Intolerance of Uncertainty and Impulsivity in Opioid Dependency

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Statement of Authentication

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

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List of Abbreviations

AUC	Area under the curve
BAS/BIS	Behavioral Activation/Behavioral Inhibition Scales
BIS	The Barratt Impulsivity Scale
DAST	Drug Abuse Screening Test
DSM-V	Diagnostic and Statistical Manual
DD	Delay discounting
EIQ	Eysenck Impulsivity Questionnaire
GAD	Generalised anxiety disorder
IU	Intolerance of uncertainty
IUS	The Intolerance of Uncertainty Scale
OFC	Orbitofrontal cortex
PD	Probability discounting
mPFC	Medial prefrontal cortex
PFC	Prefrontal cortex
SSS	Zuckerman Sensation-Seeking Scale
STAI	State Trait Anxiety Inventory
SUD	Substance abuse disorder
TPQ	Tridimensional Personality Questionnaire

Abstract

Opioid abuse has reached epidemic status in the United States, and opioids are the leading cause of drug-related deaths in Australia and worldwide. One factor that has not received attention in the addiction literature is intolerance of uncertainty (IU). IU is personality trait characterised by exaggerated negative beliefs about uncertainty and its consequences. This thesis investigates the links between IU and impulsive decision-making in the context of opioid-dependency. Four experimental studies examined impulsive decision-making from multiple perspectives, and assessed for the first time how impulsivity interacts with IU in opioid-dependent individuals. Across all four studies, opioid-dependent adults reported markedly higher levels of IU compared to a healthy control group. This consistent result provides strong evidence that IU is a personality trait that is related to drug addiction, whether it may be a pre-morbid risk factor, a result of chronic drug use or a co-occurring phenomenon based on shared neural correlates. A common thread between studies was that IU and impulsivity were meaningfully related in opioid-dependent individuals, but not in control groups. Specifically, IU was correlated with self-reported impulsive personality traits, poor attentional control, risk taking for monetary losses and risk-aversion for health improvements. No meaningful correlations were found between IU and impulsivity in control participants. These findings have important implications for addiction prevention and therapy. It is commonly accepted that pharmaceutical opioids are a driving factor for the upsurge in heroin abuse, and IU may be helpful to screen for at-risk individuals. Furthermore, addiction

treatment could benefit by addressing IU in order to improve faulty beliefs about and reactions to uncertainty.

Chapter 1: Introduction

1.1 Opioid addiction

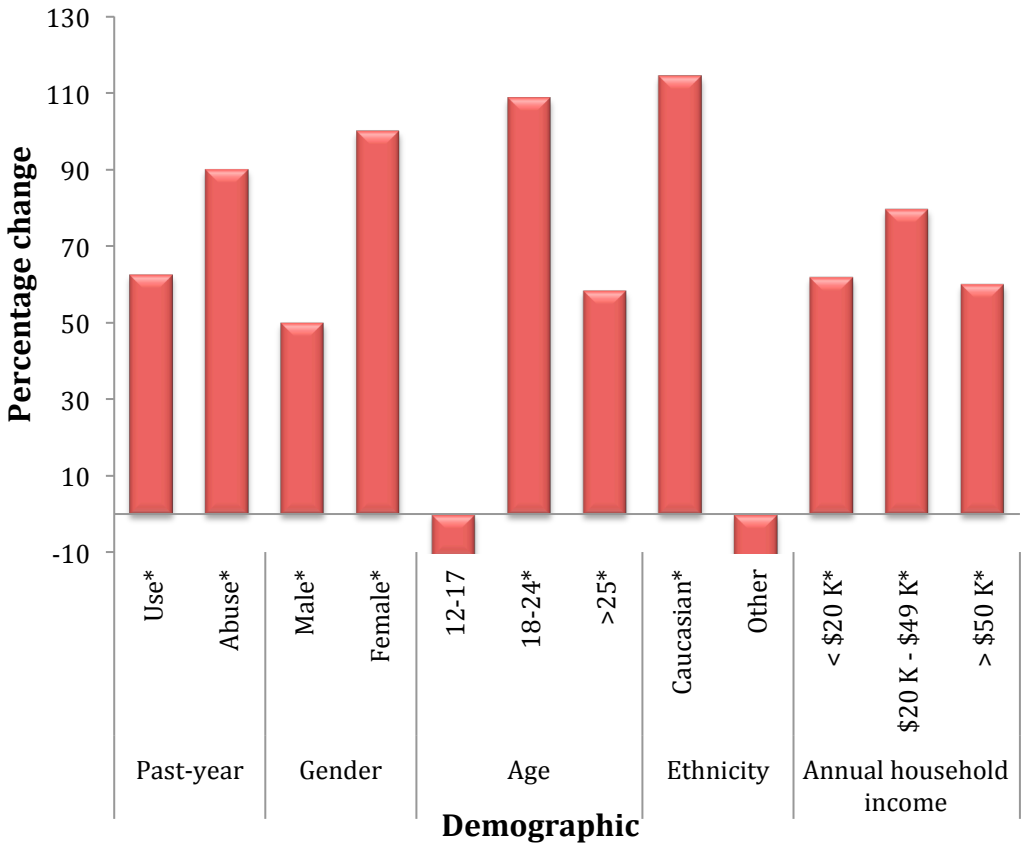
The use of opium can be dated as far back as 3000 B.C., and it left behind a wake of opium addicts as it spread across the Middle East, Europe and Asia, before arriving in the United States in the late 19th century (Escohotado, 1999). The powerful hedonic effects of opioids have made them appealing recreational drugs throughout the ages. The opioid experience involves a "rush" of initial euphoria, a prolonged feeling of well-being, and a state of detachment from reality that can involve sleepiness or unconsciousness (Koob & Le Moal, 2006). Morphine was originally prescribed in the United States as a pharmaceutical for a broad range of ailments, and heroin was later developed as a non-addictive alternative that was marketed towards mothers as a cough-suppressant. Non-medicinal opioids were criminalised in 1914 in response to the escalation of recreational use and abuse among the general population (Acker, 2002). In recent years, opioids have been increasingly prescribed as analgesics for severe short term and chronic pain such as codeine, hydrocodone, morphine, oxycodone and fentanyl (Pergolizzi, LeQuang, Berger, & Raffa, 2017). Opioids, in all formulations, are considered to be the most dangerous types of psychoactive substances due to their depressant effect on the central nervous system and high risk for physical dependency (Darke, Kaye, & Duflou, 2006).

Opioid abuse and related deaths have been rising worldwide at an alarming rate, particularly in the United States. In the last 15 years, heroin use has increased in the United States by 150% and heroin overdose deaths by 400% (Jones, Logan, Gladden, & Bohm, 2015). Additionally, there were 33,000 opioid-

related overdose deaths in 2015 compared to 7,000 in 1999. Opioids are also responsible for a large proportion of drug-related deaths in Australia. Heroin is the second most used illicit drug in Australia, and opioid-related fatalities outnumber those from all other illicit drugs (Peacock, Lusk, & Bruno, 2016). While heroin use has remained fairly stable in Australia for the last twenty years, accidental opioid related deaths have been on the upturn, with a 160% increase in pharmaceutical opioid related deaths from 2001 – 2012 (Roxburgh et al., 2017).

Opioid abuse, particularly heroin, has spread to demographic groups that are historically low-risk for heroin abuse, such as women and high-income earners (Jones et al., 2015). The demographic changes in heroin users between 1999 and 2013 in the United States is depicted in Figure 1.1 The dramatic upsurge in heroin addiction has been largely attributed to the proliferation of prescribed opioid pain medication (Bohnert et al., 2011; Jones, 2013), although the path to opioid addiction is not clear-cut. The change in the demographic profile of heroin users may reflect a transition to cheaper and often easier to procure heroin (Drug Enforcement Administration, 2015; Jones, 2013), as obtaining illicit pharmaceutical opioids can entail doctor shopping, forging prescriptions, or stealing from friends and family (Degenhardt et al., 2007). It is possible that the new cohorts of heroin users simply did not have previous exposure to opioids, compared to those with drugs readily available within their community, peers or family (Durrant & Thakker, 2003; Hawkins, Catalano, & Arthur, 2002). The demographic shift shows us that addiction vulnerability transcends the typical social and cultural risk factors, such as parental permissiveness, lack of supportive social systems for educational success,

unemployment and low socioeconomic status (see Spooner & Hetherington, 2004 for a review). Indeed, the first documented morphine addicts were comprised of people from all walks of life, including doctors and the clergy, and the majority belonged to the middle class (Escohotado, 1999). Furthermore, the stereotypical profile of a "junkie", as argued by Acker (2002) is not a manifestation of a morally defunct character or innate criminality, but instead is a consequence of the vice subculture created by the criminalisation of opioids. There are clearly nuanced individual differences that contribute the development of an addiction that need to be better understood if we hope to curb the opioid epidemic.



* Significant trend ($p < .05$)

Figure 1.1. Demographic changes in heroin use in the United States between 2002-2004 and 2011-2013.

Regardless of one's trajectory to opioid addiction, the negative physical, psychological and social costs are the same. A large study of heroin-related consequences revealed that 89% of current heroin users reported financial problems, 78% reported family problems, 78% had driven under the influence of heroin, 41% lost a job because of heroin use, 38% experienced legal ramifications, 29% had a history of overdose, and 27% had attended an emergency room because of heroin (Moses, Woodcock, Lister, Lundahl, & Greenwald, 2018). Addiction to all drug types is characterised by a pathological pattern of behaviours involving loss of control over the amount of drugs used and the amount of time spent using, obtaining or recovering from drugs (American Psychiatric Association., 2013). Consequent social detriments often ensue, in which one fails to fulfil obligations at work, school or at home, or to attend important social events. Opioids are particularly problematic because of their depressant effect on the central nervous system that results in sedation, drowsiness and mental clouding (Inturrisi, 2002). Furthermore, people often use opioids with the primary aim of disengaging with the world (Kreek, Laforge, & Butelman, 2002).

The physical health consequences of opioid abuse are also very serious, particularly when opioids are administered intravenously. Intravenous drug users are at a high risk of contracting HIV, with studies reporting 40% HIV infection in methadone-treatment patients (Schoenbaum et al., 1989), and an estimated 55% attributable risk of HIV due to intravenous use (Chitwood, Comerford, & Sanchez, 2003). Furthermore, Hepatitis C and B are extremely common in intravenous drug users, with one study observing a 76% prevalence of hepatitis C and 67% prevalence of hepatitis B (Garfein, Vlahov, Galai, Doherty,

& Nelson, 1996). Opioid abuse also carries a great risk of overdose, compared to all other illicit substances (Susnjara, 2015), primarily due to respiratory depression (Inturrisi, 2002). The primary cause of death among heroin users is overdose, and both fatal and non-fatal overdose is highly common in intravenous users (Sporer, 1999; Warner‐Smith, Darke, Lynskey, & Hall, 2001). Suicide is also a major problem, as opioid-dependent individuals are 14 times more likely to die from suicide compared to the general population, and between 17% and 47% of heroin users and abusers have a history of attempted suicide (Wilcox, Conner, & Caine, 2004). On a societal level, the economic cost of the opioid epidemic was estimated to be $51.2 billion US dollars in 2015, due to lost productivity and the costs of incarceration, crimes committed by users, addiction treatment and treatment for addiction-related complications such as HIV, hepatitis, tuberculosis, overdose and Neonatal Abstinence Syndrome (Jiang, Lee, Lee, & Pickard, 2017).

Finally, opioid addiction is notoriously hard to overcome for both abstinence-orientated and opioid-maintained drug therapy. For example, Smyth, Barry, Keenan, and Ducray (2010) found that 91% of patients experienced a relapse after six-week in-patient abstinence therapy; 59% of which occurred within one week of discharge. Relapse rates after buprenorphine treatment have shown to be around 56% to as high as 90% (Bentzley, Barth, Back, & Book, 2015). The National Treatment Outcome Research Study, conducted on 23 opioid rehabilitation programmes in England, observed a 31% relapse rate within 30 days of completing abstinence-focussed residential drug dependence programmes (Gossop, Stewart, Browne, & Marsden, 2002). Interestingly, there were no differences in relapse rates according to length of treatment, socio-

demographic characteristics, drug-using friends or partners, or psychological/physical health problems. The extent of pre-treatment heroin use or length of addiction also did not predict relapse. Similar findings were observed across 21 methadone clinics, in that demographic variables (age, race, education level or marital status) did not predict treatment efficacy (Joe, Simpson, & Sells, 1994). It is clear that there are other vulnerability factors for drug relapse that cannot be accounted for purely by drug exposure, socioeconomic status or other demographic variables.

1.2 Drug exposure perspectives on addiction

Drug addiction is conceptualised as a progressive dysregulation of multiple brain circuits that results from neuroadaptive changes in response to chronic drug use (Everitt & Robbins, 2005). The sensitization of the mesolimbic dopamine system has traditionally thought to be the primary mechanism underlying transition from drug use to addiction (Hyman, Malenka, & Nestler, 2006). Addictive substances activate the dopaminergic reward system responsible for the hedonic and reinforcing effect of drugs (Di Chiara & Imperato, 1988; Koob & Bloom, 1988; Volkow, Fowler, & Wang, 2003). The incentive-sensitisation theory of drug addiction posits that repeated drug exposure creates neural adaptations to the dopaminergic system, which enables drugs to be more effective in stimulating dopamine (Robinson & Berridge, 2001). There is clear evidence that chronic drug use results in neural changes at the molecular and cellular level (Nestler & Aghajanian, 1997). Drugs become more desirable, and "wanting" the drug develops into craving and compulsive drug taking, which occurs relatively independent of desired or undesired

consequences (Robinson & Berridge, 2001). Dopamine influences other responses to rewards, such as signalling and consolidating memory (Volkow, Fowler, Wang, Swanson, & Telang, 2004), which create learned associations that lead to later cravings and further drug use (Robinson & Berridge, 2003; Volkow et al., 2004). This allows drug-related cues, such as syringes or paraphernalia, to act as reminders of the drug and elicit cravings. A critical component of the dopaminergic system is the striatum, which mediates the associative learning after repeated drug administration (Di Chiara, 1999) that is responsible for the compulsive use of drugs observed in addiction (Berridge & Robinson, 1998). The reinforcing effect of a drug is thought to become so great that it overshadows natural reinforcers, thus motivating chronic drug use (Volkow et al., 2003) at the expense of other rewarding activities. Negative reinforcement models have also been proposed in which addiction develops from learned associations with the alleviations of the physical and affective symptoms of withdrawal, as well as with stress relief (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004). In the negative affect reinforcement model of addiction proposed by Baker et al. (2004), the chronic drug user eventually becomes sensitised to internal and external signals of negative affect, which prime learned associations with drug taking.

Drug addiction has been attributed to dysfunction in areas of the brain responsible for self-regulation and cognitive control such as the prefrontal cortex (PFC; Bechara, 2005; Goldstein & Volkow, 2002). Damage to the PFC has been associated with impaired decision-making in substance dependent individuals (Bechara et al., 2001). Insensitivity to future consequences, as demonstrated by chronic drug taking, has been shown to also relate to damage to the PFC (Bechara, Damasio, Damasio, & Anderson, 1994). Substance abusers

exhibit impaired decision making similar to those with damage to the PFC (Bechara et al., 2001; Rogers et al., 1999). The orbito-frontal cortex (OFC) is an essential component to associative learning, and may contribute to the reinforcing effects of drugs (Winstanley, Olausson, Taylor, & Jentsch, 2010). Dysfunction in the OFC can prevent new associated learning to occur for future non-drug rewards (Schoenbaum, Roesch, & Stalnaker, 2006). Drugs also active stress pathways that adapt in response to regular drug administration and as a consequence of withdrawal, such as a hyper-sensitisation of hypothalamic-pituitary-adrenal axis hormones observed in opioid and cocaine abusers (Sinha, 2008). As a result, drug abusers may be less able to control their stress response and turn to using drugs as a coping method. A combination of a heightened reward value of drugs, sensitisation to drug rewards, associative learning, and lack of behavioural control manifest in the destructive choices observed in drug addiction (Jentsch & Taylor, 1999; Lyvers et al., 2014). Over time, neural changes can contribute to the transition to loss of control over one's drug use. However, the pathway from drug taking to drug addiction is unclear and highly complex, as some regular drug users never develop an addiction.

Opioids produce powerful analgesic properties as well as intense euphoria, which result from the activation of endogenous mu-opioid receptors that are involved in modulating stress, mood, and reinforcement of natural rewards such as food and sex (Le Merrer, Becker, Befort, & Kieffer, 2009). Damage to opioid system is implicated in drug addiction in tandem with disruptions of the dopaminergic system. Chronic opioid use leads to changes in the excitability of mu-opioid receptors, resulting in the need for greater amounts of the drug to achieve the desired effects (i.e. tolerance). Dependency also can

result from suppression of noradrenaline, a neurotransmitter that regulates the physical expressions of opioid use, such as slowed breathing, drowsiness, and low blood pressure. Noradrenaline production increases in response to the depressant effects of opioid, and an excessive amount of noradrenaline is released with the sudden cessation of opioid use (Kosten & George, 2002). Opioid dependency is thought to also cause changes in brain regions associated with reward, motivation, stress, learning and executive function (Le Merrer et al., 2009; Seip-Cammack, Reed, Zhang, Ho, & Kreek, 2013). These neurobiological changes have been shown to persist after abstinence (Dalley et al., 2005; Seip-Cammack et al., 2013), which may account for the high rates of relapse associated with opioids. The persistence of neural dysfunction has been implicated in overdose following a long period of abstinence. Tolerance to the euphoric effects of opioids is thought to develop more quickly and diminish more slowly than physiological tolerance (White & Irvine, 1999). This discrepancy may lead to overdose if a recently abstinent user takes a larger dose to achieve a hedonic effect that the body can no longer tolerate.

1.3 Transition from drug use to addiction

It has been argued that experiencing euphoria universally motivates non-drug recreational activities, such as playing sports, listening to music, watching movies, or eating gourmet food (Siegel, 2005). These activities alter brain function much like drugs do; therefore, taking drugs is not necessarily an aberrant behaviour as it aligns with our innate desire to experience pleasure. Furthermore, drug use does not necessarily lead to an addiction, as data from a survey of a large representative US sample shows. The National Comorbidity

Survey revealed that only 15% of those who use drugs develop a substance use disorder (SUD), and 7.5% of analgesic users (e.g. opioids) reported dependency (Anthony, Warner, & Kessler, 1994). This survey also revealed that among those who use drugs sporadically, only some of them go on to start using regularly, and even a smaller subset develop an addiction. Regarding addiction to prescription opioids, not every patient who legitimately takes opioid medication becomes addicted. An estimated 3% of chronic pain patients receiving opioid medication management develop an addiction to opioids (Portenoy et al., 2007), and around 20.4% exhibit aberrant drug-related behaviours that often precede addiction (Fishbain, Cole, Lewis, Rosomoff, & Rosomoff, 2008). Animal models support the supposition of individual differences in addition vulnerability. When rodents are freely able to self-administer drugs, only some rats increase their drug intake (Mantsch, Yuferov, Mathieu-Kia, Ho, & Kreek, 2004; Piazza, Deminiere, Le Moal, & Simon, 1989) or consistently take high doses of the drug (Piazza, Deroche-Gamonent, Rouge-Pont, & Le Moal, 2000).

There are many individual differences predating drug addiction that are theorised to contribute to drug abuse. Some differences include personality traits that psychotropic properties of drugs correct or balance out, such as neuroticism, depression or low-self esteem (Ausubel, 1961). Deficits in one's ability to control anxiety, negative affect or aggression are also individual factors that are implicated in consuming drugs (Khantzian, 1980). Drug abuse has also been conceptualised as a ratio of deconstructive to constructive individual factors relating to personality strength, motivations, risk taking and habit formation (Frederick, 1980). Many of these theories predate evidence of neural alterations resulting from chronic drug exposure, but are still very relevant to

our understanding of why particular individuals lose control of their drug intake. Furthermore, addiction can develop to many other hedonic activities such as sex, food or gambling, which clearly indicates that there are non-drug exposure factors that underlie substance abuse.

Piazza and Deroche-Gamonet (2013) proposed a general model of the transition to drug addiction that involves three stages, through which only individuals with particular psychobiological vulnerabilities progress. As one moves through these phases, the amount of time spent on productive and non-drug related activities grows smaller as involvement with drug use increases. The first phase is recreational/sporadic use, in which the drug activates reward pathways and taking the drug is purely a pleasurable activity. In the intensified/sustained phase, the motivation for drug use changes from pleasure to desire, tolerance develops and the drug becomes needed for allostasis. The third stage is addiction and is characterised by a loss of control. The drug is also intensely mourned and withdrawal can occur, which results in devoting a great deal time to obtaining and using the drug. The authors posit that progression from one stage to the next is facilitated by individual neurobiological differences interacting with the degree of drug exposure. This three-phase model can account for why only a small percentage of people escalate their recreational drug intake and/or lose control over their use.

However, among those who do become addicted, opioid addiction tends to persist over long periods of time. Hser, Hoffman, Grella, and Anglin (2001) found that after 33 years, the rate of heroin use was almost identical in a sample of 581 patients receiving court-ordered addiction treatment (23.1% versus 20.7%). Similarly, Vaillant (1973) found that only 35-42% of heroin addicts were

abstinent after a 20-year follow-up. As discussed earlier in the current chapter, relapse rates are also very high for opioid addicts, even after receiving inpatient therapy or opioid maintenance therapy. Understanding the vulnerability factors for addiction is vital for initiating treatment strategies before damage can occur and prevent addiction becoming a lifelong affliction.

1.4 Impulsivity

There is clear evidence that repeated drug exposure causes neural and structural brain changes, but the role of individual differences in the development of drug addiction is less understood. Contrary to drug exposure theories, there is evidence that individual differences predating drug use may increase one's vulnerability to addiction. One key trait is impulsivity; a multi-factor construct that is broadly conceptualised as a tendency to act without considerable forethought or inhibition (Bari & Robbins, 2013; Gullo, Loxton, & Dawe, 2014). Spontaneity and risk taking are natural human behaviours, and we would not have scientific developments or the creative arts without some aspects of impulsivity. The ability to make quick, error-free decisions is also an advantageous quality in fast-paced work environments and in competitive sports. However, impulsivity becomes dysfunctional when it results in undesirable consequences.

Impulsivity can be conceptualised as a form of maladaptive decision-making, in that it is counterproductive for achieving one's best interests. For the purpose of the present thesis, the term impulsivity will be operationally defined as a pattern of maladaptive decision-making. The literature largely supports impulsivity as a relatively stable personality trait that correlates well with

psychopathologies such as SUD, problem gambling and violent criminal offending (see Stanford et al. 2009 for a review). Impulsivity is highly relevant to drug addiction, as maladaptive decision-making is a principal feature of drug addiction in that users choose to take drugs despite serious negative consequences, and at the expense of pursing pro-social non-drug rewards (American Psychiatric Association., 2013). It has been theorised that heightened approach behaviour and difficulty inhibiting behaviour combine as a risk factor for drug addiction (Gullo et al., 2014; Loxton & Dawe, 2001). In other words, a pre-morbid predisposition towards risk-taking may incline one to initially try drugs, and deficits in impulse control may impede regulation of the intensity of drug taking, resulting in drug dependency. Once addicted, a lack of inhibitory control may also interfere with attempts to quit or impede adherence to a treatment programme.

Self-report measures of impulsivity

Impulsivity is multi-dimensional, and a variety of measures have been developed to evaluate its diverse manifestations. Self-report questionnaires that assess impulsivity as a general personality trait include the Barratt Impulsivity Scale (BIS; Barratt, 1965; Patton, Stanford & Barratt, 1995), the Eysenck Impulsivity Questionnaire (EIQ; Eysenck, Pearson, Easting, & Allsopp, 1985), and the UPPS impulsive behaviour scale (Whiteside & Lynam, 2001). Other questionnaires measure particular impulsive behaviours and characteristics such as the Sensation Seeking Scale of the Zuckerman-Kuhlman Personality Questionnaire (SSS; Zuckerman, Kuhlman, Joireman, Teta, & Kraft, 1993), the novelty seeking and harm avoidance subscales of the Tridimensional Personality

Questionnaire (TPQ; Cloninger, Przybeck, & Svrakic, 1991), behavioural inhibition and behavioural activation scales (BIS/BAS; Carver & White, 1994) and the Adult and Retrospective Measure of Behavioural Inhibition inventories (RMBI/AMBI; Gladstone and Parker, 2005). Of all the self-report questionnaires, the BIS is considered the gold-standard measure of impulsivity (Stanford et al., 2009), and is comprised of three subtraits: attentional impulsiveness (impaired cognitive control), motor impulsiveness (acting without thinking) and non-planning impulsiveness (lack of future thinking). Table 1.1 provides an overview of the most common self-report questionnaires and a summary of the facets of impulsivity they purport to measure.

The models of impulsivity that underpin self-report measures have demonstrated neurological correlates. For example, individuals who score highly on the BIS exhibit reduced neural responses to punishment (Potts, George, Martin, & Barratt, 2006) and increased reward related activation in response to rewards (Martin & Potts, 2009). BIS scores also predict dampened activity in and reduced volume of the PFC (Brown, Manuck, Flory, & Hariri, 2006; Matsuo et al., 2009). Thus, it can be argued that impulsive personality traits characteristic of addiction can arise from inborn neural variations in executive control and reward processing.

Table 1.1

Summary of self-report impulsivity questionnaires and example items

Measure	Impulsivity subfactor		Example item
BIS-11 *Patton et al. (1995)*	⇧Attentional	- Lack of attentional control - Difficulty focusing	"I don't 'pay attention'"
	⇧Motor	- Acting without thinking - Behavioural disinhibition	"I act on the spur of the moment"
	⇧Non-planning	- Lack of future thinking - No long-term planning	"I am more interested in the present than the future"
Eysenck Impulsiveness Questionnaire *Eysenck et al. (1985)*	⇧Impulsiveness	- Acting and thinking quickly without much forethought	"Do you usually think carefully before doing anything?"
	⇧Venturesomeness	- Adventure and risk seeking	"Do you quite enjoy taking risks?"
UPPS Impulsive Behaviour Scale *Whiteside & Lynam (2001)*	⇧Urgency	- Strong emotions and impulses, particularly under negative affect	"It's hard for me to resist acting on my feelings"
	⇩Premeditation	- Diminished deliberation of consequences before acting	"I usually make up my mind through careful reasoning"
	⇧Sensation seeking	- Pursing exciting activities - Openness to new experiences	"I seek new and exciting experiences and sensations"
	⇩Perseverance	- Low self-discipline - Inability to focus on boring tasks	"I tend to give up easily"
Tridimensional Personality Questionnaire *Cloninger (1987)*	⇧Novelty seeking	- Excitement in response to appetitive stimuli - Behavioural activation	"When nothing new is happening, I usually start looking for something that is thrilling or exciting"
	⇧⇩Harm avoidance	- Intense negative response to aversive stimuli - Behavioural inhibition	"I often feel tense and worried in unfamiliar situations"
Zuckerman-Kuhlman Personality Questionnaire *Zuckerman et al, (1993)*	⇧Impulsive sensation seeking	- Risk taking for excitement - Acting without thinking	"I sometimes do 'crazy' things just for fun"
Behavioural Inhibition/ Behavioural Activation System Scales *Carver & White (1994)*	⇩Behavioural inhibition	- Sensitivity to punishment and novelty	"I worry about making mistakes"
	⇧Behavioural activation	- Pursuit of desired goals - Fun seeking - Responsiveness to reward	"I crave excitement and new sensations"

Behavioural measures of impulsivity

Self-report measures have many inherent limitations that restrict the interpretation of their results. Primarily, questionnaires rely upon respondents' ability to accurately and objectively assess themselves. Questionnaires are also vulnerable to intentional misreporting due to social desirability. These limitations are particularly problematic for research with impulsive individuals, as they may not answer with as much forethought or deliberation as would non-impulsive comparison groups. Cognitive and behavioural measures have been created to more precisely evaluate impulsivity. In a review conducted by Verdejo-García, Lawrence, and Clark (2008), the authors categorised laboratory measures of impulsivity into three groups that will be utilised here for ease of discussion: Response inhibition, delay-discounting, and cognitive impulsivity. Measures of response inhibition evaluate the ability to restrain automatic behaviours, such as suddenly stopping a repetitive action on the Go-NoGo and Stop-Signal tasks. Poor performance on response inhibition tasks indicates insufficient impulse control. Delay discounting tasks assess one's willingness to wait for a reward rather than take a smaller, but immediate reward. Choosing the smaller immediate reward is thought to reflect a desire for immediate gratification at the expense of a more profitable option (Madden & Johnson, 2010). Cognitive impulsivity is defined in terms of maladaptive decision-making, and will be the focus of the present thesis. Cognitive impulsivity relates to choices that are made before acquiring an adequate amount of information (Clark, Robbins, Ersche, & Sahakian, 2006; Evenden, 1999), or involve an unnecessary amount of risk, such as gambling tasks (Bechara et al., 1994) and probability discounting (Green & Myerson, 2010). Probability discounting tasks

require decisions about certain rewards or larger, probabilistic rewards, and purport to measure risk taking. Cognitive impulsivity also can be observed in feedback learning tasks that require one to select optimal behaviours in response to rewards and punishments (Bódi et al., 2009). A tendency to shift away from a rewarding learning strategy after negative feedback is suggestive of choices made without careful consideration of an optimal long-term plan. The wide range of measures illustrates the multi-faceted nature of impulsivity, and the present thesis aims to utilise a number of measures to assess impulsivity in addiction from multiple angles.

Impulsivity and addiction

Impulsivity is a key characteristic of SUD as diagnosed by the DSM-V criteria (American Psychiatric Association., 2013). Impaired behavioural control, failure to consider future consequences, inability to delay gratification and excessive risk taking are impulsive features of drug abuse, which are well supported in the literature. For example, individuals with a history of or current drug abuse score highly on self-reported measures of impulsivity such as the BIS, EIQ and the TPQ (Allen, Moeller, Rhoades, & Cherek, 1998; Sher, Bartholow, & Wood, 2000; Stanford et al., 2009). Stimulant-dependent individuals are higher in sensation seeking, poor attentional control, acting without forethought, and lack of future planning (Ersche, Turton, Pradhan, Bullmore, & Robbins, 2010). People dependent on a number of substances, including alcohol, nicotine, stimulants and opioids show a preference for a smaller, immediate reward rather than a larger, delayed reward (Allen et al., 1998; Kirby, Petry, & Bickel, 1999; Madden, Petry, Badger, & Bickel, 1997). Substance users also demonstrate

less information gathering before making decisions than non-drug using controls (Clark et al., 2006). The National Epidemiologic Survey on Alcohol and Related Conditions, a large representative sample of the United States, found that 62% of respondents with diagnosable SUD reported acting impulsive most of the time in their daily life (Chamorro et al., 2012).

Impulsivity and opioid abuse

High levels of impulsivity have been documented in opioid users using both questionnaires and behavioural measures. Opioid abusers and opioid-dependent individuals have reported higher levels of EIQ impulsivity and venturousness, and BIS non-planning and motor impulsivity (Kirby & Petry, 2004; Kirby et al., 1999; Madden et al., 1997) compared to non-drug using controls, as well as higher sensation seeking (Franques et al., 2003). Opioid addicted participants also have demonstrated high novelty seeking and low harm avoidance on the TPQ (Teh, Izuddin, Hatta, Zakaria, & Salleh, 2012; Wang et al., 2013), and express less interest in planning for the future, feel that the present is more important than the future, and do not believe that planning ahead is useful (Petry, Bickel, & Arnett, 1998). Furthermore, opioid users also exhibit greater discounting of delayed monetary rewards (Kirby & Petry, 2004; Kirby et al., 1999; Madden et al., 1997; Petry et al., 1998). A meta-analysis of neuropsychological functioning of chronic opioid users conducted by Baldacchino, Balfour, Passetti, Humphris, and Matthews (2012) revealed abnormalities across a range of cognitive domains, particularly working memory, cognitive impulsivity and cognitive flexibility, which are central features of impulsive traits and behaviours. While there is reliable evidence for

heightened impulsivity in opioid users, opioids have received comparatively less attention in the literature compared to substances such as nicotine and alcohol; highlighting the need for continued research on impulsivity as a vulnerability factor for addiction.

Impulsivity as a vulnerability factor for addiction

Premorbid sensitisation of dopamine responsiveness to reinforcers such as drugs may be a vulnerability factor initiating drug use (Piazza & Le Moal, 1996), and/or may make one more sensitive to drugs' reinforcing effects (Blum et al., 2000; Young, Lawford, Nutting, & Noble, 2004). Cognitive deficits related to the PFC may also result in reduced impulse control and willpower needed to resist addictive drugs (Horn, Dolan, Elliott, Deakin, & Woodruff, 2003). Premorbid abnormalities may help explain why only a small proportion of drug taking individuals lose control over their use, or why some individuals develop an addiction more rapidly than others (Gullo et al., 2014). For example, males who report impulsive behaviours exhibit heightened sensitivity to the stress alleviating effects of alcohol, which may put these individuals at greater risk of developing an alcohol use disorder (Sher & Levenson, 1982). In regards to opioid addiction, Pud et al. (2006) found that greater scores on the TPQ harm avoidance subscale predicted a greater increase in pain threshold in response to morphine and a larger decrease in pain magnitude compared to placebo. It is possible that those who have low levels of harm avoidance (which can be suggestive of impulsivity) may react to opioids in a way that makes these individuals more likely to abuse the drug, and thus increase their risk for dependency.

Evidence supporting heightened impulsivity prior to opioid dependency can be found in a study conducted by Baldacchino, Balfour, and Matthews (2015). Illicit heroin users and methadone-maintained patients demonstrated greater cognitive, motor and non-planning impulsivity compared to a healthy control group, but a cohort of opioid pain management patients without a history of drug abuse behaved similarly to controls. The opioid pain management patients reported an average length of opioid use similar to current heroin users (M = 5 years and M = 6.1 years, respectively), which suggests that the neurophysiological effects of long-term opioid exposure cannot fully explain differences in impulsivity. Brain development from childhood also contributes to our understanding of impulsivity as an underlying factor of substance abuse. Risk-taking and poor impulse control are hallmarks of adolescence and are believed to arise from the developmental immaturity of brain structures involved in reward processing and behavioural inhibition. A neurobiological triadic model has been proposed by Ernst, Pine, and Hardin (2006), which posits that impulsivity in adolescence can be explained by immature development of the nucleus accumbens, amygdala and PFC, which results in a hypersensitive reward system, diminished harm-avoidance and weak self-regulatory control. Consequently, adolescence is a high-risk period for developing a SUD, and drug experimentation in adolescence may transition into addiction during adulthood (Chambers, Taylor, & Potenza, 2003). Early life trauma and chronic stress are widely known risk factors for drug addiction and relapse in vulnerable individuals (Sinha, 2008). Sustained activation of neural stress pathways can result in long-term physiological, emotional and behavioural changes that are implicated in drug abuse (Cleck & Blendy, 2008; Sinha et al., 2011). Exposure to

stress early in life may alter the development of brain regions responsible for regulating emotional and behavioural stress responses, decision-making, reward-behaviours, and impulsivity, including the PFC (Blanco et al., 2015; Heinrichs, 2005; McCrory, De Brito, & Viding, 2012), which in turn may influence drug use later in life. One of the key behaviours implicated in the development of opioid addiction is the use of opioids to cope with emotional pain, anxiety, aggression or distress (Khantzian, 1985).

There are also a number of longitudinal studies linking childhood/adolescent impulsivity to substance use and abuse in adulthood, such as high novelty seeking (Cloninger, Sigvardsson, & Bohman, 1988; Masse & Tremblay, 1997; Sher et al., 2000), low harm avoidance (Cloninger et al., 1988; Masse & Tremblay, 1997), risk-taking (Ohannessian & Hesselbrock, 2007), heightened behavioural activation (Johnson, Turner, & Iwata, 2003; Knyazev, Slobodskaya, Kharchenko, & Wilson, 2004), and poor behavioural control (Dawes, Tarter, & Kirisci, 1997; King & Chassin, 2004; McGue, Iacono, Legrand, Malone, & Elkins, 2001; Sher, Walitzer, Wood, & Brent, 1991; Tarter et al., 2003; Tarter, Kirisci, Reynolds, & Mezzich, 2004). Children who develop behavioural self-control at slower than average rates are also more likely to start using drugs in adolescence and to have drug-related problems (Wong et al., 2006).

There are converging lines of evidence for genetic and biologically based impulsive risk factors for drug addiction. Siblings of substance dependent individuals have reported greater levels of impulsivity compared to non-drug taking controls, such as higher BIS scores (Ersche et al., 2010), impaired response inhibition (Ersche et al., 2012a; Ersche et al., 2012b), reduced executive function (Ersche et al., 2012b), and smaller volume of brain regions implicated in

self control, learning and habit formation (Ersche et al., 2012a). There is also evidence for neurophysiological correlates of impulsivity in the children of substance abusing parents. For example, reduced neural event-related potentials and event-related oscillations during a behavioural inhibition task are phenotypic markers for alcoholism, and are observed in adult children of alcoholic parents (Kamarajan et al., 2006; Kamarajan et al., 2005). Only longitudinal studies can confirm a causal relationship between impulsivity and addiction, but there is likely an interaction between premorbid vulnerabilities and neurobiological changes after prolonged drug use. It is the aim of the present thesis to add to our understanding of impulsivity in opioid-dependency, as well as to clarify the link between impulsivity and other individual factors that contribute to maladaptive decision-making in drug addiction.

1.5 Uncertainty

Simply stated, decision-making involves the prediction of expected outcomes and the selection of the most suitable action accordingly (Redish, Jensen, & Johnson, 2008). Humans frequently face complex decisions that have varying degrees of uncertainty, and the ability to predict possible consequences of behaviour from incomplete or ambiguous information is fundamental for adaptive behaviour (Bland & Schaefer, 2012). Impulsivity can thereby be viewed as maladaptive decision-making resulting from impairments in evaluating uncertainty, predicting outcomes from incomplete information, and/or planning behaviour appropriately. For example, a decision whether to speed through a yellow light involves evaluating the potential outcomes and their value (e.g. getting to work on time versus incurring a traffic citation), predicting the

likelihood of the outcomes based on the available information (e.g. previous experiences at the intersection or current traffic conditions), and choosing to accelerate/decelerate accordingly. An impulsive decision may occur because of a failure at any one of these points. For example, one may ignore the possibility of getting caught and act on the first impulse instead (e.g. the desire to get to the destination on time), or underestimate the risk (e.g. chance of a red light camera), both of which can result in an action that is not beneficial for the future (e.g. paying a citation). As such, impulsivity can be manifested as maladaptive decision-making in the face of uncertainty.

Uncertainty can arise from a number of sources, such as unpredictability, unfamiliarity, and tentativeness (Hillen, Gutheil, Strout, Smets, & Han, 2017). One type of uncertainty that is of interest to the present thesis is outcome uncertainty. Decision-making under uncertainty involves an analysis of the anticipated outcomes through controlled and effortful information processing (Starcke, Pawlikowski, Wolf, Altstötter-Gleich, & Brand, 2011). Uncertainty signals to the brain that any decisions made while lacking complete information in the given scenario may be harmful, and the detection of uncertainty initiates cognitive and behavioural processes to resolve the uncertainty (Hsu, Bhatt, Adolphs, Tranel, & Camerer, 2005). Prediction error (i.e. the discrepancy between a predicted outcome and the actual outcome) stimulates dopaminergic activity, which increases as a function of uncertainty (Fiorillo, Tobler, & Schultz, 2003). Uncertainty about outcomes is associated with areas of the brain involved in learning and decision-making. The anterior cingulate cortex is a key structure for learning the values of decision options based on previous reward prediction errors (Behrens, Woolrich, Walton, & Rushworth, 2007). The anterior cingulate

cortex helps us decide whether violations of reward expectancy indicate that our behaviour is no longer optimal and whether we should change our actions (Behrens et al., 2007; Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006; O'Reilly, 2013). The medial prefrontal cortex is also triggered by reward-prediction error and guides responses to uncertainty (Matsumoto, Matsumoto, Abe, & Tanaka, 2007), and the orbitofrontal cortex and amygdala have also been implicated in detecting and responding to uncertain rewards (Hsu et al., 2005).

Uncertainty about outcomes may stimulate brain regions responsible for detecting rewards and initiating adaptive behaviours, but research has shown that uncertainty impairs decision-making (Shafir, 1994). Humans tend to act irrationally when faced with uncertain situations, as demonstrated by Tversky and Shafir (1992). They presented participants with a hypothetical gambling scenario that had equal odds of winning $200 or losing $100. Participants were asked whether they would gamble a second time if they won the first gamble, lost the first gamble, and if they didn't know the result. Among those who would gamble a second time regardless if they won or lost the first round, only 65% reported that they would gamble again if they didn't know the outcome of the first round. This phenomenon was coined the "disjunction effect", which states that people prefer inaction when faced with uncertain outcomes, even if their actions would not be impacted by the possible outcomes if they were known. Humans also have difficulty intuitively judging probabilities and demonstrate the disjunction effect when dealing with probabilistic scenarios. For example, individuals have shown a preference for games with one probabilistic element over games with two probabilistic elements, even though the probability of winning for each game is the same (Bar-Hillel, 1973).

If the decision-making process is naturally impaired by uncertainty, then deficits in cognitive function, reward processing, and associative learning likely further impede adaptive decisions. Brevers et al. (2014) defines the cognitive abilities necessary for adaptive decision-making under uncertainly as the "integration of prechoice emotional processes and rational analytical system aspects that require the capacity to represent a dilemma, maintain and organize information in working memory, strategically plan and execute a response, and to evaluate the efficacy of the solution" (p. 1925). Furthermore, deficits in neural areas responsible for processing uncertainty inevitably hamper one's ability to make effective decisions under uncertainty. It is important to note that the neural functioning underlying cognitive processing of uncertainty, such as the dopaminergic system and PFC, have shown to be deficient in impulsive and substance abusing individuals.

The other aspect of uncertainty that is significant to the present thesis is the individual reaction to uncertainty that may impact subsequent decision-making. Uncertainty has been defined as a metacognitive state that reflects the way one appraises circumstances as uncertain (Han, Klein, & Arora, 2011). This working definition conceptualises uncertainty as on overreaching state, rather than a specific feature of the environment, and allows us to synthesise the results of research in this area. It has been suggested that a particular frontolimbic neural circuit mediates our subjective, emotional and physiological, responses to uncertainty: the amygdala, anterior insula, bed nucleus of the stria terminalis, and areas of the PFC (Gorka, Nelson, Phan, & Shankman, 2016). Positive cognitive, emotional and behavioural reactions to uncertainty include curiosity, excitement, and deliberation (Hillen et al., 2017). For example, people who are

fascinated with UFO sightings can derive pleasure from pursuing information, even though it is unlikely that they will find definitive answers about alien life. Uncertainty can also motivate exploration around one's environment (Anselme, 2010), which can be beneficial for acquiring knowledge about the world.

However, research has shown that certainty is most often preferable to uncertainty (Heine, Proulx, & Vohs, 2006; Lejuez, Eifert, Zvolensky, & Richards, 2000; Mineka & Kihlstrom, 1978), particularly uncertain threat (Grillon, Baas, Cornwell, & Johnson, 2006; Lejuez et al., 2000). Animal research has established that unpredictable shocks are more aversive to predictable ones (Fanselow, 1980; Marlin, 1981), and human research has shown that more anxiety is elicited by unpredictable shocks than predicable shocks (Badia, McBane, & Suter, 1966; Lanzetta & Driscoll, 1966). The startle reflex is potentiated by the anticipation of unpredictable shocks in humans (Bradford, Shapiro, & Curtin, 2013; Grillon, Baas, Lissek, Smith, & Milstein, 2004), along with physiological arousals such as increased heart rate, skin conductance and blood pressure (Epstein & Roupenian, 1970; Jennings, Averill, Opton, & Lazarus, 1970; Monat, Averill, & Lazarus, 1972). Furthermore, humans have shown a preference for contexts previously paired with predicable shock compared to contexts paired with unpredictable shock (Grillon et al., 2006).

Uncertainty in itself can be a stressor, as unpredictable neutral tones have shown to elicit anxiety (Grupe & Nitschke, 2013; Jackson, Nelson, & Proudfit, 2015), avoidance behaviour and anxiety related behaviour, such as increased attention to emotional facial expressions (Herry et al., 2007). Even uncertain rewards activate the anterior insula, which responds to uncertain threat in individuals with high anxiety (Gorka et al., 2016). Stress and anxiety prompted

by uncertainty can reduce neural reward system functioning (Nelson, Shankman, & Proudfit, 2014), reward anticipation (Nelson, Kessel, Jackson, & Hajcak, 2016), as well as require considerable cognitive resources to suppress (Milkman, 2012). Importantly, uncertainty in one's environment has shown to deplete the willpower needed to resist temptation, as demonstrated in a series of studies conducted by Milkman (2012). When faced with "want" or "should" options (e.g. eating candy versus eating fruit), participants who were in a state of uncertainty regarding an unrelated topic (e.g. what movie they would be watching during the experiment) tended to choose more "want" options than participants who did not have uncertainty in their decision-making environment. In summary, uncertainty is generally unpleasant and often invokes aversive cognitive and physiological reactions that can impair adaptive decision-making.

1.6 Intolerance of uncertainty

The way in which one responds cognitively, behaviourally and emotionally to uncertainty has important implications on how uncertainty impacts decision-making. Intolerance of uncertainty (IU) is one way that beliefs and attitudes about uncertainty have been conceptualised in the literature. IU is a dispositional trait characterised by strong negative reactions to uncertainty, which arise from appraising uncertainty as threatening disproportionally to the actual likelihood of aversive outcomes (Freeston, Rhéaume, Letarte, Dugas, & Ladouceur, 1994; Ladouceur, Gosselin, & Dugas, 2000). Furthermore, IU is characterised by an "incapacity to endure the aversive response triggered by the perceived absence of salient, key or insufficient information" (Carleton, 2016, p. 31). In other words, an individual with high IU experiences a heightened

aversion to uncertainty and simultaneously has a diminished faculty to cope with the negative thoughts and emotions that uncertainty engenders.

IU has been associated with employing dysfunctional strategies to reduce uncertainty, which impedes the ability to make optimal decisions. Those high in IU have demonstrated a need to acquire more information before making decisions than those with low IU, as demonstrated by their performance on the Beads Task. High IU has been associated with sampling a greater number of beads before guessing whether a bag contains mostly white or mostly black beads, indicating that those with high IU have a lower threshold for ambiguity (Ladouceur, Talbot, & Dugas, 1997). High IU has also been linked to behavioural inhibition in a timed typing study conducted by Thibodeau, Carleton, Gómez-Pérez, and Asmundson (2013), in which high IU predicted slower typing speed. One interpretation posited by the authors is that IU prompted checking typed letters and/or hesitation before each keystroke. However, there is evidence that sub-optimal decision-making is not just a consequence of an excessive need for certainty or overly cautious behaviour. Luhmann, Ishida, and Hajcak (2011) observed that high IU was associated with risky gambles and less willingness to wait for a reward with better odds. The aversiveness of a prolonged state of uncertainty may have impelled high IU participants to make suboptimal decisions. IU is also characterised by a lack of confidence in one's ability to manage uncertainty (Dugas, Freeston, & Ladouceur, 1997), and it is apparent that efforts to reduce or avoid uncertainty can be detrimental to decision-making.

IU elicits a number of cognitive and emotional reactions to threat in everyday life. Those with high IU exhibit a greater propensity to seek out and

focus on threat-related information, which often results in exaggerated threat perception and heightened psychological distress (Rosen, Knäuper, & Sammut, 2007). Worry elicited by IU has shown to disrupt cognitive processing of ambiguous stimuli due to the intrusion of negative thoughts (Metzger, Miller, Cohen, Sofka, & Borkovec, 1990). There is also evidence that IU intensifies the effect of daily stressors on anxiety symptoms in non-clinical populations (Chen & Hong, 2010; Ciarrochi, Said, & Deane, 2005). Consequently, those with high IU may perceive their daily lives to be more stressful and less manageable. There are also neural connections between IU and the insula; a structure involved in the emotional response to negative future events (Gorka et al., 2016). Emotion-based responses to uncertainty may usurp rational thinking and adaptive decision-making.

The cognitive, psychological and emotional consequences of IU also have a serious impact on adaptive coping behaviours due to elevated perceptions of threat, negative problem orientation, cognitive avoidance, and overestimation of the likelihood and intensity of negative outcomes (Bredemeier & Berenbaum, 2008; Dugas et al., 1997). Negative-problem orientation is characterised by interpreting problems as threats rather than challenges, which can result in avoidance instead of solution-finding (Davey, 1993). Those with high IU demonstrate low appraisals of self-control in a threatening situation and greater levels of emotion-focused coping (e.g. rumination, self-blame, or resignation), compared to problem-solving coping methods (Taha, Matheson, Cronin, & Anisman, 2014). IU is considered to be a fundamental aspect to worry, and worry is often used as a maladaptive strategy for managing or preventing negative outcomes, rather than actually resolving the undesirable situation (Freeston et

al., 1994). IU may be particularly detrimental to drug abusers' perception of life stress, as IU may compound drug-related abnormalities in stress regulation. Overall, IU elicits stress and anxiety, which may further impede adaptive decision-making.

The role IU has in psychopathology is of great interest, as it is considered to be a transdiagnostic vulnerability factor and "phenotypic core" for internalising disorders (Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2014), such as major depressive disorder, obsessive compulsive disorder, generalised anxiety disorder (GAD), panic disorder (Carleton et al., 2012; Mahoney & McEvoy, 2012b; McEvoy & Mahoney, 2012), and social anxiety (Carleton, Collimore, & Asmundson, 2010). Anxiety disorders and mood disorders are highly comorbid with SUD, which is of great importance to the current thesis. The National Institute of Mental Health Epidemiological Catchment Area Survey found 28.3% comorbidity between SUD and anxiety disorder and 26.4% comorbidity with mood disorders in a large representative sample of the United States (Regier et al., 1990). The link between anxiety and SUD has been well documented in the literature (Huang & Wang, 2015; Kushner, Krueger, Frye, & Peterson, 2008; Lai, Cleary, Sitharthan, & Hunt, 2015), and the comorbidity of substance dependence and anxiety disorders is approximately 25% (Grant et al., 2004). Non-clinical anxious traits are also associated with addiction as reported in multiple studies (Litt, Cooney, & Morse, 2000; Mehroof & Griffiths, 2010; Wilsey et al., 2008). Of the anxiety disorders, GAD has the highest comorbidity rate with drug dependence (Grant et al., 2009; Grant et al., 2004; Kushner et al., 2008). IU is thought to be a key causal factor of worry, and excessive and uncontrollable worry about potential future events are the primary symptoms of

GAD (American Psychiatric Association., 2013). Furthermore, anxiety disorders and SUD share many common features. Both disorders are based on maladaptive associative learning: Addiction develops from hypersensitisation to the conditioned associations between drugs and reward (Robinson & Berridge, 2001), and anxiety disorders arise from learned associations between stimuli and aversive outcomes (Pittig, Treanor, Lebeau, & Craske, 2018). Chronic drug use has also shown to alter neural stress pathways, which implicates anxiety in escalating drug use and triggering relapse (Sinha, 2001). Emotional distress has also been implicated in engaging in self-destructive behaviours, reduced impulse control, and a need for immediate gratification (Tice, Bratslavsky, & Baumeister, 2001). Despite the high co-morbidity and shared features between anxiety disorders and substance abuse, there has not yet been an investigation of IU and drug-dependency.

Psychoactive drugs are often used as a method to reduce negative affect elicited by stress or distress (Khantzian, 1985; Sinha, 2001). Drugs may be used as a way to cope with unpleasant emotions and anxiety that are elicited by IU (Carleton, 2016; Robinson, Sareen, Cox, & Bolton, 2009), or to avoid the distress felt when thinking about an uncertain future. However, there is a dearth of investigation into how IU relates to substance abuse. Based on a comprehensive review of IU research, there is a strong argument for examining the link between IU and addiction, given IU's role in psychopathologies that are highly co-morbid with addiction and which share similar features. The existing research on IU and substance use is limited to motivations for drinking alcohol. Two recent studies found that IU predicts using alcohol as an avoidance strategy to cope with worry and negative affect (Kraemer, McLeish, & Bryan, 2015; Oglesby, Albanese,

Chavarria, & Schmidt, 2015). Negative drinking motivations, such as coping or peer conformity, are linked to alcohol abuse and increase the risk of developing an alcohol use disorder (Carpenter & Hasin, 1999; Cooper, Frone, Russell, & Mudar, 1995; Cooper, Russell, Skinner, & Windle, 1992; Park & Levenson, 2002). There is a need to investigate the relationship that IU has with substances other than alcohol, and how IU may impact problematic substance use behaviours that lead to addiction. IU may be a risk factor for developing an addiction if drug use is employed as a long term coping strategy in the face of unavoidable uncertainty.

1.7 Aims and structure of the thesis

Associations between IU and individual differences common to addiction highlight the importance of further research of this topic. Impulsive traits and behaviours are cardinal features of addiction that can impair decision-making, particularly under uncertainty. The overall aim of this thesis is to investigate relationships between IU and impulsivity in the context of opioid dependency. The thesis consists of four empirical chapters that address these topics individually, followed by a synthesis of the results that draws a clearer picture of the role of IU in addiction. A stronger understanding of the role of IU in opioid dependency will contribute to improved substance abuse treatment, as well as inform transdiagnostic therapy for related psychological disorders.

Chapter 2

Although there is clear evidence that anxiety and impulsivity are associated with substance abuse, there is a paucity of research examining the role of IU in this disorder. IU has been linked to a number of anxiety disorders, and it has been postulated by recent research that anxiety felt in the face of uncertainty may result in impulsive decision-making (Luhmann et al., 2011; Pawluk & Koerner, 2013). The study presented in chapter two tested for the first time whether opioid-dependent individuals are less tolerant of uncertainty compared to a healthy comparison group. Chapter 2 also investigates whether self-reported impulsive personality traits moderate the relationship between opioid-dependency and IU, and aims to illuminate how IU may be related to deficits in impulse control that are characteristic of compulsive drug taking behaviour. The following publication is a product of the work conducted in Chapter 2:

Garami, J., Haber, P., Myers, C., Allen, M., Misiak, B., Frydecka, D., & Moustafa, A. (2017). Intolerance of uncertainty in opioid dependency – Relationship with trait anxiety and impulsivity. *PLoS One, 12*(7).

Chapter 3

Chronic drug use has been associated with a dysfunction of the dopaminergic reward system that may predate or be a product of drug addiction. Furthermore, abnormal reward feedback learning has been observed in drug-addicted individuals and clinical populations that exhibit dopamine dysregulation (Frank, Samanta, Moustafa, & Sherman, 2007; Frank, Seeberger, & Reilly, 2004; Haber & Behrens, 2014; Moustafa, Krishna, Eissa, & Hewedi, 2013). The way in which one responds to feedback, particularly negative feedback, may

suggest impairments in impulse control and may negatively affect optimal learning. Previous studies have largely utilised deterministic feedback learning measures that have limited generalisability, as the outcomes of daily decisions often fluctuate in unpredictable ways. Chapter 3 presents a study that uses a probabilistic feedback learning paradigm to assess the ability to learn from uncertain reward and punishments in opioid-dependent individuals, as well as impulsive responses to unpredictable feedback. Only one study to date has investigated probabilistic feedback learning in the context of opioid dependency (Meyers et al., 2016), and Chapter 3 builds upon this study to be the first to correlate IU with probabilistic learning and responsiveness to uncertain feedback. These relationships provide further insight into how negative beliefs about uncertainty observed in opioid-dependent individuals may negatively impact their capacity to effectively learn from reward and punishment in everyday life.

Chapter 4

Excessive risk taking is also a common feature of drug addiction and is exemplified by problematic drug use, particularly opioids, which carry a high risk of overdose. Uncertainty is inherent in risk-taking situations, as at least one of the possible outcomes is undetermined. Risk taking involves a decision between uncertain outcomes based on the subjective value one places on each option relative to the probability of its occurrence. Humans tend to devalue a reward as the odds against receiving it grow larger, and this inclination becomes maladaptive when it fails to maximise benefits (or minimise losses) over the long run. The study presented in this chapter is the first to utilise the probability

discounting (PD) paradigm to assess maladaptive risk-taking in opioid-dependent individuals. The PD measures developed in Chapter 4 involve hypothetical monetary outcomes, and include both probabilistic losses as well as rewards in consideration of the potential losses incurred by opioid abuse. Furthermore, differences between PD of monetary gains compared to losses have received comparably less attention in the PD literature, particularly in the context of addiction. Chapter 4 also provides an analysis of how IU may influence risk-taking in opioid dependent individuals compared to controls.

Chapter 5

It can be argued that the way in which one discounts monetary outcomes may not generalise to behaviour outside the laboratory. In respect to this limitation, the novel PD tasks developed in Chapter 5 comprise hypothetical health improvements and detriments, similar to health outcomes experienced by chronic drug users. Health outcomes were specifically chosen for this study because of their applicability to the physical and psychological consequences of continued drug use versus those of abstinence. Similarly to Chapter 4, differences in PD rates were assessed between opioid-dependent individuals and healthy controls, and the relationships with IU were examined. Finally, comparisons are made between the discounting patterns observed in Chapters 4 and 5.

1.8 Research setting

The studies presented in this thesis were conducted at the Drug Health Services and Opioid Treatment Program at the Royal Prince Alfred Hospital in

Sydney, Australia. All patient participants in the empirical studies reported in the thesis were recruited from this program. Patients are diagnosed for opioid use disorder and receive daily methadone or buprenorphine maintenance therapy. Given the chronic nature of opioid addiction and the high rate of relapse after abstinence-based therapy, opioid maintenance programs are important in reducing the personal and societal harms associated with opioid addiction (World Health Organisation, United Nations Office of Drugs and Crime, & Joint United Nations Programme on HIV/AIDS, 2004). Methadone is the most common form of maintenance treatment, and is a long-acting opioid that binds to endogenous opioid receptors and reduces cravings, prevents withdrawal and dampens the effect of other opiates (Kunc, Ketchen, Gorzelanczyk, & Fareed, 2015). Buprenorphine is an alternative opioid maintenance medication that has a lower risk for overdose than methadone and is often prescribed for short-term treatment in patients with good prognostic factors (Kahan, Srivastava, Ordean, & Cirone, 2011).

While methadone and buprenorphine are longer-acting opioids compared to morphine or heroin, patients are required to attend the clinic daily to receive their dose. Failure to take one's daily medication can result in craving and withdrawal symptoms (Koob & Le Moal, 2006), which can motivate patients to seek out illicit opioids. Some patients are also required to adhere to opioid treatment as part of a court order. Consequently, all of the experimental tasks used in the present thesis took place at the clinic shortly after patients received their daily medication (0-2 hours) to ensure participation would not interfere with treatment. The studies conducted in this thesis were approved by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health District.

Chapter 2 – Intolerance of uncertainty and self-reported impulsivity

2.1 Introduction

As there has been no research to date investigating IU and drug addiction, the primary purpose of the study presented in this chapter is to assess whether opioid-dependent individuals experience higher levels of IU compared to a non-drug abusing control group. Because impulsivity and anxiety are common traits to addiction, we also examined whether there is an association between IU and impulsivity and whether this relationship might hold equally in opioid-dependent patients and healthy controls.

Typically, IU is associated with overly cautious and carefully considered behaviour, but there is also evidence that IU may promote hasty and maladaptive decisions (Pawluk & Koerner, 2013). The fear of uncertain future events has been associated with heightened psychophysiological reactivity and amplified startle reflexes in anticipation of an unpredictable negative event (Nelson et al., 2016). IU has been linked to the propensity to make rash decisions (Furnham, 1994) as a way to alleviate distress in stressful situations (Pawluk & Koerner, 2013). IU has also been related to a preference for an immediate reward as relative to a more beneficial delayed reward, which has been interpreted as an aversion to the uncertainty involved in attempting to improve a future state (Worthy, Byrne, & Fields, 2014). Individuals higher in IU also show a tendency to select an immediately available, but less probable reward rather than wait for one with better odds (Luhmann et al., 2011), ostensibly because the aversive state of uncertainty motivates a quick, but suboptimal, resolution.

Decisions made by individuals with poor impulse control (such as chronic drug users) may be disproportionally impacted by uncertainty, and uncertainty in one's environment has been shown to deplete the willpower needed to resist temptation (Milkman, 2012). Therefore, uncertainty may further impair the ability of an impulsive person to make choices that are beneficial in the long term. Increased activity in brain areas responsible for coding stimuli salience suggests that drug abusers may feel a greater pressure to act in uncertain situations because they find uncertain stimuli more salient and/or rewarding (Leland, Arce, Feinstein, & Paulus, 2006). There is evidence that IU is related to dysfunction in the dopaminergic system and prefrontal executive control, which may contribute to the disordered processing of pleasurable stimuli (Gorka et al., 2016) that has been observed in drug abusing individuals.

The current chapter will assess impulsivity specifically in terms of self-reported thoughts, attitudes and behaviours as measured by the Barratt Impulsivity Scale (BIS). Originally created in 1959 as a framework for impulsivity as an overarching personality construct, the BIS is currently in its 11th revision (BIS-11) and considered to be the gold-standard self-report measure of impulsivity (Stanford et al., 2009). Three subfactors have been identified by Patton, Stanford, and Barratt (1995): Attentional impulsivity (inability to control ones' attention or focus), motor impulsivity (acting quickly without forethought), and non-planning impulsivity (not planning for the long-term future). Each subtrait is comprised of two first-order factors, which are summarised in Table 2.1. The full BIS-11 questionnaire can be found in Appendix A. The BIS-11 has robust internal consistency (α = .83) and retest reliability (r = .83), as well as good convergent validity with the EIS, the BIS/BAS, and the ZSS

(Stanford et al., 2009). Total BIS score is typically used as an index of impulsivity, but the individual subscales are also informative and have good internal consistency (α = .74, .59 and .72 for attentional, motor, and non-planning, respectively). Total BIS-11 scores will be the primary indicator of impulsivity, as its three-factor structure has been questioned (Reise, Moore, Sabb, Brown, & London, 2013; Steinberg, Sharp, Stanford, & Tharp, 2013). Nonetheless, assessing the subtraits is important to better understand the individual contributing factors to impulsivity in drug addiction.

Table 2.1

First and second order factors of the BIS-11 identified by Patton et al. (1994)

Second-order	First-order	Description	Example item
Attentional	Attention	Focussing on a current task	"I don't 'pay attention'"
	Cognitive instability	Intrusive or racing thoughts	"I often have extraneous thoughts when thinking"
Motor	Motor	Acting on the spur of the moment	"I act on 'impulse'"
	Perseverance	A stable lifestyle	"I change jobs"
Non-planning	Self-control	Thinking and planning carefully	"I say things without thinking"
	Cognitive complexity	Enjoying challenging mental tasks	"I like to think about complex problems"

Research questions and hypotheses

1. Do opioid-dependent patients who receive opioid maintenance therapy report higher levels of IU than non-drug-abusing control participants?

2. In what way does IU relate to self-report impulsivity, and which types of impulsivity measured by the BIS-11 have the strongest association with IU once anxiety is accounted for?

3. Is the relationship between IU and self-reported impulsivity different in opioid-dependent patients compared to controls?

Given that drug abuse is associated with neurological abnormalities in stress and reward pathways, it was anticipated that patients would report greater IU. Furthermore, IU will predict greater impulsivity in opioid-dependent patients, but not control participants.

2.2 Method

Participants

The study sample comprised of 177 participants, of which 112 were opioid-dependent patients and 69 were healthy comparisons. Patients were being treated for opioid addiction by either methadone or buprenorphine. The control group participants were recruited from psychology students at Western Sydney University and from the wider western Sydney community, through

snowballing and advertisements. A history of opioid use or a score higher than 11 on the Drug Abuse Screening Test (described in detail below) were exclusion criteria for the control participants. All participants completed a demographic questionnaire assessing age, gender, years of education, and efforts were made to match control participants with patients on these variables. Patients also answered clinical questions regarding their age of first opioid use, current non-prescribed opioid use and any secondary drugs of abuse. Patients were considered to be poly-drug users if they reported using another drug of concern other than alcohol. Patients were also categorised as extra-medical opioid users if they reported non-prescribed opioid use in the past 30 days.

Measures

Drug Abuse Screening Test (DAST):

The DAST was developed by Skinner (1982) as a self-report screening tool for substance abuse disorders. The measure is comprised of 28 yes/no questions about the use of illicit drugs or misuse of medically prescribed drugs. Each "yes" response receives a score of 1, and each "no" response receives a score of zero (three items are reverse scored). Scores are tallied and a sum equal to or greater than 12 indicates a definite substance abuse problem. A cut-off score of <12 was utilised in the current thesis as an exclusion criterion for control participants, as this cut-off score has shown to accurately identify both individuals with and without a SUD (Gavin, Ross, & Skinner, 1989).

The Intolerance of Uncertainty Scale (IUS):

The IUS is a 27-item self-report scale measuring negative beliefs about the nature of uncertainty and its consequences (Freeston et al., 1994). The

English version developed and validated by Buhr and Dugas (2002) was used in the current thesis and can be found in Appendix B. IU is measured by the extent to which the respondent relates to statements that describe thoughts and reactions to uncertainty on a 5-point scale (1 = not at all characteristic of me to 5 = entirely characteristic of me). Total IUS score is typically used as an index of IU, however two subfactors have been identified by Sexton and Dugas (2009). Factor 1 (IUS-1), is comprised of 15 items regarding the belief that uncertainty has negative self-referent implications and is detrimental to behaviour. Example items are: "Being uncertain means that I lack confidence" and "When I am uncertain, I can't go forward". The second factor (IUS-2) consists of 12 items that assess the belief that uncertainty is unfair and can spoil everything. Example items include: "It's unfair having no guarantees in life" and "One should always look ahead so as to avoid surprises". Subsumed within the subfactors are those identified by (Carleton, Norton, & Asmundson, 2007), which involve "paralysis" in the face of uncertainty (IUS-1) and "a need for predictability" (IUS-2).

Ratings are totalled for an overall IUS score and for the individual subscales. Total IUS score has shown high correlations with GAD, worry, anxiety, and depression and has excellent internal consistency (IUS-1 : α = .92 for and IUS-2: α = .90; Sexton & Dugas, 2009). The IUS also has good test-retest reliability (r = .74; Buhr & Dugas, 2002). The IUS has been subject to many factor analyses and researchers have not reached a final consensus on how the subfactors should be defined (Birrell, Meares, Wilkinson, & Freeston, 2011). As such, the IUS-1 and IUS-2 will be included in the statistical analyses of the present thesis, but the primary focus will be overall IUS scores as the measure of IU.

The Barratt Impulsivity Scale – 11th revision (BIS-11):

The BIS-11 is a 30-item self-report measure that evaluates impulsivity as a multifactorial behavioural and personality construct (Patton et al., 1995). Respondents rate whether a statement reflects the way they act or feel on a 4-point scale (1 = rarely/never, 2 = occasionally, 3 = often, 4 = almost always/always). Ratings are summed to obtain total and subscale scores (eleven items are reverse scored). The average total score for healthy adults is estimated to be around 62.3 (*SD* = 10.3), and a score of 72 or higher is thought to indicate a high level of impulsiveness (Stanford et al., 2009). Individuals with scores of 74 or higher have demonstrated greater aggression (Lawrence & Stanford, 1998) and low baseline levels of arousal (Mathias & Stanford, 2003). The BIS-11 has also shown strong convergent validity across clinical populations, including substance abuse disorder, depression, and bipolar disorder. And is correlated with deficient executive function, working memory and attention (Stanford et al., 2009).

The State Trait Anxiety Inventory for Adults (STAI):

The STAI is a 40-item self-report questionnaire developed by Spielberger, Gorusch, Lushene, Vagg, and Jacobs (1977), measuring state anxiety (defined by transient emotions elicited by specific scenarios) and trait anxiety (a relatively consistent predisposition to react to circumstances in an anxious way). The STAI is comprised of two forms: Form Y-1 assesses state anxiety, and was not administered in the current study as temporary feelings of anxiousness were not of interest. Form Y-2 assesses trait anxiety and requires respondents to indicate on a 4-point scale whether a statement reflects how they feel generally (1 = not

at all to 4 = very much so). Form Y-2 shows strong internal consistency (α =. 89) and retest reliability (r = .88; Barnes, Harp, & Jung, 2002). For the purposes of this chapter, form Y-2 will be referred to as the STAI, and can be found in Appendix C.

Procedure

All participants were administered paper-and-pen versions of the DAST, IUS, BIS-11 and the STAI, in order. For participants who had difficulty reading or writing, the researcher read aloud the questions and wrote down participants' answers.

Statistical analyses

The IBM SPSS Statistics software package (version 24) was utilized for the statistical analysis of the data in the current chapter, and all subsequent empirical chapters of the thesis. Independent-samples t-tests were used to assess mean differences in demographic variables between sample groups, and the distribution of males and females across groups was determined with the chi-square test. Independent-samples t-tests were used with poly-drug use and current opioid-use as independent variables and scores on the IUS, BIS-11, and STAI as dependent variables. Analysis of covariance (ANCOVA) was implemented to test differences in IUS, BIS-11 and STAI scores between groups, using age, years of education, and gender as covariates. Zero-order correlations were obtained between all measures and clinical variables, and hierarchical regression analyses were used to examine if the relationships between impulsivity measures were different between patient and control participants.

2.3 Results

The patient group was significantly older than the control group and had significantly fewer years of education. Gender was not distributed evenly between groups in that there were a higher proportion of females in the control group. Accordingly, age, years of education and gender were entered as covariates in the ANCOVAs. The participants' demographic and clinical characteristics can be found in Table 2.2

Table 2.2

Participant demographic and clinical characteristics

Characteristic	Mean (*SD*)		Statistic
	Control	Patient	
Age	36.58 (12.12)	40.27 (9.42)	t = -2.30*
Female (%)	49 (71.00%)	54 (47.40%)	χ^2 = 9.76**
Years of education	12.57 (2.06)	9.83 (12.06)	t = 8.67**
Age of first opioid use	---	19.00 (5.64)	---
Years of opioid use	---	21.01 (9.86)	---
Poly-drug user (%)	---	54 (49.10%)	---
Extra-medical user (%)	---	63 (34.4%)	---

* p < .05, ** p < .001

Eleven participants were not included in the analyses of certain measures due to failure to complete all the questions on the IUS (n=4), STAI (n=2), or BIS-11 (n=5). Data from these participants were included in analyses that did not involve the incomplete questionnaire. Results of ANCOVA revealed that patients scored significantly higher than the control group on the IUS, BIS-11 and STAI and subscales (all p < .001). Poly-drug or extra-medical opioid use did not have

significant effects on any of the questionnaire measures (all $p > .100$). When gender differences were assessed, males and females scored similarly on the IUS, but males reported significantly greater attentional impulsiveness, non-planning impulsiveness, and overall BIS-11 scores. Means, standard deviations, and statistical analyses can be found in Table 2.3.

Table 2.3

Means, standard deviations and ANCOVA results comparing IUS, BIS-11, and STAI trait scores between participant groups

Measure	Mean (*SD*)		*F*
	Control	Patient	
IUS	56.61 (16.83)	72.61 (24.07)	15.90*
IUS-1	28.43 (9.24)	37.68 (13.50)	17.81*
IUS-2	28.18 (8.34)	34.37 (11.51)	11.43*
BIS-11 total	59.19 (9.08)	73.55 (11.08)	48.26*
Attentional	15.51 (3.93)	18.75 (4.18)	14.92*
Motor	21.75 (3.66)	26.28 (5.05)	30.20*
Non-planning	21.93 (4.32)	28.83 (5.29)	43.17*
STAI trait anxiety	35.96 (8.20)	48.25 (12.45)	51.91*

* $p < .001$

Zero-order correlations revealed significant positive relationships between all the questionnaires and subscales (all $p < .001$), with the exception of motor subscale scores. Motor impulsiveness was correlated with IUS total and IUS-1 scores at the $p < .05$ level, and did not have a significant relationship with the IUS-2. Correlations between self-report measures and the demographic and clinical variables showed that education was significantly negatively correlated with the questionnaires and subscales, indicating that more years of education

predicted lower IU, anxiety and impulsivity. Years of opioid use did not correlate significantly with any of the independent variables. A multiple regression analyses was conducted to identify which impulsivity subtraits were the best predictors of IU when education and anxiety were accounted for. Education and anxiety were included because of their correlations with IUS scores. Results of the regression model showed that total IUS score was significantly predicted only by attentional impulsiveness (B = 1.26, SE = .43, p = .004).

A hierarchical moderated regression tested whether the relationship between overall impulsivity and IU were similar between patients and controls. Addiction status and total BIS-11 scores were entered in at step 1, for which the overall model was significant (F(2,171) = 14.71, p < .002) and accounted for 14.7% of the variance in IU. When an interaction term was included in step 2, it did not improve the model although it approached significance (B = .633, SE = .339, p = .064).

The second hierarchical moderated regression analysis assessed whether the relationship between attentional impulsivity and IU was different between participant groups. Addiction status and scores on the attentional impulsiveness subscale of the BIS-11 comprised step 1 of the model, for which the overall model was significant (F(2,174) = 26.41, p < .001) and accounted for 23.3% of variance in IU. Introducing an interaction term into step 2 explained an additional 2% of variance, which was significant (F(1,173) = 4.65, p = .032). The results of this regression can be found in Table 2.4. Simple slopes analysis revealed that there was a significant positive relationship between IU and attentional impulsiveness in the patient group (B = 2.550, SE = .455, p < .001), but not in the control group (p = .157). The interaction between attentional

impulsivity and IU between groups is depicted in Figure 2.1. It appears that IU predicts greater impulsivity only in opioid-dependent patients compared to healthy controls.

Table 2.4.

Moderation regression analysis summary predicting IUS from addiction status and attentional impulsiveness

Predictor	β	R^2	ΔR^2	F	ΔF
Step 1		.233		26.41**	
Group	.192*				
ATT	.378**				
Step 2		.253	.020	19.53**	4.65*
Group	-.392				
ATT	-.149				
Group x ATT	.929*				

ATT = Attentional impulsiveness BIS-11 subscale
* $p < .05$

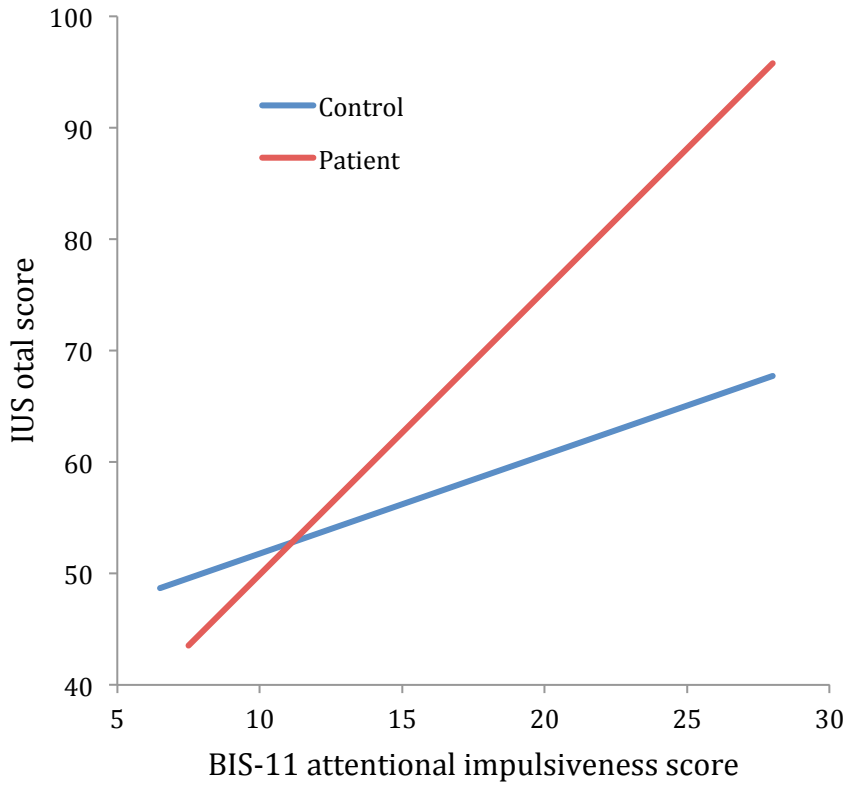


Figure 2.1. Attentional impulsivity predicting IUS scores between patient and control groups

2.4 Discussion

This study assessed the relationship between opioid-dependency, IU and facets of impulsivity as measured by the BIS-11. Firstly, our results showed that opioid-dependent patients in the course of opioid maintenance therapy report higher IU than a healthy control group. One possible interpretation is that addiction results from regularly taking drugs in order to cope with an often-unpredictable world. Chronic high levels of stress and poor coping strategies are associated with substance abuse (Sinha, 2008), and animal models have shown that stress may permanently alter the structure of the neural reward system in a way that increases the risk of developing addiction (Piazza & Le Moal, 1998; Sinha, 2001). Uncertainty can result in hypervigilance, which in drug-dependent

populations may result in enhanced attention to drug-related stimuli (Grupe & Nitschke, 2013). In addition, stress and anxiety associated with IU may lead to increased drug use and relapse (Jacobsen, Southwick, & Kosten, 2001; McCabe, Cranford, & Boyd, 2016; Sinha, 2001).

Alternatively, IU may develop after the onset of opioid addiction, or even reflect acute effects of current opioid therapy. Arguing against this interpretation is our finding that neither the duration of opioid use nor poly-drug abuse had a significant relationship with scores on the IUS. This suggests that IU may be a relatively stable personality trait predating addiction, rather than arising in the wake of opioid use. Only longitudinal studies can definitively answer whether IU is an antecedent to opioid exposure that confers a risk for the development of addiction.

The second aim of the study was to explore how IU relates to impulsive traits that are common to drug addiction, for which prior research findings were mixed. IU and trait anxiety in our study were associated with greater overall impulsivity, which supports research linking dimensions of impulsivity to worry (Belzer, Zurilla, & Maydeu-Olivares, 2002; Cougle, Goetz, & Timpano, 2012; Gay, Schmidt, & Linden, 2011), GAD (Miller, Flory, Lynam, & Leukefeld, 2003; Pawluk & Koerner, 2013; Worthy et al., 2014), and IU (Luhmann et al., 2011; Pawluk & Koerner, 2013; Worthy et al., 2014). We also found that when anxiety was accounted for, attentional impulsiveness was the only BIS-11 subtrait that significantly predicted IU. Attentional impulsiveness is characterised by an inability to control one's attention or concentration, and is a deficient cognitive process that may underpin many impulsive behaviours (Patton et al., 1995). Impulsivity is delineated by disordered decision-making that results in adverse

consequences. Accordingly, difficulty focusing on important tasks can prevent advantageous choices and behaviours. Attentional impulsiveness may also motivate one to seek out more stimulating activities at one's detriment. For example, attention deficit/hyperactivity disorder (ADHD) is characterized by extreme difficulties in focusing attention that most often results in social, academic and occupational disadvantages (American Psychiatric Association., 2013). ADHD is correlated with attentional impulsivity (Malloy-Diniz, Fuentes, Leite, Correa, & Bechara, 2007; Müller et al., 2007), and illustrates the way in which lack of attentional control results in maladaptive decision-making. From these results, we can conclude that poor attentional control is a predominant driving factor of the relationship between impulsivity and IU observed in the current study.

When the links between impulsivity and IU were analysed between participant groups, a significant positive relationship between attentional impulsivity and IU was observed only in the patient group. IU and attentional impulsivity were not meaningfully associated in control participants. There was also a similar positive correlation between overall BIS-11 impulsivity and IU that was unique to patients. While not significant, the trend neared the threshold, which makes the relationship noteworthy nonetheless. It appears that there is a particular interplay between impulsivity and IU in opioid-dependent individuals that is not present in non-drug-abusing populations. Impulsivity and IU may additively combine to heighten one's risk for opioid addiction, so that individuals with only one of these traits are less likely to develop addiction. Increased activity in the striatum in response to decision-making under uncertainty has been correlated with BIS-11 impulsivity scores, and stimulant drug users have

exhibited stronger neural responses to uncertainty in the striatum (Leland et al., 2006). In regards to attentional impulsivity, the damaging effects that chronic opioid use may have on executive control may also arguably diminish control over directing and focusing attention on important, but not particularly enjoyable tasks.

Limitations

There are several limitations of the current study that need be taken into account and used to direct future research. Firstly, the self-report methods used here are prone to recall errors or intentional misreporting of sensitive information for social desirability (e.g. "I plan for financial security"). The addition of an experimental manipulation for impulsivity would validate the current results and guide our interpretations. This is addressed in the following chapters, which will involve behavioural measures of impulsivity. The results of the current study may have also been influenced by the mismatch between the control and patient groups in age, gender, and education. Previous research using opioid-maintenance therapy patients often has difficulty in matching this group closely to community controls in educational attainment because patients tend to have completed far fewer years of schooling (Myers et al., 2017; Myers et al., 2016; Sheynin et al., 2016). However, our statistical analyses accounted for differences in demographic characteristics and showed that these variables did not account for significant variations in the dependent variables. The relationship between impulsivity and IU in opioid addiction is not straightforward and requires further research to clarify the role that IU plays as a factor in theories of drug addiction.

Chapter 3 –Probabilistic feedback learning and impulsive decision-making

Chapter 2 revealed that impulsivity as a self-reported personality construct predicts greater IU in opioid-dependent patients. While self-report methods are valid assessment methods, they require respondents to objectively assess their own behavioural tendencies. Accordingly, Chapter 3 utilises a behavioural measure to assess impulsive decision-making. Humans are frequently presented with complex situations in which they need to learn from feedback and modify their behaviour in an adaptive manner. The current chapter investigates how impulsive reactions to uncertain negative feedback differ between opioid-dependent individuals and healthy controls, and how such reactions are impacted by one's ability to tolerate uncertainty.

3.1 Introduction

The transition from initial drug use to addiction involves incentive-based associative learning (Di Chiara, 1999; Robinson & Berridge, 2001). Learning the relationships between stimuli, response and outcome guides our behaviour, and over time these links become strengthened and turn into habits, such as drug abuse. Difficulty learning from previous positive and negative experiences may interfere with adaptively modifying behaviours (Haber & Behrens, 2014). For example, we learn from an early age that placing a hand (response) on a hot surface (stimulus) results in pain (negative outcome). One type of associative learning is probabilistic category learning, in which a response to a stimulus does not result in the same outcome 100% of the time. Probabilistic feedback

tasks allow us to assess decision-making under uncertainty by changing the contingencies between the outcome and stimulus response (Bland & Schaefer, 2012). In the probabilistic learning paradigm, one pattern of responding maximises rewards (or minimises losses), regardless of inconsistent feedback. A typical probabilistic feedback task requires the participant to assign various stimuli to different categories over multiple trials, and learning is assessed by the proportion of optimal guesses made over the course of the task. Unlike a deterministic task, the probabilistic design occasionally violates the expectancy that a certain stimuli will be associated with a specific category. The optimal strategy is to select the most-often correct category for a particular stimulus, regardless of occasional trials that are not rewarded.

Associative learning is largely controlled by the dopaminergic system in the basal ganglia (Belin, Jonkman, Dickinson, Robbins, & Everitt, 2009), which has been implicated in diminished probabilistic feedback learning (Haber & Behrens, 2014). Support for the connection between dopamine and feedback learning can be found in clinical populations of dopaminergic dysfunction related disorders, such as Parkinson's disease. Patients diagnosed with Parkinson's disease have exhibited a diminished learning from reward compared to healthy controls and medicated Parkinson's patients, but perform similarly to or better than controls and medicated Parkinson's patients when learning from punishment (Frank et al., 2007; Frank et al., 2004; Moustafa et al., 2013; Piray et al., 2014). Reward learning can be improved by the administration of dopamine agonists, but these medications can simultaneously impair punishment learning (Bódi et al., 2009; Cools, 2006). It appears that Parkinson's disease is associated

with enhanced punishment learning as well as with impaired reward learning, and that this pattern is most likely accounted for by dopamine deficiency.

Individuals with schizophrenia exhibit deficits in dopamine production and have demonstrated difficulty learning from probabilistic reward compared to healthy controls (Waltz, Frank, Robinson, & Gold, 2007). Abnormalities in dopamine function are also associated with post-traumatic stress disorder (PTSD), as research has found that veterans experiencing severe PTSD symptoms exhibit superior reward learning compared to veterans with little or no PTSD symptoms (Myers et al., 2013). However, the veteran groups demonstrated similar punishment learning performance (Myers et al., 2013), and Parkinson's patients do not always perform differently on punishment learning tasks than healthy individuals (Moustafa et al., 2013). This suggests that dopamine deficiency may have stronger involvement with reward learning than with punishment learning.

Research has shown that there are also abnormalities in probabilistic feedback learning in substance abusers. Long-term cocaine users show deficiencies in dopamine transmission in the striatum, a key area for associative learning (Martinez et al., 2004; Martinez, Narendran, Foltin, & Slifstein, 2007), and exhibit a dampened ability to learn from both positive and negative probabilistic outcomes (Vadhan, Hart, Haney, van Gorp, & Foltin, 2009; Vadhan et al., 2014). Other research shows that cocaine-dependent individuals are impaired in learning from probabilistic positive outcomes relative to negative outcomes, and are worse at learning from positive outcomes compared to controls (Strickland, Bolin, Lile, Rush, & Stoops, 2016). However, research has not consistently found differences in probabilistic feedback learning in cocaine

dependency (Vadhan et al., 2008), or opioid dependency (Myers et al., 2016), and one study showed that the administration of amphetamine to a control group actually improved reward-learning performance (Lane et al., 2014).

Using past experiences to take the most optimal course of action is essential to adaptive decision-making (Kennerley et al., 2006). Decisions are often made under uncertainty and require one to decide based upon the expected outcomes of the possible options at hand. These expectations are often impacted by recent history, and the probabilistic learning paradigm allows us to assess the way in which one reacts to previous outcomes and how those responses relate to learning performance. There are two types of responses that are of interest in a probabilistic learning task. A "win-stay" response is one that repeats the previously rewarded category choice for a particular stimuli. A "lose-shift" response is a switch to the alternate option following a punished category selection. A pattern of lose-shift responses may reflect maladaptive decision-making in which an optimal strategy is deserted in response to an expectancy violation. In this sense, a lose-shift response can be conceptualised as an impulsive, "knee jerk" reaction. Differences in win-stay/lose-shift patterns of behaviour have been observed in addiction literature. Balconi, Finocchiaro, and Campanella (2014) found that cocaine users tended to repeat previously rewarded responses more than non-drug using controls and scored higher on sensitivity to rewards. Heroin users have made fewer lose-shift responses on another probabilistic learning task than healthy controls, and lose-shift responding was associated with sub-optimal performance overall (Brevers et al., 2014; Yan et al., 2014). Conversely, opioid-dependent individuals have shown more lose-shift responses on a probabilistic feedback learning task employed by

Myers et al. (2016). It is of interest to understand how opioid-dependent individuals respond to punishments, as punishment sensitivity appears to be both attenuated and heightened in drug abusers.

The role of uncertainty

Adaptive decision-making is dependent upon learning the relationship between a stimulus, response and outcome, and uncertainty arises when this relationship is unexpectedly violated. Uncertainty exists in a probabilistic feedback task because the outcomes of the available options are at times unpredictable. Decision-making under these uncertain circumstances requires one to have the cognitive capability to infer whether the unexpected feedback signals a change in the relationship with the response, and if one needs alter the responses strategy (Kennerley et al., 2006). This process necessitates executive functioning, working memory and self-regulation (Milkman, 2012; Venkatraman & Huettel, 2012), and proper functioning of neurotransmitters that signal unexpected uncertainty, such as acetylcholine and noradrenaline (Kennerley et al., 2006). Decision-making subject to uncertainty also activates areas of the brain responsible for learning in response to performance feedback (Behrens et al., 2007; Matsumoto et al., 2007). Deficits in this activation have been exhibited by opioid addicts (Ersche et al., 2012a; Yan et al., 2014), which can impede adaptive responses to feedback. In summary, difficulty in cognitively processing uncertainty may impair learning from probabilistic feedback due to the unpredictability of outcomes and occasional expectancy violations. Uncertainty has also been related to changes in reward system functioning, in that neural activity in response to a reward (reward-related positivity; RewP) is diminished

when a reward is experienced in an unpredictable context. This was demonstrated in a study conducted by Nelson et al. (2016) who found that RewP was inhibited during a gambling task when participants listened to unpredictable tone sequences. Furthermore, stress and anxiety elicited by uncertainty has the potential to dampen neural sensitivity to reward (Nelson et al., 2016; Porcelli, Lewis, & Delgado, 2012) and can attenuate learning from rewards (Bogdan & Pizzagalli, 2006).

IU may also impact probabilistic learning by biasing response strategies after feedback. High IU has been associated with increased win-stay behaviour in a conditioned place preference task that has been widely used in the study of addiction (Radell, Myers, Beck, Moustafa, & Allen, 2016). In this task developed by (Radell et al., 2016), participants explore two virtual rooms with different frequencies of rewards (a "rich" room versus a "poor" room). During a post-test, the participant's preference for each room is assessed. Participants with higher IU exhibited a tendency to enter the rich room first compared to those with lower IU, who entered the rich and poor room at similar rates. The authors concluded that high IU biases an individual towards exploiting known rewards and away from exploring other potentially (more) rewarding options. Interestingly, decreases in lose-shift responding have been related to paralysis or impaired functioning in response to uncertainty (Hong & Lee, 2015; Nelson et al., 2016), suggesting that individuals with high IU make more preservative responses and may be less influenced by unexpected negative feedback. This pattern of responding may ultimately result in poor learning performance. In Chapter 2 of the present thesis, self-reported impulsivity predicted IU in opioid-dependent patients. Chapter 3 investigates how IU relates to impulsive

responses to feedback in opioid-dependent individuals, and their capacity to learn from probabilistic feedback. The current chapter also examines whether win-stay or lose-shift responding are beneficial to probabilistic learning performance. IU may bias opioid-dependent patients towards exploiting known rewards and away from exploration of new rewarding options, and these strategies may negatively impact learning from feedback.

The study presented here builds upon the research conducted by Myers et al. (2016), who discovered that opioid-dependent individuals more frequently shift their responses after negative feedback than healthy controls. Correlational analyses were not conducted between learning performance and win-stay/lose-shift responses, and as a result, whether lose-shift responding in the probabilistic feedback task was suboptimal to learning is unknown. The current study seeks to expand upon Myers et al. (2016) by comparing how lose-shift responding relates to learning performance. This is of great importance, as one focus of the present thesis is how uncertainty relates to maladaptive decision-making. Increased lose-shift responses may reflect impulsive, poorly thought out choices, which ultimately result in poor feedback learning. Deficits in feedback learning are directly related to the development of addiction in that the negative consequences of drug abuse do not appear to discourage harmful drug-taking behaviour.

Research questions and hypotheses

1. Do opioid-dependent individuals demonstrate an impaired ability to learn from probabilistic feedback compared to non-drug abusing controls?

2. Do opioid-dependent patients adhere to optimal response strategies when faced with unexpected negative feedback, and how do win-stay and lose-shift response strategies relate to overall learning performance?

3. Does IU relate to probabilistic feedback learning performance or to impulsive reactions to negative feedback? Are these associations similar between opioid patients and controls?

Based on previous work with opioid-dependent cohorts, it is expected that optimal responses on a probabilistic feedback learning task will be comparable between opioid patients and controls. However, it is also expected that patients will be more reactive to negative feedback (i.e. demonstrate greater lose-shift responses) in a way that hampers learning performance. Given that IU reflects heightened threat appraisals of uncertainty, we hypothesise that IU will positively correlate with lose-shift responses.

3.2 Method

Participants

The study sample was comprised of 69 opioid-dependent patients receiving opioid-maintenance medication at the Drug Health Services and Opioid

Treatment program. Thirty-five healthy control participants were recruited from psychology students and Western Sydney University and from the wider western Sydney community via snowballing and advertisements. Exclusion criteria for the control group was a history of opioid dependence or a score greater than 11 on the DAS, as described in the previous chapter. Patients completed a clinical interview regarding their history of drug use, and were categorised as poly-drug patients if they reported using non-opioid substances other than alcohol, and were considered to be extra-medical opioid users if they reported using non-prescribed opioids in the past 30 days.

Materials

Probabilistic feedback learning task

The probabilistic learning task is computer-based and is comprised of 80 reward learning trials and 80 punishment learning trials, which are randomly intermixed. On each trial, participants are asked to guess whether four unique images belong to "Category A" or "Category B" by pressing the corresponding A or B key on the computer keyboard.

Reward learning trials: Two images are presented on-screen and belong to Category A and Category B with differing probabilities. Image 1 (S1) belongs to Category A with 80% probability and to Category B with 20% probability. Conversely, image 2 (S2) belongs to Category A with 20% probability and Category B with 80% probability. On each reward learning trial, participants either receive 25 points if they categorise the image correctly (displayed as +25

on the computer screen) or receive zero points if they answer incorrectly. Therefore, incorrect guesses are not punished, and the participants are not provided with feedback that explicitly signals an incorrect guess.

Punishment learning trials: Punishment learning trials involve two unique images. Similar to the reward-learning trials, image 3 (S3) belongs to Category A with 80% probability and to Category B with 20% probability, and image 4 (S4) belongs to Category A with 20% probability and Category B with 80% probability. Incorrect answers incur a loss of 25 points (displayed as -25 on the computer screen) and correct answers result in no point change. Correct guesses are not explicitly rewarded, nor is there feedback indicating a correct guess. The category and reinforcement structure of the probabilistic feedback task can be found in Table 3.1.

Table 3.1

Stimuli, category and feedback structure for the reward and punishment feedback trials

Stimulus	Probability category A	Probability category B	Correct response feedback	Incorrect response feedback
1	80%	20%	+25 points	No feedback
2	20%	80%		
3	80%	20%	No feedback	- 25 points
4	20%	80%		

The task was administered on a Macintosh i-book, of which the keyboard was masked except for two keys, labelled “A” and “B”. The following instructions were given to each participant prior to testing:

In this experiment, you will be shown pictures, and you will guess whether those pictures belong to category "A" or category "B". A picture does not always belong to the same category each time you see it. If you guess correctly, you may win points. If you guess wrong, you may lose points. You will see a running total of your points as you play. We will start you off with a few points now. Press the mouse button to begin practice.

Testing began with a practice session in which the participant completed some trials in order to become familiar with the reward, punishment and no feedback outcomes. Participants were then presented with a summary of instructions on-screen:

For some pictures, if you guess CORRECTLY, you WIN points (but, if you guess incorrectly, you win nothing). For other pictures, if you guess INCORRECTLY, you LOSE points (but, if you guess correctly, you lose nothing). Your job is to win all the points you can – and lose as few as you can. Remember that the same picture does not always belong to the same category. Press the mouse button to begin the experiment.

Participants were allotted with 500 points at the start of the experiment. Reward and punishment trials were presented in a random order, and the relevant feedback was displayed on the screen immediately following each guess (+25 or -25). A running total of points was displayed in the bottom right corner of the computer screen throughout the experiment. Examples of a correct and an incorrect trial can be found in Figure 3.1.

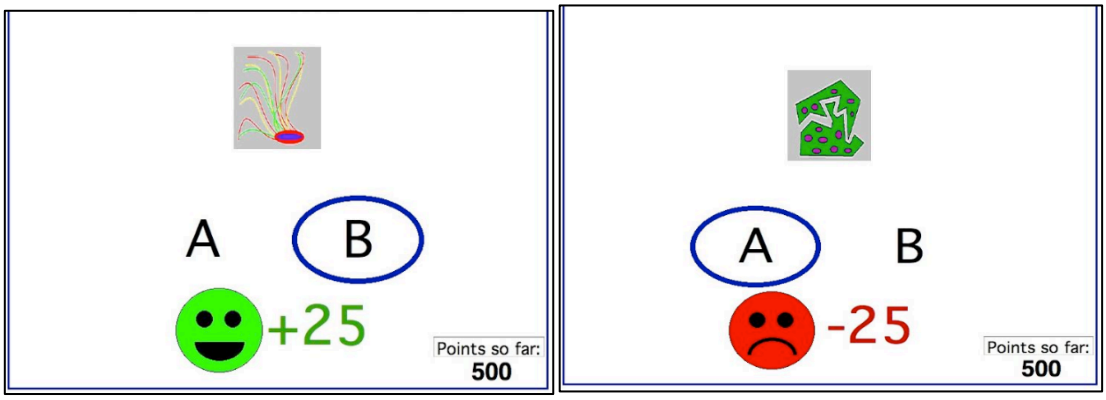


Figure 3.1. An example learning trial for Stimulus 1 and Stimulus 3 as presented to participants on-screen

Overall performance on the probabilistic classification task is calculated by the total number of points accumulated at the end of the experiment. Reward and punishment learning are calculated separately as a proportion of optimal responses made on reward and punishment learning trials. Optimal responses are defined as those in which the participant chooses the category that an image is most likely to belong to, regardless of whether the guess was correct on that trial. For example, S1 has 80% probability of belonging to category A, therefore A is an optimal response for this image on each trial even though 20% of the time this answer is incorrect.

Win-stay responses are repeated category selections on the trial immediately following a rewarded (or unpunished) trial for that stimulus. An example of a win-stay response is assigning S1 to Category A on a given trial if Category A was correctly guessed on the previous presentation of S1. Conversely,

lose-shift responses are those in which the participant does not repeat the preceding punished (or non-rewarded) categorisation for an image. The overall number of correct guesses impacts the number of win-stay and lose-shift responses, thus win-stay/lose-shift responding was quantified as a proportion of total correct and incorrect answers, respectively.

Drug Abuse Screening Test (DAST)

The DAST is described in Chapter 2.

Intolerance of Uncertainty Scale (IUS)

The IUS is described in Chapter 2.

Procedure

Patient participants were first interviewed about their current and past drug use and control participants completed the DAST. All participants completed the feedback learning task before answering a pen-and-paper version of the IUS.

Statistical method

Preliminary independent-samples t-tests and chi-squared analyses were conducted to ascertain whether there were any group differences in demographic variables. Total points earned on the probabilistic learning task were analysed with ANCOVA to determine group differences in learning performance. The proportion of optimal responses on the reward and punishment learning trials were calculated and analysed by a mixed ANOVA, with group as the between-subjects variable and trial type as the within-subjects

variable. Win-stay responding was calculated as a proportion of correct guesses across both trial types (rewarded or non-punished), and lose-shift responding was calculated as a proportion of incorrect responses across trial types (punishment or non-reward). Group differences in win-stay responses and lose-shift responses were analysed using mixed-factors ANOVA, with win-stay and lose-shift responding as the within groups factor. ANCOVA was used to assess the differences between group scores on the IUS and bivariate correlations were conducted between the IUS, behavioural data and clinical characteristics.

3.3 Results

Participants in the control and patient group were similar in age, but patients had completed significantly fewer years of education and groups were imbalanced in gender distribution. Consequently, years of education and gender were used as covariates in the between-group analyses. The clinical and demographic characteristics of the groups can be found in Table 3.2.

Table 3.2

Participant demographic and clinical characteristics

Characteristic	Mean (*SD*)		Statistic
	Control	Patient	
Age	39.03 (11.57)	39.86 (9.57)	t = .41
Education	12.14 (2.45)	10.00 (1.83)	t = -5.01**
Female (%)	25 (71.4%)	29 (40.6%)	χ^2= 8.84*
DAST	1.17 (1.24)	19.32 (5.03)	---
Age first use	---	19.69 (5.86)	---
Length use	---	20.25 (9.85)	---
Poly-drug user (%)	---	13 (12.5%)	---
Extra-medical user (%)	---	33 (53.2%)	---

* $p < .001$

ANCOVA revealed that the patient group had a marginally better mean total learning score than the control group, however this difference was not significant (p = .652). Repeated-measures ANOVA showed that there was no significant effect of group (p = .360) or trial type (p = .489) on performance, and there was not a significant interaction between group and trial type (p = .469). When win-stay and lose-shift responses were analysed, an interaction between group and response type was found ($F(1,78) = 16.474$, $p < .001$). The opioid-dependent group exhibited more lose-shift responses than controls ($F(1,78) = 15.247$, $p < .001$), but groups demonstrated a similar proportion of win-stay responses. Figure 3.2 depicts between-group differences on the feedback learning trials. ANCOVA also found that patients scored significantly higher than controls on overall IUS and subscales. Gender, extra-medical opioid use or poly-drug use did not have a significant effect on feedback learning performance,

feedback response type, or IUS scores (all $p > .05$). Results from between-group analyses can be found in Table 3.3.

Table 3.3.

Means, standard deviations and ANCOVA results comparing groups on feedback performance, response type and IUS scores

Measure	Mean (*SD*)		*F*
	Control	Patient	
Optimal reward	50.75 (21.52)	56.35 (22.23)	0.90
Optimal punishment	58.14 (12.87)	59.20 (12.24)	0.04
Total Score	605.00 (283.47)	649.64 (332.25)	0.20
Proportion win-stay	.673 (.13)	.668 (.14)	0.17
Proportion lose-shift	.356 (.11)	.438 (.09)	14.78**
IUS	52.51 (12.25)	72.38 (24.90)	13.77**
IUS-1	31.85 (15.24)	38.00 (13.92)	6.15*
IUS-2	26.57 (5.98)	34.10 (11.89)	9.05*

* $p < .05$, ** $p < .001$

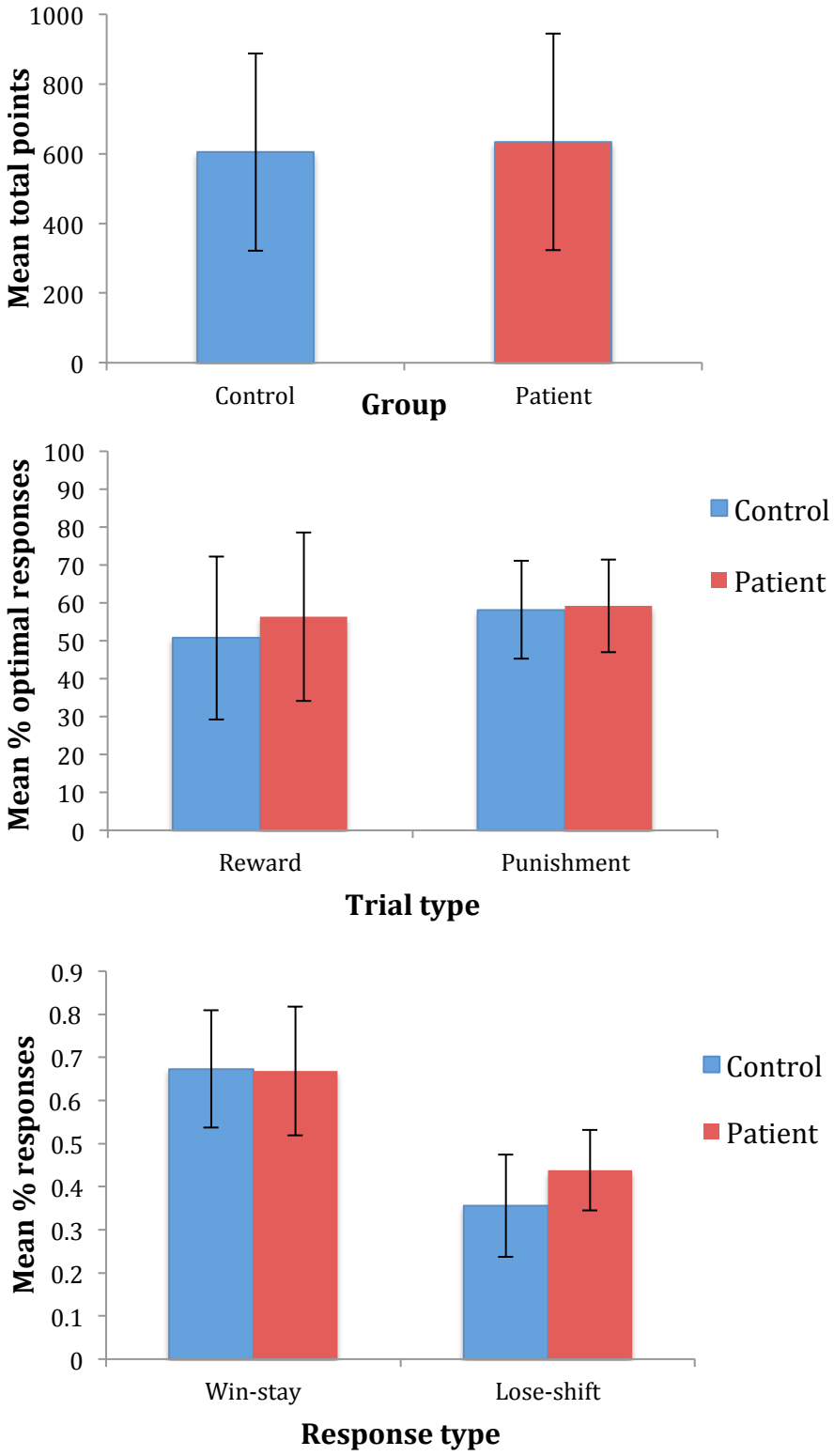


Figure 3.2. Mean group learning performance, optimal responding, and response type between groups

Zero-order correlations were obtained between all behavioural measures, the IUS and length of opioid use. IUS total score correlated positively and significantly with the number of optimal punishment learning choices, total feedback learning score, and proportion of win-stay responses. When the subscales of the IUS were analysed, a more nuanced relationship appeared. The IUS-1 was correlated solely with win-stay responding, while the IUS-2 was correlated with optimal punishment responses and total learning score. Win-stay responses were positively correlated with total learning performance and optimal responding on both reward and punishment trials. Conversely, lose-shift responding were negatively correlated with optimal choices on punishment learning trials. Length of opioid use was not meaningfully correlated with any other measure (all $p > .200$). Full zero-order correlations and statistical significances are found in Table 3.4. Visual inspection of scatterplots suggested that the relationship between IU and the feedback learning task variables were almost identical between groups. Accordingly, further regression analyses were not conducted.

Table 3.4

Zero-order correlations between learning performance, optimal responding, response type, IUS scores and length of opioid use

	IUS	IUS1	IUS2	RO	PO	TS	WS	LS	LU
IUS	---	.847**	.960**	.164	.194*	.196*	.226*	.012	-.044
IUS1		---	.776**	.118	.177	.155	.255*	.051	-.048
IUS2			---	.176	.206*	.223*	.174	.025	-.036
RO				---	.033	.830**	.348**	.454**	.036
PO					---	.487**	.738**	-.449**	-.136
TS						---	.561**	.171	.001
WS							---	-.439**	-.164
LS								---	.013
LU									---

IUS = Intolerance of Uncertainty Scale, RO = Optimal responses on the reward task, PO = Optimal responses on the punishment task, TS = Total feedback learning score, WS = Win-stay responses, LS = Lose-shift responses, LU = Length of opioid use
* $p < .05$, * $p < .001$

3.4 Discussion

This study examined the differences in probabilistic feedback learning between opioid-dependent individuals and healthy controls, and how responses to unexpected feedback relates to IU across and between groups. Patients marginally outscored controls in total points and number of optimal responses on reward trials, however this difference was not statistically significant. Our results replicate those of Myers et al. (2016) and furnish additional support for the study conducted by Vadhan et al. (2008), which revealed that optimal responding to a similar reward/punishment feedback task was comparable between cocaine-dependent participants and non-drug users. However, cocaine

users have also been shown to perform poorly compared to controls (Vadhan et al., 2009). The disparate findings of previous research, including the current study, may be attributed to different designs of probabilistic feedback measures. For example, tasks used by previous researchers provide explicit feedback on all trials, while the measure used in the current study included ambiguous feedback in the form of non-punishment and non-reward. It is possible that optimal responding may be impeded by the vagueness of some feedback. However, both groups performed similarly indicating that if there was an affect of ambiguity, it affected both groups similarly.

In regards to win-stay responding, the groups were similar in their likelihood to repeat a response to a stimulus that had received rewarding or non-punishing feedback on the previous trial. In other words, the opioid-dependent patients demonstrated comparable reward sensitivity to the control participants, which was unexpected given the reward system dysfunction and sensitisation to reinforcers prevalent in long-term drug users (Robinson & Berridge, 2001). Importantly, patients were more likely than controls to change responses after a punishment or non-reward. It appears that opioid-dependent individuals may be particularly reactive to negative feedback and/or particularly averse to punishments. Loss aversion has been related to dopamine function. The findings of the current study replicates those of Myers et al. (2016), and suggests that patients are more likely to switch response strategies when experiencing negative or non-confirmatory feedback.

Moreover, lose-shift responding was negatively correlated with optimal performance on punishment trials, indicating that a greater tendency to change response strategies after punishment can adversely impact learning from

negative feedback. This further suggests that sensitivity to punishment is a form of impulsive decision-making, in that it fails to adaptively alter behaviour to maximise the accrual of benefits. Particularly relevant to the prevention of drug relapse, we found that the patient group demonstrated greater lose-shift responses. Relapse is often triggered by stressful (McCabe et al., 2016) or distressing events, even in patients receiving methadone-maintenance therapy (Jaremko, Sterling, & Van Bockstaele, 2015), and more understanding about how negative incidences may trigger the return to drugs. On the other hand, greater win-stay responding was positively correlated with both optimal reward and punishment responses, which suggests that repetition of previously rewarded actions may be an advantageous learning strategy. These findings are also important for the development of successful addiction treatment, as adhering to abstinence is the long-term rewarding strategy that needs to be pursued despite occasional setbacks. Relapse is highly common in opioid addiction and understanding the cognitive mechanisms that hinder recovering individuals adherence to treatment, and return to treatment after relapse, is extremely valuable.

Scores on the IUS and IUS-1 were correlated with greater optimal responding on punishment trials, which suggests that IU may facilitate learning from punishments. IU is characterised by a tendency to interpret uncertain situations as threatening and highly aversive (Ladouceur et al., 2000), which may result in heightened attention to stimuli that can potentially result in negative outcomes. Greater attentiveness to aversive stimuli (e.g. uncertainty) may enhance associative learning between a particular stimulus and its negative outcome (Fiorillo et al., 2003), and sensitivity to punishment may serve as a

motivating factor to learn how to avoid aversive stimuli. Recent work with learning tasks has found that anxiety-vulnerable individuals demonstrate enhanced associative learning (e.g., classical eyeblink conditioning) in situations involving some form of uncertainty of stimulus presentation and trial timing (Allen, Myers, & Servatius, 2016; Allen et al., 1998; Holloway, Allen, Myers, & Servatius, 2014), possibly because more attention is paid to uncertainty. On the other hand, optimal responses on reward trials were not meaningfully correlated with IU, which does not support previous findings that IU is related to suboptimal decisions regarding probabilistic rewards (Luhmann et al., 2011). The current study provides evidence that IU may not be influenced by the uncertain nature of rewards in the probabilistic learning paradigm, possibly because uncertain rewards do not elicit a similar threat response produced by uncertain punishment.

Greater win-stay responding was positively correlated with total IUS and IUS-2 scores, which aligns with the results from the conditioned place preference task conducted by Radell et al. (2016). Our results suggest that an aversion to uncertainty, particularly a great desire for predictability and cognitive distress towards uncertainty, is related to continuing a rewarding response strategy rather than exploring new options. Interestingly, IU did not have a meaningful relationship with lose-shift responding, suggesting that IU does not have an impact on behaviour following violations of reward expectancy. This was unanticipated as experiencing a loss elicits negative emotions and activity in the amygdala (Sokol-Hessner, Camerer, & Phelps, 2013), and sad and angry emotional states have shown to impact decision-making (Andrade & Ariely, 2009; Harlé & Sanfey, 2007). It would be expected that because uncertain threat

is highly aversive to those with high IU, these individuals would have reacted emotionally to unpredictable punishments.

Limitations

The feedback provided in the current study involved hypothetical rewards and punishments in the form of points that did not translate into tangible outcomes. Vadhan et al. (2009) found that on a similar feedback task cocaine dependent participants' learning performance was improved when the outcomes were real monetary gains and losses. Furthermore, cocaine dependent participant's performance was improved so much as to become comparable to non-drug-using controls when actual money was at stake. In contrast, opioid-dependent participants in the current study performed similarly to controls with non-tangible outcomes, raising the possibility that the hypothetical nature of an outcome may not necessarily impact learning distinctly in drug abusing individuals and controls. Alternatively, the current study may have observed learning differences between groups had real monetary outcomes been at stake, given the extent to which cocaine abusers' learning performance improved in Vadhan et al. (2009). Actual money may have a heighted reinforcing effect for drug abusers, which would have predicted that opioid-dependent patients would outperform controls in a tangible monetary outcome task. This is only speculation, given that there was not a cash money task in the present study, but would be of interest to future investigation.

As was the case in Chapter 2, the demographic characteristics of the patient group were different than the control group in education level, which may have influenced the ability to learn. It is difficult to say how this may have

affected our results, as patients and controls scored similarly, and the patients actually accrued more points on the overall task. The cross-sectional design prevents making causal assumptions regarding addiction and performance on the experimental measures. However, the current study observed that the length of opioid use was not predictive of performance or responding type on the feedback tasks, further suggesting that responsiveness to negative feedback may predate addiction.

Chapter 4 – Probability discounting of hypothetical monetary rewards

We may conclude from Chapter 3 that opioid-dependent individuals tend to make impulsive decisions when receiving unpredictable negative feedback, and that a knee-jerk reaction to punishment is a suboptimal learning strategy. Chapter 4 continues the analysis of IU and impulsive decision-making under uncertainty in opioid addiction by focussing our attention on risk-taking.

4.1 Introduction

Effective decision-making in a risk situation involves assigning subjective values to the outcomes of the available options and selecting the option that is deemed the most advantageous relative to its risk. Strategic risk-taking can yield great rewards, but the concept of risk also denotes undesirable consequences such as danger, harm and loss (Slovic, 1987). For clarity in the present thesis, the term risk will be used in reference to the negative definition of risk and its suboptimal outcomes. Risk taking is evident in drug addiction when one chooses to engage in drug use despite the high probability that it will result in acute and/or long-term harm. As discussed in Chapter 1, opioid abuse can be especially damaging to one's physical and mental health both directly (e.g. overdose) and indirectly (e.g. intravenous disease transmission). The literature largely supports the link between addiction and risk-taking. A meta-analysis of neuroimaging studies conducted by Gowin, Mackey, and Paulus (2013) revealed that individuals with SUD exhibit neural activity while engaging in risk taking

that is distinctly different than the activity witnessed in non-drug abusing control groups. The meta-analysis also found that the neural activation observed in SUD occurs in brain areas that are responsible for dopaminergic regulation and executive functioning. There is also extensive evidence for neural correlates with risk taking and desensitisation to risk in areas of the brain affected by drug abuse discussed in Chapter 1, such as the OFC (Hsu et al., 2005) and the PFC (Manes et al., 2002; Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999)

Decisions relating to what rewards to pursue, or which losses to avoid, are often made without complete certainty. Uncertainty plays an integral part in risk-taking because the outcomes of possible options are either unknown or not guaranteed. Decision-making is generally hampered by uncertainty, and humans tend not to make maximally optimal choices about uncertain scenarios (Tversky & Kahneman, 1974). When deciding about rewards, utility theory describes how people should make decisions under uncertainty. For example, assured rewards are more valuable than uncertain rewards of the same amount, such as receiving a guaranteed $100 is more attractive than taking a gamble to win $100. In order to maximise rewards over the long run, one should also subjectively value two probabilistic options with differing odds but identical average payoffs equally. Unfortunately, utility theory does not accurately predict behaviours in real-life scenarios because humans tend to be risk-averse (Kahneman & Tversky, 1982). As a result, we tend to make suboptimal decisions by preferring an assured reward even if it is lesser in value than the probability-weighted-sum (i.e. objective value) of a larger, uncertain reward. In order to overcome aversion to uncertainty, the objective value of the uncertain reward needs to be considerably higher than that of the certain one (Huettel, Stowe, Gordon, Warner, & Platt,

2006; Platt & Huettel, 2008). This innate pattern of valuation is called discounting, and can be conceptualised as a type of aversion to uncertainty that ultimately prevents maximal benefits in the long term.

As discussed in Chapter 1, repeated drug administration can cause significant changes to stress and reward neural pathways (Koob & Kreek, 2007; Sinha, 2008). Chronic use of and repeated withdrawal from drugs can result in neurobiological adaptations that enhance sensitivity to stress and modify reward valuation (Robinson & Berridge, 2000). These neural changes can explicitly impact responses to *uncertain* threat rather than predictable threat (Bradford et al., 2013; Hefner & Curtin, 2012; Hefner, Moberg, Hachiya, & Curtin, 2013; Moberg & Curtin, 2009). Uncertainty in and of itself is a stressor (Bradford et al., 2013; Grupe & Nitschke, 2013; Hefner & Curtin, 2012), and neural adaptations can impair decision-making by altering the subjective value of uncertain rewards and impeding the ability to predict rewards (Berridge & Aldridge, 2008). Reduced accuracy of predicting reward value and an exaggerated asymmetry between the subjective and objective value of a reward may result in suboptimal decision-making under uncertainty (Schultz, 2011). As a result, a drug-addicted individual may become biased towards certain rewards, such as a drug's desired effects, and away from relatively uncertain non-drug rewards.

Uncertainty exists when outcomes are either delayed or probabilistic. Delay discounting (DD) is the increasing preference of small, immediate rewards over delayed, larger ones as a function of the length of time to receive that reward (Green & Myerson, 2004). DD involves a cost/benefit analysis that accounts for the inherent uncertainty of receiving future rewards as a result of possible interfering factors during the delay (Heilbronner, Hayden, & Platt, 2010;

Patak & Reynolds, 2007). Receiving $100 today may be more attractive than receiving $105 in ten years because the person offering the money may, for instance, lose your address, go bankrupt, or even pass away. Furthermore, you may be in immediate need of $100 (e.g. to pay overdue rent), which makes the value of receiving $100 today greater than receiving $105 far in the future. However, discounting future rewards becomes maladaptive when this strategy does not maximize one's gains. Opting for $20 today, rather than waiting until tomorrow to receive $100, is arguably suboptimal behaviour because the likelihood of intervening factors is relatively small. It is commonly accepted in the literature that high levels of DD reflect a desire for immediate gratification at the expense of better long-term benefits (Green & Myerson, 2010).

It has been widely documented in the literature that addictive behaviours are related to greater DD of money, drugs and other commodities (Mackillop et al., 2011; Madden et al., 1997; Reynolds, Richards, Horn, & Karraker, 2004; Saville, Gisbert, Kopp, & Telesco, 2010; Yi, Mitchell, & Bickel, 2010). DD has also shown associations with high scores on the Eysenk Impulsivity Questionnaire (Andrade & Petry, 2012; Madden et al., 1997), BIS-11 non-planning impulsivity (Mobini, Kass, Yeomans, & Grant, 2007) and functional and dysfunctional impulsivity (Andrade & Petry, 2012; Mobini et al., 2007). Cognitive distortions related to impulsivity are also linked with DD, such as the need for instant satisfaction and short-term thinking (Mobini et al., 2007). There is also evidence that DD may occur as a result of aversion to uncertainty, as Luhmann et al. (2011) found that high IU was associated with the tendency to choose smaller, less probable rewards rather than wait for a larger, more certain reward. As

discussed in Chapter 2, the authors attributed this economically disadvantageous behaviour to the aversiveness of waiting in a state of uncertainty.

Uncertainty is also inherent when the outcome of a reward is probabilistic. Probability discounting (PD) is the tendency to discount the value of an uncertain reward as the probability of receiving that reward decreases (McKerchar & Renda, 2012). Low levels of PD are widely considered to be an indication of risk seeking (Green & Myerson, 2010; Patton et al., 1995) when the probability against receiving a reward compared to its actual value is not factored into one's decision (Shead & Hodgins, 2009). Therefore, someone with a pattern of low PD would be more likely to choose a risky gamble rather than settle on a smaller reward with better odds. The literature has failed to consistently find correlations between PD and other impulsivity measures such as the BIS-11 (Baumann & Odum, 2012; Mitchell, 1999), the EIQ (Andrade & Petry, 2012; Crean, de Wit, & Richards, 2000; Reynolds et al., 2004), the SSS (Mitchell, 1999; Reynolds et al., 2004) and dopamine-related impulse control (Mobini, Chiang, Ho, Bradshaw, & Szabadi, 2000). It is likely that PD assesses a unique aspect of impulsivity that is not captured by other impulsivity measures. Furthermore, positive correlations have frequently been observed between DD and PD (Baumann & Odum, 2012; Crean et al., 2000; Johnson, Johnson, Herrmann, & Sweeney, 2015; Ohmura, Takahashi, & Kitamura, 2005; Richards, Zhang, Mitchell, & Wit, 1999), which suggest that those who prefer the immediacy of a reward (i.e. are impulsive) simultaneously place a high value on the certainty of a reward (i.e. are risk-averse). It is counterintuitive to predict that an impulsive person would be less risk–seeking. Either PD and DD are

capturing different impulsivity facets or DD is actually assessing risk taking rather than delayed gratification, given that delay inherently involves risk.

There is very little research regarding PD in the addiction literature, and the existing studies have generated inconsistent results. The earliest addiction PD research focused on nicotine dependency, and found that that cigarette smokers tend to discount probabilistic rewards more so than non-smokers (Reynolds et al., 2004; Yi, Carter, & Landes, 2012; Yi, Chase, & Bickel, 2007). This pattern suggests that substance users are more risk-averse, despite substantial research linking substance abuse and risk taking. However, other studies failed to find differences in PD between smokers and non-smokers (Białaszek, Marcowski, & Cox, 2017; Mitchell, 1999; Ohmura et al., 2005). More recent research has expanded the investigation to include other substances of abuse, with varied findings. Bernhardt et al. (2017) found that individuals with alcohol use disorder exhibited lower rates of PD compared to healthy controls, suggesting that alcoholic patients were less risk averse. Alternatively, marijuana users do not appear to discount probabilistic outcomes differently than non users (Mejía-Cruz, Green, Myerson, Morales-Chainé, & Nieto, 2016). There are only two studies to date to investigate PD and "harder" substances of abuse, which found that cocaine-dependent individuals discount probabilistic rewards similarly to non-drug-users (Johnson et al., 2015; Mejía-Cruz et al., 2016). Further investigation into how drug addicted individuals make risk-decisions in the PD paradigm is warranted because the existing literature is far from conclusive.

Probability discounting of losses

As has been discussed in Chapter 1, certainty is generally preferred to uncertainty, and uncertain threat is particularly aversive. However, uncertainty becomes desirable when a loss is at stake, and humans are willing to take a chance on avoiding a small loss, even if the odds of incurring a much greater loss are high (Tversky & Kahneman, 1981). Humans have an innate tendency to be more responsive to the outcomes of losses compared to those of gains because of the different emotional responses that gains and losses elicit (Sokol-Hessner et al., 2013). Dissociable regions in the brain also encode gains and losses differently (Canessa et al., 2013; Cooper & Knutson, 2008; Seymour, Daw, Dayan, Singer, & Dolan, 2007). People will also irrationally devalue a course of action that is merely framed as a loss even though the overall outcome is the same when the option is worded as a gain (Tversky & Kahneman, 1981). According to prospect theory, people are motivated to take risks when provided the opportunity to avoid a loss but are more risk-averse about gaining a reward because of the negative emotions elicited by incurring a loss (Heilbronner et al., 2010; Tversky & Kahneman, 1981). Our differential attitudes and behaviours towards losses necessitate an analysis of impulsive risk-taking for positive and negative outcomes individually.

There have only been a few studies to date that assess PD of losses in the context of addiction. Alcohol-dependent patients tend to show lower rates of PD for losses than controls, indicating that alcohol patients are more risk seeking for gains and less risk seeking for losses (Bernhardt et al., 2017). Other studies have found no correlation between frequency of alcohol use and PD of losses (Takahashi, Ohmura, Oono, & Radford, 2009). More studies are needed because

opioids carry a high probability of significant losses due to their highly addictive nature, sedative effect and overdose potential (Inturrisi, 2002). It is apparent from drug taking behaviour that addicted individuals are willing to take high-stake chances when they use drugs despite the incredibly serious negative consequences.

Assessing probability discounting

In the typical PD experimental paradigm, a participant is presented with a series of dichotomous choices between a small, certain outcome and a larger, probabilistic outcome with varying probabilities. For example, the respondent may be asked to choose between receiving an assured $75 and receiving $100 with a 90% chance. The latter option carries an implicit risk of winning zero dollars. During the course of the experiment, the value of the probabilistic option remains the same ($100) and the value of the certain option is adjusted over a series of questions until an "indifference point" is reached (i.e. the *subjective* value of the assured reward is the same as the *objective* value of $100). The procedure is repeated for a number of varying percentages, (typically 90, 75, 50, 25, 10%). Appendix D is a schematic of discounting questions and the way in which IPs are calculated using example data.

The discounting rate is calculated by fitting a hyperbolic function to the indifference points obtained. Discounting of probabilistic outcomes has been described by the following hyperbolic function (Rachlin, Raineri, & Cross, 1991).

$$V = A/(1 + h\,\Theta)$$

In this equation, h is a free parameter that specifies the degree of discounting, V is the subjective value of the certain outcome as described above, A is the value

of the probabilistic outcome, and Θ is the odds against receiving the outcome. The values of V are entered into the equation to obtain a discounting parameter for each individual. Higher h values result in a function that declines steeply, which indicates a high rate of discounting.

The area under the curve (AUC) is another method of assessing discounting that does not rely on theoretical assumptions about the form of the discounting function (Myerson, Green, & Warusawitharana, 2001). The AUC is derived by plotting a participant's subjective values, expressed as a proportion of the actual amount, as a function of the odds against the outcome and summing the area of the trapezoids below the data points. Values range from .00 (highest discounting) to .10 (no discounting). AUC data is more normally distributed than h discounting parameters, eliminating the need for non-parametric analyses that often have less statistical power (Myerson et al., 2001).

Discounting of probabilistic losses is assessed and calculated in the same way as the discounting of probabilistic gains. Indifference points are obtained by the same procedure, except the options are between a certain loss and a probabilistic loss. For example, a participant may be asked to lose $75 for certain or risk losing $100 with a 90% chance. There is no option to gain anything in this scenario, but there is a 10% possibility to avoid a loss that is inherent in the decision. Constructing a separate PD paradigm for losses that does not involve reward allows us to isolate reactions to negative outcomes.

In the PD paradigm, greater discounting of gains is indicative of risk-aversion, but greater discounting of losses is suggestive of risk seeking. Shead and Hodgins (2009) proposed that attitudes towards risk are defined by the weight given to the probability of an undesirable outcome relative to the value of

the preferred outcome. According to this interpretation, greater discounting of probabilistic losses is indicative of risk taking because the probability of incurring a great loss is underweighted. A risk-seeking person will place less importance on the least desirable outcome, thereby will be more inclined to risk winning nothing and be more open to risking incurring a large loss. The figures found in Appendix E illustrate how to interpret the discounting of probabilistic losses versus gains in relation to risk attitudes.

Intolerance of uncertainty and discounting

There is a dearth of research that utilises behavioural measures to investigate IU and risk taking. There is only one study to date that directly assesses risk-taking conducted by Macatee et al. (2015). On each trial, participants chose between receiving a small, medium or large amount of money, and each amount had a corresponding low, medium and high risk of being accompanied by an electric shock. There was also a "pass" option in which the participant could skip to the next trial without the risk of receiving a shock. The authors found that IU was positively correlated only with the number of "pass" options, indicating that high IU related to the complete avoidance of making a decision in a risky scenario. Skipping a trial resulted in no monetary gain, meaning that avoiding a decision was detrimental to the participants' overall monetary benefit; illustrating how IU can lead to maladaptive decisions. Uncertainty is a key factor of PD, so accordingly it would be expected that negative beliefs about uncertainty would play a role in the extent which one devalues uncertain outcomes. Macatee et al. (2015) found that IU predicted risk-aversion, which corroborates that those with high IU tend to be more cautious in

their decisions. In light of Chapter 2, which found that high IU predicted impulsivity in opioid-dependency, it is of interest of the current study to investigate how IU relates to the risk taking in opioid-dependent patients, and if the relationship is different compared to non-drug-abusing controls. Given that opioid patients were more reactive to unexpected punishments in Chapter 3, it was also of interest to examine risk taking for losses independently, as patients may make more impulsive, risky choices when faced with a potential negative outcome compared to a reward.

The current study

The present chapter is the first to investigate PD of monetary gains and losses in the context of opioid addiction. Expanding the literature to include opioids is crucial as each drug is unique in its availability, social acceptance, addictive potential, acute effects and long-term consequences. Although risk seeking is a key feature of addiction, the behaviours involved in drug abuse indicate that drug addicted individuals show a preference for relatively smaller, certain rewards of the drug rather than the probabilistic, larger rewards of abstinence. There has been even less investigation into the discounting of probabilistic losses, but there is evidence to suggest that the discounting of losses involve separate processes than gains (Heilbronner et al., 2010; Tversky & Kahneman, 1992). PD of losses is observed when the harmful consequences of drug abuse are ignored in order to avoid losing the effect of a drug. Essentially, the loss experienced from abstinence is the absence of the desired effect of the drug, which can result in the persistence of negative emotions, less enjoyment in social settings, exclusion from a drug-taking peer group, or withdrawal

symptoms. Abstinence can also elicit dysphoria and an inability to derive pleasure from non-drug reinforcers due to reduced dopamine activity (Koob, Caine, Parsons, Markou, & Weiss, 1997). Therefore, it was of interest to the current study to assess discounting of gains and losses individually.

Research questions and hypotheses

1. Do opioid-dependent individuals discount hypothetical monetary gains more than healthy controls? What are the implications in terms of risk taking?

2. Do opioid-dependent individuals discount hypothetical monetary losses more than healthy controls?

3. Is there an inverse relationship between IU and risk taking in opioid-dependent patients?

In accordance with previous research using cigarette smokers, it was anticipated that opioid-dependent patients will be more risk averse when deciding between potential gains (i.e. exhibit greater PD), and be more risk seeking when chosing between possible losses (i.e. exhibit less PD) than controls. Given the positive correlation between IU and impulsivity in Chapter 2, it was expected that IU would predict greater risk taking in opioid-dependent patients, but not controls.

4.2 Method

Participants

The sample group was comprised of 55 control participants and 56 patients receiving maintenance therapy at the RPA Opioid Treatment Program as described in Chapter 1. Control participants were recruited from the wider Sydney community via word of mouth and snowballing. Exclusion criteria for the control group was a history of drug dependence or a score greater than 11 on the DAST.

Materials

Probability discounting tasks

The PD tasks were comprised of 100 items that consisted of choices between a smaller, certain reward and a larger, uncertain reward. Each question was posed in this way: "Would you rather receive $_____ for sure or receive $1000 with a _____% chance?" Questions were divided into 5 blocks of 20 items for each percentage of receiving money (90, 75, 50, 25, 10%). The probabilistic amount for each block descended from $1000 to zero in $50 increments. Figure 4.1 is an example item as presented to the participant on-screen.

Figure 4.1. Example of a monetary reward item as presented on-screen to participants

For the gains task, the participants are presented with the following on-screen instructions:

> *In this part of the study, you will be asked a series of questions about receiving hypothetical money. We are interested in what you would choose if you were offered these choices in real life. There are no right or wrong answers; we are just interested in your personal preferences.*
>
> *Please imagine that you may be receiving real money. You will be presented with two choices: An amount that you will receive FOR SURE or $1000 that you MIGHT receive. The screen will show you the chances of receiving $1000. Note: If you chose the amount that you MIGHT receive, you risk receiving no money at all.*

Participants completed 5 practice questions and were invited to ask any questions before moving on to the actual experimental questions. The instructions for PD loss task were identical to the gains PD task, except the word "gain" was replaced by the word "lose". Questions were presented individually,

in which participants used a mouse or track pad to click on their preferred option and then click a "next" button to move on to the next item. Options were presented side by side, and in random order for each question so that half the questions read "Would you rather receive $1000 with a ____% chance or receive $_____ for sure?" Randomising the order of presentation of options ensured that the consistent choosing of one type of answer was not incorrectly attributed to clicking on one side of the screen. The order of presentation of the gains and losses task was counterbalanced.

Drug Abuse Screening Test (DAST)

As described in Chapter 2.

Intolerance of Uncertainty Scale (IUS)

As described in Chapter 2.

Barratt Impulsivity Scale – version 11 (BIS-11)

As described in Chapter 2.

Procedure

A pen-and-paper clinical interview was conducted with patients prior to testing regarding demographic information, history of opioid use and current substance use. A question regarding the age of regular opioid use was included to differentiate between the length of opioid use and length of opioid abuse, in order to more clearly ascertain patients' lifetime involvement with opioids. Patients were considered to be poly-drug users if they reported using other drugs besides opioids or alcohol. Patients who reported use of non-medicinal

opioids in the previous 30 days were considered to be extra-medical opioid users. The experimental tasks were administered via SurveyMonkey on a MacBook Pro laptop with a wireless mouse. Participants were asked if they had difficulty reading or using the computer. If so, the researcher read aloud each question and/or operated the mouse.

Statistical method

As discussed earlier in the chapter, the extent of a participant's discounting is measured by obtaining an indifference point (IP) for each block of questions and entering each IP into the hyperbolic discounting equation. The IP was calculated as the mean of the values around which the participant "switches" from a certain to uncertain reward. For example, as the certain monetary amount decreases in value, the "switch point" is when a participant changes from the certain options and begins selecting the uncertain option. In the case where a participant had multiple switch points, the final switch was considered to be the participants' final decision and used to calculate the IP. The IP is calculated as the mean of the monetary value of the certain option and uncertain option at this point. The IP corresponds to the subjective value of the probabilistic outcome in comparison to the certain outcome. The indifference points for each participant and group medians were entered into the hyperbolic discounting equation described above to obtain a probability discounting value (h). Differences in discounting rates were obtained by comparing mean h values between patient and control groups. The degree of discounting was also measured by calculating the area under the discounting curve (AUC) for each participant. Mean AUC was compared between groups to assess differences in discounting. Multiple

moderated regression analyses were also conducted to assess the relationships between IU and discounting between participant groups.

Data management

Scores on the DAS identified six control participants as being ineligible based on possible drug dependency (a score greater than 12 on the DAS). Data from these participants were excluded from analyses comparing group differences. The data for a number of participants showed multiple "switch points" within blocks of percentage values. Exclusion criteria for discounting analyses were more than 2 switch points in any block of questions or a pattern of increasing IP values within a block. These criteria were chosen as they were considered to be an indication of either participant inattention, random answering, or lack of understanding of the task. After excluding participants who did not meet response criteria, there were 39 control participants and 44 patients that were used in the statistical analysis. The sample size varied between the discounting gains and losses tasks as some participants either did not complete both discounting tasks or had their data excluded from one task due to non-systematic responding. Additionally, not all participants completed the self-report measures. The sample sizes are provided for each analyses below.

4.3 Results

Independent t-tests were conducted between groups to assess differences in demographic variables. The groups did not differ significantly in age; however the patient group completed significantly fewer years of education than controls. Accordingly, education was used as a covariate in subsequent analyses of group

differences. Chi-squared analysis revealed that gender was distributed evenly between groups. Length of opioid dependency was calculated by subtracting the age of regular opioid use from the participant's current age. Length of opioid use was calculated by subtracting age of first opioid use from current age. Full demographic and clinical details can be found in Table 4.1.

Table 4.1

Participant demographic and clinical characteristics

Characteristic	Mean (*SD*)		Statistic
	Control	Patient	
Age	36.59 (17.30)	41.05 (8.36)	t = -1.52
Education	11.59 (1.37)	10.43 (1.82)	t = 3.23*
Female (%)	19 (48.7%)	24 (51.8%)	χ^2 = .28
DAS	1.77 (2.62)	---	---
First opioid use	---	19.30 (6.77)	---
First regular use	---	22.00 (7.60)	---
Years of use	---	21.79 (9.22)	---
Years of abuse	---	19.07 (2.62)	---
Poly-drug user (%)	---	16 (42.1%)	---
Extra-medical user (%)	---	10 (25.0%)	---

* $p < .05$

Statistical analysis of gains data

Hyperbolic discounting functions were fitted to the group median indifference points and individual participant data using nonlinear least squares regression conducted through Microsoft Excel's SOLVER Add-in (Brown, 2001). Proportion of explained variance (R^2) and a discounting parameter (h) were obtained for group medians and individual data. The discounting value found for

the control group was h = 2.550 and the proportion of variances accounted for by the model was R^2 = .607. Patient data revealed a discounting value of h = 5.846 and proportion of variance R^2 = .470. Figure 4.2 depicts the best-fitting hyperbolic model for control and patient groups. The R^2 values of both groups were comparatively lower than those typically found in the discounting literature (R^2 > .80), indicating that the participant data did not fit the hyperboloid function well (Estle, Green, Myerson, & Holt, 2006; Mazur, 1987; Rachlin, 2006). When individual indifference points were entered into the equation, 36% of participants had a R^2 less than zero. Of those with a R^2 greater than zero, the values ranged between R^2 = .335 and R^2 = .994, indicating that a large proportion of individual data was not well described by the discounting function. Consequently, only AUC analysis was utilised to determine group differences in discounting. As earlier discussed, AUC is a valid method of discounting that is not based on the assumptions of human behaviour posited by the hypothetical function, and allowed for a larger sample size in the current study (Control n = 36, patient n = 39).

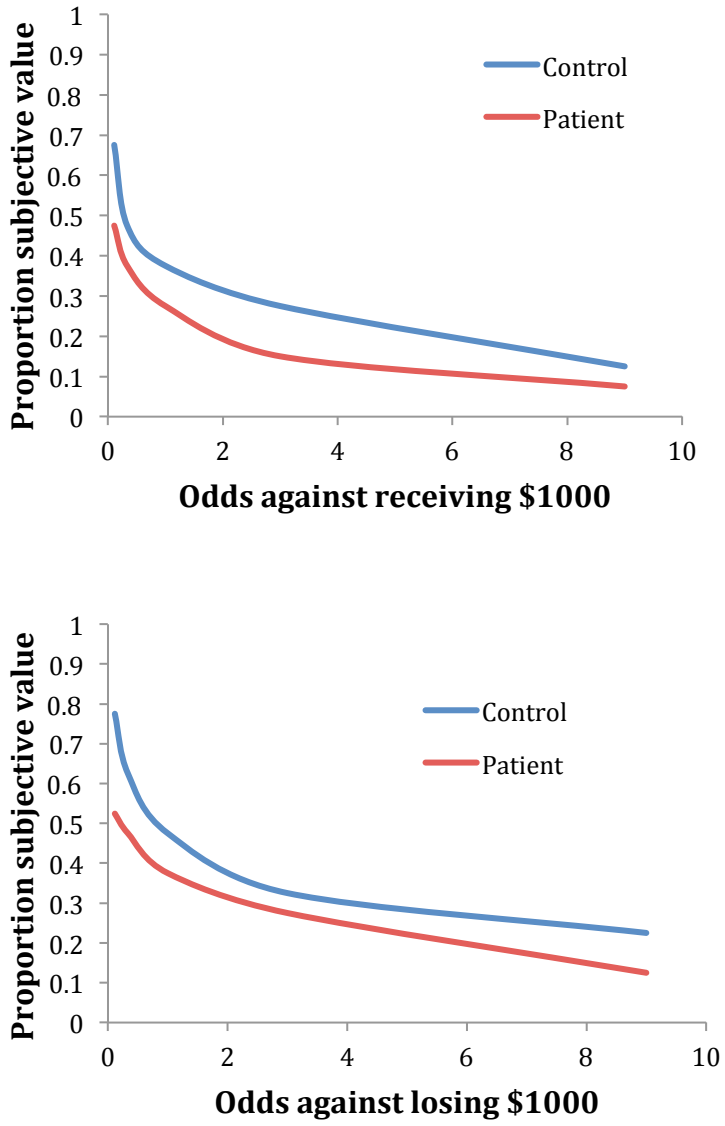


Figure 4.2. Best fitting hyperbolic probability discounting curves for patient and control groups

The participant's proportional subjective values of the probabilistic outcome were plotted as a function of the odds against receiving $1000, and the AUC was calculated by summing the area of the trapezoids underneath the data points. Preliminary analyses of data revealed that AUC data was positively skewed, which was corrected by eliminating two outliers. Results of ANCOVA found that patients had significantly lower AUC ($F(1,72) = 4.441$, $p = .039$),

indicating that patients' responses were more risk-averse than control responses.

Statistical analyses of losses data

Group median and individual indifference points were fit to the hyperbolic equation in the same way as the gains data. The best fitting curves for participant groups are depicted in Figure 4.2. The median R^2 for the control group was .741 and the discounting rate was h = 1.149. The median R^2 for patients was - .020, and a discounting rate of h = 3.205. As was the case for the probabilistic gains task, both group's data did not fit the discounting model well and when participant R^2 values were inspected independently, 40.3% of participants had a R^2 below zero. Consequently, the AUC method was used to assess discounting differences between groups (Control n = 33, patient n = 34). Results from ANCOVA showed that patients had significantly lower AUC than controls ($F(1, 64) = 5.574$, p = .021), indicating that patients were more risk-taking than control participants. Figure 4.3 depicts the mean differences in AUC between groups for gains and losses data.

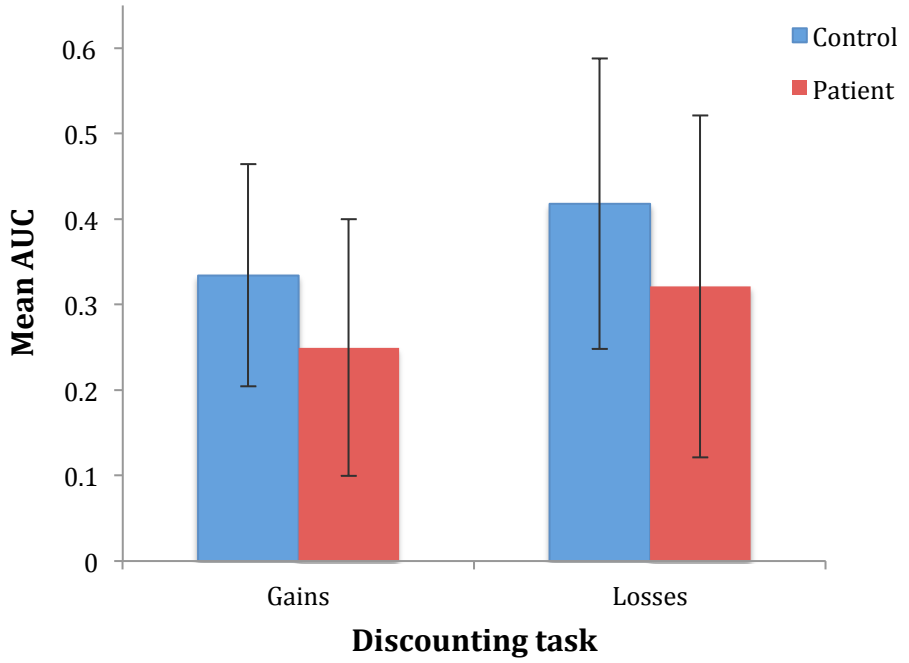


Figure 4.3. Mean differences in AUC between participant groups for the probabilistic gains and losses tasks.

Group comparisons on self-report measures

A series of ANCOVAs were performed to assess differences in IUS and BIS-11 scores between groups. Patients scored significantly higher on overall IUS and IUS 1 subscale, and scores between groups on the IUS subscale 2 failed to reach significance (p = .051). While patients reported higher levels of impulsivity on the BIS-11, only attentional impulsiveness neared significance (p = .084). The results of all ANCOVA analyses can be found in Table 4.2.

Independent t-tests were conducted to assess discounting in patients who were poly-drug users or who were currently using non-prescribed opioids. Results showed that there were no effects of poly-drug use or extra-medical opioid use on discounting rates, IU or impulsivity measures (all p > .300).

Table 4.2.

Results of ANCOVA assessing differences in AUC, IUS scores, and BIS scores between participant groups

Measure	Mean (*SD*)		*F*
	Control	Patient	
AUC Gain [a]	.34334 (.13)	.25383 (.15)	4.44*
AUC Loss [b]	.42095 (.17)	.30980 (.19)	5.57*
IUS [c]	62.92(17.64)	77.53 (28.33)	4.56*
IUS-1	32.82 (10.62)	41.53 (16.19)	4.47*
IUS-2	30.10 (8.35)	36.00 (12.80)	3.93
BIS-11[d]	64.67 (10.22)	69.37 (12.77)	1.46
Attentional	15.51 (3.47)	17.29 (4.05)	3.06
Motor	22.92 (3.87)	24.44 (4.18)	1.19
Non-planning	26.23 (5.49)	28.61 (5.38)	1.04

[a] Control n = 36, patient n = 39; [b] Control n = 33, patient n = 34; [c] Control n = 39, patient n = 39; [d] Control n = 39 , patient n = 41.
* $p < .05$

Correlations between measures

Zero-order correlations were obtained between AUC of the gains task, AUC of the loss task, scores on the IUS and scores on the BIS-11. Neither AUC gain nor AUC loss was significantly related to scores on the IUS. Surprisingly, AUC gain had a significant negative correlation with non-planning impulsiveness, indicating that more risk-taking for monetary gains predicted a greater future thinking. AUC of the losses task had no significant correlation with any of the measures. Replicating Chapter 2 of the present thesis, IUS total and IUS-1 were positively correlated with all BIS-11 impulsivity scores. Scores on the IUS-2 were not correlated with total BIS-11 or impulsivity subscales. Zero-order correlations were also calculated between experimental and clinical variables. Length of

opioid use and opioid abuse were not correlated with discounting or self-report measures.

Moderation analyses

Two hierarchical moderation regression analyses were conducted to determine whether the relationship between PD and IU is different between opioid-dependent individuals and non-drug abusing controls. The detailed results of both analyses can be found in Table 4.3. Gender, addiction status and AUC for gains were the predictive variables the first step of the first regression model with IUS score as the dependent variable. Gender was included because preliminary analyses showed that females scored significantly higher on IU. The overall model was statistically significant ($F(3,66) = 6.85$, $p < .001$), and accounted for 23.8% of variance. Gender and group were significant predictors of IU ($B = 15.70$, $SE = 5.28$, $p = .004$ and $B = 16.16$, $SE = 17.83$, $p = .005$, respectively), but AUC was not ($p = .513$). Step two of the regression added an interaction between group and AUC, which did not significantly increase the variance accounted for by the model ($R^2 = .239$, $p = .729$). It appears that the relationship between IU and PD of gains are non-significant in both the patient and control group.

The second hierarchical moderation analysis was conducted predicting IUS score from gender, addiction and AUC for losses. The overall model was significant ($F(3,60) = 6.37$, $p = .001$) and accounted for 20.4% of variance. Step two added an interaction variable between group and AUC of losses, which significantly improved the model ($R^2 = .300$, $p = .30$). The results of this regression can be found in Table 4.3. Simple slopes analysis revealed a

significant negative relationship between scores on the IUS and AUC for losses in patient participants (b = -47.803, SE = 20.82, p < .001), but not for controls. In other words, higher IU in patients related to greater risk-seeking decisions about probabilistic losses, while IU did not appear to significantly relate to decision-making in controls. Figure 4.4 depicts the relationships between IU and AUC of losses between groups.

Table 4.3

Results from the hierarchical moderation regression analyses predicting IUS scores from addiction and the AUC of the PD losses task

Predictor	β	R^2	ΔR^2	F	ΔF
Step 1		.242		6.37**	
Gender	-.389**				
Group	.177				
AUC loss	-.123				
Step 2		.300	.059		4.941*
Gender	-.366*				
Group	.684*				
AUC loss	.148				
Group x AUC loss	-.553*				

* p < .05, ** p <.001

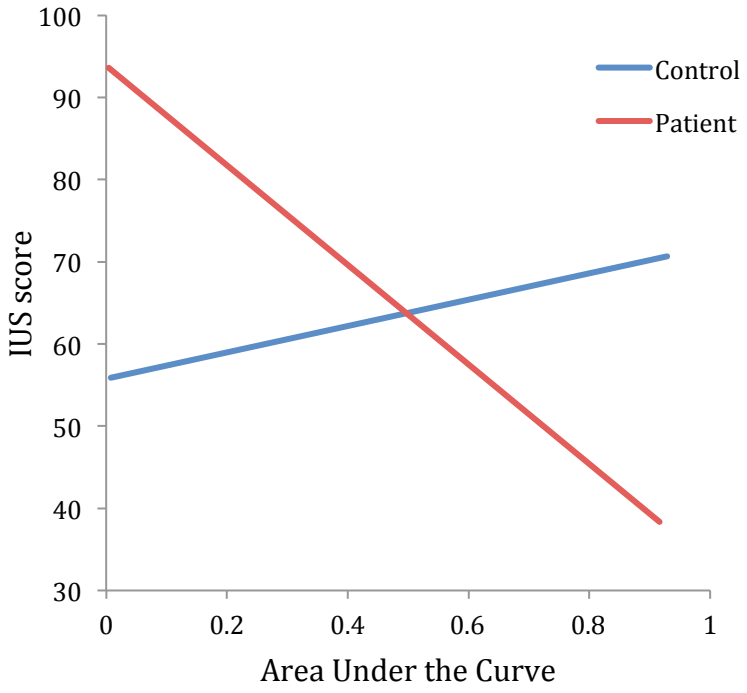


Figure 4.4. AUC for the PD monetary losses task as a function of IUS score between participant groups.

4.4 Discussion

This chapter is the first to use the PD paradigm to investigate risk-taking in opioid-dependent individuals, and how attitudes towards uncertainty relate to the subjective values placed on probabilistic monetary gains and losses. When the extent of PD was compared between groups, patients demonstrated greater gain discounting compared to controls. In other words, opioid-dependent participants tended to choose monetary rewards that were lesser in value rather than risk receiving a larger amount, suggesting that the subjective value of assured monetary gains was much greater to patients than to controls. Our results align with previous research on cigarette smokers, which found that nicotine dependent individuals discount monetary gains more than non-smokers (Reynolds et al., 2004; Yi et al., 2012; Yi et al., 2007). Adding to the literature, the current chapter is the first to provide evidence that those who are dependent on

substances other than nicotine discount monetary rewards more than non-addicted cohorts. It appears that the opioid-dependent patients' decisions about rewards may have been disproportionally impacted by risk, in that the certainty of a reward was valued over the monetary amount of the uncertain reward. The subjective value of uncertain rewards may be diminished as a result of neurological abnormalities in stress regulation that augment negative reactions to uncertainty (Koob & Kreek, 2007). As a result, drug addicted individuals may become biased towards certain rewards (e.g. the drug's desired effect) at the cost of relatively indefinite non-drug rewards (e.g. improved relationships with friends and family). Additionally, opioid-dependent individuals may have a preference for "certainty of supply" that develops from childhood adversity (Barker et al., 2015). Interpreted in these terms, our results suggest that prior negative experiences with uncertainty have a significant impact on risk decisions about monetary gains.

Considered in isolation, the observation that opioid-dependent participants discounted probabilistic gains more than controls does not speak to the quality of decisions between groups. Instead, the choices made by participants need to be interpreted in the context of the probability-weighted values of the uncertain options. In the PD paradigm, $900 is the probability-weighted value of receiving $1000 with a 90% chance, and selecting an assured monetary value less than $900 is too conservative of a strategy to maximise one's gains in the long-term. Conversely, values greater than $900 are ultimately too risky to be beneficial over time. As discussed earlier in this chapter, decisions made under uncertainty tend to be impaired, which is illustrated by the $650 median value chosen by the control group in the current example. The median

subjective value for patients was $475, indicating that opioid-dependent individuals' desire for certainty would result in less advantageous decisions than healthy controls over the long-run. Hence, avoiding risk is not always optimal, and aversion to risky rewards may be related to neurological abnormalities implicated in overvaluing assured rewards. Damage to the dopaminergic reward system that results from chronic opioid use may decrease the subjective value of probabilistic rewards and promote the pursuit of assured ones. As such, heightened PD of positive outcomes may reflect a greater aversion to uncertainty, which ultimately results in maladaptive decision-making. Risk aversion for uncertain rewards may also have implications for drug relapse as Gowin, Ball, Wittmann, Tapert, and Paulus (2015) found when comparing neural activity during risk-taking in methamphetamine-dependent individuals one year after rehabilitation. Abstinent individuals exhibited increased activation of the striatum and insula in response to large, risky rewards compared to small, safe rewards. Relapsing individuals did not show differential activation, suggesting that deficits in risk processing may be a factor in relapse. Furthermore, reward-related brain activity in response to risk was associated with better outcomes after treatment, supporting the supposition that risky gains may be less rewarding to relapse-vulnerable individuals.

Patients also exhibited a greater level of loss discounting in that they tended to risk high amounts of monetary losses with less advantageous odds than did controls. This pattern of behaviour suggests that opioid-dependent individuals are more sensitive to losses and are incentivised to take large risks in order to avoid suffering a loss. It appears that the risk-taking observed in opioid-dependent participants also resulted in less optimal decisions than controls, as

illustrated by the median values of choices made compared to probability-weighted values. The risks taken by patients when considering uncertain hypothetical monetary losses reflects drug-taking behaviour in which the probability of immense drug-related losses is ignored in favour of avoiding the certain loss of the drug's desired effect. However, the severe withdrawal symptoms associated with sudden cessation of opioids must be taken into account when generalising our results to real-world behaviour. Many addicted individuals continue to use opioids in the absence of euphoria or other enjoyable effect primarily to avoid withdrawal symptoms (Koob, Stinus, Moal, & Bloom, 1989). In such a scenario, withdrawal is so aversive that the need for relief feels worth the risk of the dangerous consequences. Future studies would benefit from using a more realistic scenario rather than hypothetical money, which Chapter 5 of the present thesis aims to address. PD of gains and losses were not related, which was interesting given that the Shead & Hodkins (2009) risk-attitudes model predicts a negative correlation between risk-aversion and risk-seeking behaviours. It would be anticipated that participants who were risk-averse on the gains task would also be risk-averse on the losses task. Instead, the lack of any correlation suggests that there are distinct cognitive processes at work when contemplating uncertain gains compared to uncertain losses.

In light of the correlations between impulsivity and IU in Chapter 2, we anticipated a similar relationship between IU and PD in the current study. There were no significant overall correlations between either PD task and the IUS, and when the associations between IU and PD of gains were analysed in terms of opioid-dependency, there were no differential relationships patients and controls. However, we found that greater IU predicted risk taking for

probabilistic losses in the patient group, but did not predict risk taking in the control group. It appears that IU is related to risky decisions concerning probabilistic losses in opioid-dependent individuals, but not in a non-drug-abusing sample. Previous research has shown that high IU is linked to risk-aversion (Ladouceur et al., 1997; Luhmann et al., 2011; Macatee et al., 2015; Thibodeau et al., 2013), and the results of the current study suggests that role that IU has in risk-avoidance is in the opposite direction than has been demonstrated by non-addicted individuals. The present chapter thus lends additional support for a unique link between IU and impulsivity in addiction.

Non-planning impulsiveness was correlated with risk-aversion on the PD gains task, which was unexpected given that making sound decisions about probabilities involves future planning. There were no relationships between self-reported impulsivity and PD of losses. When considered in tandem, the lack of meaningful relationships corroborates previous research that have observed weak correlations between PD and impulsivity measures, and further suggests that the PD paradigm is a measure of a relatively unique facet of impulsivity.

Limitations

An alternative interpretation of our results can be made depending upon how we define risk-attitudes. Risk attitudes can also be conceptualised in terms of uncertainty, in which case a probabilistic outcome is always the riskier choice. Therefore, a risk-seeker places less importance on the uncertainty involved in a decision (i.e. the chance of not achieving the desired goal) and more importance on the value of the outcomes at stake (Shead & Hodkins, 2009). Conversely, a risk-averse person would regard uncertainty to be a more important deciding

factor and place less weight on the outcome. Conceptualised in this way, the greater PD of losses exhibited by patients in the current would suggest that patients were less risk taking because of an aversion to uncertainty. Thus, patients favoured the assured option over the uncertain loss, regardless of probability.

When applying discounting of probabilistic outcomes to drug taking, we must consider the temporal elements involved in the rewards of abstinence. Compared to the immediate rewards of a drug, there is a significantly longer delay between drug cessation and positive outcomes such as improved health, pro-social relationships, and regular employment. As discussed earlier in the current chapter, drug addicted individuals exhibit greater discounting of delayed outcomes, which the literature has interpreted as an inability to delay gratification. Therefore, DD may be more descriptive of drug addiction than PD or may be an underlying factor in the relationship between addiction and PD. However, there is little evidence that DD and PD are similar constructs or that they reflect similar cognitive processes. Future studies should investigate the power of DD versus PD to predict drug addiction.

The large amount non-systematic responses may be due to flaws in the discounting tasks used in the current study. There were more participants in the patient group that were excluded due to a low R2, which may be attributed to the effects of opioid maintenance medication. Drowsiness and sedation are common effects of all opioids, and acute cognitive deficits are possible side effects of methadone medication (Gritz et al., 1975) which may have interfered with patients' ability to understand the task. Furthermore, a test was not conducted prior to the experiment to ensure that participants possessed adequate

mathematical skills to understand the concept of percentage. However, each response choice was represented in two different ways to make percentage easier to comprehend to counteract this possibility (e.g. "10% chance" and "1 out of 10 chance"). We cannot make the assumption that medication side effects or lack of mathematical ability is responsible for patient non-systematic data, as there were control participants that also responded non-systematically (some of whom had completed tertiary education).

Another factor to consider is the nature of the outcomes involved in the PD tasks. While participants were paid for their time, the money in the discounting tasks was hypothetical. It is possible that participants would have made different risk choices if tangible money was at stake, but there are mixed views on this issue. Kirby et al. (1999) found that both heroin-dependent participants and a control group discounted real monetary gains at a higher rate than hypothetical monetary gains, suggesting that people generally may be less able to resist immediate gratification about tangible money. In the current study, patient participants may have been less risky with their decisions about hypothetical money. However, multiple studies have failed to find differential discounting rates between real and hypothetical monetary outcomes (Hinvest & Anderson, 2010; Johnson & Bickel, 2002; Lawyer, Schoepflin, Green, & Jenks, 2011). Finally, participants' current financial circumstances may have impacted the amount of risk they were willing to take. It is feasible that participants with low incomes are more likely to accept smaller, certain sums of money because the relative value of that sum compared to their income is greater than those with larger incomes.

Chapter 5 – Probability discounting of hypothetical health outcomes

Opioid-dependent patients appear to be risk averse when deciding between probabilistic monetary gains, but tend to take risks for monetary losses. Moreover, negative attitudes towards uncertainty are associated with risk taking in opioid patients but seem to have no relationship in healthy controls. These patterns of behaviour are similar to the impulsive decisions that are exhibited by chronic drug users when they persist in drug taking despite the risk of serious harm. Not only the risk of damage caused by the drug itself, but also the harm involved in contracting illnesses from intravenous administration. Illicit substance use involves a number of health related decisions, which span from seeking out rehabilitation to engaging in safer drug use practices. Chapter 5 builds upon the monetary nature of the previous chapter by investigating probabilistic health related improvements and detriments, with the aim to ascertain whether the risky decision making observed in Chapter 4 can generalise to a more drug-relevant domain.

5.1 Introduction

Health-related decision-making involves a wide range of options that involve balancing the potential costs involved against the probabilities of health benefits. For example, chemotherapy carries the risk of painful side effects, and the odds of the treatment extending one's life are highly variable. Changing one's lifestyle is not necessarily guaranteed to improve one's health and also carries

subjective costs. Similar decisions are also made when choosing to engage in activities that are harmful to one's health, such as the abuse of harmful substances like opioids. Impaired decision-making can result from the effect of the drug itself, such sharing needles or participate in risky sexual activity while under the influence of drugs which carry the risk of blood and bodily fluid transmitted diseases such as hepatitis, HIV and other sexually transmitted infections (Chitwood et al., 2003; Degenhardt et al., 2007; Elliott, Hasin, Stohl, & Des Jarlais, 2016). Lowered inhibitions can result in poor judgements when deciding to operate a motor vehicle intoxicated or engage in other activities that can cause bodily harm. Drug overdose is also a serious risk for opioid users as the purity of illicit opioids such as heroin is highly variable (Uporova, 2018).

Drug taking also has damaging health consequences that manifest after chronic use. As discussed in previous chapters, there is strong evidence that regular substance engenders long-term changes in neural stress pathways in a way that may make one more sensitive to stress and make adaptive coping more difficult (Sinha, 2008). Another lasting effect of opioid abuse is an increased risk of overdose death after rehabilitation. Tolerance to the euphoric properties of opioids is believed to build more rapidly than tolerance to the lethal respiratory effects (White & Irvine, 1999), increasing the chance of overdose after abstinence. It is clear that chronic drug use can cause both short term and long-term health harms, and that decision-making regarding health outcomes appears to be seriously impaired in chronic drug users.

According to behavioural economics, health-related choices are influenced by similar factors that guide decisions about monetary outcomes (Tucker, Simpson, & Khodneva, 2010). Like money, health has functional value in

that good health facilitates our ability to engage in valued activities, while ill health costs resources and time. Engaging in health promoting behaviours also involve costs and benefits, such spending time at the gym or buying expensive organic food. Health can be viewed as a commodity in itself, as shown by Chapman and Johnson (1995), who found that healthy individuals were willing to exchange years of life expectancy with other commodities such as cars, vacation homes, and food. The DD paradigm can also be applied to health and the value of delayed health outcomes has been shown to decay according to the hyperbolic discounting function (Baker, Johnson, & Bickel, 2003; Johnson, Bickel, & Baker, 2007), and health and money are biased similarly by the outcome magnitude and length of delay (Chapman & Elstein, 1995).

It appears that there are similar cognitive process at work when making decisions about monetary and health outcomes. However, there is a plethora of evidence that individuals make different decisions about uncertain health outcomes compared to uncertain monetary outcomes. As discussed in Chapter 4, discounting is a phenomenon in which the subjective value of a reward decreases according to the length of delay or probability against its receipt. Delayed health outcomes have been shown to be more steeply discounted than monetary outcomes. For example, participants have discounted delayed health improvements from a disease more than they discounted delayed money, suggesting that the immediacy of health improvements was more desirable compared to the immediacy of a monetary gain (Chapman & Elstein, 1995; Lazaro, Barberan, & Rubio, 2002). There are also low correlations between discounting rates of delayed monetary gains and delayed health improvements (Chapman, 1996; Chapman & Elstein, 1995; Chapman, Nelson, & Hier, 1999).

The inconsistent relationship between the discounting rates of health and money can be explained by the differential cost/benefit analyses involved when considering the two domains. Unlike many tangible goods, it is not feasible to assign dollar amounts to health that can be agreed upon universally (Keeler & Cretin, 1983), and there are a myriad of non-monetary variables that impact one's economic evaluation of health outcomes. There are time and effort costs to improving health (e.g. regular exercise and cooking healthy food) that are weighed against the predicted outcomes of success (Drummond, 2015). Even when health gains or losses are defined numerically, there is no evidence for an intrinsic equivalent to money, as a study conducted by Petry (2003) illustrated. The authors found that participants' discounting rates did not correlate with the monetary value they assigned to a one-year delay of an illness. Similarly, Baker et al. (2003) found that DD rates for monetary gains did not differ according to the monetary amounts participants assigned to a 10% improvement of their overall health. It appears that decisions made regarding health do not accurately reflect the perception of what one's health is worth in monetary terms; highlighting the need for domain-specific measurements.

Discounting differences between domains

Domain-specific discounting refers to decisions as they relate to the nature of the commodity considered in the discounting task. The monetary domain, which is by far the most common domain used in discounting research, is used to infer patterns of behaviours in domains outside of the laboratory. However, it is not clear whether discounting of one type of commodity can accurately predict behaviours in different domains. Positive correlations have

been observed between DD of monetary outcomes and DD of other commodities such as food (Hirst & DiGennaro Reed, 2016; Odum, 2011), cigarettes (Bickel, Odum, & Madden, 1999), entertainment (Charlton & Fantino, 2008), marijuana (Johnson et al., 2010), heroin (Hirst & DiGennaro Reed, 2016; Odum, 2011) and sexual activity (Lawyer & Schoepflin, 2013). Furthermore, discounting rates for food, sex, and drugs have been positively correlated with each other (Holt, Newquist, Smits, & Tiry, 2014; Odum, 2011).

However, there is evidence for a "domain effect" in which discounting differs depending upon the commodity in question. The majority of research in this area has been conducted on DD and has provided solid evidence that individuals in the general population tend to prefer more immediate commodities compared to immediate monetary gains. For example, delayed consumable goods have been discounted at higher rates than delayed money, such as favourite foods, alcohol and soda (Estle, Green, Myerson, & Holt, 2007; Holt et al., 2014; Odum & Baumann, 2007; Odum, Baumann, & Rimington, 2006), non-consumable commodities such as books, music and movies (Charlton & Fantino, 2008), and sex (Holt et al., 2014). Probabilistic monetary rewards are also discounted less steeply than leisure time in the form of mobile phone access (Hirst & DiGennaro Reed, 2016). Interpreted in impulsivity terms, it appears that humans prefer immediate gratification from consumable and non-consumable commodities, compared to money, and are more conservative when risking access to leisure time.

Domain-specific discounting tasks may be more appropriate for assessing domain-relevant behaviours. Johnson and Bruner (2012) found that cocaine-dependent participants who discounted delayed condom use with partners

deemed likely to have a sexually transmitted infection predicted reported HIV risk-taking sexual behaviour. The authors did not observe a relationship between risky behaviour and discounting of delayed monetary rewards. Similarly, DD for monetary outcomes was not predictive of high-risk sexuality factors (e.g. sexual interest and desire) or behaviours (e.g. sexual disinhibition; Lawyer & Schoepflin, 2012). Lawyer (2013) also found that scores on a sexual risk taking measure, but not on a monetary risk taking measure, predicted self-reported sexual excitability outside of the laboratory setting. Furthermore, high body fat has shown to be more strongly related to DD of food than with DD of monetary rewards (Hendrickson & Rasmussen, 2013; Rasmussen, Lawyer, & Reilly, 2010). It is apparent that monetary discounting paradigms may not be the best indication of decision making in other domains, particularly decision making about health-related outcomes such as STIs or obesity.

Health-related discounting

In general, those who are at risk for negative health consequences discount delayed health-related outcomes steeply, suggesting impulsive decision-making for potential averse health consequences. For example, individuals with a high percentage of body fat have been shown to discount delayed food rewards more than those with body fat in a healthier range (Hendrickson & Rasmussen, 2013). There is substantial evidence that individuals who use both legal and illicit substances DD money less steeply compared to their drug of choice such as cigarettes (Odum & Baumann, 2007), alcohol (Odum & Rainaud, 2003), cocaine (Bickel et al., 2011; Coffey, Gudleski, Saladin, & Brady, 2003) and heroin (Madden, Bickel, & Jacobs, 1999; Madden et al., 1997). Delayed

heroin has been discounted more than money in a sample of needle sharing opioid users (Odum, Madden, Badger, & Bickel, 2000). Beyond the harmful consequences of drug taking, drug abusers display greater DD of other health outcomes, such as the onset of a hypothetical illness (Petry, 2003), indicating that drug users prefer a sooner, smaller health loss, rather than delay a larger health loss. Alcohol-dependent individuals discount a greater number of delayed sex acts to a greater extent that non-alcohol abusing controls, which suggests that alcohol-dependent individuals may have less impulse control in sexual situations; increasing their risk of disease (Jarmolowicz, Bickel, & Gatchalian, 2013). Cocaine- and opioid-dependent individuals have exhibited greater discounting of delayed condom use compared to controls (Herrmann, Hand, Johnson, Badger, & Heil, 2014; Johnson et al., 2015), even when there was an explicit risk of contracting a STI (Koffarnus et al., 2016). Cigarette smokers were also shown to steeply discount delayed hypothetical health gains and detriments compared to never smokers (Baker et al., 2003; Friedel, Dehart, Frye, Rung, & Odum, 2016; Odum, Madden, & Bickel, 2002), and there is evidence that heavy smokers discount probabilistic health outcomes less than non-smokers (Poltavski & Weatherly, 2013), suggesting greater risk taking for health compared to money. The acute effects of drug use can also impair health-protective decision-making. For example, cocaine administration was found to decrease the likelihood of using a condom when there was a chance of contracting a sexually transmitted infection compared to a placebo (Johnson, Herrmann, Sweeney, LeComte, & Johnson, 2017). Alcohol consumption can also not only decrease the likelihood of waiting for a condom before having sex, but also decrease the probability of using an immediately available condom

(Johnson, Sweeney, Herrmann, & Johnson, 2016). It is apparent that drug use and abuse is associated with impulsive decisions that put drug-abusing individuals at serious harm. Research using the health-discounting paradigm is necessary to lower the barriers to addiction treatment and motivate safer drug-taking practices.

Health discounting and intolerance of uncertainty

Although research is very limited, the existing studies have evidenced that IU may influence health decisions. Monitoring is a behaviour characterised by seeking out threat related information and focussing attention on potential threats in the environment (Miller, Brody, & Summerton, 1988). In the health domain, "monitors" are individuals who request a great deal of illness-relevant information rather than avoid focusing on their illness. Greater IU is related to health monitoring, and it has been hypothesised that seeking out excessive information about a health threat is motivated by a need to reduce uncertainty, rather than by a desire to gain control over one's illness. For example, Miller et al. (1988) found that high monitors preferred to play a passive role in their medical treatment despite requesting more diagnostic tests, information and counselling than low monitors. Rosen et al. (2007) found that high IU was related to health monitoring in women regarding the human papilloma virus (HPV). Higher IU was related to gathering more information about HPV and requesting more clinical intervention. However, reduction of uncertainty as a primary motivating factor for monitoring has yet to be established. Rosen et al. (2010) found that providing women with a great deal of information about HPV induced anxiety in high IU women compared to low IU women. Those with elevated IU

may seek out more disease relevant information to reduce uncertainty, although the information they receive may actually increase distress when the uncertainty cannot be resolved in its entirety. Furthermore, during the H1N1 virus pandemic Taha et al. (2014) found that higher IU was associated with greater perceptions of the health threat, lower perceived control, and greater use of emotion-focused coping methods. IU may heighten threat perceptions of an uncertain illness, but also may reduce effective coping strategies by augmenting distress and negative problem orientation.

Measuring probability discounting of health outcomes

Many studies have shown that discounting health outcomes fits the hyperbolic function that was developed originally for monetary rewards and losses (Baker et al., 2003; Johnson et al., 2007; Odum et al., 2002). Discounting of probabilistic health outcomes can be described by the same equation used in Chapter 4:

$$V = A/(1 + h\,\Theta)$$

Past research has defined health outcomes in a variety of ways, but the most common is years of overall health. The subjective value of gained/lost years of health (V), as it relates to its actual amount (A), is comparable to a monetary reward/loss because V is mathematically expressed as a proportion of A in both domains. The variable A is the probabilistic number of years of improved health and V is the certain number of years that is subjectively equivalent to A. The variable Θ represents the odds against the probabilistic years, and is calculated as 1 - p /p (where p is the probability of receipt divided by the number of lost years). Finally, h is the discounting parameter that reflects the rate in which the

probabilistic number of years decreases in subjective value. Steeper curves indicate greater discounting.

Discounting of non-monetary outcomes such as health can also be calculated with the AUC method, in which the subjective values of guaranteed years of health (V) are plotted as a function of the odds against the probabilistic number of years (A). The area between the x-axis and the plotted data is used as an index of discounting (0 = highest level of discounting to 1 = lowest level of discounting). The AUC method does not rely upon the assumptions of the hyperbolic model, and does not exclude participants based on how their data fits the hyperbolic assumptions. As with monetary outcomes, greater discounting of health gains suggests risk aversion, while greater discounting of losses suggests risk seeking.

The current study

There is a dearth of investigation into the discounting of health outcomes by drug-dependent individuals, and no research has been done to date regarding opioids. The current study sought to better understand opioid-dependent individuals' decisions about health by using the PD paradigm to assess risky decision-making about health losses and gains. The majority of studies in the health domain have focused on delayed health gains or preventative health behaviours (e.g. protected sex or using clean syringes), or outcomes tangential to health, such as drug use itself. Little enquiry has been made into discounting of probabilistic health gains and losses. The results of the study reported in Chapter 4 revealed distinct patterns of responding between opioid patients and controls. Specifically, patients discounted large, uncertain monetary rewards while

discounting large, uncertain monetary losses, compared to controls. The pattern of responding to monetary outcomes may reflect the decision-making involved in addiction, however the generalisability of the results of Chapter 4 is debatable. Because of the potential domain effect, the current study sought to expand the findings of the previous chapter to the PD of health gains and detriments.

Drug taking behaviour involves a trade-off between the pleasurable effects of the drug and the improved health associated with abstinence. From the drug abuser's perspective, consuming a drug may convey subjective health benefits in terms of easing psychological distress, enhancing mood, and preventing/alleviating withdrawal symptoms. Abstinence carries objective health gains, which are realistically greater in value than the perceived benefits of the drug. The current study also assessed discounting of health-related losses, as this is crucial to better understand why chronic illness, overdose or death are risked in order to avoid the loss of the drug's desired effects. There is only one study to date that has assessed PD of health-related losses in the addiction literature, which failed to find differences between cocaine-dependent individuals and healthy controls in discounting the risk of contracting a sexually transmitted infection (Johnson et al., 2015). However, the study did not separate gains and losses, as the decision was between a loss (infection) and a gain (sex with a desired partner), rather than the avoidance of a loss. The distinction between an explicit gain and an avoidance of loss is important for understanding risk attitudes towards negative outcomes in isolation from positive ones. The current study sought to expand previous findings regarding health-related behaviours (e.g. condom use, needle sharing, or drug taking) to general health improvements or detriments that are relevant to drug users.

Research questions and hypotheses

1. Do opioid-dependent individuals discount probabilistic health gains or losses differently than non-drug-abusing controls? What are the implications regarding risk taking?

2. Do negative beliefs about uncertainty relate to the discounting of probabilistic health outcomes?

3. Does IU relate to PD of health outcomes differently in opioid-dependent patients compared to controls, and is this relationship similar to the pattern observed regarding monetary outcomes?

4. How does the PD of health outcomes appear to compare to the PD of monetary outcomes in Chapter 4? What are the implications for the generalisability of PD tasks to real-world behaviours?

We anticipated similar discounting patterns to Chapter 4, in that patients would demonstrate greater PD for gains and less PD for losses than controls. Although not observed in the previous chapter, a positive correlation between risk-taking and IU for health losses was anticipated in opioid-patients, given the greater applicability of health outcomes to drug abuse.

5.2 Method

Participants

The sample groups consisted of 55 control participants and 49 patients at the RPA Opioid Treatment Program who were receiving opioid-maintenance medication. Control participants were recruited from the wider Sydney community via word of mouth and snowballing. Exclusion criteria for the control group were a history of drug-dependence and a score greater than 11 on the DAST. As described in previous chapters, patients were considered to be poly-drug users if they reported using non-opioid substances other than alcohol. Extra-medical opioid user status was determined by self-reported non-prescribed opioid use in the previous 30 days.

Materials

Probability discounting tasks

There were two PD tasks that were comprised of 50 items each. Items consisted of a binary choice between a smaller, certain health outcome and a larger, uncertain health outcome. Outcomes were quantified in terms of years of better or worse health, respective of task type. Questions were divided into 5 blocks of 10 items with different odds of experiencing the health outcome (90, 75, 50, 25, 10%). The certain number of years for each block descended from 10 years to one year in increments of one year.

Participants are presented with two hypothetical health scenarios that are adapted from those used by Chapman and Elstein (1995). The scenarios include functioning in a range of domains that are used to classify health status (sensation, emotion, cognition, usual activity, and vitality; Drummond, 2015).

Both tasks were conducted using a MacBook pro 15" laptop, and participants read the following instructions and scenario for the PD gains task:

> *In this part of the study, you will be presented with a series of questions about a health related scenario. There are no right or wrong answers; we are just interested in your preferences.*
>
> *Imagine that for the past two years you have felt this way:*
>
> - *You often feel tired and sometimes feel light-headed*
> - *You have trouble falling asleep and sometimes have nightmares*
> - *Your mouth feels dry, and foods do not seem to have as much taste as they used to*
> - *You often feel angry or irritated*
> - *It is difficult to concentrate*
>
> *Imagine that this state of health will continue for the rest of your life.*
>
> *Now imagine that there are two treatments available that will return you back to good health, for a limited number of years. One treatment is 100% effective, but the other treatment is not guaranteed to work. You can choose between:*
>
> - *A treatment which MIGHT return you to health for 10 years*
> - *A treatment which will return you to health FOR SURE, but for a fewer number of years*

Please note: If you choose the treatment that MIGHT work, you risk the treatment not working at all.

Each item posed the question "Which would you prefer?" followed by two options. Either: "_____ years of better health for sure" or "_____% of 10 years better health". For example: "Which would you prefer? 5 years better health or 90% chance of 10 years better health". An example item as presented on the computer screen is depicted in Figure 5.1. Questions were presented individually, in which participants used a mouse or track pad to click on their preferred option and then click a "next" button to move on to the next item. Options were presented side by side, and the order of the options was randomised for each item. This was done so that the consistent choosing of one type of answer was not incorrectly attributed during data analyses to a participant inattentively clicking one side of the screen.

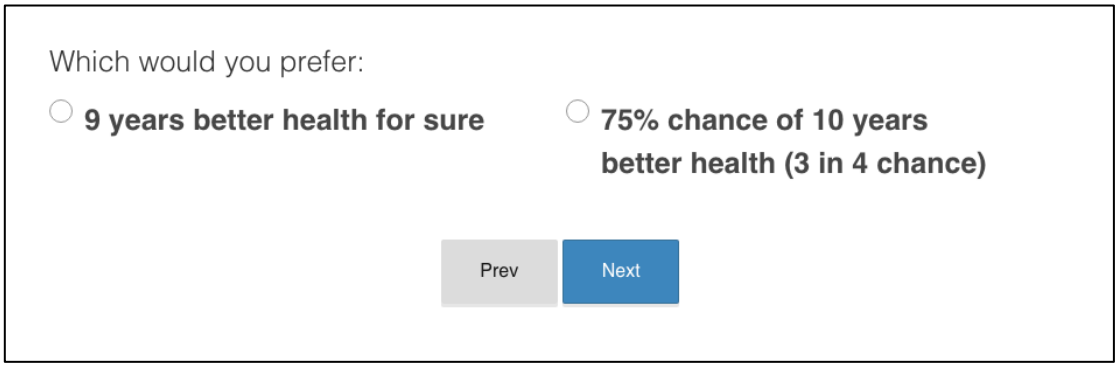


Figure 5.1. Example health gains item as presented on-screen to participants

The hypothetical health scenario presented for the losses task is as follows:

Imagine that you have been diagnosed with an illness and you need to undergo treatment. At the moment, you feel fine. However, the treatment may involve temporary side effects:

- *You will feel tired and sometimes feel light-headed*
- *You will have trouble falling asleep and sometimes have nightmares*
- *Your mouth will feel dry, and food will not seem to have as much taste it used to*
- *You will often feel angry or irritated*
- *It will be difficult to concentrate*

Now imagine that there are two choices of treatments available, which will both cure you:

- *A treatment which MIGHT make you sick with side effects for 10 years*
- *A treatment which will make you sick FOR SURE, but for a fewer number of years*

Please note: If you choose the treatment that MIGHT make you feel sick, there is a chance that you will <u>not feel sick at all</u>.

Each item was posed as "Which would you prefer? _____ years of feeling sick for sure or _____% chance of feeling sick for 10 years". For example: "Which would you prefer? Seven years of feeling sick for sure or 90% chance of feeling sick for 10 years". Items were presented in the same manner as the gains task, and participants completed 5 practice items for each task. The order of the gains and losses tasks was counterbalanced.

Procedure

A pen-and-paper clinical interview was conducted with patients prior to testing regarding demographic information, history of addiction and current substance use. The PD tasks, IUS and BIS-11 were administered via SurveyMonkey on a MacBook Pro laptop with a wireless mouse. Participants were asked if they had difficulty reading or using the computer. If so, the researcher read aloud each question and/or operated the mouse.

Statistical method

The magnitude of a participant's discounting was assessed in the same way as in Chapter 4. An indifference point (IP) for each percentage block of the PD task was obtained by calculating the mean of the values around which the participant "switched" from a certain to uncertain reward. In the case of multiple switch points within blocks of percentage values, the last switch was considered to be the participants' final decision and used to calculate the IP. The IP corresponds to the subjective value of the probabilistic outcome (V), which was operationalized as number of years improved or diminished health. The absolute value of the IPs for each participant and group median IPs were entered into the hyperbolic discounting equation to calculate discounting rates (h) between groups. The degree of discounting was also measured by the AUC method. Each participant's proportional subjective value was plotted as a function of odds against receiving/losing years of health. Mean AUC was compared between groups and correlated with scores on the IU and BIS-11. Moderated multiple regression analyses were also conducted to further investigate differential relationships between IU and discounting between participant groups.

Data management

Scores on the DAS identified five control participants who were ineligible based on possible drug dependency. Data from these participants were included only in correlational analyses. Exclusion criteria for discounting analyses were more than 2 switch points in any block of questions, or a pattern of increasing IP values. After participants were excluded according to criteria, there were 42 control participants and 45 patient participants. The participant sample sizes of the discounting tasks and self-report measures varied due to incomplete questionnaires or excluded data on one discounting task due to non-systematic responses. The sample sizes are reported in the following analyses.

5.3 Results

Means were obtained for demographic and clinical variables, and independent t-tests were conducted between groups on demographic variables. Patients and controls were similar in age and the gender distribution was even between groups. However, the patient group had completed significantly fewer years of education than the control group. See Table 5.1 for participant demographic and clinical data.

Table 5.1

Participant demographic and clinical characteristics

Characteristic	Mean (*SD*)		Statistic
	Controls	Patients	
Age	37.54 (18.42)	41.58 (9.72)	t = -1.20
Years of education	11.51(1.34)	10.37 (1.93)	t = 3.01*
Female (%)	20 (54.10)	22 (48.90)	χ^2 = 0.21
DAS	1.78 (2.68)	---	---
First opioid use	---	18.53 (6.99)	---
First regular use	---	21.91 (9.65)	---
Years of use	---	22.76 (9.54)	---
Years of abuse	---	19.40 (10.10)	---
Poly-drug use (%)	---	15 (18.3%)	---
Extra-medical use (%)	---	14 (17.1%)	---

*p < .05

Statistical analysis of probabilistic health gains

The group median and individual IPs were entered into the hyperbolic equation using Microsoft Excel SOLVER Add-in (Brown, 2001) to calculate a discounting factor (h) and the measure of fit to the model (R^2). The control group had a discounting factor of h = 2.011 and a R^2 = .435. The patient group demonstrated a discounting value of h = 2.278 and a R^2 = .480. Figure 5.2 depicts the best-fitting hyperbolic model for control and patient groups. As was the case in Chapter 4, neither group's data fit the hyperbolic function well. When individual data was entered into the equation, 47.3% of participants had a R^2 value that was less than zero and the remaining participant's R^2 values ranged between .194 and .990. Subsequently, AUC analysis was used as a validated

measure to compare discounting between groups. As the AUC method does not rely upon participant responses to conform to a hyperbolic model, it was not necessary to exclude participant data (control *n* = 32; patient *n* = 42).

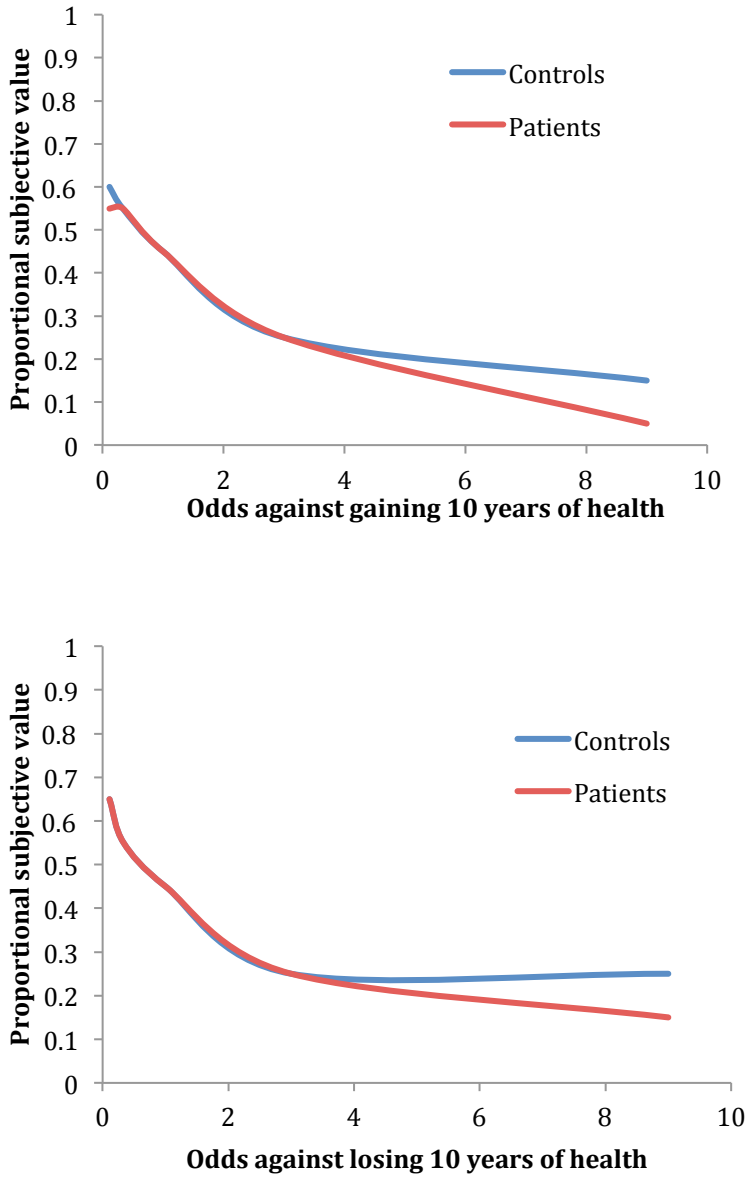


Figure 5.2. Best fitting hyperbolic discounting functions for probabilistic health gains and losses between groups

The proportional subjective values of 10 years improved health were plotted as a function of the odds against its receipt, and the area of the trapezoids under the curve were summed to obtain the AUC for each participant. Initial examination of mean AUC data showed that data was positively skewed and could not be normalised through log transformation, necessitating a non-parametrical analysis. An independent-samples Mann-Whitney U test was conducted, which found that median AUC for patients (*Mdn* = .34125) was not statistically significantly lower than the median AUC for the control group (*Mdn* = .37125; *U* = 597, *z* = -.819, *p* = .413). It appears that opioid-dependent patients and control participants discounted probabilistic health gains to similar extents.

Statistical analysis of probabilistic health losses

The hyperbolic discounting equation was fitted to group medians and individual IPs for the PD losses task in the same way as the PD gains data. The control group showed a discounting value of h = 1.780 and a R^2 = .270. The patient group demonstrated a discounting parameter of h = 1.875, and a R^2 = .623. When individual R^2 data was calculated for participants, 41.9% of participants had a R^2 of less than zero. As the participant data did not adequately conform to the hyperbolic model, particularly the controls group's data, AUC was used to compare discounting between groups (control *n* = 36; patient *n* = 38).

The AUC for the PD losses task was not normally distributed and could not be corrected for by transformation. An independent-samples Mann-Whitney U test was conducted which found that while the median AUC for the patient group (*Mdn* = .38750) was higher than the median AUC for the control group (*Mdn* = .38625), this difference was not statistically significant (*U* = 598, *z* = -.93,

p = .352). It appears that groups discounted both probabilistic health losses similarly.

Group comparisons on self-report measures

A series of ANCOVAs were conducted to assess differences in scores on the IUS and BIS-11 between groups and used years of education as a covariate. Patients scored significantly higher on all measures except for motor impulsivity, for which patients and controls had almost identical scores. Means and results of ANCOVAs are found in Table 5.2.

Analyses were also conducted on patient clinical variables. Independent t-tests were conducted to obtain gender and patient differences in discounting and self-report measures. Males and females scored similarly on all measures (all p > .005), and poly-drug and non-poly-drug using patients also scored similarly on all of the dependent variables (all p > .200). Extra-medical opioid users scored higher on attentional impulsiveness (t(37) = -2.53, p = .016) and overall BIS scores (t(37) = -2.10, p = .042) compared to abstinent patients.

Table 5.2

Results from ANCOVA comparing mean group differences in scores on the IUS and BIS-11

Measure	Mean (*SD*)		*F*
	Controls	Patients	
IUS[a]	64.35 (17.88)	81.45 (25.45)	8.34*
IUS-1	33.46 (10.78)	44.45 (14.88)	9.59*
IUS-2	30.89 (8.41)	37.00 (11.32)	5.61*
BIS-11 total[b]	64.46 (10.26)	72.70 (13.04)	4.86*
Attentional	15.38 (3.35)	18.35 (4.62)	7.57*
Motor	22.78 (4.05)	22.95 (8.18)	0.31
Non-planning	26.30 (5.26)	31.40 (6.26)	9.39*

[a] Control $n = 37$, patient $n = 37$; [b] Control $n = 37$, patient $n = 40$.
* $p < .05$

Correlations between measures

Zero-order correlations were calculated between AUC, self-report measures and opioid use variables. AUC for the gains task was significantly negatively correlated with scores on the IUS and subscales, indicating that greater IU predicted more risk-averse choices when making decisions about probabilistic health gains. AUC for the losses task was not correlated with AUC for the gains task, nor any of the self-report measures. The AUC for PD losses task did not correlate meaningfully with any other measure or the AUC for gains. Between self-report measures, positive correlations were found between total scores on the IUS and IUS-1 with scores on BIS-11, with the exception of motor impulsivity. Aligning with previous chapters, the IUS and IUS-1 were significantly positively correlated with overall BIS-11 impulsivity score, attentional impulsiveness and non-planning impulsiveness. Length of opioid use or length of

opioid abuse did not have any meaningful correlations with discounting nor with the questionnaires. The full results of the correlation analyses can be found in Table 5.3.

Table 5.3

Zero-order correlations between discounting, self-report measures and clinical variables

	1	2	3	4	5	6	7	8	9	10	11
1. AUCG	---	-.111	-.368**	-.330**	-.384**	-.069	-.153	.010	-.037	.194	.203
2. AUCL		---	-.024	-.062	.028	.048	-.001	.091	.012	-.078	.002
3. IUS			---	.968**	.943**	.227*	.288*	.030	.225*	.017	.143
4. IUS1				---	.829**	.312**	.347**	.083	.299**	-.038	.069
5. IUS2					---	.093	.181	-.042	.104	.086	.227
6. BIS-T						---	.769**	.650**	.801**	.114	.161
7. ATT							---	.182	.656**	.214	.191
8. MO								---	.149	.044	.095
9. NP									---	.024	.070
10. LU										---	.775**
11. LA											---

AUCG = Area under the curve gains task, AUCL = Area under the curve losses task, IUS = Intolerance of Uncertainty Scale, BIS-T = BIS-11 total score, ATT = Attentional impulsiveness, MO = Motor impulsiveness, NP = Non-planning impulsiveness, LU = Length of opioid use, LA = Length of opioid abuse
* $p < .05$, ** $p < .001$

Moderation analyses

Two hierarchical moderation regression analyses were conducted to test for group differences in the relationship between discounting and IU. The first regression model predicted IUS score from years of education, gains AUC and opioid dependency status. Education was used as a variable in the regression as

preliminary analyses found that education had a significant negative correlation with IUS scores. The variables contributed significantly to the regression model ($F(3,63) = 7.02$, $p < .001$) and accounted for 21.5% of the variation in IU. Both opioid-dependency and AUC significantly predicted IU. The addition of an addiction by AUC interaction variable in step 2 explained an additional 7.6% variation in IU, and this increase was significant ($F(1,62) = 7.04$, $p = .010$). The complete results of the regression analysis can be found in Table 5.4. Addiction status moderated the relationship between IU and discounting of probabilistic health gains. Simple slopes analysis revealed a significant negative relationship between IU and AUC for gains in the patient group ($b = -79.160$, $SE = 20.87$, $p < .001$), but there was no meaningful correlation between variables in the control group ($p = .801$). Figure 5.3 depicts these findings.

Table 5.4

Results from the hierarchical moderation regression analyses predicting IUS scores from addiction and the AUC of the PD gains task

Predictor	β	R^2	ΔR^2	F	ΔF
Step 1		.251		7.02**	
Education	-.117				
Group	.314*				
AUC gain	-.289*				
Step 2		.327	.076		7.04*
Education	-.130				
Group	.906**				
AUC gain	.041				
Group x AUC gain	-.702*				

* $p < .05$, ** $p < .001$

The first step of the second hierarchical moderation regression model was comprised of education, AUC for the PD losses task and opioid-dependency as predictors of scores on the IUS. The overall model was significant ($F(3,65) = 3.90$, $p = .013$) and accounted for 15.3% of variance. Opioid-dependency was the only significant predictor of IU. The introduction of a group by AUC interaction variable into step two failed to improve the overall model ($p = .198$), indicating that PD of health losses was related to IU similarly between groups, and that this relationship was non-significant in both groups.

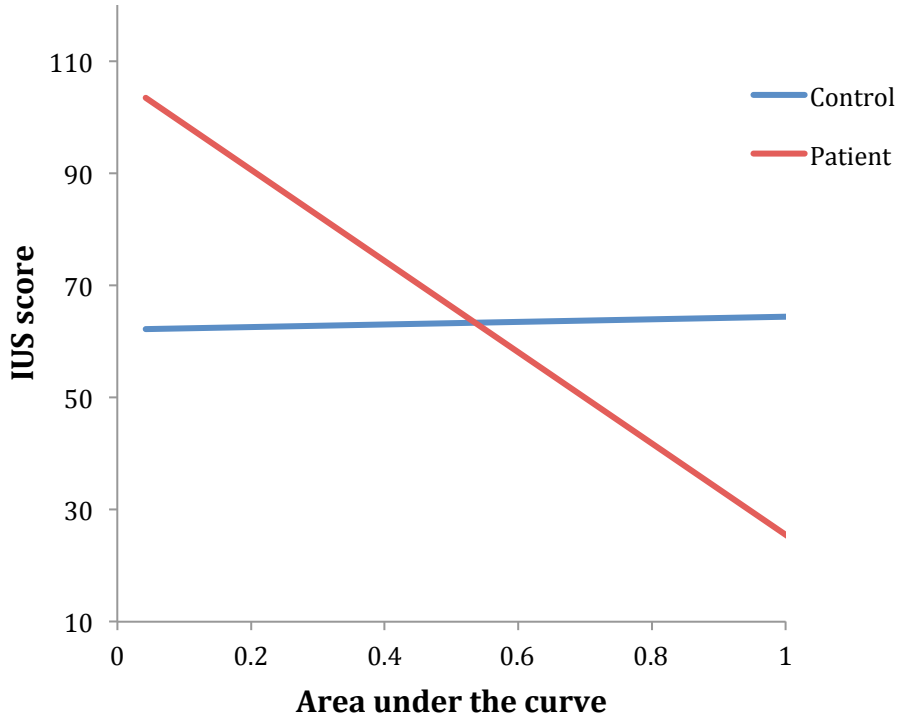


Figure 5.3. AUC for the health gains task as a function of IUS scores between groups.

5.4 Discussion

This is the first study to investigate the way in which uncertainty influences risky health-related behaviour in opioid-dependent individuals compared to healthy controls, and whether risk-taking may be influenced by attitudes about uncertainty. Opioid patients tended to make more risk-averse decisions when deciding between probabilistic health gains than controls, however the difference in the AUC between the groups did not reach statistical significance. It appears that opioid-dependent participants and non-drug abusing individuals may discount probabilistic health improvements similarly. Likewise, patients discounted health losses more than controls, but this difference also did not pass the threshold of statistical significance. The similar discounting rates of health outcomes supports the only other existing study of PD of health losses in the context of addiction, which found that the probability of contracting an sexually transmitted infection was not discounted differently between those with a cocaine use disorder and non-users (Johnson et al., 2015). While it would reasonable to expect that patients would have a different risk attitude towards health outcomes compared to controls, it is possible that the health scenarios employed by the current study are not generalisable to health related behaviour outside of the laboratory. Alternatively, these results provide indirect evidence for a domain effect, as has been witnessed in a number of DD studies (Baker et al., 2003; Chapman & Elstein, 1995; Lazaro et al., 2002; Petry, 2003). Furthermore, PD may not reflect risky decision making in the health domain.

Because inquiry of PD of health outcomes is very limited, we need to turn to the DD paradigm to interpret the lack of significant differences in the current study. Research using DD tasks offer evidence that discounting hypothetical

health scenarios in a research environment does not necessarily translate into real-life health behaviours. For example, only a weak relationship has been observed between DD of hypothetical health outcomes and opting for a free flu vaccination (Chapman et al., 2001; Chapman & Coups, 1999). However, receiving the vaccination was associated with a greater willingness to wait for a better health outcome). Research has shown that discounting of delayed health outcomes are not predictive of daily exercise habits or medication compliance (Chapman, 1998; Chapman et al., 2001). As the present chapter is the first to investigate PD of general health outcomes in the context of addiction, much more enquiry is needed on the topic in order to make more definitive conclusions.

The current study also observed a negative correlation between PD of health gains and scores on the IUS, in that greater IU predicted a preference for more certain health improvements. This is interesting given the lack of correlations between IU and PD of monetary gains in Chapter 4. IU is characterised by tendencies to view uncertainty as aversive, and perhaps a health scenario conveys more emotional weight than a situation involving hypothetical money. A significant relationship between IU and health was not observed in PD for losses, which limits our interpretations because illness is arguably more threatening than the lack of a health improvement (i.e. a punishment versus a non-reward). The results may also be an artefact of the health scenarios used, in that health detriments occurred in the course of a medical treatment. Perhaps the certainty of alleviating aversive symptoms are more valuable than the certainty of avoiding side-effects during a treatment that will ultimately make a person healthy again. An alternative explanation may be that the health scenarios involved "cold" health behaviours, which are deliberate

and made in a relatively unemotional state, as compared to health decisions that occur in a "hot", goal-driven state (Chapman, 2005). There is evidence that discounting applies primarily to hot health behaviours, which tend to be made impulsively (i.e. drug-taking), and not to cold health behaviours (i.e. preventative health measures), which are more carefully considered (Chapman, 2005). In regards to the PD paradigm utilised in the current chapter, it may be that decisions about cold health behaviours are not particularly indicative of risk taking, which may account for the absence of correlations between PD and the BIS-11, or the similarities of PD between participant groups.

When group differences were analysed, this correlation was only significant in the patient group and indicated that IU may have biased patients towards assured health gains. IU was not related to control participants' risk-taking. Aligning with the results of the previous chapters in the thesis, the results of the current study support a relationship between IU and impulsivity that is limited to opioid-dependent patients. However, the correlation for health outcomes is in the opposite direction as would be expected given the results of the previous chapters. It appears that as IU increases in patients, the more risk-averse they are when making decisions about health gains. IU may promote risk-averse choices in patients for the health scenario used in the current study because of past experiences of withdrawal. Negative attitudes about uncertainty may compound the effect that uncertainty has on health choices in patients and increase the tendency to rely on the certainty of the "health improvements" of drugs rather than risk withdrawal and negative affect for the benefits of abstinence. Interestingly, there were no relationships found in either group between IU and PD of health losses. One explanation may be that the health loss

scenario was framed in terms of a treatment that would ultimately result in a positive outcome, which may not be a strong analogue to the health losses incurred by drug use, as there is no long-term health benefit from chronic drug use.

Almost half of the participants did not fit the discounting equation, which hints at the motivational factors driving health choices that are not accounted for by the hyperbolic model. Story, Vlaev, Seymour, Darzi, and Dolan (2014) propose a theoretical model of unhealthy behaviour that posits that DD can account for the initiation of goal-directed behaviours, but ultimately associative learning is responsible for cementing health behaviours into habits. Unhealthy behaviours tend to be stable even if one changes the health goal. For example, a habit of eating unhealthy food will persist beyond the immediate goal-change to lose weight, and this behaviour does not fit the hyperbolic discounting model (Story et al., 2014). Furthermore, environmental factors influence unhealthy choices, such as stress or drug-related cues (Fields, Ramos, & Reynolds, 2015; Story et al., 2014), which also cannot be accounted for by a discounting equation. The influence of cues on behaviour is particularly applicable to laboratory research, which is purposely conducted without extraneous environmental variables. The poor fit of the current study's data to the hyperbolic model adds support to the notion that the discounting paradigm may not be an accurate measure of risky health choices.

The relationship between IU and PD of health outcomes in the patient group contrasts with the findings of the previous study in which correlations were found with monetary losses but not monetary gains. It is apparent that IU relates uniquely to PD in the health domain compared to the monetary domain.

This is important because greater levels of IU have shown to be related to low levels of perceived self-control and less use of adaptive coping strategies in the face of a serious health concern (Taha et al., 2014). Taking into consideration negative attitudes about uncertainty could be important when assisting drug addicted individuals to make positive health changes, such as using sterile needles or initiating rehabilitation.

The different relationships between PD of monetary outcomes in Chapter 4 and PD of health outcomes observed in Chapter 5 imply that the results of Chapter 4 are not generalisable to real-world drug taking behaviour. It is also possible that there are other unaccounted for variables impacting decision-making such as one's financial situation in Chapter 4 and current illness for the present chapter. While the study did not assess health status in participants, a report of drug injecting residents in the wider Sydney community found that 70% tested positive for hepatitis C, 24% for hepatitis B, and 7% for HIV (Rutter, Dolan, & Wodak, 1996). More recently, 69% of intraveneous drug users in Australian capital cities reported a diagnosis of Hepatitis C (Butler & Burns, 2015). While these illnesses were not accounted for in the current study, they could have impacted the responding of patients, although we would expect that poorer health status in patients would influence their decisions in a way that was notably different than healthier controls. IU seemed to impact decisions about health gains in the patient group, suggesting that current ill health may make assured health improvements more appealing, particularly improvements from a current illness. Anecdotally, a number of patients remarked during testing that they could relate to the symptoms described in the health scenarios in the past and/or present time. It may be that the poorer overall health of patient

participants who also had high IU influenced their desire for certain health improvements because of a greater subjective value of even modest symptom relief.

Limitations

The motivations underlying drug taking and drug addiction are exceptionally complex and there are a myriad of variables that influence whether to abstain or continue using harmful substances. Therefore, the results of the current study need to be interpreted taking into account a number of considerations. While the purpose of the current study was to assess PD of general health outcomes which are relevant to drug taking, the scenarios utilised may not have been adequately applicable to everyday life. For example, Herrmann et al. (2014) found that opioid-dependent women show increased discounting of delayed condom use, which is a situation that is more likely to be encountered in real life than the hypothetical medical scenarios used in the current study. The tasks also involved a temporal element that could have impacted the results. The number of years of feeling better (or feeling worse) involves a delay of the recurrence of a better or poorer state of health.

Chapter 6: General discussion

The subject of addiction is highly complex and encompasses an array of interconnected attributes and processes. The present thesis contributes to our understanding of opioid-dependency from a cognitive and behavioural perspective. The particular focus was the relationship between intolerance of uncertainty and different facets of impulsivity that contribute heavily to the maladaptive decisions that are hallmark of drug abuse. The thesis investigated impulsive decisions made primarily under uncertainty, as IU was expected to have a particular impact on these types of choices.

The primary research questions were as follows:

1. Do opioid-dependent individuals have different reactions to uncertainty compared to non-drug abusing individuals?

2. How do impulsive personality traits and behaviours correlate with intolerance of uncertainty?

3. Does intolerance of uncertainty relate to impulsive traits and behaviours differently in opioid-dependent individuals compared to the general population?

6.1 Synthesis of research results

Some of the research questions asked in the thesis can be answered more definitively than others. Opioid-dependent individuals undergoing medication maintenance therapy consistently reported strong negative beliefs and reactions towards uncertainty across all the studies presented here, which provide the evidence required to answer the first research question affirmatively. While the exact causes of this finding are unclear, there are many possibilities that warrant further investigation. Those with high IU express a great desire for predictability and report an impaired ability to effectively resolve uncertainty (Carleton et al., 2007). The "paralysis" experienced in the face of uncertainty may motivate the individual to resort to other coping strategies, such as drug use, to resolve the anxiety and distress that inevitably arises from uncertainty in the daily environment. Uncertainty about one's ability to cope with distress is an inherent factor in IU (Buhr & Dugas, 2002), which can further contribute to using maladaptive methods to manage stress.

Cognitive processing of uncertainty shares a number of neural correlates with addiction, such as the dopaminergic reward system, which is activated when faced with unexpected rewards (Fiorillo et al., 2003). Additionally, the striatum is a dopaminergic structure partly responsible for coding stimulus salience, which is activated in response to uncertainty (Aron et al., 2004). Accordingly, uncertainty may be more aversive to those with drug-related dysfunction in dopamine function. Abnormal striatal activity may increase the salience of uncertain stimuli (Leland et al., 2006), and given uncertainty's general undesirability, heighted salience in drug users may augment their aversion to uncertainty.

IU may be a personality factor that increases one's risk for drug addiction, or it may result from neurobiological and/or environmental detriments resulting from chronic drug use. For example, drug addiction may increase the unpredictability of one's situation and produce associations between uncertainty and adversity. For example, the amount of time allotted to achieving drug related goals eventually overtakes the time necessary to maintain steady employment and a consistent stream of income to buy life's necessities (American Psychiatric Association., 2013; Piazza & Deroche-Gamonet, 2013). Alienation from non-drug peer groups is also a diagnosis factor for severe SUD, and damaged relationships with friends and family erode support systems on which one can rely upon for stability. As a result, uncertainty may appear more threatening and be less tolerable for substance abusers. IU is thought to be a stable dispositional characteristic (Carleton et al., 2007; Freeston et al., 1994), and chronic drug use may cause long lasting changes in brain circuitry responsible for processing uncertainty and managing reactions to threat. Compounded with pre-existing IU, it is plausible that IU is both a risk factor for addiction as well as a contributor to a vicious drug-taking cycle. It is outside of the scope of the current thesis to determine a causal role that IU may play in drug addiction, but future longitudinal studies can provide more definitive answers.

The study presented in Chapter 2 was the very first to address the way that impulsivity and IU interact in opioid-addicted individuals, and provided preliminary evidence for an inverse relationship to non-drug abusers. As discussed in Chapter 1, research has demonstrated that IU is associated with greater deliberation, need for more information before making decisions (Ladouceur et al., 1997; Thibodeau et al., 2013) and more risk averse behaviours

(Carleton et al., 2016). IU is also a key factor in the development of worry and GAD, and IU is connected to both clinical and sub-clinical anxiety (Barlow et al., 2014). Individuals with greater anxiety demonstrate risk-aversion and behavioural inhibition (Pittig et al., 2018), which supports an expectation that high levels of IU would create a bias against impulsive decisions and motivate more deliberation in uncertain scenarios. However, Chapter 2 found that IU was predictive of multiple impulsive traits such as acting quickly without forethought, attentional control and myopia for the future. Furthermore, attentional impulsivity was the strongest predicting factor of IU after anxiety was accounted for, suggesting that difficulty controlling one's attention or focus may be a key feature of IU. Most importantly, positive correlations between IU and impulsivity were only observed in opioid-dependent patients when analysed separately from control participants.

Similar results are reported in subsequent chapters of the current thesis, in which unique correlations between IU and risk taking were observed in opioid-dependent patients but were non-existent in controls. Perhaps the combination of impulsiveness and low tolerance of uncertainty has a multiplicative effect on the inclination to engage in addictive behaviours. It may be that individuals with poor impulse control who also experience regular distress in response to uncertainty may be prone to using maladaptive coping methods without fully considering their ultimate effectiveness or long-term consequences. Indeed, IU has been linked to using alcohol as a coping method to deal with stress and negative affect (Kraemer et al., 2015; Oglesby et al., 2015), and opioid users tend to use the drug to disassociate from worry and anxiety (Spotts & Shontz, 1980). There is also evidence supporting a link between

striatal dopaminergic activity and impulsivity in the context of substance abuse. A study conducted by Leland et al. (2006) found that stimulant users exhibited heightened striatal activation while making decisions with high degrees of uncertainty compared to drug naïve controls. Furthermore, greater striatal responding was associated with self-reported impulsivity on the BIS-11. The interchange between dopaminergic circuits and uncertainty may acount for the positive correlation between self-reported impulsivity and IU demonstrated by opioid-dependent participants. Chapter 2 provides preliminary evidence that IU may impact impulsivity (or vice versa) differently in opioid-dependent individuals compared to the general population, and that this relationship is in the opposite direction as would be expected from non-drug abusing individuals. The subsequent chapters of the thesis further explored the relationship between impulsivity and IU via behavioural measures.

Drug abusers appear to be highly sensitive to the rewards of the drug and relatively impervious to the possibility of immense harm. Chapter 3 is the first to examine how IU relates to the ability to learn from probabilistic feedback and adaptive behaviour modification following uncertain feedback. Chapter 3 expanded upon the study conducted by Myers et al. (2016) by correlating reward and punishment sensitivity with IU, as well as with feedback learning performance. Our results replicated those of Myers et al. (2016), in that patients did not exhibit differences in learning performance compared to controls. This contrasts with other research supporting impaired reward leaning in individuals with dopamine dysfunction or cocaine dependency (Frank et al., 2007; Strickland, Beckmann, Rush, & Stoops, 2017; Vadhan et al., 2014; Waltz et al., 2007). Opioid-dependent patients exhibited more sensitivity to punishing

feedback, in that they tended to alter their responses after negative feedback. Unlike previous work showing that drug using individuals have diminished sensitivity to punishments (Balconi et al., 2014; Brevers et al., 2014; Yan et al., 2014), our results also do not appear to align with the persistence of harmful drug taking behaviours. However, when our results are construed in another way, increased lose-shift responses may reflect impulsive decisions elicited by punishing feedback. This interpretation does align with relapses triggered by stress and may also explain why some addicts resume drug taking on a regular basis. Our results also support those of Ersche et al. (2005), which revealed that experiencing a loss generated risky decisions in methadone-maintained opioid users, but not current heroin users, amphetamine users, ex-drug users or drug naïve controls. It may be that opioid medication maintained patients are uniquely hypersensitive to punishments compared to other drug users, or that there is an effect of current opioid-medication that affects impulsive decision-making. Chapter 3 also found that the tendency to modify response strategies after receiving a punishment ultimately predicts sub-optimal decisions when learning from negative feedback. In other words, impulsive reactions to negative feedback can interfere with adaptive decision making when an overall rewarding pattern of behaviour is deserted.

There are neural correlates between the medial prefrontal cortex (mPFC) and the patient group's increased punishment sensitivity observed in Chapter 3. The mPFC is involved in reward processing, error monitoring, and decision making under risk and uncertainty, and the mPFC can dynamically modify behaviour in response to changes in the environment, motivations or goals (Venkatraman & Huettel, 2012). The mPFC also has shown to process a variety of

drug and non-drug-related stimuli such as cocaine and money (Breiter et al., 1997; Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Elliott, Newman, Longe, & Deakin, 2003). Seeing as the mPFC is involved in changing behaviour in accordance with success and failures of a given action (Matsumoto et al., 2007), mPFC dysfunction may underpin the maladaptive choices made by opioid-dependent patients in response to negative feedback. Dopamine and serotonin in the basal ganglia have also been correlated to heightened sensitivity to punishment in Parkinson's patients (Balasubramani, Chakravarthy, Ravindran, & Moustafa, 2014). Dopamine in the basal ganglia signals a difference between expected and actual rewards (i.e. prediction error), and the basal ganglia computes the value of the expected future reward (Haber & Behrens, 2014). Impaired ability to predict expected rewards may impede sticking with optimal response strategies after receiving inconsistent feedback.

It appears that opioid-dependent individuals are more likely to respond impulsively following negative feedback, which may aid our understanding of drug relapse after successful rehabilitation. During abstinence or opioid-maintenance therapy, the avoidance of physiological symptoms of withdrawal is no longer a motivating factor for drug, yet craving and drug-seeking still occurs (Devos, Vanwilgenburg, Vandenbrink, Kaplan, & Devries, 1996), which is why it is of great interest to understand why many individuals experience a relapse or why a proportion resume drug abuse. There are multiple lines of evidence that experiencing a negative or stressful event can trigger relapse (Sinha, 2001), for which opioid-dependent patients undergoing treatment may be particularly sensitive to (Bentzley et al., 2015). Failure to use adaptive coping methods to maintain abstinence, such as using exercise as distraction or avoiding drug-

related situations, has been associated with relapse after completing rehabilitation (Gossop et al., 2002). A reactive sensitivity to negative events may increase the chances that opioid-dependent patients will abandon abstinence, despite the long-term benefits.

The relationship between IU and feedback sensitivity was also explored in Chapter 3. Those with high IU were more likely to repeat winning responses rather than explore other options, which corroborates the findings of Radell et al. (2016), and seems to support the desire for predictability and an aversion to the unknown characteristic of IU. However, our results diverge from those of Chapter 2 in that IU predicted more cautious, win-stay responses associated with optimal choices and overall better learning performance. IU may bias one towards exploiting previously rewarded actions, rather than encourage exploration of uncertain alternatives, and this bias may improve learning from feedback. IU was also linked to optimal punishment choices, and it is probable that IU facilitates learning from negative feedback, due to increased attention to potential threats. The findings of Chapter 3 compliment the findings of Chapter 2 in that opioid-dependent patients exhibited more impulsive reactions and reported higher levels of IU than the control group. However, regression analysis found that IU did not significantly predict impulsive responses differently in opioid-dependent patients compared to control participants.

Chapter 3 adds to our knowledge of how opioid-dependent individuals react to and learn from feedback, but we were unable to confirm that impulsive reactions to probabilistic punishments (i.e. uncertain negative feedback) are associated with IU. Our results indicate that while IU is linked to self-reported attentional impulsivity in opioid-dependent individuals, there may be no

meaningful connection between IU and impulsivity as assessed by the probabilistic feedback learning task.

Chapter 4 reported the first study to assess risk taking in opioid-dependent individuals using the PD paradigm, and the first study to compare PD of gains with PD of losses in the context of illicit substance abuse. Chapter 4 is also the first to examine a relationship between risk taking and IU in opioid-dependency. We found that when considering probabilistic rewards, patients preferred certain, smaller monetary gains more so than control participants, and that the discounting of uncertain, larger gains is a suboptimal strategy to maximise monetary gains in the long run. While Chapter 3 and Chapter 4 examined different facets of impulsive decision-making, it is interesting that uncertain rewards appeared to differentially impact patients in Chapter 4, but not Chapter 3 in which patients and controls modified their behaviour in response to rewards similarly. Risk taking and reward sensitivity are arguably different constructs that reflect different cognitive processes, and the current thesis illustrates how all elements of impulsive decision making may not relate to addiction analogously.

The higher level of discounting demonstrated by patients may explain why the objectively positive outcomes of abstinence are eschewed in favour of chronic drug use. It is possible that the certainty of the drug's desired effects is more appealing compared to the relative uncertainty of other non-drug alternatives. This explanation is fairly simplistic on its own, given the neurobiological and conditioned learning factors that make addictive drugs highly appetitive and subjectively more valuable than natural reinforcers (Volkow et al., 2003). Furthermore, there are differences in the immediacy and

effort involved in drug taking compared to initiating and maintaining abstinence. Reaping the long-term rewards of abstinence takes a great deal of effort and time, which are two factors that undoubtedly influence the decisions involved addictive behaviours. It has been well established that the immediacy of a reward is greatly desired by drug abusers (Mackillop et al., 2011). The highly aversive symptoms of opioid withdrawal must also be taken into account, as the desire to avoid withdrawal may become the primary motivation for continuing opioid use (Koob & Le Moal, 1997).

However, the role of the individual in the path to drug addiction cannot be overstated and certainly has bearing on drug taking in all stages of use, addiction and recovery. The striatum has shown activation during risky choices about rewards (Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003) suggesting that the patient participants in Chapter 4 may have viewed uncertain reward as more salient, more distressing, and therefore opted for more certain rewards. Dysfunction in the OFC may account for the differential PD rates observed in the present thesis between opioid-dependent patients and healthy controls. Uncertainty about outcomes is encoded in the OFC in probabilistic task paradigms (Huettel, Song, & McCarthy, 2005; O'Neill & Schultz, 2010; Stern, Gonzalez, Welsh, & Taylor, 2010), and abnormalities in the OFC may reduce sensitivity to risk and ambiguity (Hsu et al., 2005). Dampened activity in the OFC has been linked to substance dependency (London, Ernst, Grant, Bonson, & Weinstein, 2000), and reduction in OFC matter has been observed in abstinent drug users (Tanabe et al., 2009), suggesting either lasting damage after chronic drug use or a pre-existing deficit in OFC functioning. Decision-making in risk scenarios also involves the integration of emotional responses with rational

responses, which is regulated by the cognitive control exerted by mPFC (Venkatraman & Huettel, 2012).

When considering probabilistic losses, patients tended to take chances with more unfavourable odds than controls in order to avoid incurring a relatively small loss. The level of PD patients demonstrated for potential losses was a less optimal decision pattern compared to that of the control group, as it was too risky of a response strategy to minimise losses over time. When the findings of Chapter 4 are considered in tandem with Chapter 3, it appears that opioid-dependent individuals may be more sensitive to experiencing a loss than the non-drug users, and that this sensitivity may promote risky decision-making in order to avoid future negative outcomes. For example, a heroin user may be aware of the risk of an overdose, given the unpredictability of heroin's potency, but the aversiveness of withdrawal or continuing emotional distress appear to be powerful motivating factors to risk a potentially fatal outcome.

When correlations between IU and PD were initially assessed in Chapter 4, IU did not appear to relate meaningfully to either PD of gains or PD of losses. However, when regression analyses were conducted, higher IU was associated with risk-taking for losses in the patient group. This result aligns with the study reported in Chapter 2, which found that greater IU was positively correlated with self-reported impulsivity only in opioid-dependent patients. Chapter 4 delivers further support for an inverse relationship between impulsivity and IU in opioid-dependent individuals compared to the general population. Those with an addiction may be impacted by uncertainty in a paradoxical way, which results in risky rather than cautious decisions when a potential loss is at stake. We did not observe an interaction between PD of gains and opioid-dependency in regards to

IU, suggesting that the differential impact of IU on risk-taking in opioid-dependency is limited to risking negative outcomes. Considering the great risk of harm involved in opioid abuse, the findings of Chapter 4 provide some further illumination on how faulty attitudes towards uncertainty may lead to destructive choices in those with drug addiction.

The studies reported in Chapters 3 and 4 utilised tasks that operationalized rewards and punishments numerically (i.e. number of points accrued) or monetarily (i.e. hypothetical money). Chapter 5 presented a novel task assessing PD of health outcomes, which is a PD domain that has not yet been applied to illicit substance abuse. The findings of Chapter 4 may not have been generalizable to behaviour outside the laboratory, and it was the purpose of Chapter 5 to construct a PD task that would be more relevant to drug abuse or more personally meaningful to participants than intangible sums of money. The health scenarios were derived from those created by Chapman and Elstein (1995) and while they were not written to be specifically relevant to substance abuse, many patients remarked over the course of testing that they could relate to the symptoms described in the scenarios. However, we failed to find any significant differences between patients and controls in discounting of either gains or losses. This is surprising given the health decisions made by drug abusers on a daily basis, and contrasts with a study conducted by Poltavski and Weatherly (2013) that found heavy smokers PD general heath outcomes less than non-smokers. An interaction was found in Chapter 5 between IU and PD of health gains, in which patients showed a preference for small, certain health gains as their IU increased. There was no meaningful correlation between IU and

PD of health gains in the control group, which suggested that IU may be related to risk-aversion regarding health outcomes in opioid-dependent individuals.

It is noteworthy that money was discounted differently between groups in Chapter 4, but health was discounted similarly in Chapter 5. Past research has evidenced that delayed health improvements are discounted at a greater rate than delayed sums of money (Chapman & Elstein, 1995; Lazaro et al., 2002), and delayed illness is discounted less compared to delayed monetary gains (Petry, 2003). Due to difficulties making direct comparisons between domains across the separate studies, statistical analysis was not conducted to ascertain statistical differences between PD of health and PD of money. Regardless, the differences in discounting domains between Chapters 4 and 5 are interesting because health consequences are highly relevant for opioid addicts. It would be reasonable to expect differences in the way patients discount health outcomes compared to non-drug abusers, given the risks opioid users are willing to take with their health, and that patients and controls demonstrated different risk-taking patterns about monetary outcomes.

Impulsivity and IU in opioid-dependency

IU reflects negative attitudes towards uncertainty and is the basis of worry and highly co-morbid with anxiety. It was expected that IU would also be a factor in drug addiction, given the similar maladaptive decision-making apparent in chronic drug use. The four empirical studies reported in this thesis support impulsivity as a multi-dimensional decision-making construct, and provide evidence that the relationships between certain facets of impulsivity and IU are unique in opioid-dependent individuals. A visual summary of the meaningful

relationships between IU and impulsivity across chapters can be found in Figure 6.1.

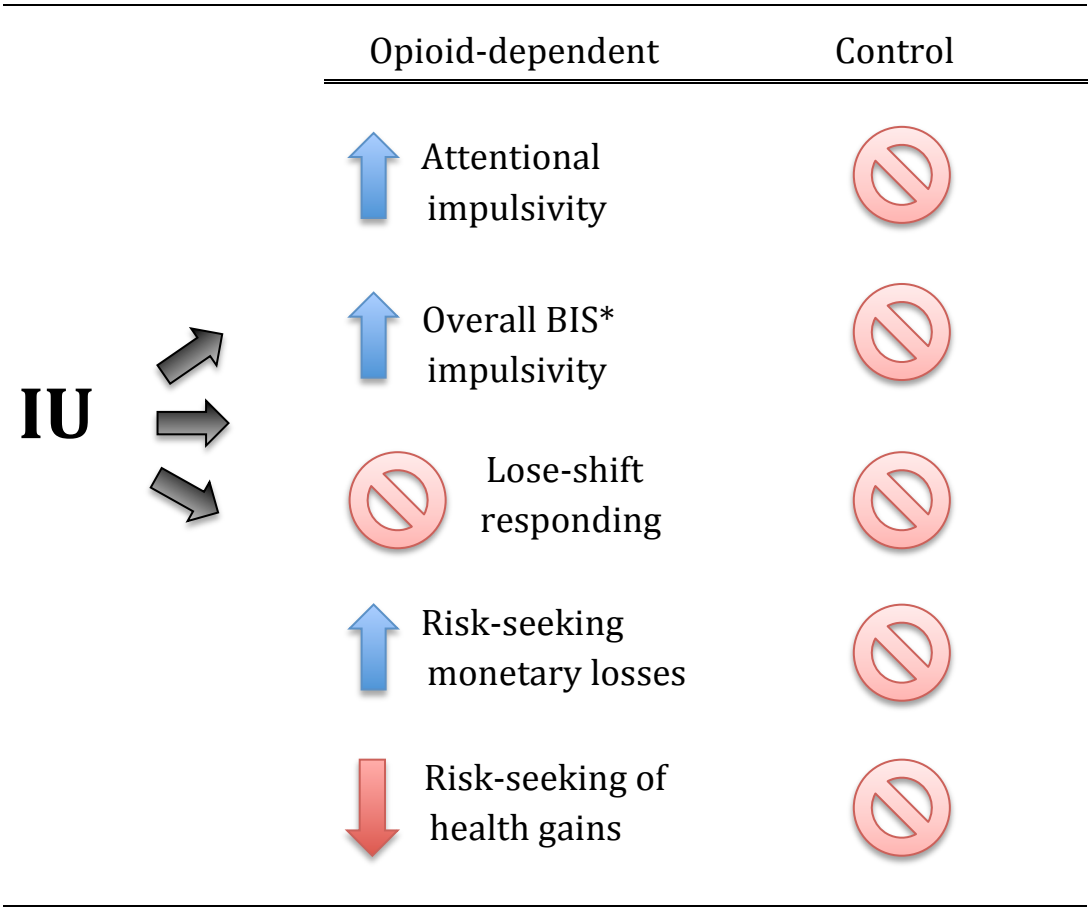


Figure 6.1. The relationship between IU and impulsivity dimensions between participant groups
* p = .064

There was a pattern of impulsive response to positive versus negative outcomes across Chapter 3 and Chapter 4. Patients reacted more impulsively to punishments than controls, and they appeared to be more risk-taking when faced with a financial loss. Taken together, these results suggest that opioid-dependent are more sensitive to punishments (i.e. are more loss-averse) and

appear to contradict other research showing that drug addiction is associated with dampened sensitivity to negative outcomes (Hester, Bell, Foxe, & Garavan, 2013; Potts et al., 2006). However, there is evidence for stress circuitry impairments and dysfunctional stress regulation in drug addicts, which may make these individuals more reactive to the negative affect associated with punishments. Uncertain negative outcomes create stress, which is a possible explanation why patients were more impulsive on the uncertainty impulsivity measures. Our results also have implications for relapse. It is well documented in animal research that stress in the form of foot shocks elicit the reinstatement of drug seeking (Shaham, Erb, & Stewart, 2000), and stress imagery can elicit drug cravings in humans similar to drug cues (Sinha, Fuse, Aubin, & Malley, 2000). Consequently, researchers have theorised that relapse is triggered by stress because stress disrupts the behavioural inhibition system responsible for supressing drug taking.

More relevant to the present thesis is the interaction observed between IU and impulsivity in relation to negative outcomes in the patient group. The uncertainty inherent in the feedback tasks of Chapter 3 and in the probabilistic outcomes in Chapter 4 ostensibly elicits stress and anxiety in those with high IU. Stress created by uncertain threat in IU individuals therefore can lower inhibition, and thus result in impulsive behaviours, particularly in people who have pre-existing dysfunction in stress circuitry and stress regulation. In relation to relapse, rehabilitated drug addicts who have low tolerance for uncertainty may be especially vulnerable to reinstating drug-taking behaviour following stress.

These conclusions are tempered by the lack of discounting differences of probabilistic health losses between participant groups in Chapter 5, and that the relationship between IU and health losses were similar between groups. This can potentially be explained by the finding that the relationship between IU and losses in Chapter 5 very small and non-significant in both groups, indicating that something about the health losses scenario was not impacted by attitudes towards uncertainty. This may be attributable to the health scenario itself, in that it involved health detriments occurring during the course of a treatment that was guaranteed to result in a positive outcome. Similarly, the relationship between IU and health gains that was not observed in previous chapters may be a result of the temporary nature of the health improvements, which occurred in the context of a life-long illness.

Overall, the results from the empirical chapters of the thesis clearly show that IU and impulsivity interacted only in opioid-dependent patients, which suggests that negative attitudes towards uncertainty need to be addressed in drug treatment programs.

6.2 Contributions and applications

The connection between IU and addiction-related impulsivity factors clearly illustrates the need to address IU in all stages of addiction prevention and treatment. Promisingly, a number of recent studies have demonstrated that IU can be modulated through cognitive interventions in clinical and non-clinical populations. Oglesby, Allan, and Schmidt (2017) developed a cognitive bias modification method to improve negative perceptions of ambiguity that are hallmark of IU. Participants with elevated levels of IU were “trained” to assign

neutral or positive interpretations to ambiguous phrases through positive and negative feedback. For example, an ambiguous phrase such as “the doctor called” can either be interpreted neutrally as an appointment reminder (rewarded with positive feedback) or negatively as a disease diagnosis (punished with negative feedback). This IU-focused cognitive bias modification paradigm yielded a significant reduction in IU at post-intervention, as assessed by the IUS (Oglesby et al., 2017). These improvements were maintained at a one-month follow up, suggesting that a relatively simple cognitive bias modification procedure can have a lasting impact on negative interpretations of uncertainty.

Cognitive behavioural interventions have also found success in reducing IU in clinical samples. A cognitive behavioural therapy (CBT) intervention targeting IU has been developed by Hui and Zhihui (2017), and involves psychoeducation about IU, recognition of uncertainty, uncertainty exposure, and problem re-orientation when dealing with uncertainty. The authors found that in a sample of adults with GAD diagnosis, IU-focused CBT had success in reducing IU, depression, anxiety and GAD symptoms at post-intervention. Furthermore, improvements were sustained at a six-month follow up. Decreases in IU have also been accomplished indirectly through therapies for anxiety and depression. IU reductions have been observed after group CBT for anxiety (Talkovsky & Norton, 2016) and social phobia (Mahoney & McEvoy, 2012a), as well as mindfulness-based cognitive therapy for panic disorder (Kim, Lee, Kim, Choi, & Lee, 2016). IU was improved following transdiagnostic CBT for patients diagnosed with anxiety and/or depression (Boswell, Thompson‐Hollands, Farchione, & Barlow, 2013). McEvoy and Erceg-Hurn (2016) propose that not only is IU a transdiagnostic factor for a variety of emotional disorders, but is also

a “trans-therapy” factor that can be both directly or indirectly modulated by diverse types of therapies. There are no studies to date that assess improvements in IU following SUD treatment, which is unsurprising given that IU has not received attention in the addiction literature. However, the current thesis presents robust evidence that IU is a factor for consideration when treating maladaptive decision-making in chronic drug users.

Early interventions targeting the association observed between IU and coping motives for alcohol use may be successful in preventing alcohol abuse, considering that using alcohol as a coping strategy is risk factor for alcohol abuse disorder (Carpenter & Hasin, 1999; Kraemer et al., 2015; Oglesby et al., 2015). Similar interventions could also be effective for opioids, as it is commonly accepted that opioids are also used to manage stress and relieve emotional pain (Khantzian, 1985). The role of individual differences can also be vital for screening patients who may be vulnerable to developing an addiction from prescribed opioid medication. Oxycodone (OxyContin), which has double the potency as morphine, was marketed to primary care physicians for moderate pain, despite it being originally dispensed by oncologists and physicians with pain management training to cancer patients (General Accounting Office, 2003)(General Accounting Office, 2003). While increased media and government attention in United States has brought more awareness to the dangers of pharmaceutical opioids, opioids are still commonly prescribed with 99% of all OxyContin prescriptions made in the United States (Manchikanti, 2007). Unfortunately, those who have been opioid naïve prior to receiving pharmaceutical opioids clearly have pre-existing vulnerabilities that need to be accounted for before prescribing highly addictive drugs.

Given that IU may be a trans-diagnostic, trans-therapy factor, the inclusion of IU reduction efforts in substance abuse treatment could also ostensibly improve rehabilitation outcomes. Correcting negative perceptions about uncertainty may improve self-appraisals of control and enable problem-focused coping methods, rather than emotional-focused strategies (Taha et al., 2014), which has also has implications for preventing relapse in response to stress. Furthermore, reducing stress elicited by uncertainty in opioid-dependent individuals receiving maintenance therapy is important, as stress has shown to increase extra-medical opioid craving in this cohort (Hyman, Fox, Hong, Doebrick, & Sinha, 2007). Improving perceptions about uncertainty may also increase confidence for methadone/buprenorphine patients to progress past maintenance therapy and become fully independent of any opioids. Finally, focusing on creating a stable everyday environment for a recovering addict may be crucial for attaining long-term success, as the literature has demonstrated that supressing cognitions about uncertainty can deplete the willpower necessary to resist temptation (Milkman, 2012).

6.3 Limitations and future directions

The limitations particular to individual studies have been discussed in their relevant chapters, however there are a number of general considerations that need to be accounted for when interpreting the results of the current thesis.

A key consideration is that the methodology used does not allow us to differentiate between the acute effects of opioid maintenance treatment and the long-term effects of opioid-dependency. However, we consistently found that the length of opioid use or abuse was not correlated with the behavioural or

personality measures, a result that provides tenuous evidence that impulsivity observed in patients may predate addiction. The cognitive side effects involved with methadone and buprenorphine maintenance therapy may have also impacted patients' responses. For example, Rass et al. (2014) found that working memory was significantly worse in methadone patients at peak timing of methadone administration (120 minutes after dosage) compared to trough timing (26 hours after last dosage). Alternatively, Gorzelaczyk, Fareed, Walecki, Feit, and Kunc (2014) found that risky decision-making and response time (on the Iowa Gambling Task) were reduced in methadone-maintained patients shortly following their daily methadone dose. In the present thesis, it was necessary to conduct each study shortly after participants had been administered their medication, as daily administration of medication is mandatory and it would not be ethical to interfere with patients' treatment programs. It is possible that the decision-making demonstrated by patient participants may change over the course of the day as the acute effects of their medication tapers off. The best attempt was made to exclude data from participants who appeared to be cognitively impaired, however future research using this cohort would benefit from a cognitive acuity screening measure before testing.

Treatment-seeking opioid users may also demonstrate altered cognitive factors related to impulsivity, such as in executive control. Severtson, Von Thomsen, Hedden, and Latimer (2010) found that low scores on an executive functioning task predicted less treatment seeking in active heroin and/or cocaine users, and scores were negatively correlated with self-recognition of problematic drug use. There also may be differences in cognitive functioning

between abstinent opioid-medication maintained patients and non-treatment seeking active heroin users, as evidenced by Verdejo, Toribio, Orozco, Puente, and Pérez-García (2005). The authors observed that compared to abstinent heroin users about to commence rehabilitation, methadone-maintenance patients demonstrated impairments in working memory, analogical reasoning, cognitive flexibility, processing speed and visuo-spatial attention. Furthermore, there is evidence that methadone-maintenance therapy may impact risky decision-making in opioid users compared to heroin users who are not in treatment, in ways that cannot be accounted for by individual differences in impulsivity (Ersche et al., 2005).

A final question that the current thesis is unable to answer is whether data obtained from opioid-medication maintained individuals, who have ceased involvement with illicit drugs, can generalise to opioid abusers who have not sought treatment. Psychological dependence is delineated from physical opioid-dependence in that the former involves a craving for the drug's hedonic effects (Inturrisi, 2002). While all the patient participants in the current thesis were physically opioid-dependent, the patients widely differed in regards to psychological dependence. On one extreme were patients who were regularly using drugs other than their medication to "get high" and who were still involved in a drug-taking lifestyle. On the other extreme were patients who had not used illicit substances in decades, and who were living healthy, pro-social lifestyles. There may be inherent personality differences in psychologically dependent drug users compared to those who are only physically dependent, and future research would benefit from addressing this question.

6.4 Conclusion

Intolerance of uncertainty is higher in opioid-dependent individuals and may uniquely influence impulsive decision-making, in that it may result in heightened impulsivity that is not typically characteristic of IU. Impulsive individuals who are prone to addiction may also react to uncertainty in negative ways that reflect their lived experience with uncertainty. IU may also arise due to shared neural connections with impulse control, reward valuation and addiction. The cause and effect nature of these associations are yet to be determined in future studies. However, the new information provided by this thesis significantly contributes to our understanding of the individual vulnerabilities that contribute to the current opioid epidemic, and provides initial insight to guide the creation of future studies on the topic.

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Appendices

Appendix A

The Barratt Impulsivity Scale – Version 11

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and fill in the appropriate circle on the right side of the page. Do not spend too much time on any statement. Answer quickly and honestly.

(1) Rarely/Never (2) Occasionally (3) Often (4) Almost Always/Always

1. I plan tasks carefully.	(1) (2) (3) (4)
2. I do things without thinking.	(1) (2) (3) (4)
3. I make up my mind quickly.	(1) (2) (3) (4)
4. I am happy-go-lucky.	(1) (2) (3) (4)
5. I don't "pay attention."	(1) (2) (3) (4)
6. I have "racing" thoughts.	(1) (2) (3) (4)
7. I plan trips well ahead of time.	(1) (2) (3) (4)
8. I am self-controlled.	(1) (2) (3) (4)
9. I concentrate easily.	(1) (2) (3) (4)
10. I save regularly.	(1) (2) (3) (4)
11. I "squirm" at plays or lectures.	(1) (2) (3) (4)
12. I am a careful thinker.	(1) (2) (3) (4)
13. I plan for job security.	(1) (2) (3) (4)
14. I say things without thinking.	(1) (2) (3) (4)
15. I like to think about complex problems.	(1) (2) (3) (4)
16. I change jobs.	(1) (2) (3) (4)

17. I act "on impulse."	1	2	3	4
18. I get easily bored when solving thought problems.	1	2	3	4
19. I act on the spur of the moment.	1	2	3	4
20. I am a steady thinker.	1	2	3	4
21. I change residences.	1	2	3	4
22. I buy things on impulse.	1	2	3	4
23. I can only think about one thing at a time.	1	2	3	4
24. I change hobbies.	1	2	3	4
25. I spend or charge more than I earn.	1	2	3	4
26. I often have extraneous thoughts when thinking.	1	2	3	4
27. I am more interested in the present than the future.	1	2	3	4
28. I am restless at the theater or lectures.	1	2	3	4
29. I like puzzles.	1	2	3	4
30. I am future oriented.	1	2	3	4

Appendix B

The Intolerance of Uncertainty Scale

IUS

IUS

You will find below a series of statements which describe how people may react to the uncertainties of life. Please use the scale below to describe to what extent each item is characteristic of you. Please circle a number (1 to 5) that describes you best.

	Not at all characteristic of me			Somewhat characteristic of me		Entirely characteristic of me
1. Uncertainty stops me from having a firm opinion.	1	2	3	4	5	
2. Being uncertain means that a person is disorganized.	1	2	3	4	5	
3. Uncertainty makes life intolerable.	1	2	3	4	5	
4. It's unfair not having any guarantees in life.	1	2	3	4	5	
5. My mind can't be relaxed if I don't know what will happen tomorrow.	1	2	3	4	5	
6. Uncertainty makes me uneasy, anxious, or stressed.	1	2	3	4	5	
7. Unforeseen events upset me greatly.	1	2	3	4	5	
8. It frustrates me not having all the information I need.	1	2	3	4	5	
9. Uncertainty keeps me from living a full life.	1	2	3	4	5	
10. One should always look ahead so as to avoid surprises.	1	2	3	4	5	

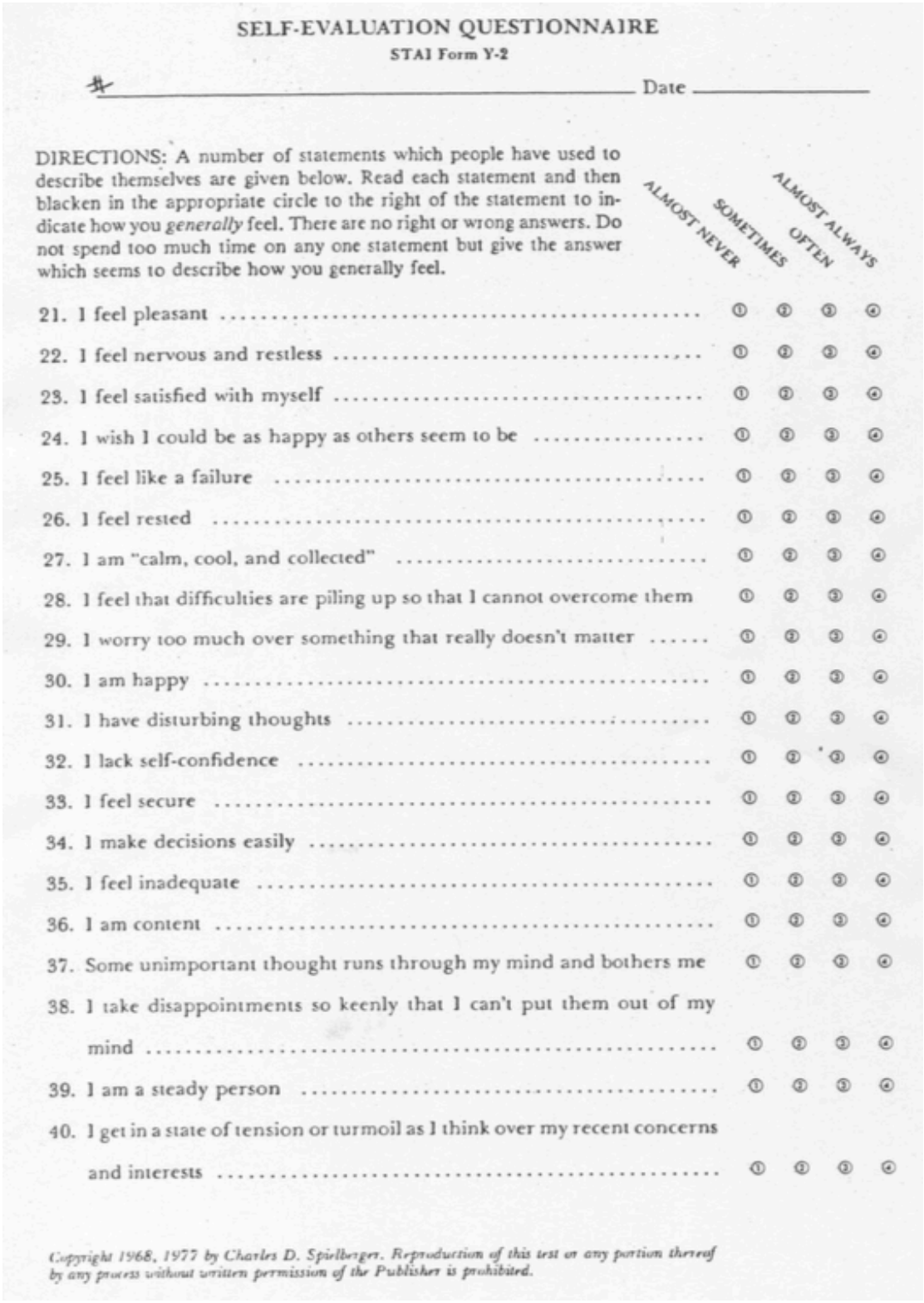
	Not at all characteristic of me			Somewhat characteristic of me		Entirely characteristic of me
11. A small unforeseen event can spoil everything, even with the best of planning.	1	2	3	4	5	
12. When it's time to act, uncertainty paralyses me.	1	2	3	4	5	
13. Being uncertain means that I am not first rate.	1	2	3	4	5	
14. When I am uncertain, I can't go forward.	1	2	3	4	5	
15. When I am uncertain I can't function very well.	1	2	3	4	5	
16. Unlike me, others always seem to know where they are going with their lives.	1	2	3	4	5	
17. Uncertainty makes me vulnerable, unhappy, or sad.	1	2	3	4	5	
18. I always want to know what the future has in store for me.	1	2	3	4	5	
19. I can't stand being taken by surprise.	1	2	3	4	5	
20. The smallest doubt can stop me from acting.	1	2	3	4	5	
21. I should be able to organize everything in advance.	1	2	3	4	5	
22. Being uncertain means that I lack confidence.	1	2	3	4	5	

	Not at all characteristic of me				Somewhat characteristic of me				Entirely characteristic of me
23. I think it's unfair that other people seem sure about their future.		1		2		3		4	5
24. Uncertainty keeps me from sleeping soundly.		1		2		3		4	5
25. I must get away from all uncertain situations.		1		2		3		4	5
26. The ambiguities in life stress me....		1		2		3		4	5
27. I can't stand being undecided about my future.		1		2		3		4	5

Origianl French Version: Freeston, M.H., Rhéaume, J., Letarte, H., Dugas, M.J., & Ladouceur, R. (1994): Why do people worry? *Personality and Individual Differences, 17* (6), 791-802.
English Version: Buhr, K., Dugas, M. J. (2002). The intolerance of uncertainty scale: psychometric properties of the English version. *Behavior Research and Therapy, 40* , 931-945.

Appendix C

The State Trait Anxiety Questionnaire – Form Y-2



SELF-EVALUATION QUESTIONNAIRE

STAI Form Y-2

#_____ Date _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	ALMOST NEVER	SOMETIMES	OFTEN	ALMOST ALWAYS
21. I feel pleasant	①	②	③	④
22. I feel nervous and restless	①	②	③	④
23. I feel satisfied with myself	①	②	③	④
24. I wish I could be as happy as others seem to be	①	②	③	④
25. I feel like a failure	①	②	③	④
26. I feel rested	①	②	③	④
27. I am "calm, cool, and collected"	①	②	③	④
28. I feel that difficulties are piling up so that I cannot overcome them	①	②	③	④
29. I worry too much over something that really doesn't matter	①	②	③	④
30. I am happy	①	②	③	④
31. I have disturbing thoughts	①	②	③	④
32. I lack self-confidence	①	②	③	④
33. I feel secure	①	②	③	④
34. I make decisions easily	①	②	③	④
35. I feel inadequate	①	②	③	④
36. I am content	①	②	③	④
37. Some unimportant thought runs through my mind and bothers me	①	②	③	④
38. I take disappointments so keenly that I can't put them out of my mind	①	②	③	④
39. I am a steady person	①	②	③	④
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	①	②	③	④

Appendix D

Schematic of probability discounting procedure and calculation of an indifference point

Item	Receive for certain	Receive at 25% chance	
1	**$1000**	$1000	
2	**$950**	$1000	
3	**$900**	$1000	
4	**$850**	$1000	
5	**$800**	$1000	
6	**$750**	$1000	**IP =** Mean of values at the switch point ($550 & $500) = **$525**
7	**$700**	$1000	
8	**$650**	$1000	
9	**$600**	$1000	
10	**$550**	$1000	
11	$500	**$1000**	← Switch point from certain to probabilistic reward
12	$450	**$1000**	
13	$400	**$1000**	
14	$350	**$1000**	
15	$300	**$1000**	
16	$250	**$1000**	
17	$200	**$1000**	
18	$150	**$1000**	
19	$100	**$1000**	
20	$50	**$1000**	

Figure C.1. Choices between monetary rewards for the 25% probability block of questions, with example answers from participant #101 in bold font.

Appendix E

Probability discounting functions as indices of risky decision-making

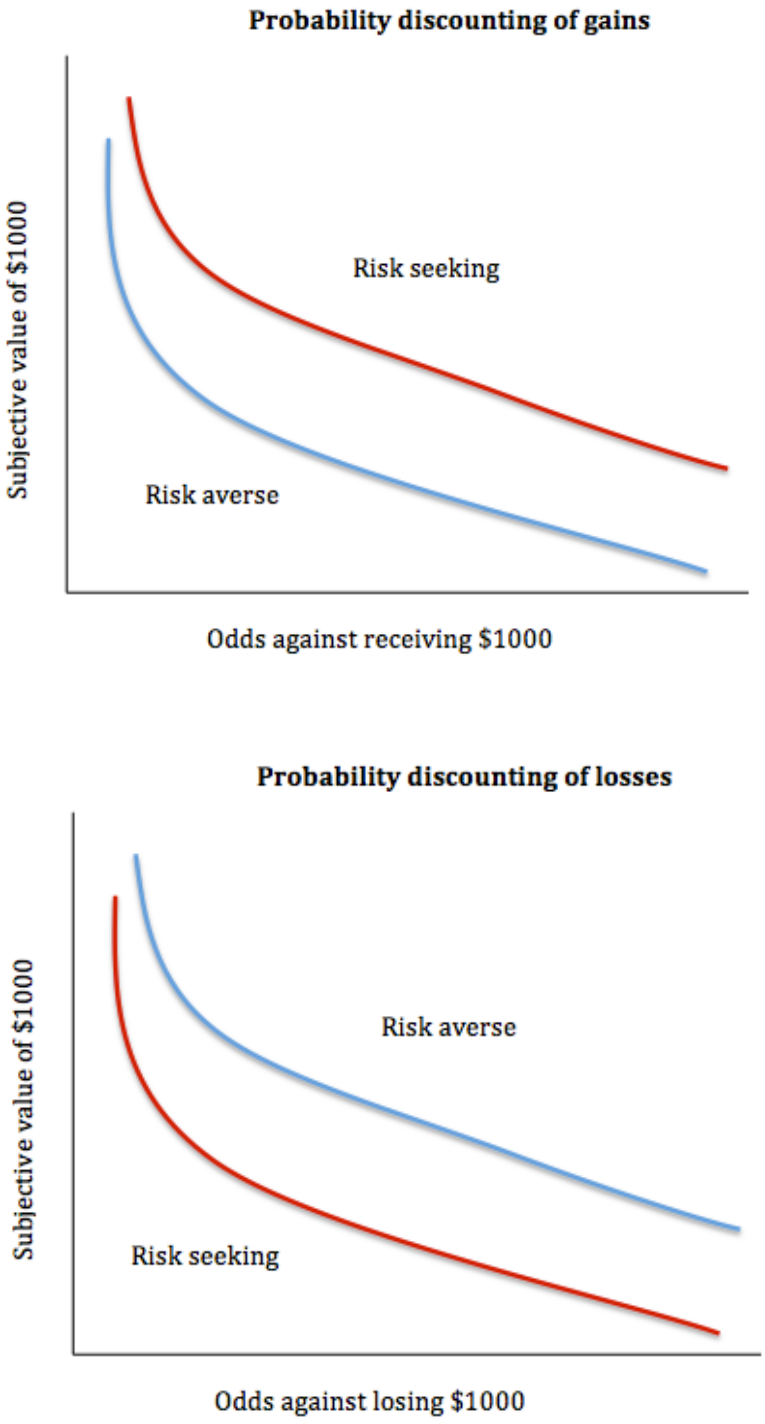


Figure D.1. Example probability discounting functions for gains and losses interpreted in regards to risk attitudes

The graphs show that risk is assessed inversely for loss discounting.

Appendix F

Participant information sheet

Studying Cognitive Function in Patients with Addiction

INFORMATION FOR PARTICIPANTS

Introduction

You are invited to take part in a research study that is looking at cognitive function in adults. The objective is to investigate cognitive function in individuals who are receiving treatment for addiction, and healthy people who have no addiction problems. The study involves the completion of questionnaires and a computer task that measure different aspects of cognitive functioning. Participation in the study will take up to a maximum of 1 hour to complete.

The study is being conducted within this institution by Professor Paul Haber from the Drug Addiction Unit, and Dr Ahmed Moustafa from Western Sydney University.

The study is being supported by a research grant from the University of Western Sydney.

Study Procedures

If you agree to participate in this study, you will be asked to sign the Participant Consent Form. You will then be asked to complete a computerised cognitive test, and few general questionnaires. These will seek information on your cognitive functioning and will take about 50 to 60 minutes to do. In addition, the researchers would like to have access to your medical record to obtain information relevant to this study.

Risks

The risks of participating in this study are:

The study requires you conducting some questionnaires and doing a computerised task, which will take approximately 50 minutes. Participants will be compensated financially for their participation in the study and there will not be any kind of risk or harm for their participation.

Benefits

While we intend that this research study furthers medical knowledge and may improve the treatment of addiction problems in the future, it will not be of direct benefit to you.

Costs

Participation in this study will not cost you anything. You will be reimbursed $20 for your travel expenses and participation in our study.

Voluntary Participation

Participation in this study is entirely voluntary. You do not have to take part in it. If you do take part, you can withdraw at any time without having to give a reason. Whatever your decision, please be assured that it will not affect your medical treatment or your relationship with the staff who are caring for you.

Confidentiality

All the information collected from you for the study will be treated confidentially, and only the researchers named above *(or other authorised personal as appropriate)* will have access to it. The study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such a presentation.

It is also possible that the results of this study may be used in other like projects conducted by Dr Ahmed Moustafa and colleagues, but will not be used in any way that reveals my identity.

Further Information

When you have read this information, *Professor Haber* will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact Dr Ahmed Moustafa (Phone: 9772 6847; email: a.moustafa@uws.edu.au)

This information sheet is for you to keep.

Ethics Approval and Complaints

This study has been approved by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health District. Any person with concerns or complaints about the conduct of this study should contact the Executive Officer on 02 9515 6766 and quote protocol number **X16-0356**.

Appendix G

Participant consent form

I,
.....
[name]

of

.....……*[address]*

have read and understood the Information for Participants on the above named research study and have discussed the study with
.....

I have been made aware of the procedures involved in the study, including any known or expected inconvenience, risk, discomfort or potential side effect and of their implications as far as they are currently known by the researchers.

I understand that my participation in this study will allow the researchers and others, as described in the Information for Participants, to have access to my medical record, and I agree to this.

I understand that the results of this study may be used in other like projects conducted by Dr Ahmed Moustafa and colleagues but will not be used in any way that reveals my identity

I freely choose to participate in this study and understand that I can withdraw at any time.

I also understand that the research study is strictly confidential.

I hereby agree to participate in this research study.

NAME:

.....

SIGNATURE:

.....

DATE:

.....

NAME OF WITNESS:

.....

SIGNATURE OF WITNESS:

.....

Appendix H

Ethics application

ETHICS APPLICATION FORM FOR HUMAN RESEARCH

SECTION 1: ADMINISTRATION AND SUBMISSION TO OTHER HUMAN RESEARCH ETHICS COMMITTEES (HRECs)

1.1 (a) Full study title

Decision Making, Learning, and Memory: Studying Cognitive Function in Healthy Patients with Addiction

(b) Short name by which the study will be known (if appropriate)

Decision Making, Learning, and Memory

1.2 (a) Name of Chief Investigator

Dr Ahmed Moustafa

(b) Name(s) of Co-, Associate- and/or Student-Investigator(s)

Co-investigator 2: Professor Paul Haber
Study co-ordinator: Dr Christa Lam-Cassettari

1.3 Indicate the exact SLHD (RPAH Zone) location at which the study procedures / data collection will be undertaken, ie department, building, level, etc.

Drug Health Services, Royal Prince Alfred Hospital, Camperdown, NSW, 2050
(directed by Dr. Paul Haber)

.

1. Project details

HREC Application Reference Number:

Name/ID of HREC reviewing the research project:

Project Title (in full): Decision Making, Learning, and Memory: Studying Cognitive Function in Healthy Patients with Addiction

2. Project summary

Provide a brief description (half page) of the project details to enable the research governance officer to understand the nature and impact of the research project at the research site.

One limitation of prior research in the field of addiction is the largely exclusive focus on decision making and impulsivity measures. Here, we aim to extend current knowledge by departing from this route and focusing more on learning from gains or losses, in addition to systematically assessing a wider range of measures that comprehensively evaluate other cognitive functions that have been posited to influence addictive behaviours.

In collaboration with Dr Paul Haber (Addiction Unit, RPAH), in this project, we will test cognitive function in individuals with diagnosed addiction problems compared to healthy controls. Although prior studies have reported cognitive changes in individuals with addiction, it is not clear how these changes (including executive function) correlate with psychiatric symptoms, including behavioural inhibition and impulsivity. In addition, there are various theories explaining why some individuals show addictive problems, including abnormal valuation of wins vs. losses or executive dysfunction. In this project, we will test both healthy control subjects and individuals with addiction on both (a) computerized cognitive tasks (which test learning from wins vs. losses) and (b) clinical measures (Barratt Impulsiveness Scale). We will test the plausibility of existing cognitive theories of addiction. In addition, we predict that cognitive changes might explain some of the symptoms in individuals with addiction.