabis, cocaine, opiates and barbiturates. Conversely, control group participants only underwent urine tests over 2 scheduled sessions, namely baseline screening and assessment sessions, in order to verify self-reported non-substance use. At both sessions, control participants were tested for 6 substances: methamphetamine, d-amphetamine, cocaine, cannabis, opiates and barbiturates.

RDM measures.

Iowa Gambling Task (IGT). Developed by Bechara et al. (1994), the IGT is a gambling task that measures RDM. The Psychology Experiment Building Language (PEBL) 0.14 computerised-version of the measure consists of 4 virtual decks, A, B, C and D, in which participants make deck selections over a total of 100 trials. When a deck is chosen, one obtains a fixed reward on that trial, represented by a monetary reward gained, but one can also obtain a concurrent, probabilistic loss (Figure 1). The objective of the task is to maximize total money

gained by selecting decks that are associated with positive long-term net pay-outs and avoiding decks associated with negative long-term net pay-outs. In particular, decks A and B are considered to be disadvantageous decks because they are associated with long-term losses, whilst decks C and D are considered more advantageous as they are associated with positive long-term gains.

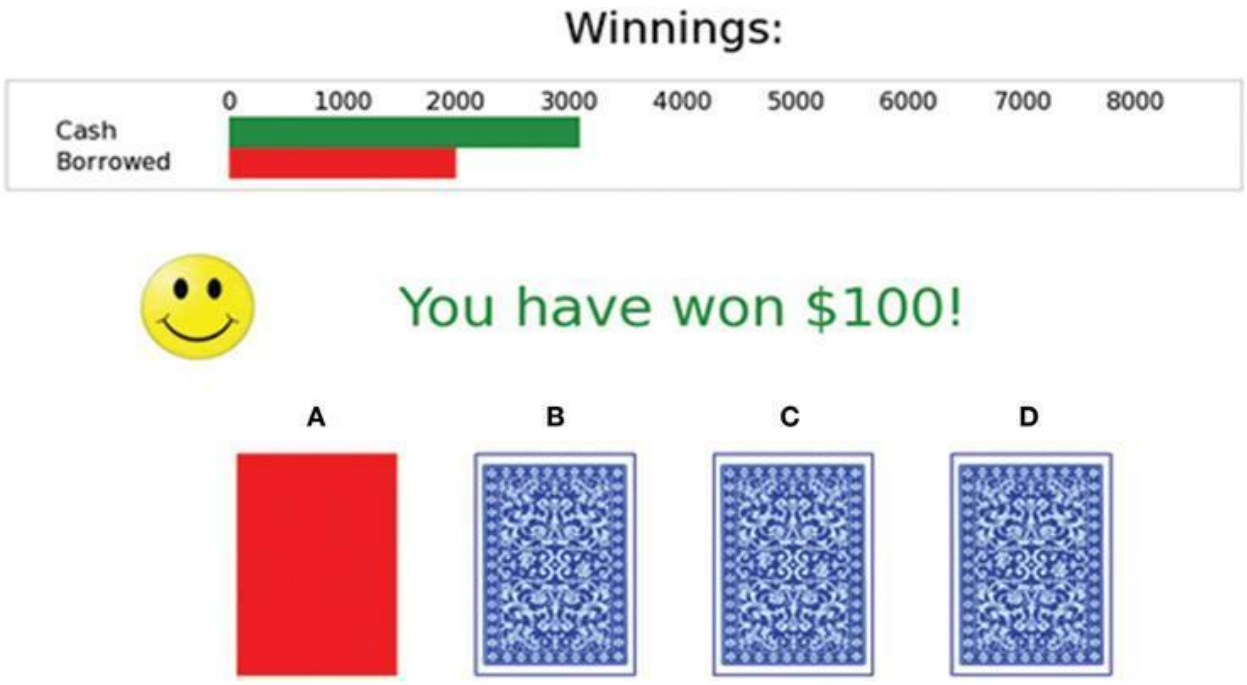

Figure 1. Screenshot of PEBL version of IGT: Deck A has been selected by a participant who has subsequently earned $100. Reprinted from "Decision-making in healthy participants on the Iowa gambling Task: New insights from an operant approach," by P.N. Bull, L.J. Tippett, D.R. Addis, 2015, *Frontiers in Psychology, 6,* p.5

In addition to *long-term* net pay-out, decks differ from one another in terms of the *magnitude* of reward and loss outcomes presented and the *frequency* with which rewards and losses occur (see Table 1). The task has been designed such that disadvantageous decks with long-term losses are also associated with large short-term rewards, whilst advantageous decks

are tied to smaller short-term rewards. Rather, long-term net losses on disadvantageous decks are explained by relatively higher *average* loss penalties that exceed their associated large but short-term gains. Despite the fact that average losses over time in combination with specific short-term reward sizes are tied to long-term outcomes, the *magnitude* of short-term losses is not *directly* tied to particular long-term net pay-outs on this version of the IGT, as they vary in size even *within* both advantageous and disadvantageous decks. Moreover, as only short-term loss outcomes vary in both magnitude *and* frequency across decks, with the magnitude and frequency of reward outcomes being fixed for each deck, the *net* frequency pay-out of rewards relative to losses can be calculated. Net frequency is derived from summing the magnitude of a reward and loss outcome that occur simultaneously with the selection of a deck, to determine a *net* value and its associated frequency of occurrence over time. Furthermore, performance on the IGT could be influenced by any one or all deck characteristics, including magnitude, frequency and/or long-term pay-out.

Table 1
IGT deck outcome specifications

	Deck A	Deck B	Deck C	Deck D
Reward magnitude	100	100	50	50
Loss magnitude	150- 350	1250	25-75	250
Long-term average	-250	-250	250	250
Absolute gain-loss frequency	10 gains 5 losses	10 gains 1 loss	10 gain 1 loss	10 gains 5 losses
Net gain-loss frequency	9 gains 5 losses	9 gains 1 loss	9 gains 5 draws	9 gains 1 loss

Moreover, performance on the IGT can also be impacted by learning ability. Participants are not made aware of the long-term outcome contingencies of each deck, but are rather told that some decks are more advantageous than others, and that one should select such decks in order to

maximize net payout on the task. This suggests that deck outcome contingencies are learnt through experience on the task. Moreover, in order to ensure that performance represented decision-making capabilities, participants were incentivised with a flat rate voucher to the value of R25, if a positive net-payout was obtained on the task. Moreover, the IGT itself has been demonstrated in the literature to be both an ecologically valid measure of RDM, given its strong association with self-reported real-life RDM, including excess substance usage and sexual risk behaviours (Golub, Starks, Kowalczyk, Thompson & Parsons, 2012; Bechara et al., 2001).

Balloon Analogue Risk Task (BART). An E-prime 2.0 computerised version of the BART (Schneider, Eschman & Zuccolotto, 2002) was used in this study. The task is a valid risk-taking measure developed by Lejuez et al. (2002). The measure consists of a virtual balloon that is electronically "pumped-up" by the participant in order to obtain a virtual monetary reward, which is conducted over 40 balloon trials (Figure 2). The aim of this test is for the participant to maximise the total amount of monetary reward accrued, which is increased with every pump of the balloon, with 5-point increments gained for each pump However, increasing the number of pumps in a trial also increases the probability of the balloon exploding, whereby the total reward occurred in that particular trial is lost following an explosion (Figure 3). In this way, participants must decide how many times to pump the balloon up within one trial (otherwise viewed as how much money to "cash-out" within one trial) before moving on to the next trial. Moreover, balloons are represented by two different types of risk, with red balloons signifying greater risk (higher probability of explosion) and blue balloons representing relatively lower risk (lower probability of explosion), although the potential reward obtained on each pump is the same across balloon types. Importantly, explosion probabilities for red and blue balloons are represented by 1/32 and 1/128 respectively, drawn from a uniform distribution. In this way, each

balloon trial is associated with a random explosion probability drawn from within the specified probabilistic range.

Unlike the IGT, the BART has no pre-specified long-term outcomes attached to short-term actions taken, and outcomes are relatively more sensitive to individual differences. As a result of this, the BART better isolates one's preference for riskier, variable outcomes over safer, certain outcomes, otherwise referred to as risk-taking propensity. Moreover, similarly to the IGT, participants were not made aware of the explosion probabilities associated with each balloon type, which thus allows one to assess learning of balloon explosion probabilities from experience on the task. In turn, risk-taking propensity and risk learning can be assessed from performance on the BART. Similarly to the IGT, participants received a flat R25 reward voucher for obtaining a positive net-payout on the BART. In support of this, Ferrey and Mishra (2014) found that performance on the BART by substance users differed when offered real monetary rewards relative to hypothetical rewards. This task has been used successfully in the South African context comparing risk-taking in psychotic and non-psychotic MUD participants (Cotton, 2014).

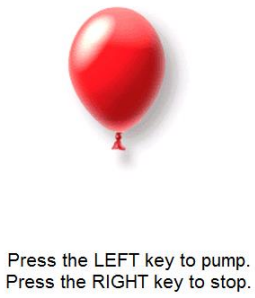

Figure 2. E-prime 2.0 version screenshot of high-risk, red balloon trial on BART

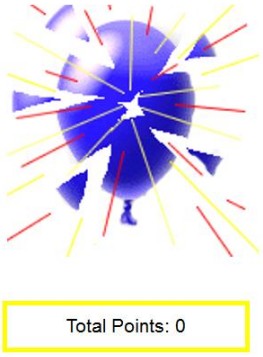

Figure 3. E-prime 2.0 version screenshot of low-risk, blue balloon explosion on BART

The BART and IGT are complementary tasks in that each task measures risk-taking under uncertainty, where outcome probabilities are not made explicitly known to the participant but are learnt through experience. However, tasks do differ in their associated outcome variability, where risk probabilities in the IGT are relatively more fixed, whilst explosion probabilities vary more substantially on the BART. Moreover, the IGT factors in long-term outcomes, which is not evident within the BART, and in turn suggests that the BART better accounts for unconstrained risk-taking preferences, whereas the IGT assesses the extent to which one demonstrates risk learning (Upton et al., 2011). Tied to this, the BART encourages an adaptive level of risk–taking whilst the IGT punishes any risk-seeking behaviour (Dean et al., 2011; Dislich, Zinkernagel, Ortner & Schmitt, 2010). Furthermore, the BART has explicitly pre-defined the magnitude of reward and loss outcomes, where rewards and losses on the BART are directly related to one's pumping patterns, where the latter is experienced by a loss in accrued credit due to balloon explosion whilst the former is represented by successful "cashing-out" on a balloon (Bishara et al., 2009). Moreover, whilst rewards and losses on the BART are separated in the form of "explosions" and "cash-outs," reward and loss are experienced simultaneously on the IGT.

Impulsivity measures.

UPPS-P. Otherwise referred to as the Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale (UPPS-P), this self-report instrument measures psychopathological vulnerability to impulsivity as it exists along 5-dimensions, including namely: lack of premeditation, lack of perseverance, sensation seeking, positive urgency and negative urgency (Whiteside & Lynam, 2001). A UPPS-P total score across each of the proposed 5-dimensions was calculated and utilized to represent a general vulnerability to impulsive behaviour, otherwise referred to as "impulsivity". The UPPS-P was borne from several reliable, but heterogeneous survey instruments, reducing impulsivity to 5 dimensions and demonstrating high internal consistency (Whiteside & Lynam, 2001). Using the UPPS-P, Uhlmann et al. (2016) found that MUD participants with and without psychosis demonstrated high impulsivity relative to healthy controls in a South African context.

Procedure

Recruitment. Clinic personnel from partnered rehabilitation clinics were provided with an overview of CM treatment, eligibility criteria, as well as posters to be placed up around the clinic. I went to the clinics on specified days of the week in order to make contact with potentially eligible MUD recruits, where CM treatment was explained in detail, provisional eligibility was determined and voluntary informed consent was obtained. For those interested MUD and control recruits who responded to newspaper advertisements or who were obtained through snowball sampling, I made contact with recruits telephonically in order to explain the requirements of the study (and a description of CM treatment for MUD recruits), establish provisional eligibility as well as to obtain voluntary consent.

Baseline screening and assessments.

MUD participants. After establishing eligibility, interest and commitment to partaking in the study, regular meetings were set up with MUD participants. These meetings took place at Psychiatry department at Groote Schuur Hospital, Cape Town. Participants first underwent a 2-week baseline period in order to establish their commitment to the program (i.e. attendance at ≥4 meetings), in addition to ensuring that at least one methamphetamine-positive urine sample was obtained to confirm current use of methamphetamine. Meetings were scheduled to take place three times a week (every Monday, Wednesday and Friday) in order to ensure that there were no more than 2 days between urine tests.

Within this 2-week period, a screening session was set-up in order to complete both the WASI and SCID-5 screening measures, and took place over a period of 2 hours. If an individual did not present with a psychiatric co-morbidity and had an WASI score above 55, they were taken for an HIV-test at the drop-in clinic situated at the University of Cape Town, where they received pre- and post-test counselling. If a participant was HIV seronegative, a baseline task assessment took place towards the end of this same two-week period, where computerized gambling tasks (IGT and BART) and a self-report measure were administered over a 1-hour period. Two to three days prior to baseline task assessment, urine sample testing was utilized to verify abstinence prior to the scheduled day of assessment, and was additionally utilized on the day of assessment. If a participant presented with a methamphetamine-positive urine sample on the day of assessments, the assessment was re-scheduled.

Moreover, if an eligible candidate failed to provide at least one methamphetamine-positive urine sample during the 2-week baseline period (i.e. the presence of methamphetamine

and/or d-amphetamine), failed to attend ≥ 4 meetings, or did not meet all the eligibility criteria, they were excluded from the study.

Recruits who provisionally presented with a psychiatric comorbidity were referred for further assessment with a psychiatrist at Groote Schuur hospital. Moreover, those who presented with an HIV seropositive status were referred to their nearest day clinic for anti-retroviral treatment, in addition to further HIV counselling. Candidates in too severe a condition for outpatient treatment were referred for inpatient treatment. Importantly, candidates were not told that a methamphetamine-positive urine sample was required during the 2-week baseline period in order to be eligible for CM treatment, as this could create a potential perverse incentive to use methamphetamine as a means to become eligible for CM treatment.

Healthy controls. The WASI and SCID-5 were administered to the control group participants during a screening session, where a urine test was taken. If a participant obtained a score on the WASI equaling or exceeding the 55 cut-off criterion, did not present with any psychiatric illnesses, and had a urine test that was negative ("absent") of any substances, they were offered the opportunity to complete computerised gambling tasks (the IGT and BART) and self-report measures over one baseline session of 1 hour.

CM treatment period for MUD participants.

MUD participants. Following baseline screening, fully eligible MUD participants underwent an 8-week CM treatment period, where they were required to meet three times a week on Monday, Wednesday and Friday for urine tests. It was during this period that participants could earn vouchers of increasing value with every negative urine sample (i.e. abstinence from methamphetamine use) that they provided. Vouchers were sent to the participants' working cell

phone number or on a loaned phone if the participant did not have one and could only be redeemed at a large supermarket franchise, *Checkers* and *Checkers hypermarket.*

Healthy controls. These individuals did not receive CM treatment, and thus were not seen during the period over which the intervention was administered to MUD participants, besides at the beginning and end of the intervention period.

Compensation.

MUD participants. Throughout the CM treatment period, vouchers were rewarded to MUD participants based on methamphetamine-negative test results (i.e. verified abstinence from methamphetamine use). Vouchers were sent to participants via mobile phone, and could be redeemed for consumable goods at any local Checkers supermarkets, but excluded purchase of alcohol or cigarettes. Vouchers began at R25 and incrementally increased in value by R12.50 with each consecutive methamphetamine-negative test provided, where an additional R100 bonus was granted following three consecutive methamphetamine-negative tests. This payment schedule was based on that of Shoptaw et al.'s (2005) original reinforcement schedule design, with a rand-to-dollar conversion rate of R10 to 1$. If a participant was abstinent from methamphetamine throughout the entire duration of CM treatment, the participant could accumulate a maximum of R4850. However, if the participant presented with a methamphetamine-positive urine sample at any point during the CM treatment period, the individual lost the opportunity to earn a voucher, and the value of the next voucher that could be earned dropped to R25, regardless of the value of their previous voucher. Despite this, a "rapid reset" rule was adopted, which allows an individual to return to their highest earned voucher previously obtained following three consecutive methamphetamine-negative tests.

Additionally, participants could receive vouchers for demonstrating good performance on the BART and IGT, where a participant could receive up to a maximum of R50 (R25 each) on both tasks at baseline assessment.

Healthy controls. At baseline task assessment, participants were compensated for their time with a R150 voucher. Moreover, control participants also stood a chance of earning an additional R50 for good performance, defined as receiving an overall positive net return, on both the IGT and BART.

Statistical Analyses

Under hypothesis 1, I investigated several RDM outcomes including: (a) the magnitude effect, defined as the tendency to seek-out large short-term rewards and withstand loss outcomes; (b) the frequency effect, defined as the tendency to favour frequent gains and avoid frequent losses; and (c) risk learning, defined as the tendency to shift behaviour towards advantageous choices that maximise payoffs, in addition to (d) risk-taking propensity, defined as the extent to which riskier, variable outcomes are preferred over safer, certain outcomes. Linear mixed-effects models (LMM) were used to investigate (a) the magnitude effect and (b) frequency effect in addition to risk learning (c) on the IGT. Risk learning was additionally assessed on the BART using a generalized linear mixed-effects model (GLMM), whilst risk-taking propensity (a) was assessed on the BART using an ANCOVA. Mixed-effects models of risk learning differed between the IGT and BART in order to account for differences in task construction. These model differences will be discussed under each new section of analysis below. Moreover, the aim of all adopted models was to assess potential differences in RDM features between treatment non-responder, treatment responder and healthy controls.

Using covariate identification methods described by Raab, Day and Sales (2000), potential *confounders* of group differences in gambling task performance were defined as sociodemographic, individual and/or substance-related factors that substantially differed between non-responders, responders *and* control groups ($p<.10$), *and* were substantially correlated (using Pearson's *r*) with task performance outcomes ($p<.10$); these were in turn included in the model as confounders. Moreover, additional *covariates* were identified as those sociodemographic, individual and/or substance-related factors that did not largely differ ($p>.10$) between groups, but did substantially correlate with performance outcomes; these were included in models where major relationships were demonstrated. In order to combat potential model misspecification in a small sample, a more liberal alpha p-value of .10 was utilized to increase the power of detecting potential covariates. The potential influence of substance use factors on performance, which were exclusive characteristics of MUD participants, were investigated in models that included MUD participants only.

Moreover, for both tasks, all models with significant or trending findings were followed by group contrasts in order to assess potential differences in RDM features between non-responder, responder and control subgroups, using Tukey's p-adjustment correction method. Group contrasts were used to minimize type-1-error associated with multiple group comparisons. Both p-values and effect sizes were presented, where in the case of significant ($p <.05$) or trend-level ($.05 \geq p \leq .10$) differences, effect sizes were drawn upon to interpret the likely robustness of obtained results. This approach was adopted considering that significance tests are relatively more sensitive to sample size differences (Fritz, Morris & Richler, 2012). When investigating effect sizes of between-group contrasts in LMMs, Hedges' *g* estimation was utilized based on its utility within smaller samples, namely where .20 was interpreted as a small effect, .50 as a

medium effect, and .80 as a large effect. When assessing continuous variable relationships in LMMs, Pearson's *r* was utilized as the effect size, where .10 was regarded as a small effect, followed by .30 as medium and .50 as large effect. Both estimations were based on Cohen's (1988) conventions. An additional effect size estimation of relative risk or odds ratio was utilized for GLMM and related nonlinear models, where 1.68 was considered small, 3.47 medium and 6.71 large, which is equivalent to Cohen's (1988) conventions (Chen, Cohen, Chen, 2010). 95% confidence intervals were presented with all effect sizes, and all analyses were conducted using R programming software (R Core Team, 2018).

Hypothesis 1a

MUD participants, treatment non-responders more than responders, demonstrate greater RDM at baseline relative to healthy controls; where RDM is defined by several RDM features, including: magnitude effect, frequency effect, learning and risk-taking propensity.

Given previous reports of within-group heterogeneity in performance on the IGT amongst both substance-using and healthy samples (Bechara & Damasio, 2002; Horstmann et al., 2012; Verdejo-Garcia et al., 2014), LMM & GLMMs were utilized to account for this. Mixed-effect modelling does this by capturing both fixed and random effects, where estimation of random effects increases the precision of fixed-effects estimates. Attention was mostly paid to fixed-effects, which represented group differences after controlling for potential confounding effects of individual-subject variability on performance (i.e. the random effect). All LMM models were fitted using restricted maximum likelihood, whilst GLMM was fitted using the Laplace approximation of maximum likelihood, considering that the former method is not available for GLMM. For LMM model comparisons, models were re-fitted using maximum likelihood before being compared with use of a likelihood ratio (LR) test. Moreover, GLMM

models were re-fitted using pseudo-likelihood tests before being compared using pseudo-likelihood ratio tests.

Magnitude effect.

IGT analysis 1.1. Non-responders will demonstrate a greater tendency to seek-out large short-term rewards *and* withstand large short-term losses on the IGT at baseline, relative to responders and healthy controls consecutively.

An LMM was implemented to assess potential differences between non-responders, responders and controls in relation to the IGT magnitude effect at baseline. The magnitude effect was calculated by subtracting the number of selections from decks associated with large short-term gains and long-term losses (A & B) from decks tied to small short-term gains and long-term gains (C & D), over several blocks (see Table 2). Block scores represented a *net* sum of advantageous relative to disadvantageous deck selections, where blocks each consisted of 20 trials, spanning from blocks 2-5. However, the first block was removed from analysis given that performance on this block reflects more exploratory behavior, relative to latter blocks associated with more deliberate decision-making (Gansler, Jerram, Vannorsdall & Schretlen, 2011). High scores represent a low magnitude effect, as high scores are associated with a tendency to seek-out long-term gains tied to smaller short-term gains. In contrast, low scores demonstrate a high magnitude effect, as lower scores emerge from a tendency to seek-out large short-term gains that are also tied to long-term losses.

Appropriate when data is hierarchically clustered, the LMM sought to estimate potential group differences (fixed-effect) in the magnitude effect whilst simultaneously accounting for between-subject variability in block net scores (random effect). More specifically, the block net score was modelled as the unit of observation at level-1, accounting for its clustering within each

individual participant, where each participant acted as the unit at level-2. If significant (or trend-level) between-group differences were found between non-responders, responders and controls, additional planned comparisons were conducted in order to assess wherein such group differences lay *within* each individual disadvantageous deck, namely decks A and B. The purpose of this was to confirm whether group differences were additionally characterized by an ability to withstand large short-term losses alongside a drive to seek-out large short-term gains.

Frequency effect.

IGT analysis 1.2. Non-responders will demonstrate a greater tendency to seek-out frequent rewards *and* avoid frequent losses on the IGT at baseline, relative to responders and healthy controls consecutively.

An LMM was run in order to assess potential differences between non-responders, responders and control groups in the frequency effect on baseline IGT. The frequency effect was measured by subtracting the sum of deck selections associated with infrequent gains and frequent losses (A&C) from the sum of deck selections tied to frequent gains and infrequent losses (B&D) (Table 2). This scoring method was applied to each block of 20 trials, spanning from blocks 2-5, and excluding block 1, for the same reasons presented under IGT analysis 1.1. Moreover, high net scores represented high frequency effects, where decks were associated with seeking-out frequent gains and avoiding frequent losses. In contrast, low net scores represented low frequency effects, demonstrating a tendency to seek-out infrequent rewards and withstand frequent losses.

Similarly to IGT analysis 1.1, the block score was modelled as a level-1 unit of observation, with the participant modelled as the hierarchical grouping unit at level-2. Unlike

IGT analysis 1.1, no additional planned comparisons of individual decks were run. This was due to the fact that decks only varied exactly by two possible combinations: by frequent gains *and* infrequent losses, or infrequent gains *and* frequent losses. Because of this, the frequency of gains over losses could not be investigated separately, and is specific to the version of the task utilized in the present study.

Risk learning.

IGT analysis 1.3. Non-responders will demonstrate the poorest learning on IGT at baseline, relative to responders and healthy controls consecutively.

Risk learning on the IGT is defined by the extent to which one shifted from or avoided disadvantageous, long-term loss decks for more advantageous, long-term payout over the duration of the IGT at baseline. More specifically, learning is represented by continual improvement in IGT net score across consecutive blocks, whilst a declining or stable score over time reflects poor learning on the task. A linear mixed-effects growth curve model (LMM-GC) was used to investigate risk learning by assessing potential group differences in the *change* in net score across 5 consecutive blocks on the IGT at baseline. In extension, different growth curves (linear, quadratic and cubic) were modeled to determine the most appropriate fit. Importantly, in this model the fixed effect was represented by the change in block performance or the individual growth curve of each non-responder, responder and control group, whilst the random effect was captured as potential between-subject differences in block scores trends.

Like LMMs described under “IGT analysis 1.1” and “IGT analysis 1.2”, level-1 and -2 units were consistent across models, with the exception of the block number being modeled as a fixed-effect in this particular model, representing a proxy variable of time that allows the change in score to be tracked over the duration of the task for each of non-responder, responders and

control groups. The model also specified an additional random slope estimate at level-2, accounting for potential variability in the slope of the growth curve between individuals. In addition to assessing performance over time, post-hoc contrasts were utilized to assess potential differences in block-by-block performance *within* each group. This was done in order to locate where the majority of learning took place for each group.

Table 2
IGT deck outcome profiles and associated scoring methods

		Deck A	Deck B	Deck C	Deck D	Measure
Magnitude effect	Reward magnitude	High immediate reward	High immediate reward	Low immediate reward	Low immediate reward	(C + D) – (A + D) for each of blocks 2-5
	Loss magnitude	Intermediate immediate loss	High immediate loss	Low immediate loss	Intermediate immediate loss	
Frequency effect	Gain-loss frequency	Infrequent gain; Frequent loss	Frequent gain; Infrequent loss	Infrequency gain; Frequent loss	Frequent gain; Infrequent loss	(B + D) – (A + C) for each of blocks 2-5
Risk learning	Long-term	Long-term net negative	Long-term net negative	Long-term net positive	Long-term net-positive	(C + D) – (A + D) block 5 – block 1

Note. Decks A & B relate to a high magnitude effect, with a tendency to seek-out large short-term reward and withstand large losses. The latter is explicitly verified when B> A.
Decks A & B also correspond with a lower long-term payout
Decks C & B relate to a low magnitude effect, with a tendency to avoid large short-term rewards (i.e. seek-out small immediate rewards instead)
Decks B & D relate to a high frequency effect, with a tendency to seek-out frequent rewards and avoid frequent losses
Decks A & C relate to a low frequency effect, with a tendency to seek-out infrequent rewards and withstand frequent losses

BART analysis 1.4. Non-responders demonstrate the poorest learning on the BART at baseline, relative to responders and healthy controls consecutively, as demonstrated by relatively increased pumping following burst trials.

A GLMM first proposed by Mata and et al. (2012) was utilized to assess differences in learning between non-responder, responder and healthy control groups on the BART at baseline. Learning is argued to be exhibited by decreased pumping following burst trials, where evidence of learning is indicative of adaptive decision-making. Unlike the LMMs presented, a GLMM was required to model learning on the BART given the non-normal distribution of the outcome

variable, pumps per trial. In particular, estimates were derived from the gamma distribution using log estimation, which was verified through model selection. Given the wide probabilistic range of balloon bursts on the BART, with 1/32 and 1/128 representing risky and non-risky balloons respectively, there may be considerable variability in subject-level pumping across trials. Considering this, the use of GLMM provides a means to explicitly account for such inter-subject variability as random effects, in order to increase the precision of fixed-effect group differences in learning. In the GLMM, pumps per trial were specified as the unit for level-1 estimates, where trial pumps were clustered within subjects, who formed the unit at level-2 of the model.

Besides assessing potential group differences in learning on the BART at baseline, the GLMM additionally accounted for the potential influence of several proposed fixed covariates of pumping behaviour on a current trial (Ashenhurst et al., 2014; Dean et al., 2011; Mata et al., 2012). These included current trial number, current trial burst, previous trial burst and balloon colour, where the balloon colour represents the associated riskiness of the balloon. Moreover, the model was followed by post-hoc contrasts of pumping differences between previous burst and cash-out conditions for each of non-responder, responder and control groups.

This model differs from LMM-GC learning on the IGT for several reasons. Firstly, the GLMM assesses learning as the tendency to alter behaviour following a *certain* condition, namely the burst condition on the BART, whilst the LMM-GC assesses learning as a change in score over the entire duration of the IGT. Moreover, the distribution of the outcome that is indicative of learning in both models follows different distributions, and thus requires slightly altered modelling techniques. The exclusive addition of several unique covariates into the BART learning model emerges from previous studies' work on the model, which represent covariates that are specific to the task itself.

Risk-taking propensity.

BART analysis 1.5. Non-responders demonstrate greater risk-taking propensity on the BART at baseline, relative to responders and healthy controls consecutively.

A one-way ANCOVA was utilized to assess potential differences between non-responders, responders and control groups in risk-taking propensity on the BART at baseline. Risk-taking propensity was measured by the average number of pumps on non-explosion trials on the BART, otherwise known as the mean adjusted score. Lejuez et al. (2002) argue that a mean adjusted score is a valid reflection of true pumping behaviour, given that inclusion of pumps on explosion trials may actually underestimate true pumping behaviour. Moreover, an ANCOVA model is best suited to investigate risk-taking propensity, as risk-taking propensity refers to a relatively *stable* preference for riskier over safer actions, and preferences can be better captured by *average* performance. Unlike the BART, the IGT is not considered a measure of risk-taking propensity, given that risk-taking preferences are confounded by consideration for long-term outcomes on the IGT (Schonberg et al., 2011), which are absent in the BART.

Hypothesis 1b

Impulsivity positively moderates RDM features at baseline, but does not *entirely* account for potential group differences in RDM.

In all the models presented under this section, all original models of group differences proposed under hypothesis 1 were duplicated to incorporate impulsivity as a moderator of RDM features, where impulsivity was represented by the UPPS-P total score. The UPPS-P total score was continuous, where high scores reflected higher impulsivity, and lower scores represented lower impulsivity. All models assessed the potential main effect of impulsivity in relation to various RDM features. Moreover, potential interaction effects between the non-responder,

responder and control groups *and* impulsivity were investigated. In addition, if significant (or trend-level) interaction effects were found, a Sobel test was conducted in order to verify that impulsivity did not act as a *mediator* of the relationship between group differences and RDM features.

Hypothesis 2

Amongst MUD participants, greater RDM, alongside greater impulsivity, predicts relapse occurrence *and* relapse severity over the duration of CM treatment, where RDM is defined by average overall performance on IGT and/or BART.

A hurdle model was utilized to investigate whether RDM predicted CM treatment outcomes for MUD participants. CM treatment outcomes included relapse occurrence, which was defined as having at least one methamphetamine-positive urine sample and/or a missed sample during CM treatment. Treating missed samples as methamphtermine-positive urine samples offers a more conservative defintion that has been extenstively adopted in previous studies (Correia & Benson, 2006; Petry et al., 2004; Rash et al. 2008), CM treatment was also assessed by relapse severity, which referred to the number of methamphetamine-positive urine samples, including number of missed samples, obtained out of a total of 24 samples whilst undergoing CM treatment, with larger numbers representing greater relapse severity. The hurdle model represents both treatment outcomes within a 2-part model consisting of Binomial and Poisson processes, where outcomes to treatment were represented by a binomial process up until some threshold, following which they were represented by a Poisson process. Specifically, the binomial model estimated the odds of one relapsing at least once during CM treatment amongst MUD participants, whilst the Poisson model estimated the odds of severe/prolonged relapse amongst those who had relapsed at least once (i.e. non-responders only).

Moreover, RDM was incorporated as a potential predictor of CM treatment success, and was defined by overall average performance on the IGT and/or BART, where a median-split was utilized to characterise high and low performers on each task. A dichotomous variable was opted for over a continuous one, given that numeric differences in average overall performance may not entirely reflect true differences in RDM, but also random variability. Moreover, impulsivity was included as a potential covariate, as measured using the UPPS-P total score, because high impulsivity has been found to be associated with higher risk of relapse (Pattij & De Vries, 2013). Moreover, an additional covariate included the number of methamphetamine-positive urine samples during the baseline screening period, which has been previously tied to risk of relapse. In a cocaine-using sample, Ehrman Robbins and Cornish (2001) found that a greater number of baseline cocaine-positive urine samples was linked to greater relapse likelihood. Potential covariates that were considered were limited to impulsivity and methamphetamine-positive tests at the baseline screening period, due to their high associated reliability of measurement. With several possible predictors considered, only the most parsimonious model was selected using model comparison. In other words, a fully specified model was compared to reduced versions in order to acquire a model with the most relevant predictors. Models were compared using Akaike Information Criterion (AIC).

CHAPTER FOUR: RESULTS

Given that this study predominantly focused on RDM of MUD subgroups based on their treatment response on CM, the treatment process and associated outcomes were not analyzed in detail under hypothesis 1, but were merely used to define treatment response subgroups, specifically non-responders and responders. In fact, non-responders were defined as individuals who presented with at least one methamphetamine-positive urine sample and/or missing sample during CM treatment. In contrast, responders were defined as those individuals who attended all sessions and exclusively presented with methamphetamine-negative urine samples through the duration of CM treatment. Of the total sample of MUD participants, 9 represented non-responders, whilst 17 represented responders. On average, MUD participants provided clean (i.e. methamphetamine-negative) urine samples 83 percent of the time during the CM treatment period, whilst non-responders provided clean samples 54 percent of the time. Furthermore, non-responders and responders were investigated in relation to a healthy non-substance-using control group of 19 participants. Whilst not investigated under hypothesis 1, the potential relationship between RDM and CM treatment outcomes was investigated under hypothesis 2.

Group Matching on Demographics

Firstly, matching was assessed between responders, non-responders and control groups in relation to several demographic variables that have been previously tied to performance on gambling tasks including; gender, education, age and broad intellectual function (i.e. WASI), see Table 3 (Bolla, Eldreth, Matochik & Cadet, 2004; Davis et al., 2008; Evans, Kemish & Turnbull, 2004; Rogers et al., 1999; van den Bos, Homberg & de Visser, 2013; Webb, DelDonno & Killgore, 2014; Wood, Busemeyer, Koling, Cox & Davis, 2005). Non-responder, responder and controls groups were relatively well matched in gender, age and WASI scores, as they did not

significantly differ in these characteristics. In contrast, groups did significantly differ in years of education, partly because there was an absence of participants with tertiary education within the non-responder group. Moreover, groups significantly differed in impulsivity, with non-responders exhibiting the highest impulsivity, followed by responders and controls respectively. Furthermore, groups significantly differed across various additional sociodemographic factors, including current employment and household income (Table 3). More specifically, a larger number of non-responders and responders were unemployed at the time of the study than healthy controls. Interestingly, responders had the lowest average household income, followed by non-responders and controls consecutively.

Covariates of RDM

No demographic variables substantially ($p<.10$) covaried with RDM features (see Appendix A), except for gender in models of (a) IGT frequency effect ($r_s = -0.23$, p=.001**), (b) BART risk-taking propensity ($r_s = -0.45$, p=.002**), and (c) BART learning model ($r_s = 0.25$, p<.001***). As a result of this, only the models mentioned above incorporated covariates. Furthermore, impulsivity was excluded as a covariate, as it was separately investigated in relation to RDM features under hypothesis 1b. Moreover, characteristics that were exclusively applicable to MUD participants were compared between non-responders and responders; and included; methamphetamine use history, number of methamphetamine-positive baseline urine samples, whether or not a MUD participant was already enrolled in outpatient treatment at the time of CM enrollment, as well as whether MUD participants were secondary users of either methaqualone (mandrax) and/or cannabis or merely primary methamphetamine users (this excluded occasional alcohol use and/or cigarette smoking). Only a trending difference (p=.053) was found between non-responders and responders in methamphetamine use history, where non-

responders had a longer duration of methamphetamine use relative to responders. However, although methamphetamine use history significantly differed between groups, it did not substantially covary (p<.10) with RDM features, and in turn was not included as a covariate in any models.

Table 3
Full sample characteristics (N=45)

Variable	Nonresponders (*n* = 9)	Responders (*n* = 17)	Healthy Controls (*n* = 19)	F/χ^2	*p*
Sociodemographic characteristics					
Age, mean (SD)	34.20 (5.34)	33.76 (6.69)	35.50 (7.12)	0.67	.517
Gender (M: F)	7:2	10:7	11:8	1.16	.619
Education (7-10:11-12:13+)	4:5:0	5:6:6	1:11:7	9.15	.035*
Employment (Y: N)	0:9	4[a]:12	11:8	10.04	.005**
Household income (RAND), mean (SD)	45277.78 (26084)	14117.65 (19404)	34473.68 (34657)	4.27	.021*
Cognitive characteristics					
WASI IQ, mean (SD)	90.44 (12.00)	91.47 (21.55)	88.89 (17.00)	0.09	.913
Methamphetamine (MA) use history					
Duration of MA use (years), mean (SD)	13.44 (3.71)	9.88 (4.48)	--	4.15	.053^{+}
Baseline MA positive, %	45.40 (24.30)	36.20 (19.70)		1.08	.307
Other substance use and concurrent treatment					
Secondary substance (Methaqualone &/or cannabis: none)	7:2	8:9	--	1.19	.217
Concurrent outpatient treatment (Y: N)	6:3	9:8	--	0.07	.683

Note. Employment = Binary (yes or no) variable representing current employment. *a* = missing value/s in total sample. Household income = Yearly household income variable derived from an ordinal 5 income category variable, where average income was extracted from the income range reflected within an income category. WASI IQ = aggregate score derived from both verbal and performance subsets of the Weschler-abbreviated scale of intelligence test. Baseline MA positive = proportion of MA-positive tests during baseline period prior to CM treatment. Secondary substance = binary variable (Methaqualone &/or cannabis *or* none) indicating presence or absence of use of specific secondary substances besides MA. Concurrent outpatient treatment = binary variable (yes or no) indicating concurrent participation in motivational interviewing and/or group therapy alongside CM. *F* tests conducted on variables Age, Education, Household income, WASI IQ, Duration of MA use and Baseline MA positive. Fisher's exact tests conducted on count factors including; gender and employment, whilst chi-squared tests conducted on Concurrent outpatient treatment and Secondary substance.
$^{+}$ p <0.10, * p <0.05, ** p< 0.01, *** p<0.001

Main Analyses Findings

All models met assumptions of normality and homogeneity of variance, expect for the risk-taking propensity model, which deviated somewhat from normality. Linearity was upheld in all models where it is assumed (i.e. all models except IGT and BART learning models). Moreover, no highly influential data points were detected in any of the models. For additional model comparison findings for Hypothesis 1 and 2, see Appendix B and D respectively.

Hypothesis 1a.

Magnitude effect.

IGT analysis 1.1. The LMM out-performed a random-effects-only model at trending significance (*LR* = 5.09, *p* =.051*)*, where differences between non-responder, responder and control groups (i.e. the fixed-effect) explained a substantial amount of variance in the magnitude effect (R^2=0.60). These findings provide support for incorporating a group fixed-effect in the model. In addition, the LMM significantly outperforming a fixed-effects-only model (*LR* = 45, *p* <.001***), suggesting the appropriateness of a mixed-effects model in particular.

Based on specific task specifications relating to short-term reward and loss magnitudes on the IGT, the magnitude effect was investigated using separate analyses of reward and loss outcomes. Model coefficients (see Table 4) confirm that there was an absence of significant group differences between non-responders (*m* =-5.17, *sd*= 6.10) and responders (*m* =-0.53, *sd*= 8.80), as well as responders and controls (*m* =0.79, *sd*= 7.30). However, in partial support of the original hypothesis, a significant group difference was found between non-responders and controls (*p* =.020, Table 4), but following adjustment for multiple group comparisons was found

to be a trending significant difference (p=.051) with a large hedges g effect size (g = -0.97) (see Table 5). This finding suggests that, at baseline, non-responders demonstrated a greater tendency to seek-out decks with larger short-term reward magnitudes over decks with smaller short-term reward magnitudes relative to healthy controls. On the other hand, non-responders neither differed from responders nor did responders differ from healthy controls, which was contrary to that which was initially proposed. However, a medium effect size (g = -0.74) was found between non-responders and responders, implying that non-responders might also favour large short-term magnitude rewards, although this finding cannot be confirmed. Furthermore, visual inspection of the data (Figure 4) provides support for performance differences between non-responders and controls, with non-responders showing a greater tendency to seek-out short-term rewards on the IGT at baseline.

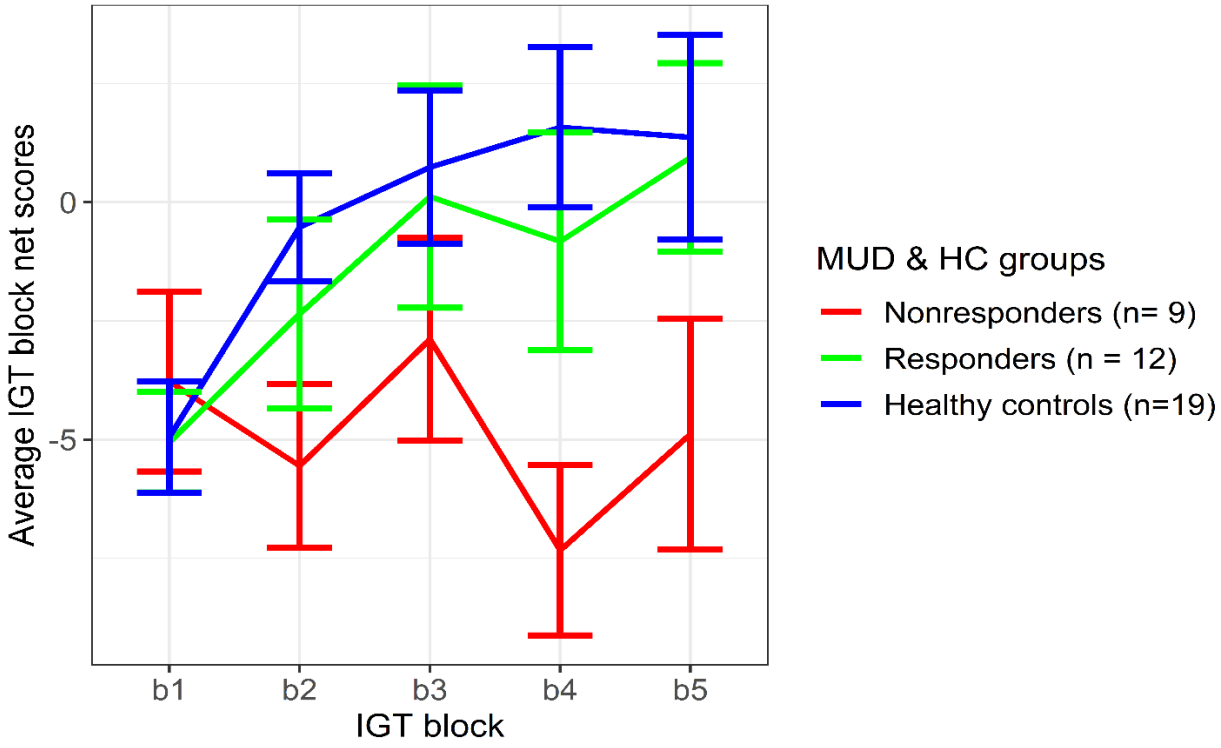

Figure 4. Magnitude effect and learning on IGT: Differences in average block scores (with associated standard error) between non-responders, responders and healthy control groups at

baseline, where the size of block scores reflects effects of outcome magnitude on choice behaviour, whilst the change in block scores represents extent of learning

Table 4
Magnitude effect on IGT at baseline: LMM estimates

Parameter	Estimate	CI	*p*
Fixed effects			
Intercept (NR) β_0	-5.16	[-9.18: -1:14]	0.012*
R β_1	4.63	[-0.43: 9.70]	0.072^{+}
HC β_2	5.95	[0.97: 10.93]	0.020*
Random effects			
Intercept variance α_0	29.34		
Error variance σ^2_ε	31.22		

Note. Within MUD group, NR = non-responders and R = responders. HC = healthy controls. Estimate = Regression coefficients. CI = 95% confidence interval. $^{+}$ p<.10, * p < .05, ** p <.01, *** p <.001.

Table 5
Magnitude effect on IGT at baseline: Group contrasts from LMM

Effect	NR	R	HC	*t*	*p*	*G*	*g*[CI]
m(sd)	-5.17 (6.10)	-0.53 (8.80)	0.79 (7.30)				
Contrast							
NR-HC				-2.41	$.051^{+}$	-0.97	[-1.59:-0.19]
R-HC				-0.64	.794	-0.20	[-0.90: 0.49]
NR-R				-1.84	.167	-0.74	[-1.37: 0.05]

Note. Within MUD group, NR = non-responders and R = responders. HC = healthy controls. m(sd)= raw mean of specified group with corresponding standard deviation. *g* = hedges g effect size. CI = 95% confidence interval. Tukey's p-adjustment used to correct for group contrasts.
$^{+}$ p<.10, * p < .05, ** p <.01, *** p <.001.

Moreover, in order to assess whether poorer performance on baseline IGT was additionally influenced by the magnitude of *loss* outcomes, the main analysis was followed by planned group comparisons conducted within individual decks specifically associated with high reward magnitudes, only if significant (or trending significant) group differences were obtained in the main model. Given the trending difference found between non-responders and controls in

relation to reward magnitude, these groups were further compared in relation to loss magnitude (Figure 5). In particular, when non-responders and controls were compared within a deck associated with large short-term reward *and* loss, namely deck B, groups did not significantly differ in their ability to withstand large short-term losses (t = 1.20, p = .229, g= 0.51, CI [-0.30:1.29]). In contrast, non-responders did select deck A significantly more often than controls (t =2.50, p = .017* g= 0.99, CI [-0.01:1.88]), a disadvantageous deck that is associated with relatively smaller losses to those of deck B. In conjunction, these findings suggest that non-responders may not differ from healthy controls in their ability to withstand losses. Moreover, it is suggestive that the original magnitude effect hypothesis is only partially supported by a difference in preference for *rewards* in particular.

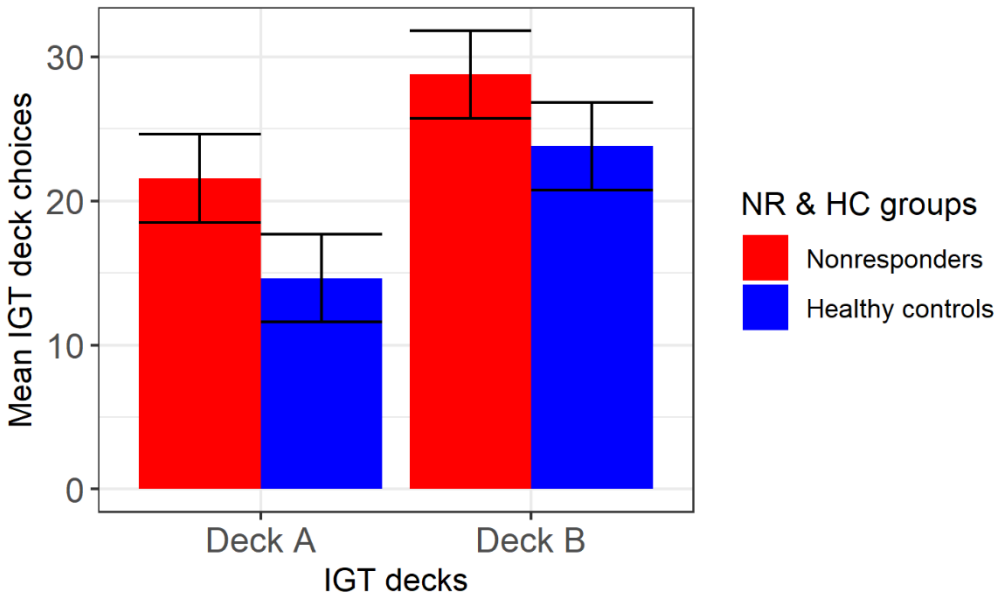

Figure 5. Mean deck selections on IGT: Selections of disadvantageous, low short-term loss deck A and disadvantageous, high short-term loss deck B by non-responder and healthy control groups at baseline.

Frequency effect.

IGT analysis 1.2. Providing support for use of an LMM model, it was found to significantly outperform a fixed-effects only model (LR=40.00, p=<.001***). Moreover, an LMM that included fixed-effects of interest performed significantly better than a random-effects-only model, suggesting the relevance of selected fixed-effects incorporated in the model (LR= 6.80, p=.034*). Moreover, the entire model accounted for a substantial amount of variance in the frequency effect (R^2=0.588).

Unlike the magnitude effect model, only a single model (i.e. no additional planned comparisons) was utilized to investigate the entirety of the frequency effect, as the result of mirrored deck frequency characteristics. Whilst non-responders (m = 0.17, sd = 4.62) appeared to significantly differ from responders (m = 5.18, sd = 7.46) according to model coefficients (Table 6), after adjusting for multiple group comparisons, only a trending difference (p = .053) was demonstrated between non-responders and responders with a medium effect size (g =-0.74, Table 7). This finding suggests that responders sought-out frequent rewards and avoided frequent losses relatively *more often* than non-responders (Figure 6), and aligns with the hypothesis to a degree. However, there were no other (trending) significant differences between the remaining groups as initially proposed, however, a trending significance was demonstrated between females and males in relation to the frequency effect, where females exhibited a greater tendency to seek-out frequent rewards and avoid frequent losses than males did (t =2.50, p=.081, g[CI]=0.61 [0.00:1.23]).

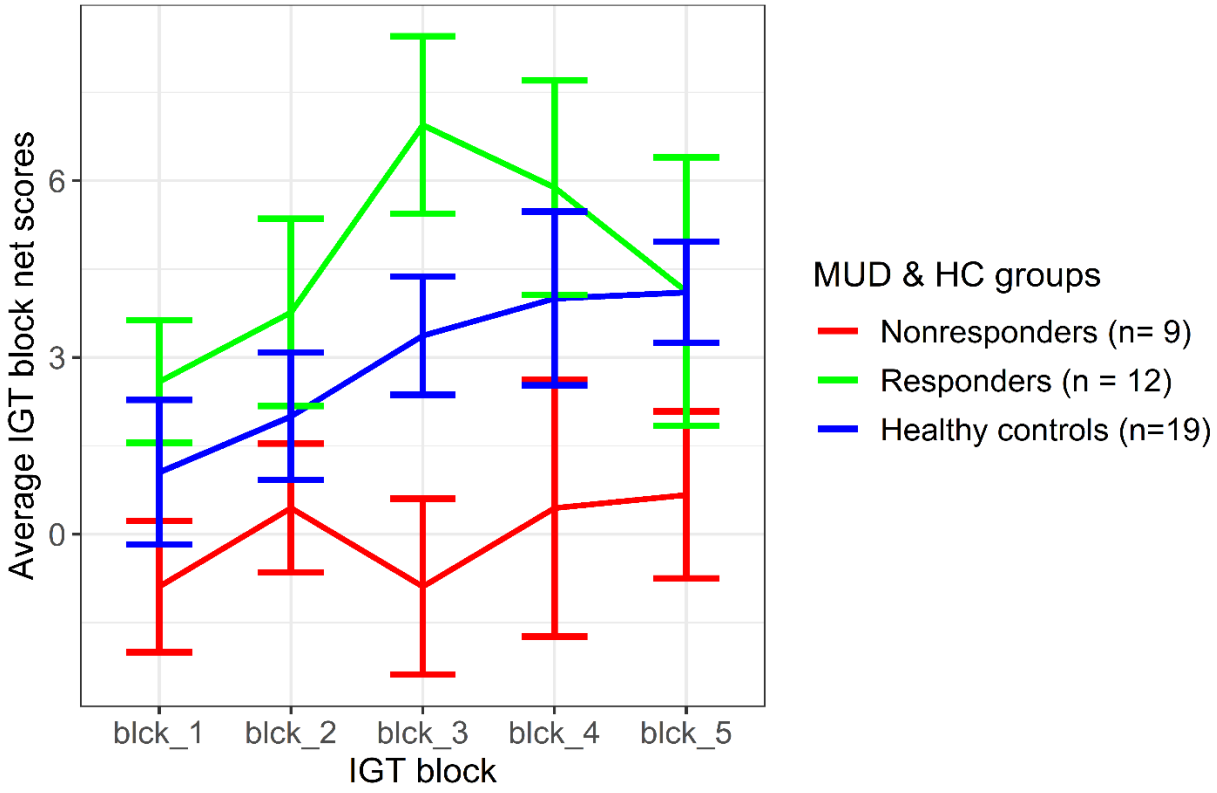

Figure 6. Frequency effect on IGT: Differences in average block scores (with associated standard error) between non-responders, responders and healthy control groups at baseline, where the size of block scores reflects effects of outcome frequency on choice behaviour.

Table 6
Frequency effect on IGT at baseline: LMM estimates

Parameter	Estimate	CI	*P*
Fixed effects			
Intercept (N) β_0	0.16	[-2.89: 3.23]	0.914
R β_1	5.00	[1.14: 8.87]	0.012*
HC β_2	3.20	[-0.59: 6.99]	0.096
Random effects			
Intercept variance	16.74		
Error variance	19.53		

Note. Within MUD group, NR = non-responders and R = responders. HC = healthy controls. Estimate = Regression coefficients. CI = 95% confidence interval. $^{+}$ p<.10, * p < .05, ** p <.01, *** p <.001.

Table 7

Frequency effect on IGT at baseline: Group contrasts from LMM

Effect	NR	R	HC	*T*	*P*	*G*	*g*[CI]
m(sd)	0.17 (4.62)	5.18 (7.46)	3.37 (4.89)				
Contrast							
NR-HC				-1.45	.323	-0.82	[-1.54: 0.06]
R-HC				1.21	.454	0.36	[-0.09: 1.00]
NR-R				-2.40	.053^{+}	-0.74	[-1.31: -0.11]

Note. Within MUD group, NR = non-responders and R = responders. HC = healthy controls. m(sd)= raw mean of specified group with corresponding standard deviation. *g* = hedges g effect size. CI = 95% confidence interval. Tukey's p-adjustment used to correct for group contrasts.

$^{+}$ $p<.10$, * $p<.05$, ** $p<.01$, *** $p<.001$.

Risk learning.

IGT analysis 1.3. A quadratic LMM-GC was found to model learning better than either linear or cubic versions, suggesting that learning on IGT is a nonlinear process (see significant quadratic term in Table 8). The LMM-GC also significantly outperformed a random-effects-only model (*LR*=17.00, *p* =.007*), suggesting that selected fixed-effects are relevant in the model. Moreover, the LMM-GC was significantly improved over a fixed-effects-only model (*LR*=65.00, *p* <.001***) confirming the appropriateness of LMM-GC in model learning.

In order to assess learning on the IGT, the LMM-GC was utilized to estimate learning curves of each of the non-responder, responder and control groups, which represented the change in performance over time. Partly supportive of the hypothesis, a trending significant difference in learning was demonstrated between non-responders (*m* = -1.11, *sd* =7.90) and controls (*m* =6.32, *sd* = 12.50) both before and after multiple comparison adjustment (*p* = .066 & *p* = .081 respectively, see Tables 8 & 9), with a medium effect size (*g* = -0.63). More specifically, findings indicate that non-responders exhibited compromised learning relative to healthy controls (Table 9, Figure 4). No other (trending) significant group differences were obtained (Table 9). When investigating potential block-by-block improvement, healthy controls exclusively

exhibited significantly improved performance across blocks, specifically from block 1 to block 3 and block 1 to block 4 *(b3-b1: t* = 2.92, *p* =.030*, *g*[CI]= 0.62[0.18:0.94]*; b4-b1: t* =3.10, *p* =.010*, *g[CI]*= 0.63*[*0.16:0.93*]* respectively) (Appendix C).

Table 8
Risk learning on IGT at baseline: LMM-GC estimates

Parameter	Estimate	CI	*P*
Fixed effects			
Intercept (NR) β_0	-6.60	[-11.66: -1.53]	0.010*
Block^2 β_1	-0.41	[-0.81: -0.02]	0.039*
Block β_2	2.09	[-0.79: 4.98]	0.154
R β_3	-1.80	[-7.16: 3.55]	0.500
HC β_4	-1.09	[-6.34: 4.16]	0.677
Block*R β_5	1.75	[-0.28: 3.79]	0.091$^+$
Block*HC β_6	1.87	[-0.12: 3.87]	0.066$^+$
Random effects			
Intercept variance α_0	13.59		
Block variance σ^2_B	3.75		
Error variance σ^2_ε	25.33		

Note. Within MUD group, NR = non-responders and R = responders. HC = healthy controls. Estimate = Regression coefficients, Block^2 = quadratic growth term. Block = linear growth term. CI = 95% confidence interval. $^+$ *p*<.10, * *p* < .05, ** *p* <.01, *** *p* <.001.

Table 9
Risk learning on IGT at baseline: Group contrasts from LMM-GC

Effect	NR	R	HC	*t*	*P*	*G*	*g*[CI]
m(sd)	-1.11 (7.90)	6.00 (8.80)	6.32 (12.50)				
Contrast							
NR-HC				-2.20	.081$^+$	-0.63	[-1.21: 0.01]
R-HC				-0.63	.801	-0.02	[-0.65: 0.62]
NR-R				-1.65	.235	-0.80	[-1.45: -0.05]

Note. Within MUD group, NR = non-responders and R = responders. HC = healthy controls. m(sd)= raw mean of specified group with corresponding standard deviation. *g* = hedges g effect size. CI = 95% confidence interval. Tukey's p-adjustment used to correct for group contrasts.
$^+$ *p*<.10, * *p* <.05, ** *p* <.01, *** *p* <.001.

BART analysis 1.5. Utilizing a pseudo-likelihood ratio test, the GLMM significantly outperformed a random-effects-only model (χ^2= 332, *p*=<.001**), suggesting that selected fixed

effects are appropriate in the model. Moreover, the GLMM was significantly improved over a fixed-effects only model (χ^2= 679, *p*=<.001**), confirming the utility of a generalized mixed effect model. Using pseudo-R squared estimation, 0.22 of total variance was explained by the model.

Despite model relevance, non-responders (*m* =12.59, *sd* = 10.80) were equally at risk of increasing pumping following a burst trial than responders (*m* =11.78, *sd* = 9.90) or controls (*m* =14.30, *sd* = 16.10, Table 10 & 11). This finding suggests a lack of differences in learning between groups, which does not align with the original hypothesis. On the other hand, several model covariates significantly predicted trial pumps, namely: trial number, current burst trial, balloon type and gender (Table 10). More specifically, incrementally increased pumping was less likely with each subsequent trial (*p* <.001); increased pumping was less likely to occur on a current burst relative to current cash-out trials (*p* <.001); pumping was more likely to increase within riskier red balloons relative to safer, blue balloons, (*p* <.001); and males exhibited a greater likelihood of demonstrating increased pumping relative to female participants (*p* =.001). Furthermore, when investigating potential *within-group* differences in pumping behavior between burst and cash-out conditions, neither significant differences between conditions were found within non-responders (*p* =.214*; RR* = 1.09 [0.94:1.26]) nor responders (*p* =.381*; RR* = 1.04 [0.94:1.17]). However, a trending significant difference between pumping across burst and cash-out conditions was found amongst healthy controls (*p* =.072*; RR* = 1.09 [0.99:1.20]), where controls pump higher on cash-out relative to burst conditions. In turn, this finding may suggest that only control groups differentiate pumping behaviour based on burst or cash conditions.

Table 10
Risk learning on BART at baseline: GLMM estimates

Parameter	Estimate	CI	*p*
Fixed effects			
Intercept (NR) β_0	-1.81	[1.27: 2.25]	<0.001***
Trial β_1	-0.13	[-0.19: -0.06]	<0.001***
Current Balloon Burst β_2	-0.27	[-0.43: -0.10]	<0.001***
Previous Balloon Burst β_3	-0.09	[-0.48: 0.26]	0.218
Red Balloon β_4	0.32	[0.17: 0.44]	<0.001***
Male β_5	0.46	[0.10: 0.82]	0.001**
R β_6	0.01	[-0.46: 0.49]	0.964
HC β_7	0.09	[-0.41: 0.56]	0.620
R*Previous Balloon Burst β_8	0.04	[-0.48: 0.54]	0.650
HC*Previous Balloon Burst β_9	0.00	[-0.42:0.44]	0.997
Random effects			
Intercept variance α_0	0.07		
Error variance σ^2_ε	0.30		

Note. Within MUD group, NR = non-responders and R = responders. HC = healthy controls. Estimate = Regression coefficients. CI = 95% confidence interval. $^+$ p<.10, * p < .05, ** p <.01, *** p <.001.

Risk-taking propensity.

BART analysis 1.6. A one-way ANCOVA model of risk-taking propensity significantly outperformed a null model in absence of any predictors (*LR* = 10.00, *p*=.015*), confirming appropriateness of model. Moreover, the model explained 0.23 of total variance in the model.

Unlike LMMs and GLMM that were utilized to model relatively dynamic features of RDM, an ANCOVA was used to investigate a relatively more stable preference, risk-taking propensity, by assessing pumping behaviour on the BART *on average*. Contrary to the hypothesis, non-responders (*m* = 12.20, *s* =6.80), responders (*m* = 11.25, *sd* =6.00) and controls (*m* = 12.45, *s* = 7.80) did not differ in risk-taking propensity on the BART (*p* = .084, see Table 11). Interestingly, gender was significantly related to risk-taking propensity on baseline BART, where males (*m* =14.30, *sd* =7.45) pumped more on average than females (*m* =8.08, *sd* =3.05, *p* = .002).

Table 11
Risk taking propensity on BART at baseline: ANCOVA estimates

Parameter	Estimate	Df	*p*
Intercept β_0	161.94	1	<0.001***
Groups β_1	0.17	2	0.841
Gender β_2	10.43	1	0.002**

Note. Groups = consists of 3 levels: non-responders, responders and healthy controls. Estimate = F-statistic. df = degrees of freedom. $^{+}$ p<.10, * p < .05, ** p <.01, *** p <.001.

Hypothesis 1b.

Magnitude effect.

IGT analysis 2.1. Contrary to the hypothesis, no significant interaction was established between UPPS-P total score and non-responder, responder and control groups in relation to the IGT magnitude effect at baseline *(F*=0.00 *p* =.994), suggesting that impulsivity does not moderate magnitude effects between specific groups. However, as a main effect, impulsivity was significantly associated with the IGT magnitude effect (*t* =-2.40, *p*=.019*, *r*[CI] = -0.38 [-0.42:-0.35], where higher levels of impulsivity were associated with a tendency to seek-out high gains (i.e. lower score) across groups. However, when impulsivity was entered as a covariate along with non-responder, responder and control groups, the difference in magnitude effect between non-responders and healthy controls no longer trended towards significance (*p* =.168). This could be the result of additional error variability contributed by the inclusion of impulsivity in the model.

Frequency effect.

IGT analysis 2.2. No significant interaction was seen between non-responder, responder and control groups and UPPS total score in relation to the IGT frequency effect at baseline (*F*=0.14 *p* = .864), implying that impulsivity does not moderate group differences in the

frequency effect, and fails to support the hypothesis. Moreover, when investigating the potential main effect of UPPS total score on the frequency effect, it was not found to be associated with the frequency effect (*t* =-0.96, *p*=.339, *r*[CI] = -0.11 [-0.14: -0.09].

Risk-learning.

IGT analysis 2.3. Contrary to the initial hypothesis, impulsivity was found not to moderate differences in learning between groups on the IGT, as found by the lack of a significant interaction effect between groups and UPPS total score *(F* =0.00 *p* =0.999). Moreover, UPPS-P total score was not significantly associated with learning, when incorporated as a main effect (*t* =-1.13, *p*=.262, *r*[CI] = -0.20[-0.24:-0.17]*)*, suggesting that learning on the IGT and impulsivity are likely unrelated.

BART analysis 2.4. There was no significant interaction found *(F* =1.08 *p* =.523) between groups and UPPS-P total score in relation to pumping following burst trial condition on the BART. This finding indicates that impulsivity did not contribute to moderating learning between groups, and thus does not support the original hypothesis. Moreover, when assessing the potential main effect of impulsivity on pumps following previous burst trials, impulsivity did not impact pumping following burst trials (*z* = 0.55, *p*=.579, *RR*[CI] = 1.04 [0.89:1.21]).

Risk-taking propensity.

BART analysis 2.5. No significant interaction was found between groups and UPPS-P total score in relation to risk-taking propensity on the BART at baseline *(F* =0.78 *p* =.466), which indicates that impulsivity does not moderate risk-taking propensity between groups. Moreover, this finding does not provide support for the original hypothesis. Furthermore, no

relationship was established between impulsivity and risk-taking propensity when entered into the model as a main effect (t =0.14, p=.888, r[CI] = 0.00[-0.00:0.01]).

Hypothesis 2.

CM treatment effect analysis 3.1. Of model comparisons (see Appendix D), the selected parsimonious hurdle model *performed* significantly better than a null model in absence of predictors *(LR* = 39.40, p=<.001***), and 0.42 of total variance was explained by the model. Assessing the likelihood of relapsing on CM, the zero-inflated model component highlighted that higher impulsivity significantly predicted greater odds of relapse during CM (p = .035), although the effect size was small (*OR* = 1.10, Table 12). Moreover, average IGT performance was not significantly related to risk of relapse (p -.108, Table 12). On the count hurdle component that modelled the likelihood of increased severity of relapse on CM, a trending significant difference was demonstrated between average IGT performance and likelihood of severe relapse (p =.071, Table 12). Specifically, poorer average IGT performance was associated with a greater likelihood of experiencing severe relapse during CM, although the effect size was small (*OR* = 1.80). Additionally, a greater number of methamphetamine-positive tests at baseline was significantly predictive of greater odds of severe relapse (p = .005), with a small effect size (OR = 1.30, Table 12).

Table 12

Hurdle prediction model of CM treatment effect

	MUD participants (*n*= 24[a])		
Contrasts	*z*	*P*	*OR* [CI]
Relapse occurrence (zero-hurdle)			
Intercept	-15.00	.024*	0.00 [0.00:0.13]
H-IGT	2.50	.108	12.00 [0.57:262.51]
IMP	0.11	.035*	1.10 [1.00:1.25]
Baseline MA pos tests	0.16	.697	1.20 [0.51:2.74]
Relapse severity (count-hurdle)			
Intercept	3.36	.008**	2.90 [2.40:351.95]
H-IGT	0.56	.071^{+}	1.80 [0.95:3.22]
HI	-0.01	.157	0.98 [0.96: 1.01]
Baseline MA pos tests	0.26	.005**	1.30 [1.10:1.57]

Note. H-IGT = poor average performers on IGT; where a median split of total IGT score was used to generate a binary categorization, with low scores reflecting poorer average performance (*n*=14) and high scores reflecting better average performance *n*=11). IMP = Vulnerability to impulsive behaviour as measured by UPPS-P total score, where higher values reflect higher vulnerability. Baseline MA pos tests = number of methamphetamine-positive urine samples during the 2-week baseline period prior to CM treatment. *Odds* refers to the odds ratio. *g* refers to hedges g effect size. *CI* refers to odds ratio confidence interval.

[a] One major outlier removed from analysis (i.e. 1 MUD participant)

+ p<.10, * p <.05, ** p <.01, *** p <.001.

CHAPTER FIVE: DISCUSSION

The current study was defined by three primary aims. The first of these aims was to investigate baseline differences in RDM between non-responders, responders and healthy controls, as characterized by several RDM features, including magnitude effects, frequency effects, learning and risk-taking propensity. The results showed that non-responders were more likely to favour short-term outcomes of a larger reward associated with long-term losses than healthy controls (at trend-level significance but with a large effect size), but did not exhibit a greater ability to withstand larger short-term losses. Moreover, responders displayed a greater tendency to seek-out frequent gains and avoid frequent losses relative to non-responders (at trend-level significance but with a medium effect size). In addition, non-responders demonstrated compromised learning relative to healthy controls (at trend-level with medium effect size), but only on the IGT. In contrast, groups neither differed in learning nor risk-taking propensity on the BART.

The second aim of the study was to assess whether impulsivity exacerbated group differences in RDM, for which no moderation effects were found. However, higher impulsivity across groups was exclusively related to a tendency to seek-out large rewards despite long-term negative consequences.

The third aim involved assessing whether RDM predicted poor CM treatment outcomes. Here, higher impulsivity was found to significantly increase the likelihood of relapse occurring (small effect size), whilst poorer overall performance on the IGT significantly increased the likelihood of a *major* relapse during CM treatment (small effect size).

RDM Features

Reward and loss magnitude. On the IGT at baseline, non-responders exhibited a greater tendency to favour large short-term rewards than healthy controls, although findings were at trend-level significance. A tendency to favour large short-term rewards, specifically on the IGT, is also associated with poor performance on the task, as larger short-term rewards are tied to long-term losses. Given that the IGT is widely regarded as a measure of adaptive decision-making in the context of risk-taking (Bechara et al., 1994), a pattern of decision-making that reflects a preference for large short-term rewards is suggestive of greater RDM amongst non-responders relative to healthy controls. In addition, it also suggests that *reward magnitude* is a major driver in decision-making, as it is a characteristic of the potential outcome. These findings were consistent with several studies that have investigated IGT performance differences between methamphetamine-using and healthy controls, in which MUD participants were found to exhibit relatively poorer performance (Gonzalez et al., 2007; van der Plas et al., 2010).

In contrast, non-responders did not *concurrently* demonstrate a greater ability to withstand large short-term losses in pursuit of large short-term rewards than healthy controls, which suggests that RDM by non-responders may be predominantly characterized by a pervasive pursuit of reward, rather than a diminished aversion to losses. This is supported by Ahn et al. (2014), who found that decision-making deficits of amphetamine users on the IGT were better characterized by a sensitivity to rewards relative to healthy controls. Conversely, Vassileva et al. (2013) found that a heterogeneous group of substance users demonstrated a tendency to withstand losses in pursuit of gains. However, these results were specific to *female* crack cocaine and heroin users, who may differ from both MUD participants and a mixed-sex sample. Evidence of the ability to withstand losses amongst substance users was also supported by

Strickland, Beckmann, Rush and Stoops (2017), who found that cocaine users exhibited diminished loss sensitivity relative to normative loss aversion coefficients represented from non-clinical populations. Importantly, contrasting findings presented in the aforementioned studies may be the result of alternative analytical methods, including the use of computational methods of reinforcement learning models (Vassileva et al., 2013), in addition to use of differing risk-taking tasks such as the mixed gambles task (Strickland et al., 2017).

However, determining the separable influence of reward and loss outcomes on decision-making is partially weakened by the inherent complexity of the IGT, reflected in the simultaneous display of reward and loss outcomes associated with each deck selected/decision made. Moreover, the impact of short-term reward on decision-making can be fairly easily observed, given that the reward magnitude presented within each deck is *fixed*, only varying across different decks. On the other hand, loss outcomes can vary in their presentation both *within* and *across* each deck, fluctuating in frequency of occurrence and at times varying in magnitude depending on the deck in use. As a result, loss outcomes in RDM are only assessed within large short-term reward conditions in order to isolate the impact of large loss from large reward. In turn, such differences call for non-equivalent analytical methods for assessing impact of reward versus loss outcomes on RDM, and suggest some caution in interpretations of the impact of loss outcomes on RDM.

IGT performance is influenced by *short-term* outcomes, but it is also confounded by *long-term* associated outcomes. Poor performance on the IGT can result from both a fixation on short-term rewards or a general insensitivity to future consequences (Bechara et al., 2002). However, using a variant of the IGT task that inverted reward and punishment schedules, Bechara et al. (2002) confirmed that performance by substance users on the IGT was only

impaired when large, long-term losses were tied to large short-term gains. This finding highlights that substance users are unlikely to be merely insensitive to *all* types of future consequences, but rather fail to account for negative future consequences specifically in the context of large short-term gains. This supports the interpretation of impaired performance demonstrated by non-responders as a reflection of RDM in the form of a tendency to select large short-term rewards.

On the other hand, responders did not differ from healthy controls in their preference for large short-term rewards, and because of this, difference in the ability to withstand large short-term losses was also not confirmed. The absence of a group difference could suggest that responders have relatively intact decision-making, given that healthy control samples typically demonstrate advantageous decision-making on the IGT (Bechara et al., 1994; Grant et al., 2000). However, the direction of differences (qualitatively speaking) aligned with the hypothesized direction, namely that responders exhibited a marginally poorer performance relative to healthy controls, which could suggest that group differences exist but are not picked up due to an underpowered sample size. Interpretation of findings is limited due to the fact that no study, to the best of my knowledge, has assessed IGT performance differences between treatment responders against a healthy comparison group.

In addition, responders did not differ from non-responders in their preference for large short-term rewards, whilst differences in the ability to withstand losses could not be confirmed. Despite this, non-responders displayed the greatest preference for large short-term rewards out of the 3 groups, and the direction of group differences between all three groups were as proposed, with non-responders performing most poorly, followed by responders and healthy controls. The lack of major group differences may suggest that non-responders do not differ from responders in decision-making as influenced by the magnitude of reward and loss outcomes, but also that

real differences are left undetected in a relatively small sample study. Preliminary research provides support for the latter interpretation: in a relatively larger sample study consisting of 75 cocaine users, Schmitz et al. (2009) found that abstinent cocaine users demonstrated better performance on the IGT at baseline relative to non-abstinent cocaine-users. In addition, several studies have found a subgroup of substance-users that fail to exhibit decision-making impairments on the IGT (Bechara & Damasio, 2002; Verdejo-Garcia et al., 2014; Verdejo-Garcia, Bechara, Recknor & Perez-Garcia, 2006), and it may be possible that individuals who respond to treatment might also fall into this subgroup. Furthermore, the tendency to pursue large short-term rewards despite long-term losses amongst non-responders in particular may be explained by mechanisms illustrated by premorbid and substance dependency theories, namely through reward and loss sensitivity.

Reward and loss sensitivity. A pervasive preference for large short-term rewards and ability to withstand large losses within substance-using populations has been argued to partially result from underlying deficits in sensitivity to both reward and loss respectively, which emerge as both a premorbid vulnerability and consequence of chronic substance use (Verdejo-Garcia, Perez-Garcia et al., 2006). However, findings from the present study suggest that MUD populations are impacted by a heightened sensitivity to reward rather than a diminished reactivity to losses. This result was further supported by Ahn et al. (2014), using an amphetamine-using sample. Within the same study, a heightened reward sensitivity was proposed to be substance-specific, given that opiate users demonstrated a diminished loss sensitivity relative to healthy controls (Ahn et al., 2014). On the other hand, using both the original and variant IGT task, Bechara et al. (2002) determined that two-thirds of a heterogenous alcohol, cocaine and methamphetamine sample performed more poorly on the original IGT as a

result of increased sensitivity to large rewards, which suggests that deficits in reward sensitivity may be a major component across *all* substance types. However, it is possible that different substance-types drive different effects within Bechara et al. (2002) study, considering that the study did not account for the possibility of varying decision-making deficits by substance-type. It is also possible that all chronic users demonstrate reward sensitivity despite substance type, but vary in loss reactivity.

In the present study, given that non-responders exhibited RDM that was in part characterized by a pervasive drive for large short-term rewards, heightened reward sensitivity is suggested. This is argued to emerge from both concurrent neurobiological reward-cue sensitization and reward desensitization. In relation to reward-cue sensitization, the incentive-sensitization theory represents the "wanting" component of deficient reward processing, and asserts increased sensitization to drug-cues with prolonged substance use (Robinson, Fischer, Ahuja, Lesser & Maniates, 2015). In this way, IGT outcomes associated with large short-term rewards may act as drug-cues that bias future decision-making towards decks that are typically associated with these outcomes, particularly amongst non-responders. These outcomes can be regarded as drug-cues given that they reflect monetary rewards, which represent a means by which drugs can be obtained (Sweitzer et al., 2016). Although outcomes on the IGT still only reflect hypothetical monetary rewards, performance on the task is additionally validated by the promise of a monetary reward tied to good performance on the IGT above a minimum threshold.

A heightened reward sensitivity may also be the result of reward desensitization mechanisms described by the opponent process theory. The "b-process" of opponent process theory explains why *large* rewards are preferred over *small* rewards. Neurobiological desensitization described by the "b-process" is associated with a diminishing hedonic state as a

consequence of prolonged drug use, which can extend to *drug-related* rewards. In order to combat this, increasingly large rewards are sought after in order to maintain or heighten hedonic experience, which act as a form of positive reinforcement. Additionally, the "a-process" of the opponent process theory may also partly explain why a diminishing hedonic effect is exhibited for drug and drug-related rewards. This process asserts that neurophysiological processes associated with maintaining homeostasis are disrupted with chronic use, and generate unregulated aversive phenomenological states typically referred to as withdrawal states in Substance Use Disorder. The "b-process" theory posits that presence of such an unregulated, aversive state may drive one to pursue the use of a substance in order to suppress this state, acting as a form of negative reinforcement. This theory can arguably be extended to include drug-related cues, such as monetary rewards. Given that non-responders demonstrated a more pervasive drive towards large short-term rewards relative to healthy controls and responders (qualitatively speaking), it might be suggested that non-responders present with the greatest neurobiological deficiencies regarding reward processing and sensitivity.

As previously outlined, diminished loss sensitivity has also been proposed to partly underlie RDM amongst substance-using populations, and has been reported in substance-using samples (Strickland et al., 2017; Gowin, Stewart et al., 2013). In fact, like heightened reward sensitivity, a diminished loss sensitivity may also partly emerge from the "b-process" of opponent process theory. The unregulated, aversive state generated by chronic substance use and described by the "b-process" theory may actually allow one to better withstand additional harm or loss, given that marginal losses are experienced as less aversive on top of an existing aversive state. This pervasive, aversive state is thought to translate into RDM by extending diminishing sensitivity from drug-loss to drug-related loss. Contrary to current theory on Substance Use

Disorder and RDM, no major group differences were found in the ability to withstand large short-term losses in the current study. This finding may be explained by less apparent physiological withdrawal symptoms amongst stimulant users relative to non-stimulant users, especially opiate users (Lago & Kosten, 1994). This could suggest that stimulant-specific associated neurobiological alterations have less of an impact on withdrawal states, thus minimizing disruption of loss processing functions. However, MUD individuals typically exhibit dysregulation in the form of aversive *affective* symptoms (Zorick et al., 2010), which could suggest that diminished loss aversion may exclusively impact emotional dysregulation over RDM. In contrast, healthy populations demonstrate a greater aversion to losses than do individuals with Substance Use Disorder, and are typically more sensitive to losses than rewards of the same size (Strickland et al., 2017; Tversky & Kahneman, 1992).

Loss sensitivity in healthy populations. Differences in decision-making between non-responders, responders and controls are potentially confounded by the influence of loss aversion in biasing decision-making amongst healthy individuals. It was originally presumed that healthy individuals would demonstrate adaptive decision-making by shifting over time to decks associated with higher long-term rewards on the IGT (Bechara et al., 1994). There is evidence to suggest that loss aversion may also drive performance on the IGT amongst healthy samples. Weller, Levin and Bechara (2010) found that healthy individuals subjectively outweighed short-term losses over gains on the IGT. Evidence of loss aversion amongst healthy individuals may disrupt good performance on the IGT, and in turn may partly explain the considerable variability in performance on the IGT demonstrated within healthy samples (Horstmann et al., 2012; Bull et al., 2015). Besides the influence of the magnitude of outcomes, the frequency at which those outcomes occur has also been shown to influence decision-making.

Healthy and clinical populations have been shown to be influenced by more than just the magnitude of outcomes: the frequency of such outcomes is also relevant. In terms of healthy samples, Horstmann et al. (2012) demonstrated that decision-making in healthy individuals on the IGT was more influenced by the frequency of short-term rewards than the long-term net value. Individuals exhibited a greater tendency to opt for frequent rewards despite long-term consequences, and this was supported by findings from Chiu et al. (2008). In the context of clinical samples, Brown et al. (2015) demonstrated that amongst schizophrenic patients, decision-making on the IGT was influenced by outcome frequency, where schizophrenics were found to avoid decks with frequent punishment similarly to controls. Considering the widespread influence of effects of frequency in various populations, this may suggest that substance-using populations are also influenced by the frequency at which outcomes occur, although to the best of my knowledge no previous study has investigated frequency effects in a MUD sample.

Reward and loss frequency. A major group difference in the effect of frequency was demonstrated between non-responders and responders on the IGT, albeit with trend-level significance but with a medium effect size. Responders demonstrated a greater tendency to favour frequent rewards and avoid frequent losses relative to non-responders, suggesting that responders are differentially influenced by outcome frequency than non-responders. This finding stood in contrast to the hypothesized direction, which proposed that non-responders would be relatively more inclined towards favoring frequent rewards and avoiding frequent losses than responders. The unexpected direction of group differences may be explained by the fact that frequency effects can be considered a “moderate” feature of RDM in the context of IGT performance. To be more specific, whilst seeking frequent gains and avoiding frequent punishment appears to be superior to a pattern of seeking-out large immediate rewards in spite of

long-term losses, this particular style of decision-making is not entirely optimal on the IGT, where short-terms losses and rewards need to be considered in relation to how they relate to *long-term* rewards. In particular, achieving long-term gains on the IGT was not best acquired by using a decision-making strategy that favoured the frequency of outcomes. In turn, a greater inclination towards frequent rewards and an avoidance of frequent losses may suggest that responders are less impaired in RDM than non-responders, although the groups did not significantly differ in the magnitude effect, so this idea cannot be confirmed.

The effect of frequency demonstrated by responders may suggest that responders are sensitized to reward, like non-responders, but tend to favour the increased occurrence of reward rather than *large* rewards. However, given that pairs of decks on the IGT vary only by two combinations, with either frequent gains *and* infrequent losses or infrequent gains *and* frequent losses, one cannot assess how reward and loss frequency individually contribute to performance by responders in the current study. As a result, it is not clear to what extent decision-making by responders may be driven by reward over loss frequency.

Furthermore, a lack of group differences in effects of frequency between healthy controls and non-responders as well as responders might confirm an absence of differences in MUD participants and healthy controls with regards to effects of frequency. However, this explanation appears to be unlikely given a medium effect size between responders and healthy controls, and is especially true when comparing non-responders to healthy controls, where a large effect size was illustrated. In the latter case and in contrast to the initial hypothesis, healthy controls favoured frequent rewards and avoided frequent losses more often than non-responders. This is supported by the Deck B phenomenon. First proposed by Lin, Song, Lin and Chiu (2012), the Deck B phenomenon describes a notable preference for the disadvantageous deck B over other

decks on IGT within healthy samples, which is inconsistent with task assumptions that healthy individuals will avoid selecting disadvantageous decks. The authors argue that this phenomenon is due to the influence of highly frequent rewards and infrequent losses associated with this particular deck, which differs from deck A, another disadvantageous deck that healthy controls tend to successfully avoid. Evidence for the Deck B phenomenon suggests that a real group difference may exist between non-responders and healthy controls, but this may not be detected within the current study as a result of a relatively small sample size.

Unlike effects of magnitude in decision-making, which have clear ties to deficits in reward and loss sensitivity, it is not entirely clear which neurobiological mechanisms may underlie preference for effects of frequency, especially amongst Substance Use Disorder populations. One possibility is that responders are sensitized to drug and drug-related cues, but are less impacted than non-responders with regards to the severity of neurobiological desensitization to reward size, which may drive one to seek-out *larger* rewards in spite of long-term losses. Moreover, whilst RDM is represented by a tendency to select certain decks based on the magnitude or frequency of associated outcomes, it is also exacerbated by a compromised ability to shift from disadvantageous to advantageous decks over time, otherwise referred to as risk learning.

Learning. A trend-level, medium effect size difference in learning was demonstrated between non-responders and healthy controls on the IGT at baseline, where non-responders exhibited markedly poorer learning. In other words, findings indicate that healthy controls were better able than non-responders to avoid selecting disadvantageous decks associated with long-term loss, and were more likely to opt for advantageous decks tied with greater long-term gains. These findings are partly consistent with those reported by Verdejo-Garcia et al. (2007), who

found that healthy controls exhibited greater learning on the IGT than substance users. Their study included cocaine and marijuana users, rather than MUD participants, which may suggest that impairments in learning are present across all substance types. Interestingly though, cocaine users demonstrated relatively more compromised learning than marijuana users, which might suggest that learning is more severely impacted within stimulant use more broadly-speaking, including methamphetamine.

Additionally, when assessing the rate of learning within-groups, a significant improvement in scores across initial block trials was exclusively demonstrated amongst healthy controls on the IGT. Such findings provide further evidence of intact learning capabilities amongst healthy controls in particular. Moreover, whilst limited improvement in performance over time within non-responder and responder groups may confirm compromised learning, it may more specifically suggest deficits in *delayed* learning. In line with this, Verdejo-Garcia et al. (2007) found that cocaine users exhibited steeper learning on the second administration of the IGT relative to the first, which contrasted with healthy controls who demonstrated steeper learning at first administration, suggesting that learning amongst cocaine users was present but *delayed*. In the same study, marijuana users also demonstrated greater learning on the IGT at first administration, which may suggest substance-specific effects on learning.

Moreover, although responders and non-responders did not significantly differ in learning on the IGT at baseline, a large effect size was obtained between groups, which suggests that a group difference in learning may exist. Specifically, my findings insinuate that responders exhibit less compromised learning relative to non-responders. One possibility for a lack of significant findings may be an insufficient number of trials to detect maximum learning capabilities, as suggested by Overman and Pierce (2013), who found that the addition of trials

greater than the standard 100 (as utilized in the current study) is associated with enhanced performance.

Responders did not significantly differ from healthy controls in learning on the IGT at baseline, and the effect size was marginal, suggesting that responders might exhibit similar learning capabilities to healthy controls. This interpretation is consistent with a graphical representation: responders and controls exhibited similar learning curves over the duration of the IGT (Figure 5). In support of group differences in learning between both responder and healthy control groups relative to non-responders, non-responders appear markedly different from other groups, exhibiting relatively stagnated performance, displayed by a flat learning curve.

No significant differences in learning were established between non-responders, responders and healthy controls on the BART at baseline. A lack of group differences lies in contrast to a difference in learning found between non-responders and healthy controls on the IGT. This is contrary to strong evidence of learning deficits on the BART in substance-using populations, including methamphetamine, relative to healthy populations (Kohno et al., 2014). Ashenhurst et al. (2014) argue that differences in learning between tasks may be due to differences in the tasks themselves, which affect how optimal decision-making is characterized. For example, whilst conservative risk-taking (or minimal risk-taking) is always an optimal decision-making strategy on the IGT, on the BART it can lead to poor performance through marginal accumulated gains, which can alternatively result from excessive risk-taking. Given that performance on the BART has been robustly associated with real-world risk-taking behaviour (Lejuez et al., 2002), the BART might capture the broader conceptualization of RDM, where RDM may refer to actions taken that increase the likelihood of negative consequences or the failure to take an action that would likely reap benefits.

Recent studies have suggested that substance-using individuals demonstrate compromised learning on the BART relative to healthy groups, by failing to learn to take optimal risks. In a smoking sample, Dean et al. (2011) found that smokers decreased pumps on high-risk balloons over time, whilst non-smokers' pumping remained stable. Moreover, non-smokers conversely increased pumps on low-risk balloons over trials, whilst smokers' pumping remained stable. Therefore, non-smokers obtained a higher net pay-out on the task, suggesting that they demonstrate greater adaptive decision-making than smokers, by learning to better maximize task pay-outs. Using a similar trial-by-trial learning model, Ashenhurst et al. (2014) found that alcohol severity moderated pumps following a large burst trial, where individuals with severe alcohol problems took markedly lower risk than those with less severe alcohol problems. Findings were similar within MUD samples, and Kohno et al. (2014) found that MUD participants pumped less often and earned less than controls, although the former was not significant.

However, preliminary research on learning differences between substance-using and healthy samples on the BART does not explain why a lack of significant group differences were obtained in the present study. One possibility is that learning deficits do not differ between non-responders and responders, although this would not explain why healthy controls also do not differ. Alternatively, and more likely, the task has high learning demands for all participants. Because a considerable amount of MUD participants and matched-controls had education lower than tertiary-level, the learning demands of the task may have been too difficult for. This is especially relevant when considering that many of studies from which group differences between substance-users and healthy controls were obtained consisted only of college samples (Dean et al., 2011; Lejuez et al., 2003). Furthermore, Pleskac (2008) found that when learning

requirements were reduced on the BART, this increased the ability to distinguish between substance-using from healthy control groups, relative to an unaltered version of the task.

Deficits in learning may be underpinned by some of the same neurobiological mechanisms underlying reward sensitivity. In fact, striatal, including amygdala activation, have been closely linked to cue-based reinforcement learning (Berridge, 2007; Gowin, Mackey et al., 2013). This suggests that the same substance-induced alterations to the striatum and other reward processing regions that can lead to abnormally heightened sensitivity to reward outcomes may also diminish adaptive learning by promoting compulsive reward-seeking. Additional theories of both affective and cognitive processes that contribute to learning and adaptive decision-making have also been presented in the literature, and were *not* specifically investigated in the current study. This included the somatic marker theory, which asserts that effective decision-making (and learning) involves use of internally-driven emotional and visceral signaling to accurately bias actions towards long-term positive outcomes. Moreover, other theories assert the importance of executive control functions in *goal-directed* learning, which include working memory, cognitive (set) shifting and disinhibition (Schiebener, Zamarian, Delazer & Brand, 2011). Tied to this, a two-part systems theory has been proposed to explain how an under-activated "reflective" brain system interacts with a hyper-activated "impulsive" system to generate impaired decision-making amongst individuals with Substance Use Disorder (Bechara, 2005).

Risk-taking propensity. Contrary to expectations, neither non-responders nor responders differed from healthy controls in risk-taking propensity on the BART at baseline. This finding differs from several studies that have confirmed differences in risk-taking propensity between substance-using and non-substance-using samples (Hopko et al., 2006; Lejuez et al., 2003; Lejuez, Aklin, Bornovalova & Moolchan, 2005). However, more recent studies have found that

both at-risk and substance-using samples demonstrate relatively lower pump averages in comparison to healthy controls (Ashenhurst, Jentsch & Ray, 2011; Campbell, Samartgis & Crowe, 2013), although none of these studies utilized an MUD sample. In addition, Dean et al. (2011) found a marginal difference in average pumps between non-smokers and smokers, where non-smokers pumped higher than smokers on average. Although this difference was not significant, the direction of differences aligned with my study findings, in which healthy controls displayed a higher pump average than either non-responders or responders. This finding could suggest that non-responders, responders and controls do not differ in risk-taking propensity, although it may also be that the BART is not sensitive enough to detect differences. Otherwise, BART may not solely measure risk-taking propensity, as supported by Kohno et al. (2014), who argue that relatively lower pumping may actually reflect a lack of sustained endurance to maximize accumulated pay-out on the BART, or an urgency to acquire immediate rewards.

Impulsivity and RDM

Non-responders exhibited significantly greater impulsivity, followed by responders and then healthy controls, which aligns with robust literature findings on impulsivity as a relevant distinguishing feature of substance-using relative to healthy populations (Verdejo-Garcia et al., 2008).

Despite this, impulsivity did not exacerbate performance between groups on any of the measured RDM features investigated in the study, suggesting that RDM may not be impacted by impulsivity. In a meta-analysis of impulsivity and BART performance in healthy samples, Lauriola, Panno, Levin & Lejuez (2013) found large effect sizes for impulsivity and performance on the BART, but only for adolescent and young adult samples. In contrast, only small effects sizes were obtained for other adult samples, which suggests that impulsivity may play less of a

role in the BART amongst adult populations, and supports my study findings. On the other hand, impulsivity was significantly associated with the short-term reward magnitude across the groups in spite of long-term losses. Given this finding, it was interesting to find that impulsivity did not also exacerbate group differences in effects of magnitude. This result may suggest that whilst impulsivity is related to effects of magnitude, there is some other pertinent factor/s that specifically explains *group* differences. This factor could potentially refer to specific neurocognitive mechanisms underlying RDM. Alternatively, it is also possible that the lack of moderation findings may be because of a lack of power to detect moderation effects in a relatively small sample size.

Moreover, a lack of findings also confirms that RDM is likely to be a separable construct from impulsivity, the two of which are considered to overlap substantially (Upton et al., 2011). Whilst impulsivity has more to do with the speed at which actions are taken or decisions are made, generally with little conscious deliberation, RDM determines how probabilities of action-outcomes are considered. However, RDM can also be *impulsively-driven* with little thought given to outcomes probabilities. The latter case describes typical decision-making by substance-users, and performance on the IGT and BART is frequently described as tasks of "impulsive choice" (Stevens, Goudriaan, Dom, Roeyers & Vanderplasschen, 2015). There is nonetheless strong evidence to suggest that impulsivity and RDM are overlapping but independent constructs, as suggested by findings from Upton et al. (2011), who established that risk-seeking behaviour on the IGT was only evident amongst low and not high impulsivity participants. In addition, impulsivity may impact RDM through its presumed effects on learning, as evidenced on both the IGT and BART using healthy samples, where high impulsivity groups demonstrated relatively poorer learning (Bornovalova et al., 2009; Franken et al., 2008). However, this does

not explain why there was an absence of moderating effects on learning models for both the IGT and BART in the present study.

Furthermore, the absence of a strong relationship between impulsivity and RDM in the current study may be influenced by the multidimensional nature of impulsivity. Whilst in the present study, impulsivity was measured by self-report, it may be that specific aspects of impulsivity are more associated with RDM than others. In line with this, and using the same self-report measure of impulsivity as in the present study, Zermatten, van der Linden, D'Acremont, Jermann and Bechara (2005) found that only one specific dimension of impulsivity, lack of premeditation, was tied to selection of disadvantageous decks on the IGT in a healthy sample. Moreover, impulsivity also exists along behavioural and trait dimensions, which may differentially influence RDM, where the current study focused on trait impulsivity through self-report. Given that the potential impact of different dimensions of impulsivity were not investigated in this study, I could not confirm potential issues of multidimensionality of impulsivity.

Sex as a Covariate of RDM

RDM features have been found to be additionally influenced by sex differences and years of education. Sex was exclusively incorporated as a covariate of RDM for models of frequency effect on the IGT, learning and risk-taking propensity on the BART. Of these models, a trend-level difference in effects of frequency was established between males and females, where females exhibited a greater tendency to favour frequent rewards and avoid frequent punishment, which is supported in the literature (van den Bos et al., 2013). In addition, sex was significantly associated with risk-taking propensity, where males demonstrated a higher pump average than

females. This finding aligns with Hunt, Hopko, Bare, Lejuez & Robinson (2005), who found that amongst a healthy sample, males displayed greater risk-taking propensity.

Predictors of CM Treatment Outcomes

Relapse occurrence. When assessing potential predictors of relapse amongst MUD participants over the 8-week CM treatment period, high impulsivity was predictive of a greater risk of relapse relative to low impulsivity. This finding is consistent with the literature, where a robust relationship has been found between impulsivity and relapse vulnerability within both clinical and preclinical samples (Pattij & De Vries, 2013). Despite this finding, the effect size was small. Considering that a global measure of impulsivity was utilized to define impulsivity in my work, evidence of a small effect size could suggest that specific dimensions of impulsivity are better predictive of relapse risk than others. This is supported by a meta-analysis conducted by Hershberger, Um and Cyders (2017), who found that specific impulsivity dimensions (lack of premeditation and negative urgency) were associated with poorer psychotherapeutic outcomes.

Moreover, whilst overall performance on the IGT at baseline was not significantly predictive of risk of relapse, the effect size was large. Given that the direction of the relationship indicates that poorer IGT performance may be predictive of relapse during CM, it aligns with preliminary research. In particular, amongst a cocaine-using sample, Schmitz et al. (2009) found that abstinent individuals following 12-weeks of a combined behavioural and pharmacotherapeutic intervention demonstrated better performance on the IGT at baseline than non-abstinent participants. In addition, Verdejo-Garcia et al. (2014) established that an insensitivity to future consequences on the IGT predicted relapse amongst cocaine users 3-months following testing. However, in a large sample of both MUD and cocaine-users, Adinoff et al. (2016) found that baseline performance on the IGT did not predict subsequent relapse

during an 8-week 12-step treatment intervention. Comparative interpretations between these studies are unfortunately limited due to differences in the treatment interventions chosen.

Relapse severity. An especially novel finding, MUD participants who performed poorly on the IGT at baseline were significantly more likely to demonstrate prolonged relapse (with small effect size) during the CM treatment period relative to MUD participants who performed better on the IGT. In conjunction with relapse occurrence findings, one could infer that high impulsivity may act more as a risk factor for *initial* relapse, whilst RDM may be directly implicated in *prolonged* relapse, which is indicative of relapse severity and is measured by repeated presentation of methamphetamine-positive urine samples. This provides preliminary evidence for separate mechanisms underlying minor relapse versus major relapse. Interestingly, these findings lie parallel to substance dependence models that distinguish *initiation* from *dependence* processes. Everitt (2014) argues that impulsivity is strongly associated with the initial experimentation of substances, whilst heightened compulsive drug-seeking behaviour emerges largely as a consequence of sustained substance use, and perpetuates continued use. Thus, in turn, impulsivity mechanisms that are involved in initiation of substance use may also be involved in the initiation of relapse, whilst RDM that may in part be worsened by continued use of substances may further exacerbate compulsive-drug seeking following initial relapse.

However, only tentative conclusions can be drawn considering small effect sizes and inconsistent literature findings by Adinoff et al. (2016), who found that better performance on the IGT at baseline predicted a greater number of stimulant use days at 6 months follow-up. However, this inconsistency in findings may likely be due to use of different treatment interventions, where Adinoff et al. (2016) used an 8-week 12-step intervention whilst an 8-week CM was adopted in the current study. Unlike the 12-step programme, relapse is a direct measure

of real-world RDM on the CM, given that relapse (and abstinence) are contingent on foregone (and awarded) vouchers as a direct consequence of behaviour. In addition, a greater number of methamphetamine-positive tests at baseline were also significantly predictive of a greater likelihood of prolonged relapse during CM, in line with previous findings by Ehrman et al. (2001)

Study strengths and limitations

The current study had several strengths. In particular, MUD participants were primary users, with the exception of several individuals who were secondary users of methaqualone (mandrax) and/or cannabis usage. To ensure that MUD participants were current users, recent methamphetamine usage was verified within a 2-week baseline period before beginning CM treatment. This partially eliminated potential confounding effects of length of abstinence on gambling task performance. In support, Wang et al. (2013) found that MUD participants with longer abstinence periods displayed better performance on the IGT relative to individuals with shorter abstinence periods. Moreover, all MUD participants demonstrated verifiable abstinence on the day of gambling task baseline assessment, which eliminated any potential acute effects of substance use on performance.

There are also several limitations in this study. The sample size was relatively small, but this pilot study intervention framework of a clinical population has provided sufficient data to propose a hypothesis and to calculate samples sizes for more robustly powered work. The absence of moderation effects of impulsivity on RDM could not be verified due to this small sample size. Groups were not perfectly matched against all potentially relevant sociodemographic, individual and substance-related factors that may covary with performance, and not all models incorporated covariates. However, steps were taken to increase the precision

of model estimates with use of LME models, which account for potential confounding effects of individual differences in performance. Furthermore, groups were not examined on executive functioning capabilities, which has been strongly tied to performance on IGT (Gonzalez et al., 2007; van der Plas et al., 2010). As such, group differences in performance may partly be explained by executive functioning differences. However, a review by Toplak, Sorge, Benoit, West and Stanovich (2010) found that performance on the IGT was weakly related to various cognitive capabilities. Finally, a flat rate monetary incentive was used for task performance, instead of a performance-sensitive monetary incentive, due to logistical limitations of obtaining customized monetary vouchers. However, this flat rate was consistently applied across non-responder, responder and controls groups, suggesting equal influence on performance across groups.

CHAPTER SIX: CONCLUSION

In summary, my findings highlight individual differences in RDM within MUD populations, where RDM by responders was particularly influenced by the *frequency* with which outcomes occurred relative to non-responders. Relative to healthy controls, non-responders tended to favour the short-term *magnitude* of rewarding outcomes in spite of their long-term negative consequences, and were less capable of learning to adopt adaptive decision-making strategies. Higher impulsivity did not exacerbate RDM between groups, but it did predict poorer CM treatment success, in conjunction with RDM. In turn, my findings suggest that poorer treatment success on CM amongst MUD participants may, in part, be explained by RDM. Although larger powered studies would be required to confirm findings, results do suggest that MUD individuals at high risk of poor treatment success on CM, may be able to be identified *prior* to commencing CM treatment. Future studies should further investigate which factors predominantly drive RDM, and which of these underlying factors is most pertinent to treatment outcomes.

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Appendix A

Table 13
Correlations between RDM features and sociodemographic, individual and substance-related factors

	IGT Magnitude effect	IGT Frequency Effect	IGT Learning	BART Learning	BART Risk-taking propensity
Age	0.09	0.02	-0.08	0.13	0.14
WASI IQ	0.27	0.20	0.14	0.11	0.18
Household Income	0.11	-0.11	0.24	-0.17	-0.08
IMP	-0.35*	-0.15	-0.40**	0.10	0.06
Gender (M: F)	-0.02	-0.30**	0.05	0.37*	-0.45**
Race (B:C)	0.05	-0.07	-0.02	-0.02	-0.13
Education (7-10: 11-12: 13+)	0.10	-0.02	0.19	-0.13	-0.20
Employment (Y: N)	-0.08	-0.01	-0.13	-0.05	0.08
MA Hx	0.08	-0.15	-0.17	-0.03	-0.02
Baseline MA pos tests	0.16	0.24	0.07	-0.24	-0.21
Outpatient tx (Y: N)	0.12	-0.09	0.20	-0.06	-0.13
Secondary substance (M&C: N)	0.38	-0.10	0.06	0.05	0.07

Note. Correlations estimated using Pearson's r. WASI IQ = aggregate score derived from both verbal and performance subsets of the Weschler-abbreviated scale of intelligence test. Education = separated by 3 subcategories; namely, 7-10 years, 11-12 years and 13+ years education. [a] = missing data. Household income = yearly South African rand-value household income variable derived from an ordinal 5 income category variable, where average income was extracted from the income range reflected within an income category. Impulsivity = total score on UPPS-P measure of vulnerability to impulsivity (where higher scores represent higher vulnerability). Race = defines two racial/ethnic groups; namely black (B) and coloured (C) populations. MA Hx = methamphetamine history, measured in years. Baseline MA pos tests = number of methamphetamine-positive urine samples during the 2-week baseline period prior to CM treatment. Outpatient tx = whether MUD participants underwent concurrent outpatient treatment with CM. Secondary substance = secondary use of methaqualone and/or cannabis relative to pure methamphetamine use.
+ p <.10, * p <.05, * p< .01, ***p<.001

Gender was significantly correlated with several RDM features at baseline (Table 13), namely: the frequency effect on the IGT, as well as learning and risk-taking propensity on the BART. This suggests that gender is likely a relevant covariate of these specific RDM features. Impulsivity was also significantly associated with magnitude effect and learning on the IGT, but rather than used as a model covariate, was investigated as a potential moderator of group differences in RDM features under hypothesis 1b.

Appendix B

Table 14
Model comparisons for Hypotheses 1a and 1b

Model	AIC		
	Final model	Fixed-effects only model	Random-effects only model
(1) IGT Magnitude effect	1207	1249	1209
(2) IGT Frequency effect	1119	1157	1122
(3) IGT Risk learning	1479	1538	1484
(4) BART Risk learning	10454	10759	11298
(5) BART Risk-taking propensity	293	--	297*
(5) IGT Magnitude effect & UPPS	1212	1253	1209
(6) IGT Frequency effect & UPPS	1124	1161	1122
(7) IGT Risk learning & UPPS	1489	1547	1484
(8) BART Risk learning & UPPS	10453	11111	11298
(9) BART Risk-taking propensity & UPPS	285	--	301*

Note. AIC = Akaike Information Criterion. * = In the case of ANCOVA models (i.e. non LMM/GLMM models.), final model is compared to an intercept-only model

Table 14 displays the Akaike Information Criterion for final models as well as their associated model comparisons, which include fixed-effect only and random-effect only models. In the case of BART risk-taking propensity models, the final model is compared to an intercept-only model.

Appendix C

Table 15
Between-block learning on IGT at baseline

		T	*P*	*G*	*g[*CI*]*
NR					
	B2-B1	-0.72	.949	-0.22	[-0.94:0.61]
	B3-B1	0.31	.997	0.10	[-0.52:0.89]
	B4-B1	-1.16	.771	-0.53	[-1.25:0.13]
	B5-B1	-0.32	.990	-0.12	[-0.86:0.66]
	B3-B2	0.97	.860	0.37	[-0.43:0.73]
	B4-B2	-0.60	.970	-0.36	[-1.15:0.42]
	B5-B2	0.25	.999	0.09	[-0.59:0.84]
	B4-B3	-1.62	.486	-1.01	[-1.61: -0.53]
	B5-B3	-0.73	.947	-0.52	[-1.47:0.14]
	B5-B4	1.22	.737	0.55	[-0.09:1.14]
R					
	B2-B1	1.52	.547	0.32	[-0.13:0.68]
	B3-B1	2.52	.090^{+}	0.57	[0.10:0.98]
	B4-B1	1.90	.318	0.41	[-0.08:0.86]
	B5-B1	2.37	.127	0.64	[0.22:1.03]
	B3-B2	1.24	.725	0.21	[-0.25:0.63]
	B4-B2	0.71	.952	0.12	[-0.36:0.66]
	B5-B2	1.69	.438	0.32	[-0.27:0.89]
	B4-B3	-0.47	.989	-0.07	[-0.53:0.41]
	B5-B3	0.41	.993	0.07	[-0.47:0.50]
	B5-B4	1.21	.743	0.30	[-0.20:0.70]
HC					
	B2-B1	2.63	.068^{+}	0.61	[0.24:0.96]
	B3-B1	2.92	.031*	0.62	[0.18:0.94]
	B4-B1	3.10	.018*	0.63	[0.16:0.93]
	B5-B1	2.64	.067^{+}	0.48	[0.00:0.79]
	B3-B2	0.67	.960	0.20	[-0.29:0.69]
	B4-B2	1.04	.833	0.28	[0.17:0.82]
	B5-B2	1.03	.840	0.25	[-0.22:0.64]
	B4-B3	0.44	.991	0.19	[-0.25:0.62]
	B5-B3	0.33	.997	0.07	[-0.44:0.47]
	B5-B4	-0.15	.999	-0.02	[-0.50:0.42]

Note. Within MUD group, NR = non-responders and R = responders. HC = Healthy controls. B1 = block 1. B2= block 2. B3 = block 3. B4 = block 4. B5= block 5. *g* = hedges g effect size. CI = 95% confidence interval. Tukey's p-adjustment used to correct for group contrasts.
$^{+}$ $p<.10$, * $p<.05$, ** $p<.01$, *** $p<.001$.

Healthy controls exclusively demonstrated significantly improved performance on the IGT at baseline from block 1 to 3, in addition to block 1 to 4 (Table 15). Healthy controls also demonstrated a tending significant improvement from block 1 to block 2, as well as from block 1

to block 5. Moreover, responders exhibited a trending significant improvement from block 1 to block 3, whilst non-responders showed no improvement across blocks.

Appendix D

Table 16
Model comparisons for CM treatment effect

	MUD participants (*n*= 24[a])
Model	AIC
(1) H-IGT	90
(2) H-IGT+IMP	80
(3) H-IGT+ Baseline MA pos tests	84
(4) H-IGT+IMP+ Baseline MA pos tests	76*
(5) H-BART	92
(5) H-BART+IMP	83
(6) H-BART+ Baseline MA pos tests	87
(7) H-BART+ IMP+ Baseline MA pos tests	82
(8) H-IGT+H-BART	92
(9) H-IGT+H-BART+IMP	84
(10) H-IGT+H-BART+ Baseline MA pos tests	87
(11) H-IGT+H-BART+IMP+ Baseline MA pos tests	79
(12) IMP+ Baseline MA pos tests	79
(13) IMP	80
(14) Baseline MA pos tests	84

Note. AIC = Akaike Information Criterion. H-IGT = poor average performers on IGT; where a median split of total IGT score was used to generate a binary categorization, with low scores reflecting poorer average performance (*n*=14) and high scores reflecting better average performance *n*=11). IMP = Vulnerability to impulsive behaviour as measured by UPPS-P total score, where higher values reflect higher vulnerability. Baseline MA pos tests = number of methamphetamine-positive urine samples during the 2-week baseline period prior to CM treatment.

[a] One major outlier removed from analysis (i.e. 1 MUD participant)

* = Final selected model.

Model 4 was selected as the final model, given that it was associated with the lowest AIC, which suggests its parsimony over all other possible models (Table 16).