Decision-making impairment in long term opiate users

Kathryn Biernacki

Bachelor of Arts/Bachelor of Science, Bachelor of Psychological Science (Honours)

Submitted in total fulfilment of the requirements for the degree of
Doctor of Philosophy

School of Psychology,
Faculty of Health Sciences

March, 2018

DECISION-MAKING AND OPIATE USE

Declaration

This thesis contains no material that has been extracted in whole or in part from a thesis that I have submitted towards the award of any other degree or diploma in any other tertiary institution.

No other person's work has been used without due acknowledgment in the main text of the thesis.

All research procedures reported in the thesis received the approval of the relevant Ethics/Safety Committees (where required).

Signed ....

Date   ....

DECISION-MAKING AND OPIATE USE

Acknowledgments

DECISION-MAKING AND OPIATE USE

Table of Contents

DECISION-MAKING AND OPIATE USE

DECISION-MAKING AND OPIATE USE

DECISION-MAKING AND OPIATE USE

DECISION-MAKING AND OPIATE USE

Abstract

The overall aim of this PhD thesis was to conduct a comprehensive investigation of decision-making impairment in long term opiate users, using three studies. The first study aimed to determine the extent of the decision-making impairment and to establish whether other co-morbid factors impacted on the severity of this deficit. Using meta-analysis, the results indicated that opiate use is associated with relatively severe decision-making impairment, and that co-morbid factors, such as head injury and poly-substance dependence did not significantly change the magnitude of the impairment. Furthermore, the decision-making impairment in opiate users was not mitigated by abstinence, and the duration of opiate use and the duration of abstinence did not have a significant impact on size of the impairment. The second study analysed whether the somatic marker hypothesis, an emotion-based model of decision-making, could provide an explanation for the decision-making impairment in opiate users. This empirical study found that, although decision-making was impaired in a group of long term opiate users relative to a group of healthy controls, this impairment was not due to reduced emotional responsiveness, nor an inability to form anticipatory warning signals (i.e., somatic markers), as measured by the skin conductance response. Notably, stronger somatic responses when contemplating making disadvantageous choices were associated with worse decision-making in opiate users, which does not support the predictions of the somatic marker model of decision-making. Finally, the third study analysed decision-making under conditions of risk, to determine whether the impairment in opiate users was restricted to certain types of decision-making. This empirical study found that opiate users, although impaired in decision-making under conditions of ambiguity, were not impaired on decision making tasks involving calculable risk, relative to healthy controls. This study also demonstrated that opiate users' decisions were not driven by an increased responsiveness to reward. Together, the results of this thesis suggest that opiate users are particularly impaired in situations of decision-making under ambiguity, but not risk, and this is not due to impairment in emotional processing. This has implications for the treatment of opiate users, who may need additional training to appropriately utilise physiological signals to make adaptive decisions. The results of this thesis may therefore be used to inform treatment practice to better support opiate users during ambiguous decision-making situations in daily life.

DECISION-MAKING AND OPIATE USE

Research Output

Published peer reviewed papers as chapters of the thesis

Biernacki, K., McLennan, S. M., Terrett, G., Labuschagne, I., Rendell, P. G. (2016). Decision-making ability in current and past users of opiates: A meta-analysis. *Neuroscience and Biobehavioral Reviews, 71*, 342-351. doi: 10.1016/j.neubiorev.2016.09.011 (Chapter 3)

Biernacki, K., Terrett, G., McLennan, S. N., Labuschagne, I., Morton, P., Rendell, P. G. (2018). Decision-making, somatic markers and emotion processing in opiate users. *Psychopharmacology*, 235(1), 223-232. doi: 10.1007/s00213-017-4760-0 (Chapter 5)

Published conference proceedings

Biernacki, K. C., McLennan, S. N., Terrett, G., Labuschagne, I. (2016). Decision-making impairments in current and ex users of opiates: A meta-analytic review. *Journal of Psychopharmacology, 30*(8, Suppl. 1), A60.

Biernacki, K., Terrett, G., McLennan, S., Labuschagne, I., Morton, P., Rendell, P. G. (2017). Decision-making, somatic markers and emotion activation in opiate users. *Psychophysiology, 54*(Suppl. 1), S44.

Conference presentations

Biernacki, K., McLennan, S., Terrett, G. (2015) *Physical reactions to decision making in long term opiate users*. School of Psychology Research Conference, Australian Catholic University, Melbourne, Australia. September 28.

Biernacki, K., McLennan, S. N., Terrett, G., Labuschagne, I., Rendell, P. G. (2016). *Decision-making in current and past users of opiates: A meta-analysis*. British Association of Psychopharmacology Summer Meeting, Brighton, England. July 18.

DECISION-MAKING AND OPIATE USE

Biernacki, K., McLennan, S., Terrett, G. (2016). *Testing the somatic marker hypothesis in healthy adults and opiate users.* School of Psychology Research Conference, Australian Catholic University, Melbourne, Australia. September 27.

Biernacki. K., Terrett, G., McLennan, S. N., Labuschagne, I., Morton, P., Rendell, P. G. (2017). *Decision-making, emotion activation and somatic markers in opiate users.* 57th Annual Meeting of the Society for Psychophysiological Research, Vienna, Austria. October 11.

Biernacki. K., Terrett, G., McLennan, S. N., Labuschagne, I., Morton, P., Rendell, P. G. (2017). *Decision-making, emotional responding and somatic markers in opiate users.* 7th Australasian Cognitive Neuroscience Society Conference, Adelaide, Australia. 23-26 November.

Bursaries and Grants

DECISION-MAKING AND OPIATE USE

List of Tables

DECISION-MAKING AND OPIATE USE

List of Figures

DECISION-MAKING AND OPIATE USE

List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder		IGT	Iowa Gambling Task
BART	Balloon Analogue Risk Task		IQ	Intelligence Quotient
BAS	Behavioural Activation System		NART	National Adult Reading Test
BIS	Behavioural Inhibition System		OFC	Orbitofrontal cortex
CGT	Cambridge Gambling Task		SCR	Skin conductance response
CI	Confidence interval			
DDT	Delay Discounting Task			
dlPFC	Dorsolateral prefrontal cortex			
GDT	Game of Dice Task			
HADS	Hospital Anxiety and Depression Scale			
IAPS	International Affective Picture System			

DECISION-MAKING AND OPIATE USE

CHAPTER 1: Introduction and Thesis Outline

1.1 Background to Opiate Dependence and Rationale for the Thesis

Opiates are naturally occurring chemicals found in poppy plants, but may also be synthesised to produce semi-synthetic illicit opiates such as heroin (Koob & Le Moal, 2005). Opiates, in particular heroin, can produce pleasurable sensations or a "rush" (World Health Organization, 2004) as they mimic the effect of endogenous opiates which signal reward and pleasure (Di Chiara & North, 1992; Kosten & George, 2002). These properties make exogenously introduced opiates susceptible to abuse and addiction.

The most recent estimate suggests that 15.5 million people worldwide are dependent on opiates (Degenhardt et al., 2014), the most heavily abused of which is heroin (United Nations Office on Drugs and Crime, 2010, 2012). Opiate dependence is therefore a major public health concern globally (Bart, 2012). Despite recent declines in opium production in key supply areas (Afghanistan, South-East Asia and Latin America), opiate use is rising in the United States and other countries, (Jones, Logan, Gladden, & Bohm, 2015; United Nations Office on Drugs and Crime, 2016). Indeed, the United States is currently part of an "opioid epidemic" with a 150% increase in the number of people abusing or dependent on heroin between 2007 and 2013, and overdose rates nearly doubling between 2011 and 2013 (Jones et al., 2015). This epidemic may be driven by the over prescription of opioid analgesics such as oxycodone, with users shifting to heroin following a period of opioid misuse (Compton, Boyle, & Wargo, 2015). A key issue is the perseverative nature of opiate dependence, with users typically cycling through periods of heavy use, then moving to treatment, and even cessation, but then relapsing, therefore starting the cycle again (Darke, 2011). In this cycle, treatment often involves the prescription of therapeutic drugs, such as methadone, buprenorphine or naltrexone.

Opiate use is associated with a range of high risk behaviours. For example, opiate users may choose to administer the drug intravenously, therefore placing them at increased risk of infection with hepatitis C and HIV (Gowing, Farrell, Bornemann, & Ali, 2008). Many opiate users also often engage in property and other crime to finance their opiate use (Gossop, Marsden, Stewart, & Rolfe, 2000; Stewart, Gossop, Marsden,

DECISION-MAKING AND OPIATE USE

& Rolfe, 2000), placing them at higher risk of incarceration (Klee & Morris, 1994; Maradiaga, Nahvi, Cunningham, Sanchez, & Fox, 2016). In addition, polysubstance abuse is very common (Veilleux, Colvin, Anderson, York, & Heinz, 2010), with a large proportion of opiate users also dependent on cocaine, alcohol and other sedatives (Astals et al., 2008). Combined, all of these issues contribute to the "cycle of addiction", and ultimately poor quality of life (De Maeyer, Vanderplasschen, & Broekaert, 2010) and to individual and societal burden (which are discussed in more detail in Chapter 2).

Although current and past opiate users may understand the consequences of actions, it appears that they have difficulty making adaptive decisions when it comes to abstaining from drug use and other maladaptive behaviours. It has been suggested that difficulty making adaptive decisions may contribute to the high risk behaviours and the day-to-day difficulties that opiate users experience (e.g., Wilson & Vassileva, 2016). Poor decision-making and high risk behaviours occur at all points in the cycle of opiate dependence (e.g., Baldacchino, Balfour, & Matthews, 2015; Zhang, Shi, et al., 2011).

Decision-making can be viewed as a cognitive process, and it can be measured in controlled laboratory settings to assess the presence and extent of impairment. A number of studies using laboratory-based measures have demonstrated decision-making impairment in opiate users. However, the nature and causes of this impairment are not well understood.

1.2 Aims of the Thesis

The overarching aim of this PhD thesis was to investigate the nature and the causes of impaired decision-making in opiate users, with a specific focus on people who were using legally prescribed opiates in the context of treatment for heroin dependence. This overall thesis aim was addressed in three studies. The aim of Study 1 in this PhD thesis was to determine the magnitude of the decision-making impairment in current and in past users of opiates, and to determine whether factors such as the presence of poly-drug use, head injury, duration of opiate use, or the phase of opiate use (i.e., past or present use) influenced the magnitude of this impairment. Following on from this, the aim of Study 2 was to investigate the cognitive and physiological mechanisms that may contribute to the decision-making impairment. It has been suggested that decision-making ability relies on more than a logical or rational evaluation of options, and that emotional responding can be critical to making adaptive decisions. Therefore, the

second study adopted a neurobiological model of decision-making (specifically, the somatic marker hypothesis; Damasio, 1994) to determine whether underlying abnormalities in the emotional response system could help to explain the decision-making impairment in opiate users. Finally, Study 3 aimed to clarify the nature of the decision-making impairment in opiate users. Decision-making is not a unitary construct and, although a range of studies have analysed decision-making impairment in opiate users, the pattern of the decision-making impairment across different types of decision-making tasks in this group remains unclear. By comparing opiate users' performance on two different types of decision-making tasks, the third study therefore aimed to provide a more fine-grained profile of the decision-making impairment in opiate users.

1.3 Structure of the Thesis

This thesis comprises published and unpublished scholarly works and is presented as a thesis with publication, in accordance with section five of the Australian Catholic University's Guidelines on the Preparation and Presentation of a Research or Doctoral Thesis for Examination (Australian Catholic University, 2015). It includes a meta-analysis study (Chapter 3), and results from two empirical studies that adopted a group-comparison design, comparing the performance of current opiate users and controls (Chapters 5 and 6).

A review of what is currently known about the consequences and effects of opiate dependence, and the associated neurological abnormalities, cognitive deficits, and emotion processing difficulties, is presented in Chapter 2. Chapter 3 presents the published meta-analysis describing factors associated with decision-making impairment in current and ex-users of opiates (Biernacki, McLennan, Terrett, Labuschagne, & Rendell, 2016). Chapter 4 provides a detailed description of the methodology of the empirical studies. Chapter 5 presents a manuscript accepted for publication, which describes findings from the first group-comparison study which assessed physiological and emotional responses and their relationship to decision-making in opiate users and controls. It also presents results of additional investigation of interoceptive ability in both groups. Chapter 6 presents findings from the second empirical study, which analysed performance on a different type of decision-making in opiate users. Finally, Chapter 7 presents a discussion of all the findings presented in the thesis and provides future directions for research in this field.

DECISION-MAKING AND OPIATE USE

CHAPTER 2: Cognitive, Neurological and Emotional Impairment in Opiate Users and Their Relationship to Decision-Making

2.1 Chapter Introduction

The research presented in this thesis investigates the nature and causes of the decision-making impairment commonly observed in long-term users of opiates. Impaired decision-making may contribute to the poor health, social, and treatment outcomes commonly observed in this group. While there is limited evidence of a broad cognitive impairment in opiate users, there is substantial evidence of decision-making impairment. However, the mechanism that causes this impairment remains unclear. It has been suggested that reduced capacity to emotionally respond to the rewarding and/or punishing outcomes of decisions may impair decision-making ability. However, while there is some evidence of emotional blunting and an inability to tune into emotional signals in opiate users, the current literature is limited and inconclusive. Similarly, it is unclear whether decision-making is impaired under all conditions; for example in situations of calculable risk. This chapter summarises existing research about the neurological abnormalities, cognitive deficits, and emotional processing difficulties that are associated with long-term opiate use, with a focus on their relevance to decision-making, and describes the limitations of the existing literature. The aim of this chapter is to provide a foundation for the subsequent investigations of impaired decision-making in opiate users reported in this thesis.

2.2 Cycle of Addiction in Opiate Users

Many opiate users are engaged in a persistent cycle of addiction and treatment. The trajectory of opiate dependence is sometimes referred to as an opiate user's "career" and people who use opiates typically cycle in and out of heavy heroin use, treatment with opiate substitutes, abstinence, and relapse over the course of adulthood (Darke, 2011; Darke et al., 2009). While some are able to maintain abstinence for long periods of time following multiple repetitions of the cycle (Hser, Huang, Brecht, Li, & Evans, 2008; Hser, Huang, Chou, & Anglin, 2007), others ultimately die from overdose, trauma, suicide or disease (Darke, Mills, Ross, & Teesson, 2011; Degenhardt et al., 2011). For heroin users receiving treatment in the community, poor decision-making has been shown to predict relapse during the treatment phase (Passetti et al., 2011; Passetti, Clark, Mehta, Joyce, & King, 2008). Thus, although opiate substitute programs

DECISION-MAKING AND OPIATE USE

provide a window for support and meaningful change, poor decision-making appears to be an ongoing issue, placing people engaged in such programs at risk of relapse and contributing to the addiction cycle. Thus, a better understanding of the factors which may contribute to this decision-making impairment has the potential to lead to improved outcomes[1].

2.3 Consequences of Opiate Use

2.3.1 Health and social problems associated with opiate use

People in all phases of the opiate addiction cycle, face a number of challenges which are thought to stem from cognitive impairments, in particular impaired judgement and decision-making (Ahn et al., 2014; Brand, Roth-Bauer, Driessen, & Markowitsch, 2008). For example, opiate users often choose to inject opiates, which can lead to collapsed veins, bacterial infection of blood vessels, abscesses and even arthritis (U.S. Department of Health and Human Services, National Institutes of Health, & National Institute of Drug Abuse, 2014). Poor decision-making may also lead to a higher risk of contracting blood-borne viruses through risky sexual practices (Gowing et al., 2008) and higher rates of poly-drug dependence through engagement in polysubstance abuse (Astals et al., 2008; Veilleux et al., 2010). Opiate users are also exposed to more violence (Darke, Sims, McDonald, & Wickes, 2000), which may lead to increased rates of traumatic brain injury (Darke, McDonald, Kaye, & Torok, 2012b). They also experience reduced employment levels (De Maeyer et al., 2011; Meulenbeek, 2000). These issues all contribute to reduced quality of life in opiate users (De Maeyer et al., 2010). Reduced quality of life can also precede drug abuse, with opiate users often experiencing physical and sexual abuse, social disadvantage and exposure to parental substance abuse from an early age (see Darke, 2011 for a review). These early experiences are often predictive of heroin and other drug dependence later in life (Darke, 2011; Dube et al., 2003), suggesting these experiences may be contribute to impaired judgement which pre-dates drug abuse (Edalati & Krank, 2016; Verdejo-Garcia, Lawrence, & Clark, 2008)

---

[1] It should be noted here that the term "opiate" refers to natural extracts of the opium poppy (such as heroin and morphine), whereas "opioid" refers to any natural or synthetic drug that has morphine-like actions, such as methadone (Darke, 2011; Koob & Le Moal, 2005). Given that the participants under investigation in this thesis identified primarily as heroin users (who also used other opioids), they will be referred to as "opiate users" throughout the thesis.

DECISION-MAKING AND OPIATE USE

2.3.2 Neurological abnormalities associated with opiate use

In addition to health and occupational issues, opiate use, particularly use of heroin, is associated with abnormalities in both the structure and function of the brain (Pandria, Kovatsi, Vivas, & Bamidis, 2016). Imaging studies assessing the acute and long-term effects of opiates have demonstrated abnormalities in key areas associated with emotional responding (Lubman, Allen, Peters, & Deakin, 2008; Schmidt et al., 2014), and cognitive processing (Wollman et al., 2016). The presence of these abnormalities provides a basis for expecting that neurobiological factors may contribute to the decision-making difficulties experienced by long-term opiate users.

Available imaging studies indicate that functional abnormalities are concentrated in the frontal cortices of the brains of opiate users. The frontal cortices are areas critical for higher-order cognitive functions, such as decision-making. Research conducted to date in opiate users has consistently reported abnormalities in cerebral blood flow (Daglish et al., 2001; Gerra et al., 1998; Pezawas et al., 2002), disruptions to white matter integrity in frontal regions (Li et al., 2016; Lin, Chou, Chen, Huang, Chen, et al., 2012; Liu et al., 2008; Lyoo et al., 2004; Qiu, Jiang, Su, Lv, Zhang, et al., 2013; Schlaepfer et al., 2006; Sun, Wang, et al., 2015; Wang et al., 2011; Wollman et al., 2015) and abnormal functional connectivity between the anterior cingulate cortex, the orbitofrontal cortex and other frontal areas that are involved in cognitive control (Cheng et al., 2013; Jiang et al., 2011; Liu, Liang, et al., 2009; Ma et al., 2010; MacDonald, Cohen, Stenger, & Carter, 2000). Additionally, positron emission topography imaging studies have demonstrated reduced function of dopamine transporters in the basal ganglia of opiate users (Liu et al., 2013; Yeh et al., 2012; Yuan et al., 2015), which may also contribute to reduced cognitive function (Liang et al., 2016). Research has also found abnormalities in the grey matter of the prefrontal cortex and medial frontal cortex of current and ex-users of opiates (Lin, Chou, Chen, Huang, Lu, et al., 2012; Liu, Hao, et al., 2009; Lyoo et al., 2006; Qiu, Jiang, Su, Lv, Tian, et al., 2013; Wang et al., 2012; Yuan et al., 2010; Yuan et al., 2009). In addition, a recent meta-analysis found that, across a range of studies, there were reductions in grey matter volume in opiate users in areas critical to cognitive and affective processing (Wollman et al., 2016). Several studies have also found that duration of heroin use correlates negatively with grey matter volume in the prefrontal cortex (Ma et al., 2015; Qiu, Jiang, Su, Lv, Tian, et al., 2013; Yuan et al., 2010; Yuan et al., 2009), which may suggest that opiate use directly

DECISION-MAKING AND OPIATE USE

causes the neurological abnormalities seen in imaging studies. The neurological abnormalities seen in the frontal lobes of opiate users may contribute to their reduced decision-making capacity.

2.4 Decision-Making: Definition and Types

Decision-making, as a psychological construct, has been studied for the better part of the last century (Goldstein & Hogarth, 1997). While many definitions have been offered, the one that best defines effective decision-making in the context of research is that it is the process that combines desires (personal values, goals) and beliefs (expectations, knowledge) to choose a course of action that will have long term positive outcomes (Hastie, 2001). In order to make a decision, a decision-maker must assess possible alternative actions and make a judgement about how likely it is that a certain outcome will occur if that alternative is chosen. Thus, the anticipated consequences of choices play a key role in decision-making.

However, it has been argued that decision-making should not be viewed as a unitary construct (Bechara, 2004; Einhorn & Hogarth, 1985; Ellsberg, 1961). As such, the mental processes (and underlying neurological processes) involved in making decisions probably vary, depending on the conditions under which a decision is being made. Indeed, decision-making involves the integration of a number of complex cognitive processes (such as working memory and problem solving, e.g., Brand, Recknor, Grabenhorst, & Bechara, 2007). However, these processes are not the focus of the current thesis. While the field of decision-making is still evolving, there is general agreement that there are at least three relevant sets of decision-making conditions. The first set of conditions is referred to as *ambiguous*, and it involves scenarios where the likelihood of reward or punishment is unknown. Decision-making under ambiguous conditions has most commonly been measured using the Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994). The second set of conditions is referred to as *conditions of delayed discounting*, where people must choose between small rewards delivered immediately and larger rewards delivered after a delay. A third set of conditions is known as *conditions of calculable risk*, and involves scenarios where the likelihood of reward can be predicted with a relatively high degree of accuracy. Decision-making under conditions of risk has been measured using the

DECISION-MAKING AND OPIATE USE

Balloon Analogue Risk Task (BART; Lejuez et al., 2002), the Cambridge Gambling Task, and the Game of Dice Task.

2.5 Empirical Studies of Decision-Making in Opiate Users across Different Types of Decision-Making

Most studies of decision-making in opiate users have investigated decision-making under conditions of ambiguity and have generally used the IGT as the decision-making measure. The bulk of these studies have found that opiate users perform more poorly than controls under conditions of ambiguity (Barry & Petry, 2008; Lemenager et al., 2011; Li, Zhang, et al., 2013; Ma et al., 2015; Pirastu et al., 2006; Rotheram-Fuller, Shoptaw, Berman, & London, 2004; Sun, Zhao, et al., 2015; Upton, Kerestes, & Stout, 2012; Verdejo-Garcia, Perales, & Perez-Garcia, 2007; Yan et al., 2014; Zhang et al., 2012), regardless of whether they are completely detoxified or are still using actively heroin or other opiate substitutes (even up to 12 hours before the session). However, some studies have found that opiate users perform no differently to controls on this task (Ahn & Vassileva, 2016; Pirastu et al., 2006; Zeng et al., 2013; Zeng, Su, Jiang, Zhu, & Ye, 2016). Other studies have found that opiate users in treatment make poor decisions on delay discounting measures, with opiate users choosing smaller short-term rewards over larger delayed rewards (Cheng, Lu, Han, Gonzalez-Vallejo, & Sui, 2012; Kirby & Petry, 2004; Kirby, Petry, & Bickel, 1999; Madden, Petry, Badger, & Bickel, 1997). In general, however, the weight of evidence is that opiate users are impaired under conditions of ambiguity. In the case of decision-making under conditions of risk, as measured by tasks such as the BART and Cambridge Gambling Task, results are more limited and more varied. On the Cambridge Gambling Task and Game of Dice Task, opiate users make poorer quality decisions than controls by consistently choosing options that are unlikely to result in reward (Baldacchino et al., 2015; Brand et al., 2008; Tolomeo, Gray, Matthews, Steele, & Baldacchino, 2016). However, in other studies, the quality of opiate users' decision-making mirrors that of controls (Ahn & Vassileva, 2016; Ersche et al., 2005). Only two studies exist which analyse opiate users' performance on the BART, and the two sets of results conflict (Ahn & Vassileva, 2016; Khodadadi, Dezfouli, Fakhari, & Ekhtiari, 2010).

While evidence suggests that decision-making is impaired in opiate users (at least in some types of decision-making), the severity of this impairment, and whether other

factors contribute to worsened or improved decision-making ability in this group, are as yet unclear. For example, previous research has demonstrated that a longer duration of opiate use is negatively correlated with grey and white matter volume in the prefrontal cortex of opiate users (Ma et al., 2015; Qiu, Jiang, Su, Lv, Tian, et al., 2013; Yuan et al., 2010; Yuan et al., 2009), which may in turn contribute to more severe decision-making impairment (Ma et al., 2015). However, while some studies have found that duration of use is negatively correlated with decision-making capacity in opiate users (Cheng et al., 2012; Yan et al., 2014), others have found no significant relationship (Brand et al., 2008; Lemenager et al., 2011). Similarly, it is thought that common co-morbid health issues such as head injury or poly-substance dependence may compound cognitive deficits. There is some evidence to suggest that head injury and poly-substance dependence in opiate users may impair other cognitive functions reliant on the frontal lobes, such as inhibitory control, planning ability and working memory, over and above the effect of opiates (Darke et al., 2012b; Darke et al., 2000; Henry et al., 2012; Loeber et al., 2012). However, their impact on decision-making has not been investigated. Furthermore, it is also unclear whether abstinence from opiates leads to improvements in decision-making. It has been argued that abstinence from opiate use may lead to better decision-making capacity (Zhang, Shi, et al., 2011), possibly due to some recovery in neurological function (Shi et al., 2008; Yeh et al., 2012). However, some neuroimaging studies have found enduring functional abnormalities in ex-users tested after 6 or 12 months of abstinence (Cheng et al., 2013; Liu, Liang, et al., 2009). Cross-sectional studies of decision-making capacity in ex-users have produced mixed results, with some studies finding that ex-users demonstrate no decision-making impairment relative to controls (Zeng et al., 2013; Zhang, Shi, et al., 2011), suggesting a degree of recovery in function, while others have found that decision-making remains impaired in ex-users (Li, Zhang, et al., 2013; Verdejo-Garcia & Perez-Garcia, 2007; Yan et al., 2014). Thus, although decision-making impairment appears relatively severe in opiate users, the impact of a number of factors on this impairment require further clarification.

2.5.1 Theories to describe (impaired) decision-making

A number of theoretical approaches have been offered to explain the mental processes involved in decision-making, and to isolate the part of the decision-making process may become impaired in opiate users. The first of these approaches used mathematical and economical models, such as the Expected Utility Model (Von

DECISION-MAKING AND OPIATE USE

Neumann & Morgenstern, 1947), to describe how people would make decisions if they behaved rationally. The main aim of these theories was to provide a series of rules for decision-making that could be used by researchers to mathematically predict how people would behave and what decisions they would make in a given situation (Plous, 1993), in particular to avoid risk (risk aversion; Schoemaker, 1982). However, simplifying human decision-making into a set of mathematically-predictable problems with solvable solutions was rather restrictive and did not describe how people actually made decisions (Plous, 1993). Later theories, such as the Subjective Expected Utility model (Savage, 1954) and Prospect Theory (Kahneman & Tversky, 1979), incorporated subjective probabilities of outcomes, and allowed the subjective wants of a decision-maker to be included in the decision process to help understand how decision-makers avoided choosing risky options. However, these theories often ignored important components of the decision-making process, such as emotion (Zeelenberg, Nelissen, Breugelmans, & Pieters, 2008), and lacked predictive power. In other words, these mathematically-based rational theories were unable to predict the choices normal decision-makers make in real life, and so could not be used to explain normal (or indeed impaired) decision-making.

Another approach to describe the mental processes involved in decision-making focused on cognitive functioning. Similar to mathematical models of decision-making, researchers investigating cognitive processing initially believed that decision-making was a relatively logical and process-driven cognitive function (Chan, Shum, Toulopoulou, & Chen, 2008; Norman & Shallice, 1986), and was related to other logical and mechanistic cognitive functions, such as cognitive flexibility, inhibitory control, and planning. These cognitive functions were termed "cold" cognitive functions, as they lacked emotional involvement (Chan et al., 2008; Roiser & Sahakian, 2013). However, researchers found that some groups with impaired decision-making, in particular people with damage to the ventromedial prefrontal cortex, were able to successfully carry out most of these cold cognitive processes, but were nevertheless unable to make adaptive decisions (Bechara et al., 1994; Bechara, Damasio, Tranel, & Anderson, 1998). Similarly, studies assessing cold cognitive functions have found these cognitive abilities are not always impaired in opiate users (Brand et al., 2008; Darke, McDonald, Kaye, & Torok, 2012a; Ersche, Clark, London, Robbins, & Sahakian, 2006; Fishbein et al., 2007; Gupta et al., 2014; Messinis et al., 2009; Mintzer, Copersino, &

DECISION-MAKING AND OPIATE USE

Stitzer, 2005; Mintzer & Stitzer, 2002; Pau, Lee, & Chan, 2002; Rotheram-Fuller et al., 2004; Verdejo-Garcia, Perales, et al., 2007; Verdejo-Garcia & Perez-Garcia, 2007), therefore suggesting that deficits in cold cognitive functions may not underpin decision-making impairment in this group. Consequently, investigations of the mental processes involved in decision-making have been approached from a "hot" cognitive processing viewpoint.

Hot cognitive functions involve more emotive components such as the experience of reward and punishment (Bechara, 2004; Chan et al., 2008; Grafman & Litvan, 1999) and the processing of motivationally and emotionally-salient stimuli (Hunter & Sparrow, 2012). Decision-making tasks in the laboratory present decision-makers with rewards and punishments for their choices, which often evoke an emotional response (Naqvi, Shiv, & Bechara, 2006). Rewarding outcomes (wins) are associated with positive emotional response, while punishing outcomes (losses) trigger negative emotional responses. These emotional responses might help inform future decisions. Thus, it has been argued that decision-making falls under the umbrella of "hot" cognitive functioning (Chan et al., 2008; Grafman & Litvan, 1999), and good decision-making may be more reliant on the ability to appropriately process emotional information based on the punishing and rewarding outcomes of choices (Bechara, 2004; Bechara & Damasio, 2005), than on cold cognitive functions. Consequently, in opiate users, poor decision-making may stem from an inability to process emotionally-salient information related to the punishing and rewarding outcomes of choices, which itself may stem from a broader emotion processing deficit (Verdejo-Garcia, Perez-Garcia, & Bechara, 2006). However, very few studies have analysed the emotion processing capacity of opiate users, and so their emotion processing capacity (and consequently any relation to their decision-making ability) remains unclear.

2.6 Emotion Processing in Opiate Users

Studies have only recently started to focus on the emotional responding capacity of opiate users, and results are inconsistent. The following section summarises what is currently known about the emotional responding capacity of this group.

2.6.1 Subjective emotional experience in opiate users

Emotional response is often assessed via subjective ratings of static images, such as the International Affective Picture System (IAPS) images. Study participants are

DECISION-MAKING AND OPIATE USE

asked to subjectively rate these images for valence (how pleasant or unpleasant the images are) and arousal (how calming or exciting the images are) (Britton, Taylor, Sudheimer, & Liberzon, 2006). Blunted emotional responses to these images may be indicative of a general emotional blunting, which may extend to emotional responses to reward and punishment in decision-making tasks, and may in turn lead to impaired decision-making (Verdejo-Garcia, Rivas-Perez, Vilar-Lopez, & Perez-Garcia, 2007).

As noted, thus far only a few studies have analysed the emotional responses of opiate users. Gerra et al. (2003) found a significant effect of valence, where opiate users rated unpleasant images as more unpleasant, and pleasant images as less pleasant, than controls. However, ratings of arousal were no different between groups. Conversely, Aguilar de Arcos et al. (2008) found that opiate users reported reduced arousal ratings for pleasant IAPS images but higher arousal ratings for negative images in comparison to healthy controls, although there were no differences between groups for ratings of valence. However, other studies have found no significant difference between opiate users and controls either for ratings of valence or of arousal in response to IAPS images (Carcoba, Contreras, Cepeda-Benito, & Meagher, 2011; Lubman et al., 2009; Smoski et al., 2011; Wang et al., 2010). It should be noted, however, that the studies which did not find a difference in subjective emotional responses presented images for relatively short periods of time (normally less than five seconds), which may not have allowed participants to fully experience the target emotion. Overall, while the findings from the two studies with the stronger methodology (i.e., Aguilar de Arcos et al., 2008; Gerra et al., 2003) suggest that subjective emotional experience may be abnormal in opiate users, there are currently too few methodologically sound studies available to make firm conclusions.

2.6.2 Objective emotional experience in opiate users

Emotional responses go beyond subjective awareness (Fernández et al., 2012) and can also be measured objectively via changes in physiology. This includes eye blinks, hormonal changes and changes in heart rate. Only two studies have assessed opiate users' emotional response using objective measures. Gerra et al. (2003) assessed hormonal responses to IAPS images in addition to the measures of self-reported valence and arousal described above. There were no significant changes in neuroendocrine levels (noradrenaline, cortisol and adrenocorticotropic hormone) or cardiovascular

reactions (heart rate and blood pressure) following viewing of the emotional stimuli in the opiate users. In contrast, control participants displayed increased neuroendocrine and cardiovascular responses following unpleasant emotional stimuli. This suggests that opiate users respond differently to emotional stimuli, and that these differences can be measured physiologically. In contrast to this, however, Walter et al. (2011) failed to detect a significant difference between opiate users and controls when assessing the startle response to IAPS images via eye blinks. Thus, it may be the case that some physiological responses to emotional stimuli are impaired in opiate users, but others are preserved. It appears, however, that more research is needed, using more rigorous methodology, to better understand the objective and subjective aspects of emotional processing in opiate users.

2.7 Emotional Model of Decision-Making: The Somatic Marker Hypothesis

As described previously, rational theories of decision-making and cold cognitive functioning have been unable to explain the poor decision-making observed in opiate users. Given that people's emotional evaluations of the outcomes of decisions are an important component of the decision-making process, alternative models of decision-making incorporating emotion have been put forward to explain how people make decisions. One such model is the Somatic Marker Hypothesis (Damasio, 1994), which aims to provide a neurological account of normal decision-making and the impact on decision-making ability when specific neurological pathways become impaired.

The *somatic marker hypothesis* proposes that decision-making, at least under conditions of ambiguity, relies on the ability to emotionally respond to rewards and punishments (Bechara, Damasio, Damasio, & Lee, 1999). This emotional response can be measured via changes in physiological arousal such as sweat on the skin (skin conductance response) and changes in heart rate (Bechara & Damasio, 2005). Crucially, when a decision-maker later contemplates making a decision similar to the one which resulted in reward or punishment, the model proposes that this same pattern of physiological response is activated in anticipation of the decision. This anticipatory *somatic marker* acts as a warning signal to inform the decision-maker of the likely outcome of a considered choice (Damasio, 2009). Thus, emotions serve as "gut feelings" which act to endorse some options and discourage others, and therefore bias

decision-making towards outcomes which are likely to be advantageous in the long run (Bechara & Damasio, 2005).

The IGT simulates decision-making under ambiguous conditions (Bechara & Damasio, 2005) and has been used to test the somatic marker model of decision-making. Previous research has found that, in healthy adults, the skin conductance response is greater after receiving a punishment than after receiving a reward on the IGT (Bechara, Tranel, Damasio, & Damasio, 1996; Crone, Somsen, Beek, & Van Der Molen, 2004). Importantly, it has also been found that the skin conductance response is higher *before* disadvantageous compared to advantageous decisions on the IGT in healthy adults (Carter & Smith Pasqualini, 2004; Crone et al., 2004). Thus, the skin conductance response can be used as an indicator of anticipatory somatic marking (Bechara et al., 1996). In addition, a larger difference in anticipatory somatic marking prior to disadvantageous relative to advantageous decisions has been associated with better decision-making in healthy adults (Carter & Smith Pasqualini, 2004; Guillaume et al., 2009; Miu et al., 2012). However, in groups with impaired decision-making, such as people with damage to the frontal lobes, people with obsessive-compulsive disorder and pathological gamblers, anticipatory somatic markers prior to disadvantageous decisions are reduced or absent (Bechara et al., 1999; Cavedini et al., 2012; Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2006).

It is thought that the abnormalities in the frontal lobes of these groups interfere with their ability to produce anticipatory somatic markers (or to respond emotionally to rewards and punishments), thus leading to poor decision-making (Bechara et al., 1999; Cavedini et al., 2012; Goudriaan et al., 2006). The orbitofrontal cortex is an area of the brain critical in the experience of emotion, in particular the emotional response to reward and punishment (Rolls, 2000, 2004). In the context of the somatic marker hypothesis, it is thought that the orbitofrontal cortex acts to pair the outcome of a decision, such as a reward or punishment, to the emotional state, or "what it feels like" to be in a given situation (Bechara & Damasio, 2005). Thus, damage to the orbitofrontal cortex may impair the formation of somatic markers either via emotional blunting in response to outcomes of decisions (i.e., reduced emotional response to reward and punishment), and/or reduced capacity to form anticipatory somatic makers. This may in turn lead to reduced decision-making capacity (Bechara, Damasio, & Damasio, 2000).

However, it is also possible that reduced *awareness* of somatic markers may contribute to reduced decision-making capacity. Interoception describes the process whereby individuals receive and interpret subtle bodily or physiological changes (e.g., changes in heart rate or skin temperature) (Craig, 2002; Verdejo-Garcia, Clark, & Dunn, 2012), which ultimately allows them to use these signals to modify ongoing behaviour (Paulus & Stewart, 2014). The ability to perceive changes in bodily states seems to be an important part of the process in recognising a somatic marker. Indeed, researchers investigating the somatic marker hypothesis have recently begun to consider the role of interoceptive ability (Craig, 2009; Dunn et al., 2010), and have shown that more accurate perception of heartbeats in healthy adults is associated with better decision-making ability (Werner, Jung, Duschek, & Schandry, 2009). However, other research has found no correlation (Dunn et al., 2010; Werner et al., 2013). While an association between interoceptive accuracy and decision-making has not been assessed in substance users, a recent study by Sönmez, Kahyacı Kılıç, Ateş Çöl, Görgülü, and Köse Çınar (2016) did demonstrate that a mixed group of abstinent substance users (including heroin users) showed reduced ability to perceive heartbeats (i.e. reduced interoceptive accuracy), relative to controls.

In the context of the Somatic Marker Hypothesis, it appears that there are two points in the chain of events during the decision-making process that could break down in opiate users, and ultimately lead to poor decisions. The first point is at the beginning of the chain; specifically, a reduced capacity to emotionally respond to more general stimuli (as outlined in section 2.6.1) may also mean that opiate users are unable to emotionally respond to the consequences of choices (i.e., punishments and rewards). This may stem from abnormal function of the orbitofrontal cortex in opiate users (Ma et al., 2010; Qiu et al., 2011). Reduced emotional responses to rewards and punishments may then interrupt the production of anticipatory somatic markers, consequently leading to impaired decision-making. Previous research has found a link between emotion processing capacity and decision-making ability in users of other substances (Verdejo-Garcia, Rivas-Perez, et al., 2007). However, the link between emotion processing capacity and decision-making ability in opiate users has not previously been examined. Alternatively, it may be that opiate users experience normal emotional responses, and create normal somatic markers but, at the very end of the chain of events, they are unable to perceive the changes in physiology as accurately as healthy adults (i.e.,

reduced interoceptive accuracy). Thus, it is a failure to detect their somatic markers that may ultimately result in the decision-making impairment. Interoceptive accuracy has been linked to the functioning of the insula in healthy adults (Craig, 2009; Critchley, 2005; Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004) and neuroimaging studies have demonstrated impaired insula structure and function in opiate users (Gardini & Venneri, 2012; Lin, Chou, Chen, Huang, Lu, et al., 2012; Wang et al., 2016; Xie et al., 2011; Zhang, Tian, et al., 2011). Thus, while opiate users may produce normal physiological signals in response to reward and punishment, and normal physiological signals prior to making decisions (i.e., normal somatic markers), they may not be able to accurately "tune into" these somatic markers, thereby reducing decision-making ability. Furthermore, given that somatic markers are hypothesized to be necessary for decision-making under conditions of ambiguity, but not under conditions of calculable risk, it may also be expected that opiate users are more impaired on tasks measuring this type of decision-making (i.e., the IGT) compared to tasks simulating conditions of risk (i.e., the BART).

2.8 Chapter Summary

In summary, opiate use is associated with a range of poor outcomes and reduced quality of life. Opiate users face a number of health and social issues every day, and opiate use is also associated with significant abnormalities of the structure and function of the brain. These brain abnormalities are centred in the frontal lobes, which control many complex cognitive functions, including decision-making. Given that opiate users demonstrate impaired neurological function, it is no surprise that they also demonstrate impaired decision-making ability on tasks in the laboratory which aim to simulate decision-making in real life. However, it is unknown whether a number of other factors may worsen or improve the decision-making capacity of opiate users. For example, co-morbid factors such as head injury or polysubstance dependence may compound cognitive deficits. On the other hand, abstinence from opiates may lead to some recovery of neurological functioning, suggesting better decision-making capacity. However, the effects of these factors on decision-making have not been systematically analysed. Similarly, longer duration of use seems to be associated with more impaired neurological functioning, however the relative importance of duration of use on decision-making has not been explored. These outstanding questions will be addressed in Study 1. As good decision-making ability is critical to adaptive functioning, theorists

DECISION-MAKING AND OPIATE USE

have tried to determine the mental processes involved in decision-making and how these process can become impaired. Rational and cold cognitive theories of decision-making have so far been unable to explain why opiate users consistently make poor decisions. Instead, it may be that reduced decision-making ability may stem from deficiencies in hot cognitive processing, which involves the emotional evaluation of outcomes. Thus, it can be suggested that the decision-making impairment observed in opiate users may be related to reduced emotional processing capacity. However, it is currently unclear whether opiate users have reduced emotional responding. Furthermore, the relationships between the capacity for emotional response, interoceptive ability, and the capacity for decision-making have not been analysed. These questions will be addressed in Study 2. Finally, opiate users have demonstrated some variation in performance on tasks assessing decision-making under different conditions (i.e., ambiguous vs. risky). This suggests that decision-making capacity may be differentially impaired under different conditions. This will be addressed in Study 3.

CHAPTER 3: Study 1 - Meta-Analysis of Decision-Making in Current and Ex-Users of Opiates

3.1 Preamble

A number of studies have found that opiate users perform more poorly than controls on a range of decision-making measures (e.g Ahn & Vassileva, 2016; Baldacchino et al., 2015; Cheng et al., 2012; Sun, Zhao, et al., 2015). However, this is not always the case, with decision-making ability in opiate users sometimes comparable to that of healthy controls in some studies (Areias, Paixao, & Figueira, 2016; Ersche et al., 2005; Mintzer et al., 2005; Zeng et al., 2013). This may be due to the heterogeneity of samples used across studies. While some studies report data for current users of opiates (e.g. Baldacchino et al., 2015; Ma et al., 2015; Upton et al., 2012), others report data for opiate users who have been abstinent for some time (e.g. Ahn & Vassileva, 2016; Li, Zhang, et al., 2013; Yan et al., 2014). It has been suggested that abstinence may reduce the decision-making impairment in opiate users (Mintzer et al., 2005; Zhang, Shi, et al., 2011), while other factors such as longer duration of heroin use may increase the severity of the impairment (Cheng et al., 2012; Yan et al., 2014). Given the heterogeneity of opiate-using samples included in previous studies, the exact level of the decision-making impairment in opiate users is, as yet, unknown. Therefore, the aim of the first study of this PhD thesis was to pool data from available studies to determine the level of the decision-making impairment in current and ex-users of opiates. Furthermore, this study aimed to determine whether additional factors such as length of heroin use, length of abstinence, head injury and polysubstance dependence, may have some impact on the severity of the decision-making impairment.

This chapter presents the published manuscript which describes the results of the meta-analysis. This study was published in *Neuroscience and Biobehavioral Reviews:*

Biernacki, K., McLennan, S. N., Terrett, G., Labuschage, I., Rendell, P. G. (2016). Decision-making ability in current and past users of opiates: A meta-analysis. *Neuroscience and Biobehavioral Reviews, 71*, 342-351. doi: 10.1016/j.neubiorev.2016.09.011

DECISION-MAKING AND OPIATE USE

3.2 Statement of Contribution for Publication 1

I acknowledge that my contribution to the paper is 50%

Name: Kathryn Biernacki

Signature:

I acknowledge that my contribution to the paper is 25%

Name: Skye N. McLennan
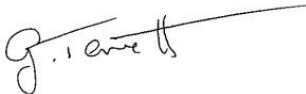
Signature:

I acknowledge that my contribution to the paper is 15%

Name: Gill Terrett
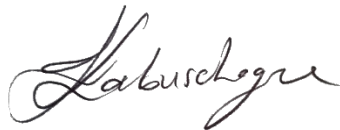
Signature:

I acknowledge that my contribution to the paper is 5%

Name: Izelle Labuschagne

Signature:

I acknowledge that my contribution to the paper is 5%

Name: Peter G. Rendell

Signature:

DECISION-MAKING AND OPIATE USE

3.3 Abstract

Opiate use is associated with deficits in decision-making. However, the impact of abstinence and co-morbid factors, like head injury and poly-substance abuse, on this ability, is currently unclear. This meta-analysis aimed to assess 1) the magnitude of decision-making deficits in opiate users; 2) whether co-morbid factors moderate the severity of these deficits; 3) whether ex-opiate users demonstrate smaller decision-making deficits than current users; and 4) whether the length of abstinence is related to the magnitude of decision-making deficits. We analysed 22 studies that compared the performance of current and ex-opiate users to healthy controls on decision-making measures such as the Iowa Gambling Task. Current users demonstrated a moderately strong impairment in decision-making relative to controls, which was not significantly moderated by co-morbid factors. The magnitude of the impairment did not significantly differ between studies assessing current or ex-users, and this impairment was not related to length of abstinence. Thus, it appears that opiate users have relatively severe decision-making deficits that persist at least 1.5 years after cessation of use.

3.4 Introduction

Long term opiate use is associated with a range of problems in everyday life, including poor physical and mental health, impaired social functioning, and high unemployment rates (De Maeyer et al., 2010; De Maeyer et al., 2011; Meulenbeek, 2000). These difficulties may be linked to deficits in cognitive functioning, with a number of cognitive processes including attention, verbal memory, and executive functions shown to be impaired in both heroin and prescribed opiate users (see Baldacchino et al., 2012; and Wang et al., 2013 for reviews). Of the cognitive processes negatively impacted by opiate use, decision-making ability appears to be one of the most consistently and severely affected (Baldacchino et al., 2012).

While it is relatively well-established that decision-making is compromised in opiate users (Baldacchino et al., 2012), little is known about which individuals within this heterogeneous population are most at risk. Similarly, the trajectory of the decision-making impairment following treatment is currently unclear. In particular, it is not known whether decision-making deficits abate during periods of abstinence. Such information has the potential to improve understanding of the difficulties that opiate

users face and to assist policy makers and service providers to develop effective support services.

A more detailed understanding of the relationship between opiate use and decision-making ability has been limited by the fact that most available studies in this field have relatively small sample sizes, and findings have been inconsistent, making it difficult to draw reliable conclusions. Therefore, the current study used a meta-analysis to pool and re-examine available data to investigate the temporal trajectory of decision-making deficits in opiate users, and examine the potential influence of individual factors on the severity of these deficits.

In the current context, effective decision-making refers to the ability to avoid making choices that result only in small or short-term benefits, and/or choices that carry a high risk of adverse outcomes. Studies of decision-making have shown that, compared to non-drug-using controls, opiate users tend to select options with short-terms gains but long term losses (e.g., Lemenager et al., 2011; Mintzer et al., 2005; Mintzer and Stitzer, 2002; Verdejo-Garcia and Perez-Garcia, 2007) as well as smaller immediate rewards over larger delayed rewards (i.e. delay discounting, Kirby and Petry, 2004; Kirby et al., 1999). In addition, opiate users generally choose riskier options, such as choosing a large but unlikely reward, over a smaller, but likely reward (Brand et al., 2008; Ersche et al., 2006; Ersche et al., 2005b). The magnitude of these decision-making difficulties is substantial, with medium to large effect sizes (Cohen's d = 0.70) reported in studies that compare opiate users to non-drug-using controls (Baldacchino et al., 2012). These decision-making difficulties have the potential to impact on real life choices about money, housing, and health related behaviours (e.g. Wilson and Vassileva, 2016).

Compromised decision-making ability in this population is not surprising given that opiate use is associated with abnormalities in the orbitofrontal cortex (OFC) and associated neural networks. The OFC supports the integration of sensory and emotional inputs when calculating the value of rewards (Elliott et al., 2000; Krawczyk, 2002; Rolls, 2000; Wallis, 2007). The OFC is also part of a larger neural network involving the dorsolateral prefrontal cortex (dlPFC) and nucleus accumbens (Cohen et al., 2005; Ernst and Paulus, 2005; Krawczyk, 2002) which is particularly important for planning behaviour that leads to distant, as opposed to immediate, rewards (Bechara, 2004, 2005; Bechara et al., 2000a; Bechara et al., 2000b; Gläscher et al., 2012; Wallis, 2007). Opiate

users show evidence of reduced OFC and dlPFC grey matter density (Lyoo et al., 2006; Yuan et al., 2010) and damage to white matter (Li et al., 2016; Liu et al., 2008; Lyoo et al., 2004; Qiu et al., 2013a). Abnormal functional connectivity in OFC networks has also been found in opiate users (Cheng et al., 2013; Liu et al., 2009; Ma et al., 2010), and this has been linked to poorer decision-making performance (Qiu et al., 2011). In addition, in comparison to controls, users of different types of opiates have demonstrated either hyper- or hypo-activation of the OFC while making risky decisions during a gambling task (Ersche et al., 2006). Furthermore, reductions in dopamine and serotonin transmission systems are also evident amongst opiate users (Liu et al., 2013; Shi et al., 2008; Yeh et al., 2012; Zaaijer et al., 2015). Although the relationship between neurotransmitters and decision-making has not been specifically investigated in opiate users, abnormalities, for example in dopamine transmission, have been linked to reduced performance in other aspects of cognitive functioning in opiate users (Liang et al., 2016). Taken together, the research reveals that there are abnormalities in relation to OFC and dlPFC structure, function, and neurotransmission in opiate users that might underpin, at least to some extent, their impaired decision-making ability. Although it should be noted that the extent to which neural pathology precedes opiate use is currently unclear, a recent longitudinal brain imaging study by Li et al. (2016) showed that opiate use was associated with white matter degeneration over the period of one year. This research has confirmed that at least some measurable degeneration occurs over a period of active opiate use.

If neural pathology does contribute to the decision-making deficit in opiate users, it may be anticipated that people with a longer history of opiate use will display more severe decision-making impairments, given that structural brain changes have been shown to be greater in people who have used opiates for longer periods of time (Yuan et al., 2010; Yuan et al., 2009). However, findings from the five available studies directly addressing this relationship have been mixed. Some have reported a negative association between duration of opiate use and decision-making ability (Cheng et al., 2012; Yan et al., 2014), whereas others failed to detect such a relationship (Brand et al., 2008; Clark et al., 2006; Lemenager et al., 2011). The limited number of these studies however, makes it difficult to make firm conclusions regarding the relationship between decision-making and duration of opiate use. It is nevertheless possible to investigate this issue further by considering other studies of decision-making in opiate users that do not

DECISION-MAKING AND OPIATE USE

directly investigate this relationship. More specifically, because the mean duration of opiate use across such studies varies, we were able to collate the data from these studies in the current meta-analysis and use meta-regression to further examine whether the size of the decision-making deficit varies as a function of the duration of opiate use.

Over and above opiate use duration, co-morbid conditions may also affect the severity of decision-making deficits in opiate users. For example, a large proportion of people who use opiates are also dependent on other street drugs (Astals et al., 2008). In addition, many long term opiate users have experienced neurological damage, either as a result of overdose, or physical trauma (Darke et al., 2012b). To the best of our knowledge, the potential impact of poly-substance abuse and head injury on decision-making has not been examined in this group to date (Darke et al., 2000; Loeber et al., 2012). However, in opiate users, poly-substance abuse and head injury are both associated with greater levels of impairment in other cognitive domains including memory, information processing, verbal learning, and executive and general cognitive function (Darke et al., 2012b; Darke et al., 2000; Henry et al., 2012; Loeber et al., 2012). Thus, it is possible that poly-substance abuse and head injury may also detrimentally affect decision-making. In the current meta-analysis, we compared the size of the decision-making impairment reported in studies that included only opiate users who were free of co-morbid issues, to that reported in studies that included people with poly-substance abuse and head injuries.

A further issue that lacks clarity in relation to the decision-making ability of opiate users is whether deficits in this capacity abate when opiate-users enter a period of abstinence. There is evidence that there is some recovery of neurotransmitter receptor availability and function after opiate cessation (Shi et al., 2008; Yeh et al., 2012), and therefore some improvement in decision-making might be anticipated. However, abnormal neural connectivity has been observed in abstinent ex-users (Cheng et al., 2013; Liu et al., 2009), perhaps reflecting permanent opiate-related damage to dlPFC regions, or abnormalities that predated drug use. On this basis, any improvement in decision-making would be expected to be limited. No research has yet tracked a cohort of opiate users from a period of active use through to a period of abstinence. However, some group comparison studies have reported that decision-making ability in ex-users is equivalent to that of non-drug-using controls (Zeng et al., 2013; Zhang et al., 2011), implying that recovery may occur. Contrary to this, other studies have reported that

decision-making ability in ex-users is poorer than controls (Ahn et al., 2014; Clark et al., 2006; Li et al., 2013; Verdejo-Garcia and Perez-Garcia, 2007; Yan et al., 2014). In the current meta-analysis, we brought together available group comparison studies to investigate whether decision-making deficits in ex-users (relative to controls) are smaller than decision-making deficits in current users (relative to controls). Such a pattern of results would imply that some recovery of decision-making ability following abstinence does occur. In addition, we also considered the possibility that functional brain changes may occur gradually following cessation of opiate use. If this is the case, decision-making ability may not improve immediately, but may instead improve slowly over a period of time. The current meta-analysis allowed us to investigate the extent to which any recovery of decision-making ability is related to length of abstinence.

In summary, we expected that the current meta-analysis would show that (1) the magnitude of decision-making deficits (relative to controls) would be greater in studies that included opiate users with poly-substance dependence and head injury, than in studies that included only opiate users who were free from these co-morbidities; (2) the length of time using opiates would moderate the magnitude of the decision-making deficits (relative to controls), such that participants who had used opiates for longer would have more severe decision-making deficits; (3) the magnitude of the decision-making deficits (relative to controls) would be greater in current users than in ex-users; and (4) in ex-users, the length of abstinence would moderate the magnitude of the decision-making deficits (relative to controls) such that longer periods of abstinence would be associated with smaller decision-making deficits.

3.5 Method

3.5.1 Literature search and study selection

This meta-analysis was conducted following PRISMA guidelines (Liberati et al., 2009; Moher et al., 2009). We searched for studies that measured decision-making and which compared a control group to a group that was dependent on opiates (current users) at the time of testing, and/or a group that had been dependent in the past but was now abstinent (ex-users). We used search terms related to opiate dependence, and specific decision-making measures commonly used in neuropsychological literature (see inclusion criteria), as well as terms related more broadly to decision-making and cognitive impulsivity. The following databases were searched: MEDLINE Complete,

DECISION-MAKING AND OPIATE USE

PsychINFO, CINAHL Complete, Scopus, and Web of Science Core Collection. Final searches were performed in February 2016. Reference lists of included articles were screened to identify other studies that met criteria for inclusion. However, this did not result in any additional eligible studies.

3.5.2 Inclusion criteria

Studies were eligible for inclusion if they: (a) included a comparison between an opiate group (current or ex-users) and healthy control group; (b) reported on participants aged between 18 and 65 years; (c) were available in full text format; (d) described quantitative results; (e) provided statistics from which an effect size could be calculated; for example, group means, standard deviations, *F, t*, or *X* statistics; and (f) were published in English.

Additional inclusion criteria relating to the participant groups (current users, ex-users, controls) were applied. Specifically: (a) current opiate users had to have been dependent on opiates at the time of testing; (b) current opiate users were required to have been regularly using heroin and/or an opiate substitute (such as methadone, buprenorphine or suboxone) in the month prior to testing; (c) ex-users had to have been dependent on opiates in the past; (d) ex-users had to have been completely abstinent from all drugs of abuse (except alcohol and nicotine) and not have used any opiate (including substitutes such as methadone) for a minimum average of one month.

Studies were excluded if: (a) healthy controls had a significant history of drug or alcohol use, i.e. had been diagnosed with substance dependence or abuse (although past experimental use of illicit substances was tolerated); (b) healthy controls were using illicit substances at the time of testing; or (c) participants in any of the three groups had a concurrent psychiatric diagnosis (with the exception of depression and/or anxiety that was not being treated with medication). It is important to note that studies were not excluded if opiate user groups were concurrently using (or had concurrently used) other drugs, as poly-substance use is prevalent in this population (Veilleux et al., 2010). However, poly-substance use and poly-substance dependence were coded separately in analyses. Furthermore, unlike other reviews (Baldacchino et al., 2012), this meta-analysis did not exclude based on head injury as this was a variable of interest.

3.5.3 Decision-making measures

To be included in the meta-analysis, papers had to report on a decision-making measure that assessed the ability to make choices with a favourable long-term outcome, despite potential short-term losses. In the wider literature, such measures are sometimes referred to as tests of cognitive impulsivity (e.g. Baldacchino et al., 2012) because more impulsive individuals tend to select options that provide some immediate reward, but which also tend to have more negative long term consequences. Specifically, the tasks that were included assessed decision-making under conditions of ambiguity where outcomes are unknown or cannot be predicted (e.g., Iowa Gambling Task (IGT); Bechara et al., 1994), or under conditions of risk where probabilities may be estimated (e.g., Game of Dice Task (GDT); Brand et al., 2008; Balloon Analogue Risk Task (BART); Lejuez et al., 2002; Cambridge Gambling Task (CGT); Rogers et al., 1999). Tasks that assessed inadequate reflection before a choice is made (Information Sampling Task (IST); Clark et al., 2006) or where the value of a delayed reinforcer is worth less than an immediate (albeit smaller) reinforcer (i.e., delay discounting; Bickel and Marsch, 2001) were also included.

3.5.4 Data screening and extraction

For each study, the following participant data for opiate and control groups were extracted: number of participants in each group; duration of opiate use for both current users and ex-users; duration of abstinence for ex-users; and poly-substance use and head injury status for current users. For decision-making measures, data extracted were group means (and standard deviations) of the main outcome measure or statistics that effect sizes could be calculated from (e.g., t, F). The first author (KB) extracted all data, and where needed, contacted the first or corresponding author of each article to request missing information. Three attempts were made to contact authors, after which studies were excluded if necessary data could not be obtained (the authors of the following studies could not be contacted: Heyman and Dunn, 2002; Robles et al., 2011; Zhang et al., 2011). Similarly, articles were excluded if data to calculate effect sizes were not available or not retained (Fishbein et al., 2007; Petry et al., 1998; Rogers et al., 1999). Data was extracted a second time by an independent reviewer (see acknowledgements). Discrepancies between the first and second reviewers were resolved by a third independent reviewer (SM). Studies where the same data were published across

multiple publications were combined to avoid reporting overlapping data (authors were contacted where appropriate to determine whether data overlapped; Ahn et al., 2014; Dai et al., 2015; Ersche et al., 2005a; Ersche et al., 2006; Qiu et al., 2011; Qiu et al., 2013a; Sun et al., 2015a; Verdejo-Garcia et al., 2007; Wilson and Vassileva, 2016).

Where articles reported more than one control group, and one of these controls groups included some illicit drug use (Rotheram-Fuller et al., 2004), only the control group that reported no drug use was included. Where articles reported on multiple groups of current opiate users, these data were collapsed into a single group (Ersche et al., 2005b; Pirastu et al., 2006; Rotheram-Fuller et al., 2004). In studies that reported on groups that had been abstinent for an average of less than one month, these groups were classified as current users (Cheng et al., 2012; Kirby and Petry, 2004). For studies that reported baseline and follow-up testing using a behavioural measure, only the baseline values were entered into analyses (Baldacchino et al., 2015; Zhang et al., 2012). For studies that reported data for two or more decision-making measures (Ahn and Vassileva, 2016; Li et al., 2013; Upton et al., 2012), effect sizes for each separate decision-making measure were pooled to create a combined decision-making effect size estimate.

3.5.5 Data analyses

The data were run using Comprehensive Meta-Analysis Version 2 software (CMA; Borenstein et al., 2005). All analyses were conducted using random-effects models, including calculations of effect sizes, subgroup and moderator analyses, and assessment of publication bias. Random-effects models were used because of known variation amongst populations (Hedges and Olkin, 1985) and because this type of modelling has a less restrictive set of statistical assumptions. Effect sizes were calculated as Cohen's d (standard difference in means; Cohen, 1992). Heterogeneity was assessed using the I^2 statistic, which describes the percentage of total variation across studies due to heterogeneity rather than chance (Higgins et al., 2003).

To address the question of whether longer duration of opiate use is associated with greater decision-making deficits, meta-regression was run (with a Method of Moments correction for random-effects variance). To address the questions of whether current opiate users with head injury or poly-substance dependence have greater decision-making deficits than current opiate users without these co-morbidities,

DECISION-MAKING AND OPIATE USE

subgroup analyses using a Q-test for heterogeneity were run ($Q_{between}$; Borenstein et al., 2009). Studies were grouped by participants' head injury status (yes, no) and poly-substance dependence status (dependent, intermittent use), and effect sizes for each group were compared. It should be noted that it is rare that an established opiate user exclusively uses opiates (Darke, 2011). More often than not, they concurrently use other drugs (Astals et al., 2008). Therefore, all participants in the opiate groups were coded as either users of, or dependent on, other drugs. Studies that did not explicitly specify criteria regarding poly-substance dependence status or head injury status were coded in the positive (dependent for poly-substance use or yes for head injury).

To address the question of whether the magnitude of the decision-making deficit (the degree of difference from the control group) was smaller for ex-users than for current users, a subgroup analysis was run using the dichotomous predictor of ex-users versus current users. Additionally, a meta-regression was run (restricted to the studies involving ex-users) to assess the impact of years of abstinence on decision-making differences.

3.5.6 Publication bias and outliers

Publication bias was assessed by visually inspecting funnel plots and by calculating Orwin's fail-safe N (Orwin, 1983; Zakzanis, 2001). The fail-safe N (N_{fs}) value provides a hypothetical number of unpublished studies with nonsignificant results ($d \leq 0.2$) which would need to exist (outside of published literature) to call the current findings into question (Rosenthal, 1979; Zakzanis, 2001). A larger N indicates more confidence in the findings (McLennan and Mathias, 2010).

The presence and influence of outliers was assessed by examining the standardised residual for each study (Viechtbauer and Cheung, 2010). In cases where a study had a z-score of greater than ±1.96, its influence was examined using the "one study removed" method. Studies were retained in the overall analyses if they did not substantially change the overall effect size.

3.6 Results

3.6.1 Included articles

After an initial literature search, a total of 4635 articles were found, which was reduced to 3537 articles once duplicates were removed. Their titles and abstracts were

DECISION-MAKING AND OPIATE USE

screened, and 192 articles were retained. These were examined to determine whether they met the inclusion criteria for the study. From this, 38 articles were subjected to a full-text analysis. Following full-text analysis, 22 studies were deemed to meet inclusion criteria (see Figure 1 for a summary of the screening process). Fifteen reported data for current users and 7 reported on ex-users.

3.6.2 Participant and study characteristics

Table 1 presents a summary of the main characteristics of each study. Cohen's d represents the magnitude of the difference between the opiate and control groups on the decision-making measures. Overall, a total of 512 current users and 513 ex-users were compared to 969 controls. The majority of participants in both the current and ex-user groups were dependent on, or had been dependent on, heroin (93.46%). Most (71.23%) current users were also using an opiate substitute, such as methadone or buprenorphine. The most commonly used opiate substitute was methadone (68.77% of all opiate-substitute participants).

3.6.3 Influence of individual and temporal factors on decision-making in current users

To assess the influence of outliers, the standardised residual was examined for all studies involving current users. One study was identified as an outlier in this group (Ersche et al., 2005b). However, results of the "one study removed" analysis indicated that it did not significantly influence the overall effect size and was therefore included in further analyses. Figure 2 presents the forest plot for studies assessing current users.

Fifteen studies reported data for current users. The mean age of current users was 34.55 years (14 studies). The overall effect size for the magnitude of the difference in decision-making performance between current users and controls was significant ($d = -0.70$, 95% CI = -0.89, -0.51, $p < .001$). There was moderate heterogeneity ($I^2 = 52.07$) and the fail-safe N was 37.58.

Eleven studies reported data for duration of opiate use for current opiate users. The mean duration of opiate use was 10.34 years (11 studies). There was moderate heterogeneity ($I^2 = 60.63$) and the fail-safe N was 25.36. Meta-regression indicated that there was no significant relationship between years of opiate use and the magnitude of the difference in decision-making performance between current opiate users and controls: $Q_{model} = 0.73$, $Q_{residual} = 10.19$, $Z = 0.85$, $p = 0.39$.

DECISION-MAKING AND OPIATE USE

Excluded articles (and reasons)

All articles identified using study
selection keywords:
$K = 4635$

All articles identified using study
selection key words once duplicates
removed:
$K = 3537$

Articles not relevant to search (animal studies, theoretical
concepts, chronic pain, clinical decision making, non-drug use
studies):
$K = 3345$

Articles examined for
inclusion/exclusion criteria:
$K = 192$

- Subjects non-human = 2
- Conference paper not published = 6
- No or inappropriate control group = 27
- Qualitative/no data = 12
- No heroin group or heroin group not specified = 18
- No behavioral decision-making measure = 79
- Full text not available/not English = 10
  $K = 154$

Articles on adult patients with heroin
dependence & decision making
deficits as in inclusion criteria:
$K = 38$

- Conference paper/procedia (data not published) = 1
- Data not retained or cannot calculate effect size (following author email) = 3
- Overlapping data (combined with other included articles) or decision-making data reported elsewhere = 9
- Author reply not received = 3
  $K = 16$

Articles included: $K = 22$

Figure 1. Summary of studies excluded from the meta-analysis (with reasons for exclusion and number of studies in each category).

Table 1.

Sample Characteristics of Studies Included in the Meta-Analysis and Effect Sizes for Decision-Making Measures (Cohen's d).

Author (year)	DM measure	Opiate group *n*	Control group *n*	Features of opiate group				Cohen's *d* (95%CI)[a]
				Opiate use (years)	Abstinence (years)	Head injury included	Poly-substance use pattern	
Current Opiate Users								
Baldacchino et al. (2014)	CGT	53	28	7.58	NA	No	Dependence	-0.66 (-1.12, -0.19)
Barry and Petry (2008)	IGT	28	37	-	NA	Yes	Dependence	-0.57 (-1.07, -0.07)
Brand et al. (2008)	GDT	18	18	11.64	NA	No	Intermittent use	-1.02 (-1.72, -0.33)
Cheng et al. (2012)	DDT	56	56	7.60	NA	No	Intermittent use	-0.96 (-1.35, -0.56)
Clark et al. (2006)	IST	40	26	11.00	NA	No	Intermittent use	-0.86 (-1.38, -0.35)
Ersche et al. (2005b)[c]	CRT	39	27	9.93	NA	No	Intermittent use	0.13 (-0.36, 0.63)
Khodadadi et al. (2010)	BART	25	50	-	NA	Yes	Intermittent use	-1.08 (-1.59, -0.57)
Kirby et al. (2004)	DDT	27	44	-	NA	Yes	Dependence	-0.91 (-1.41, -0.41)
Kirby et al. (1999)	DDT	56	60	8.30	NA	Yes	Dependence	-0.55 (-0.92, -0.18)
Lemenager et al. (2011)	IGT	46	43	15.50	NA	No	Dependence	-0.53 (-0.95, -0.11)
Ma et al. (2015)	IGT	14	14	8.79	NA	No	Intermittent use	-1.58 (-2.43, -0.74)
Madden et al. (1997)	DDT	18	38	9.40	NA	No	Dependence	-1.19 (-1.79, -0.58)
Pirastu et al. (2006)[c]	IGT	48	21	14.69	NA	No	Intermittent use	-0.30 (-0.82, 0.22)
Rotheram-Fuller et al. (2004)[c]	IGT	18	10	-	NA	No	Intermittent use	-0.79 (-1.59, 0.01)

DECISION-MAKING AND OPIATE USE

Upton et al. (2012)[b]	IGT, SGT	26	27	9.35	NA	Yes	Dependence	-0.31 (-0.85, 0.23)
Ex Opiate Users								
Ahn and Vassileva (2016)[b]	IGT, CGT, DDT, BART	44	81	7.10	1.74	NA	NA	-0.13 (-0.50, 0.24)
Li et al. (2013)[b]	IGT, DDT	124	43	6.42	1.06	NA	NA	-1.06 (-1.42, -0.69)
Sun et al. (2015b)	IGT	121	103	15.16	0.39	NA	NA	-0.47 (-0.74, -0.21)
Verdejo-Garcia and Perez- Garcia (2007)	IGT	27	36	-	-	NA	NA	-0.52 (-1.03, -0.02)
Yan et al. (2014)	IGT	58	60	7.50	1.09	NA	NA	-0.58 (-0.95, -0.21)
Zeng et al. (2013)	IGT	86	88	4.30	0.98	NA	NA	0.18 (-0.12, 0.48)
Zhang et al. (2012)	IGT	53	56	7.54	0.44	NA	NA	-0.47 (-0.85, -0.09)

[a] Represents the magnitude of the difference between the opiate and control groups on the decision-making measures, with negative values indicating poorer performance by the opiate group (compared to controls)

[b] Where more than one decision-making measure was reported, a combined effect score was computed

[c] Where more than one opiate group was reported, a combined decision-making score was computed and used for calculating effect size

Abbreviations: BART = Balloon Analogue Risk Task; CGT = Cambridge Gambling Task; CRT = Cambridge Risk Task; DM = decision making; DDT = Delay Discounting Task; IGT = Iowa Gambling Task; IST = Information Sampling Task; NA = not applicable; SGT = Soochow Gambling Task

DECISION-MAKING AND OPIATE USE

Ten studies excluded participants based on head injury, while 5 studies did not exclude opiate users based on this criterion (or did not report it as an exclusionary criterion). Subgroup comparison indicated that the magnitude of the difference between current opiate users and controls for studies which included participants with head injury (d =-0.68, 95% CI = -0.93, -0.42) did not significantly differ from studies which did not include participants with head injury (d = -0.73, 95% CI = -1.00, -0.45; $Q_{between}(1) = 0.07$, p = 0.80). Heterogeneity was low for studies with head injury (I^2 = 28.78) and the fail-safe N was 11.88, while for studies without head injury, heterogeneity was moderate ($I^2 = 61.83$) and the fail-safe N was 26.25.

Eight studies reported data for current opiate users without current dependence on other substances (i.e. those coded as intermittent users), while 7 reported data for current opiate users who had other drug dependencies. Subgroup analysis indicated that there was no significant difference between studies that reported data for opiate users who did have a current or past poly-substance dependence (dependent: d = -0.64, 95% CI = -0.82, -0.46) compared to studies which reported data for opiate users who did not have a current or past poly-substance dependence (intermittent use: d = -0.77, 95% CI = -1.12, -0.41; $Q_{between}(1) = 0.40$, p = 0.53). Heterogeneity was very low for studies with poly-substance dependence ($I^2 = 4.63$) and the fail-safe N was 15.33, while for studies without poly-substance dependence heterogeneity was moderate ($I^2 = 68.81$) and the fail-safe N was 22.68.

3.6.4 Decision-making in ex-users

To assess the influence of outliers, the standardised residual was examined for all studies involving ex-users. One study was identified as an outlier in this group (Zeng et al., 2013). However, "one study removed" analysis indicated that it did not appear to significantly influence the overall effect size and it was therefore included in further analyses.

Seven studies reported data for ex-users. The mean age of ex-users was 31.88 years (6 studies), and mean duration of heroin use in ex-users was 8.00 years (6 studies). The mean duration of abstinence was 0.89 years (6 studies). Heterogeneity was relatively high for studies that assessed ex-users ($I^2 = 80.53$) and the fail-safe N was 7.98. Figure 2 presents the forest plot for current and ex-users. The analysis of overall effect size for ex-users was significant (d = -0.43, 95% CI = -0.73, -0.13, p = .006).

DECISION-MAKING AND OPIATE USE

However, the subgroup analysis comparing studies which assessed current users to studies which assessed ex-users was not significant ($Q_{between}(1) = 2.23$, $p = 0.136$). Duration of abstinence was not significantly associated with decision-making performance: $Q_{model} = 0.15$, $Q_{residual} = 4.01$, $Z = 0.38$, $p = 0.70$. Heterogeneity was relatively high for studies reporting duration of abstinence ($I^2 = 83.63$) and this finding was associated with a fail-safe N of 6.48.
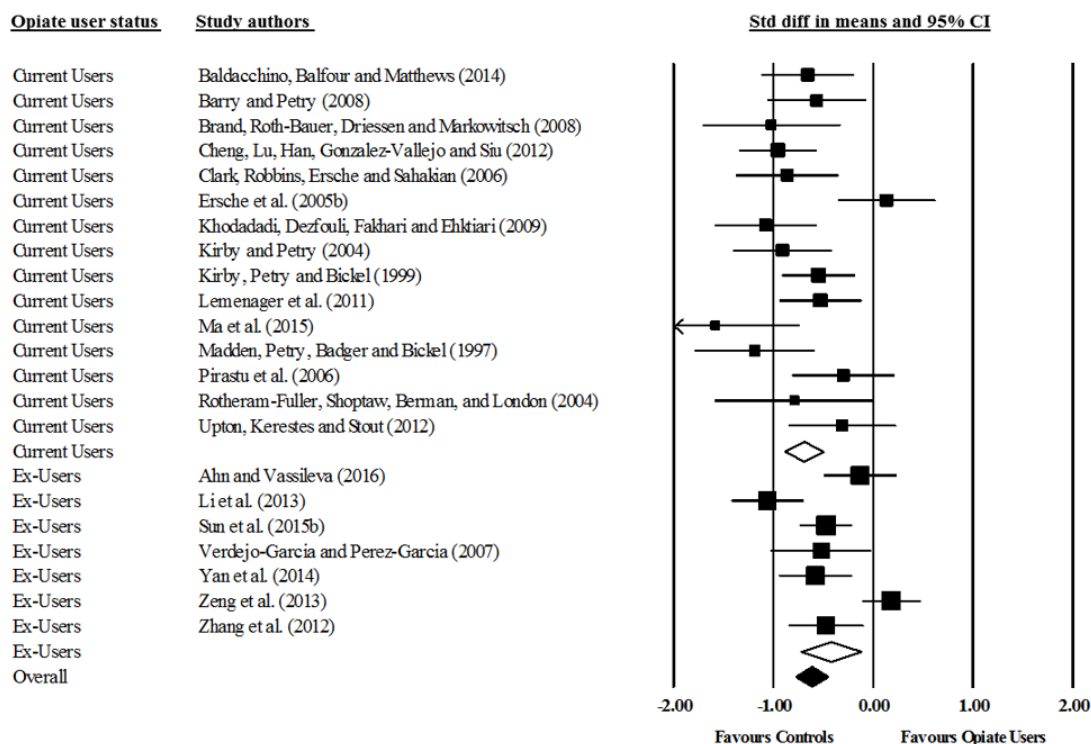
Figure 2. Forest plot of all studies included in the meta-analysis. Studies involving current opiate users are presented at the top, and those involving ex-users are presented below. Each plot point represents the magnitude of the difference (effect size) between the opiate user group and control group on decision-making measures. The open diamond represents the pooled effect size for each subgroup and the closed diamond represents the pooled effect size for all studies.

3.7 Discussion

The primary aim of this meta-analysis was to explore the influence of co-morbidities and temporal factors on the decision-making ability of opiate users. We identified 15 studies that compared the decision-making abilities of current opiate users

with controls. Consistent with an earlier meta-analysis, which applied stricter inclusion criteria (Baldacchino et al., 2012), we found that the size of the deficit in decision-making in opiate users relative to non-drug-using controls was moderate to large. This confirms that when opiate users are faced with choices, they find it difficult to avoid making risky decisions, or to forgo small short-term gains in order to achieve larger gains in the long term. In real life, this pattern of decision-making behaviour has the potential to negatively impact many areas of life. Poor decision-making in the real world could play out as difficulty resisting non-essential purchases in order to save up a deposit for accommodation, or even difficulty forgoing the short-term benefits of drug use in order to maintain abstinence. Although the real world sequela of decision-making deficits in opiate users has received little research attention, a recent study by Wilson and Vassileva (2016) found that poor decision-making in opiate users predicted sexually risky behaviour, putting users at risk of contracting HIV. In other drug-using populations, poor performance on the lab-based decision-making tests considered in this meta-analysis has been linked to dropout from drug treatment services (Stevens et al., 2013; Stevens et al., 2015b) and higher rates of relapse (Stevens et al., 2015a).

Having confirmed decision-making as an area of substantial impairment in opiate users, we then assessed the influence of comorbid conditions on this ability. To do this, we included studies that reported on opiate users who had head injuries and those who had dependencies on other drugs. These co-morbidities are very common in this group, and thus including these studies (which were excluded from the previous meta-analysis; Baldacchino et al., 2012), allowed us to examine a more representative sample. We had anticipated that people with these co-morbidities may exhibit even more severe decision-making deficits than other opiate users. However, the magnitude of the deficit did not differ significantly between opiate users with poly-substance dependence or head injury, and those without these co-morbid issues. Although relatively few studies were available for these subgroup analyses and, as such, they may have been underpowered, the magnitude of the deficit between the opiate users and controls was similar (moderate to high) regardless of whether co-morbidities were present or not. These findings therefore suggest that poly-substance use and head injury do not play a key role in influencing the level of decision-making deficit in opiate users. This raises the possibility that the observed impairment in decision-making relates more directly to

DECISION-MAKING AND OPIATE USE

opiate use, possibly through its impact on brain function (Cheng et al., 2013; Lyoo et al., 2006).

Over and above co-morbidities, the current study also investigated whether decision-making deficits are related to the duration of opiate use. More specifically, given the established links between opiate use and brain abnormalities (Cheng et al., 2013; Ersche et al., 2006; Liu et al., 2009; Liu et al., 2013; Lyoo et al., 2006; Ma et al., 2010; Shi et al., 2008; Yeh et al., 2012; Yuan et al., 2010; Zaaijer et al., 2015), and findings showing that structural brain changes are more severe in people who have used opiates for longer periods of time (Yuan et al., 2010; Yuan et al., 2009), it was anticipated that the size of the decision-making deficit might increase in line with the length of opiate use. Our meta-regression did not show such a relationship. However, the duration of opiate use reported in the 11 studies included in this analysis ranged from a mean of 7.58 years (Baldacchino et al., 2015) to a mean of 15.5 years (Lemenager et al., 2011). One possible interpretation of these findings is that brain changes may happen relatively early in the trajectory of opiate use. It is therefore possible that, if opiate use is associated with brain changes (for example, in the OFC; Ersche et al., 2006; Liu et al., 2009; Ma et al., 2010), then such neuropathology may be well established at least within 7 years, with further adverse effects being minimal. Future studies investigating the trajectory of decision-making ability across the earlier years of opiate use, such as from the first week to 7 years post-initiation of opiate use, would help clarify this issue.

The final question addressed in the current study was the impact of abstinence on the decision-making ability of opiate users. To do this, we examined decision-making deficits in ex-users who had previously been addicted to opiates, and found that abstinence from opiates (for an average of just under a year) was not associated with a smaller deficit in decision-making. More specifically, while the effect size for the difference in decision-making performance between ex-users and non-drug using controls was smaller than the effect size for the difference between current users versus controls, the difference between these effect sizes was minimal and failed to reach significance. These results suggest that decision-making deficits appear to continue even after opiate use ceases. These results are consistent with those of Mintzer et al. (2005) who found no significant difference in decision-making performance between current and ex-users on the IGT.

In addition, the duration of abstinence was not significantly associated with the magnitude of the decision-making deficit in opiate users. The period of abstinence in the available studies ranged from just over four and a half months (Sun et al., 2015b) to just over one and a half years (Ahn and Vassileva, 2016). Although previous research suggests recovery of decision-making ability may occur after extended periods of time (e.g. Zhang et al., 2011), the results of this meta-analysis suggest that, at least for the first 1.5 years of abstinence, improvements may be minimal. This is consistent with neuroimaging research conducted within the first 18 months of abstinence from opiates, which has found lasting impairments in the functional connectivity of the dlPFC and OFC, as well as reduced dopamine transmission (Cheng et al., 2013; Liu et al., 2009; Shi et al., 2008; Yeh et al., 2012). However, given that only 7 studies of ex-users were included in the analyses, and all but one of these focused on users who had been abstinent for a relatively short time, additional longitudinal research is needed in order to gain a clearer understanding of whether, and by what magnitude, decision-making abilities improve after longer periods of abstinence.

This meta-analysis has confirmed an association between opiate use and decision-making deficits, but it cannot address the direction of causality. Indeed, there are at least two possible causal pathways that may explain the current results. First, long-term opiate use may lead to decision-making deficits via structural brain changes. While not definitive, research showing an association between the duration of opiate use and the severity of structural abnormalities (Yuan et al., 2010; Yuan et al., 2009), as well as research showing measurable white matter degeneration in opiate users over a period of a year (Li et al., 2016), is consistent with the pathway of structural brain changes. Furthermore, most (Harvey-Lewis et al., 2012; Kieres et al., 2004; Schippers et al., 2012), although not all (Harty et al., 2011), animal studies have demonstrated that decision-making impairments can be experimentally induced by administering opiates. Additional research also shows that opiate administration in animals reduces function of the OFC (Sun et al., 2006), an area known to play a significant role in decision-making (Krawczyk, 2002; Wallis, 2007). A second possible pathway, however, may also be in operation, whereby people with long-standing poor decision-making ability may be more likely to begin, and to continue using opiates (Bechara, 2005). This may be due to an overactive impulsive system which weakens the influence of the executive control system in the PFC, leading to a focus on immediate, rather than delayed, consequences

of drug use (Bechara, 2005; Bickel et al., 2007). Longitudinal studies provide support for this model, with delayed discounting in childhood and adolescence predicting higher rates of drug use in adulthood (Audrain-McGovern et al., 2009; Ayduk et al., 2000). Additionally, people with developmental disorders characterised by decision-making deficits, such as Attention Deficit Hyperactivity Disorder (ADHD; see Mowinckel et al., 2015, for a meta-analysis), demonstrate a higher propensity for drug use (Biederman et al., 1998; Biederman et al., 1995; Wilens et al., 1997). Therefore, at least for a subgroup of opiate users, poor decision-making seems to predate drug abuse. The results of the current meta-analysis are consistent with either, or indeed both, of these pathways. Clarification of their relevant influence, however, awaits further empirical research. Nevertheless, given that there was no clear indication of recovery after drug use was discontinued, and no effect of co-morbidities on decision-making differences, the results of the current study provide strong evidence that the observed decision-making deficits were not merely a result of transient drug effects or of co-morbid conditions.

Although this meta-analysis provides new insights into the decision-making impairment in opiate users, results may not translate to all opiate-using groups. For example, studies were excluded from the current meta-analysis if they included opiate-users who had a concurrent serious psychiatric diagnosis. Co-morbid psychiatric disorders are common in opiate users (Astals et al., 2008) and decision-making deficits are likely to be present in these groups as well, but may be more severe (e.g. Vassileva et al., 2007). Additionally, not enough studies were available to separately analyse the effect of different types of opiates (i.e. methadone, buprenorphine, or street heroin). While some studies suggest there may be differences in decision-making ability depending on the specific opiate used (Ersche et al., 2005b; Pirastu et al., 2006), other research suggests different opiates do not differentially affect cognitive function (Darke et al., 2012a; Soyka et al., 2008). Similarly, there were too few studies available to investigate the differences between different decision-making measures, with the majority of studies assessing performance on the IGT, and only a few studies using other measures. Future research should take both the opiate type and the decision-making measures used into consideration when investigating decision-making ability in opiate users.

Taken together, the results of this meta-analysis provide clear evidence that opiate-users display decision-making deficits. Furthermore, these deficits appear to be

relatively consistent, even when comparing opiate users who have other substance dependencies or head injury, to those without these co-morbid problems. Perhaps most importantly, the current research show that decision-making deficits persist even after drug use is discontinued, which may put opiate users at risk of drug use relapse (Passetti et al., 2008) and other risky behaviour (e.g., Wilson and Vassileva, 2016). Treatment programs for opiate users typically focus on the reduction, and eventual cessation of illicit drug use, and on reducing associated harms (such as crime, drug-related disease and mortality; Darke et al., 2007; Ford et al., 2011; Nicholls et al., 2010). However, the current research demonstrates that opiate users would benefit from support that goes beyond simply reducing their drug use or achieving abstinence. Even when this aim has been achieved, ex-opiate users are likely to struggle with making decisions in high-risk situations, and are likely to benefit from ongoing support. There is now a firm basis for treatment programs to consider decision-making difficulties in order to provide more relevant and targeted support to people seeking treatment for current or past opiate addiction. If decision-making is taken into account this may increase opiate users' success in remaining in treatment and maintaining abstinence, as well as achieving broader life changes.

3.8 Acknowledgements

3.9 References for the Published Manuscript (formatted for *Neuroscience and Biobehavioral Reviews*)

Ahn, W.-Y., Vasilev, G., Lee, S.-H., Busemeyer, J.R., Kruschke, J.K., Bechara, A., Vassileva, J., 2014. Decision-making in stimulant and opiate addicts in protracted abstinence: evidence from computational modeling with pure users. Front. Psych. 5, 849-849. doi: 10.3389/fpsyg.2014.00849

Ahn, W.-Y., Vassileva, J., 2016. Machine-learning identifies substance-specific behavioral markers for opiate and stimulant dependence. Drug Alcohol Depend. 161, 247–257. doi: 10.1016/j.drugalcdep.2016.02.008

Astals, M., Domingo-Salvany, A., Buenaventura, C.C., Tato, J., Vazquez, J.M., Martín-Santos, R., Torrens, M., 2008. Impact of substance dependence and dual diagnosis on the quality of life of heroin users seeking treatment. Subst. Use Misuse 43, 612-632. doi: 10.1080/10826080701204813

Baldacchino, A., Balfour, D.J.K., Matthews, K., 2015. Impulsivity and opioid drugs: differential effects of heroin, methadone and prescribed analgesic medication. Psychol. Med. 45, 1167-1179 doi: 10.1017/S0033291714002189

Baldacchino, A., Balfour, D.J.K., Passetti, F., Humphris, G., Matthews, K., 2012. Neuropsychological consequences of chronic opioid use: A quantitative review and meta-analysis. Neurosci. Biobehav. Rev. 36, 2056-2068. doi: 10.1016/j.neubiorev.2012.06.006

Barry, D., Petry, N.M., 2008. Predictors of decision-making on the Iowa Gambling Task: Independent effects of lifetime history of substance use disorders and performance on the Trail Making Test. Brain Cogn. 66, 243-252. doi: 10.1016/j.bandc.2007.09.001

DECISION-MAKING AND OPIATE USE

Bechara, A., 2004. The role of emotion in decision-making: Evidence from neurological patients with orbitofrontal damage. Brain Cogn. 55, 30-40. doi: 10.1016/j.bandc.2003.04.001

Bechara, A., 2005. Decision making, impulse control and loss of willpower to resist drugs: A neurocognitive perspective. Nat. Neurosci. 8, 1458-1463. doi: 10.1038/nn1584

Bechara, A., Damasio, A.R., Damasio, H., Anderson, S.W., 1994. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50, 7-15. doi: 10.1016/0010-0277(94)90018-3

Bechara, A., Damasio, H., Damasio, A.R., 2000a. Emotion, decision making and the orbitofrontal cortex. Cereb. Cortex 10, 295-307. doi: 10.1093/cercor/10.3.295

Bechara, A., Tranel, D., Damasio, H., 2000b. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. Brain 123, 2189-2202. doi: 10.1093/brain/123.11.2189

Bickel, W.K., Marsch, L.A., 2001. Toward a behavioral economic understanding of drug dependence: Delay discounting processes. Addiction 96, 73-86. doi: 10.1046/j.1360-0443.2001.961736.x

Borenstein, M., Hedges, L., Higgins, J., Rothstein, H., 2005. Comprehensive Meta-Analysis: Version 2. Englewood, NJ: Biostat.

Borenstein, M., Hedges, L., Higgins, J., Rothstein, H., 2009. Introduction to Meta-Analysis. John Wiley and Sons, Chichester, UK.

Brand, M., Roth-Bauer, M., Driessen, M., Markowitsch, H.J., 2008. Executive functions and risky decision-making in patients with opiate dependence. Drug Alcohol Depend. 97, 64-72. doi: 10.1016/j.drugalcdep.2008.03.017

Cheng, G.L.F., Zeng, H., Leung, M.K., Zhang, H.J., Lau, B.W.M., Liu, Y.P., Liu, G.X., Sham, P.C., Chan, C.C.H., So, K.F., 2013. Heroin abuse accelerates biological aging: A novel insight from telomerase and brain imaging interaction. Translational Psychiatry 3, e260. doi: 10.1038/tp.2013.36

Cheng, J., Lu, Y., Han, X., Gonzalez-Vallejo, Sui, N., 2012. Temporal discounting in heroin-dependent patients: No sign effect, weaker magnitude effect, and the

DECISION-MAKING AND OPIATE USE

relationship with inhibitory control. Exp. Clin. Psychopharmacol. 20, 400-409. doi: 10.1037/a0029657

Clark, L., Robbins, T.W., Ersche, K.D., Sahakian, B.J., 2006. Reflection impulsivity in current and former substance users. Biol. Psychiatry 60, 515-522. doi: 10.1016/j.biopsych.2005.11.007

Cohen, J., 1992. A power primer. Psychol. Bull. 112, 155-159. doi: 10.1037/0033-2909.112.1.155

Cohen, M.X., Heller, A.S., Ranganath, C., 2005. Functional connectivity with anterior cingulate and orbitofrontal cortices during decision-making. Cogn. Brain Res. 23, 61-70. doi: 10.1016/j.cogbrainres.2005.01.010

Dai, J., Kerestes, R., Upton, D.J., Busemeyer, J.R., Stout, J.C., 2015. An improved cognitive model of the Iowa and Soochow Gambling Tasks with regard to model fitting performance and tests of parameter consistency. Front. Psych. 6, 229-229. doi: 10.3389/fpsyg.2015.00229

Darke, S., 2011. The life of the heroin user: Typical beginnings, trajectories and outcomes. Cambridge University Press, New York, NY.

Darke, S., McDonald, S., Kaye, S., Torok, M., 2012a. Comparative patterns of cognitive performance amongst opioid maintenance patients, abstinent opioid users and non-opioid users. Drug Alcohol Depend. 126, 309-315. doi: 10.1016/j.drugalcdep.2012.05.032

Darke, S., McDonald, S., Kaye, S., Torok, M., 2012b. Prevalence and correlates of traumatic brain injury amongst heroin users. Addiction Research and Theory 20, 522-528. doi: 10.3109/16066359.2012.672600

Darke, S., Ross, J., Mills, K.L., Williamson, A., Havard, A., Teesson, M., 2007. Patterns of sustained heroin abstinence amongst long-term, dependent heroin users: 36 months findings from the Australian Treatment Outcome Study (ATOS). Addict. Behav. 32, 1897-1906. doi: 10.1016/j.addbeh.2007.01.014

Darke, S., Sims, J., McDonald, S., Wickes, W., 2000. Cognitive impairment among methadone maintenance patients. Addiction 95, 687-695. doi: 10.1046/j.1360-0443.2000.9556874.x

De Maeyer, J., Vanderplasschen, W., Broekaert, E., 2010. Quality of life among opiate-dependent individuals: A review of the literature. Int. J. Drug Policy 21, 364-380. doi: 10.1016/j.drugpo.2010.01.010

De Maeyer, J., Vanderplasschen, W., Lammertyn, J., van Nieuwenhuizen, C., Sabbe, B., Broekaert, E., 2011. Current quality of life and its determinants among opiate-dependent individuals five years after starting methadone treatment. Qual. Life Res. 20, 139-150. doi: 10.1007/s11136-010-9732-3

Elliott, R., Dolan, R.J., Frith, C.D., 2000. Dissociable functions in the medial and lateral orbitofrontal cortex: Evidence from human neuroimaging studies. Cereb. Cortex 10, 308-317. doi: 10.1093/cercor/10.3.308

Ernst, M., Paulus, M.P., 2005. Neurobiology of decision making: A selective review from a neurocognitive and clinical perspective. Biol. Psychiatry 58, 597-604. doi: 10.1016/j.biopsych.2005.06.004

Ersche, K.D., Fletcher, P., Lewis, S., Clark, L., Stocks-Gee, G., London, M., Deakin, J., Robbins, T., Sahakian, B., 2005a. Abnormal frontal activations related to decision-making in current and former amphetamine and opiate dependent individuals. Psychopharmacol. 180, 612-623. doi: 10.1007/s00213-005-2205-7

Ersche, K.D., Fletcher, P.C., Roiser, J.P., Fryer, T.D., London, M., Robbins, T.W., Sahakian, B.J., 2006. Differences in orbitofrontal activation during decision-making between methadone-maintained opiate users, heroin users and healthy volunteers. Psychopharmacol. 188, 364-373. doi: 10.1007/s00213-006-0515-z

Ersche, K.D., Roiser, J.P., Clark, L., London, M., Robbins, T.W., Sahakian, B.J., 2005b. Punishment induces risky decision-making in methadone-maintained opiate users but not in heroin users or healthy volunteers. Neuropsychopharmacol. 30, 2115-2124. doi: 10.1038/sj.npp.1300812

Fishbein, D.H., Krupitsky, E., Flannery, B.A., Langevin, D.J., Bobashev, G., Verbitskaya, E., Augustine, C.B., Bolla, K.I., Zvartau, E., Schech, B., Egorova, V., Bushara, N., Tsoy, M., 2007. Neurocognitive characterizations of Russian heroin addicts without a significant history of other drug use. Drug Alcohol Depend. 90, 25-38. doi: 10.1016/j.drugalcdep.2007.02.015

DECISION-MAKING AND OPIATE USE

Ford, C., Halliday, K., Lawson, E., Browne, E., 2011. Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care. Royal College of General Practitioners.

Gläscher, J., Adolphs, R., Damasio, H., Bechara, A., Rudrauf, D., Calamia, M., Paul, L.K., Tranel, D., 2012. Lesion mapping of cognitive control and value-based decision making in the prefrontal cortex. Proc. Natl. Acad. Sci. 109, 14681-14686. doi: 10.1073/pnas.1206608109

Hedges, L.V., Olkin, I., 1985. Statistical methods for meta-analysis. Academic press, London, UK.

Henry, P.K., Umbricht, A., Kleykamp, B.A., Vandrey, R., Strain, E.C., Bigelow, G.E., Mintzer, M.Z., 2012. Comparison of cognitive performance in methadone maintenance patients with and without current cocaine dependence. Drug Alcohol Depend. 124, 167-171. doi: 10.1016/j.drugalcdep.2011.12.009

Heyman, G.M., Dunn, B., 2002. Decision biases and persistent illicit drug use: an experimental study of distributed choice and addiction. Drug Alcohol Depend. 67, 193-203. doi: 10.1016/s0376-8716(02)00071-6

Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. Br. Med. J. 327, 557. doi: 10.1136/bmj.327.7414.557

Khodadadi, A., Dezfouli, A., Fakhari, P., Ekhtiari, H., 2010. Effects of methadone maintenance treatment on decision-making processes in heroin-abusers: A cognitive modeling analysis. Basic Clin. Neuro. 1, 44-49

Kirby, K.N., Petry, N.M., 2004. Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. Addiction 99, 461-471. doi: 10.1111/j.1360-0443.2003.00669.x

Kirby, K.N., Petry, N.M., Bickel, W.K., 1999. Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. J. Exp. Psychol. Gen. 128, 78-87. doi: 10.1037/0096-3445.128.1.78

Krawczyk, D.C., 2002. Contributions of the prefrontal cortex to the neural basis of human decision making. Neurosci. Biobehav. Rev. 26, 631-664. doi: 10.1016/S0149-7634(02)00021-0

DECISION-MAKING AND OPIATE USE

Lejuez, C.W., Read, J.P., Kahler, C.W., Richards, J.B., Ramsey, S.E., Stuart, G.L.,
Strong, D.R., Brown, R.A., 2002. Evaluation of a behavioral measure of risk
taking: The Balloon Analogue Risk Task (BART). J. Exp. Psychol. Appl. 8, 75.
doi: 10.1037/1076-898X.8.2.75

Lemenager, T., Richter, A., Reinhard, I., Gelbke, J., Beckmann, B., Heinrich, M.,
Kniest, A., Mann, K., Hermann, D., 2011. Impaired decision making in opiate
addiction correlates with anxiety and self-directedness but not substance use
parameters. J. Addiction Med. 5, 203-213. doi:
10.1097/ADM.0b013e31820b3e3d

Li, W., Li, Q., Wang, Y., Zhu, J., Ye, J., Yan, X., Li, Y., Chen, J., Liu, J., Li, Z., Wang,
W., Liu, Y., 2016. Methadone-induced Damage to White Matter Integrity in
Methadone Maintenance Patients: A Longitudinal Self-control DTI Study. Sci.
Rep. 6, 19662-19662. doi: 10.1038/srep19662

Li, X.Y., Zhang, F., Zhou, Y., Zhang, M., Wang, X., Shen, M.W., 2013. Decision-
making deficits are still present in heroin abusers after short- to long-term
abstinence. Drug Alcohol Depend. 130, 61-67. doi:
10.1016/j.drugalcdep.2012.10.012

Liang, C.S., Ho, P.S., Yen, C.H., Yeh, Y.W., Kuo, S.C., Huang, C.C., Chen, C.Y., Shih,
M.C., Ma, K.H., Huang, S.Y., 2016. Reduced striatal dopamine transporter
density associated with working memory deficits in opioid-dependent male
subjects: a SPECT study. Addict. Biol. 21, 196-204. doi: 10.1111/adb.12203

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P.A.,
Clarke, M., Devereaux, P.J., Kleijnen, J., Moher, D., 2009. The PRISMA
statement for reporting systematic reviews and meta-analyses of studies that
evaluate health care interventions: explanation and elaboration. PLoS Med. 6,
e1000100. doi: 10.1371/journal.pmed.1000100

Liu, H., Li, L., Hao, Y., Cao, D., Xu, L., Rohrbaugh, R., Xue, Z., Hao, W., Shan, B.,
Liu, Z., 2008. Disrupted white matter integrity in heroin dependence: A
controlled study utilizing diffusion tensor imaging. Am. J. Drug Alcohol Abuse
34, 562-575. doi: 10.1080/00952990802295238

DECISION-MAKING AND OPIATE USE

Liu, J., Liang, J.Y., Qin, W., Tian, J., Yuan, K., Bai, L., Zhang, Y., Wang, W., Wang, Y.H., Li, Q., Zhao, L.Y., Lu, L., von Deneen, K.M., Liu, Y.P., Gold, M.S., 2009. Dysfunctional connectivity patterns in chronic heroin users: An fMRI study. Neurosci. Lett. 460, 72-77. doi: 10.1016/j.neulet.2009.05.038

Liu, Y.P., Han, M., Liu, X., Deng, Y., Li, Y.H., Yuan, J., Lv, R., Wang, Y.H., Zhang, G., Gao, J., 2013. Dopamine transporter availability in heroin-dependent subjects and controls: longitudinal changes during abstinence and the effects of Jitai tablets treatment. Psychopharmacol. 230, 235-244. doi: 10.1007/s00213-013-3148-z

Loeber, S., Nakovics, H., Kniest, A., Kiefer, F., Mann, K., Croissant, B., 2012. Factors affecting cognitive function of opiate-dependent patients. Drug Alcohol Depend. 120, 81-87. doi: 10.1016/j.drugalcdep.2011.07.001

Lyoo, I.K., Pollack, M.H., Silveri, M.M., Ahn, K.H., Diaz, C.I., Hwang, J., Kim, S.J., Yurgelun-Todd, D.A., Kaufman, M.J., Renshaw, P.F., 2006. Prefrontal and temporal gray matter density decreases in opiate dependence. Psychopharmacol. 184, 139-144. doi: 10.1007/s00213-005-0198-x

Lyoo, I.K., Streeter, C.C., Ahn, K.H., Lee, H.K., Pollack, M.H., Silveri, M.M., Nassar, L., Levin, J.M., Sarid-Segal, O., Ciraulo, D.A., 2004. White matter hyperintensities in subjects with cocaine and opiate dependence and healthy comparison subjects. Psychiatry Res. Neuroimaging 131, 135-145. doi: 10.1016/j.pscychresns.2004.04.001

Ma, N., Liu, Y.P., Li, N., Wang, C.X., Zhang, H., Jiang, X.F., Xu, H.S., Fu, X.M., Hu, X., Zhang, D.R., 2010. Addiction related alteration in resting-state brain connectivity. Neuroimage 49, 738-744. doi: 10.1016/j.neuroimage.2009.08.037

Ma, X.F., Qiu, Y.W., Tian, J.Z., Wang, J.H., Li, S.M., Zhan, W.F., Wang, T.Y., Zeng, S.Q., Jiang, G.H., Xu, Y.K., 2015. Aberrant default-mode functional and structural connectivity in heroin-dependent individuals. PLoS ONE 10. doi: 10.1371/journal.pone.0120861

Madden, G.J., Petry, N.M., Badger, G.J., Bickel, W.K., 1997. Impulsive and self-control choices in opioid-dependent patients and non-drug-using control

patients: Drug and monetary rewards. Exp. Clin. Psychopharmacol. 5, 256-262. doi: 10.1037/1064-1297.5.3.256

McLennan, S.N., Mathias, J.L., 2010. The depression-executive dysfunction (DED) syndrome and response to antidepressants: A meta-analytic review. Int. J. Geriatr. Psychiatry 25, 933-944. doi: 10.1002/gps.2431

Meulenbeek, P.A.M., 2000. Addiction problems and methadone treatment. J. Subst. Abuse Treat. 19, 171-174. doi: 10.1016/S0740-5472(00)00116-1

Mintzer, M.Z., Copersino, M.L., Stitzer, M.L., 2005. Opioid abuse and cognitive performance. Drug Alcohol Depend. 78, 225-230. doi: 10.1016/j.drugalcdep.2004.10.008

Mintzer, M.Z., Stitzer, M.L., 2002. Cognitive impairment in methadone maintenance patients. Drug Alcohol Depend. 67, 41-51. doi: 10.1016/s0376-8716(02)00013-3

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 6, e1000097. doi: 10.1371/journal.pmed.1000097

Nicholls, L., Bragaw, L., Ruetsch, C., 2010. Opioid dependence treatment and guidelines. Journal of Managed Care Pharmacy 16, 14-21. doi: 10.18553/jmcp.2010.16.S1-B.14

Orwin, R.G., 1983. A fail-safe N for effect size in meta-analysis. J. Educ. Stat. 8, 157-159

Passetti, F., Clark, L., Mehta, M.A., Joyce, E., King, M., 2008. Neuropsychological predictors of clinical outcome in opiate addiction. Drug Alcohol Depend. 94, 82-91. doi: 10.1016/j.drugalcdep.2007.10.008

Petry, N.M., Bickel, W.K., Arnett, M., 1998. Shortened time horizons and insensitivity to future consequences in heroin addicts. Addiction 93, 729-738. doi: 10.1046/j.1360-0443.1998.9357298.x

Pirastu, R., Fais, R., Messina, M., Bini, V., Spiga, S., Falconieri, D., Diana, M., 2006. Impaired decision-making in opiate-dependent subjects: Effect of pharmacological therapies. Drug Alcohol Depend. 83, 163-168. doi: 10.1016/j.drugalcdep.2005.11.008

Qiu, Y.W., Han, L.J., Lv, X.F., Jiang, G.H., Tian, J.Z., Zhuo, F.Z., Su, H.H., Lin, C.L., Zhang, X.L., 2011. Regional homogeneity changes in heroin-dependent individuals: Resting-state functional MR imaging study. Radiology 261, 551-559. doi: 10.1148/radiol.11102466

Qiu, Y.W., Jiang, G.H., Su, H.H., Lv, X.F., Zhang, X.L., Tian, J.Z., Zhuo, F.Z., 2013a. Progressive white matter microstructure damage in male chronic heroin dependent individuals: A DTI and TBSS study. PLoS ONE 8, e63212-e63212. doi: 10.1371/journal.pone.0063212

Qiu, Y.W., Jiang, G.H., Su, H.H., Ma, X.F., Li, L.M., Tian, J.Z., Zhang, X.L., 2013b. [Alterations in orbitofrontal cortex functional connectivity and decision making deficits in heroin-dependent individuals]. Journal Of Southern Medical University 33, 1117-1121

Robles, E., Huang, B., Simpson, P.M., McMillan, D.E., 2011. Delay discounting, impulsiveness, and addiction severity in opioid-dependent patients. J. Subst. Abuse Treat. 41, 354-362. doi: 10.1016/j.jsat.2011.05.003

Rogers, R.D., Everitt, B., Baldacchino, A., Blackshaw, A., Swainson, R., Wynne, K., Baker, N., Hunter, J., Carthy, T., Booker, E., London, M., Deakin, J., Sahakian, B., Robbins, T.W., 1999. Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: Evidence for monoaminergic mechanisms. Neuropsychopharmacol. 20, 322-339. doi: 10.1016/S0893-133X%2898%2900091-8

Rolls, E.T., 2000. The orbitofrontal cortex and reward. Cereb. Cortex 10, 284-294. doi: 10.1093/cercor/10.3.284

Rosenthal, R., 1979. The file drawer problem and tolerance for null results. Psychol. Bull. 86, 638-641. doi: 10.1037/0033-2909.86.3.638

Rotheram-Fuller, E., Shoptaw, S., Berman, S.M., London, E.D., 2004. Impaired performance in a test of decision-making by opiate-dependent tobacco smokers. Drug Alcohol Depend. 73, 79-86. doi: 10.1016/j.drugalcdep.2003.10.003

Shi, J., Zhao, L.Y., Copersino, M.L., Fang, Y.X., Chen, Y.Y., Tian, J., Deng, Y., Shuai, Y., Jin, J., Lu, L., 2008. PET imaging of dopamine transporter and drug craving

during methadone maintenance treatment and after prolonged abstinence in
heroin users. Eur. J. Pharmacol. 579, 160-166. doi: 10.1016/j.ejphar.2007.09.042

Soyka, M., Lieb, M., Kagerer, S., Zingg, C., Koller, G., Lehnert, P., Limmer, C.,
Kuefner, H., Hennig-Fast, K., 2008. Cognitive functioning during methadone
and buprenorphine treatment: Results of a randomized clinical trial. J. Clin.
Psychopharmacol. 28, 699-703. doi: 10.1097/JCP.0b013e31818a6d38

Sun, Y., Wang, G.B., Lin, Q.X., Lu, L., Shu, N., Meng, S.Q., Wang, J., Han, H.B., He,
Y., Shi, J., 2015a. Disrupted white matter structural connectivity in heroin
abusers. Addict. Biol. doi: 10.1111/adb.12285

Sun, Y., Zhao, L.Y., Wang, G.B., Yue, W.H., He, Y., Shu, N., Lin, Q.X., Wang, F., Li,
J.L., Chen, N., Wang, H.M., Kosten, T.R., Feng, J.J., Wang, J., Tang, Y.D., Liu,
S.X., Deng, G.F., Diao, G.H., Tan, Y.L., Han, H.B., Lin, L., Shi, J., 2015b.
ZNF804A variants confer risk for heroin addiction and affect decision making
and gray matter volume in heroin abusers. Addict. Biol. doi: 10.1111/adb.12233

Upton, D.J., Kerestes, R., Stout, J.C., 2012. Comparing the Iowa and Soochow
gambling tasks in opiate users. Front. Neurosci. 6, 34-34. doi:
10.3389/fnins.2012.00034

Vassileva, J., Petkova, P., Georgiev, S., Martin, E.M., Tersiyski, R., Raycheva, M.,
Velinov, V., Marinov, P., 2007. Impaired decision-making in psychopathic
heroin addicts. Drug Alcohol Depend. 86, 287-289. doi:
10.1016/j.drugalcdep.2006.06.015

Veilleux, J.C., Colvin, P.J., Anderson, J., York, C., Heinz, A.J., 2010. A review of
opioid dependence treatment: Pharmacological and psychosocial interventions to
treat opioid addiction. Clin. Psychol. Rev. 30, 155-166. doi:
10.1016/j.cpr.2009.10.006

Verdejo-Garcia, A.J., Perales, J.C., Perez-Garcia, M., 2007. Cognitive impulsivity in
cocaine and heroin polysubstance abusers. Addict. Behav. 32, 950-966. doi:
10.1016/j.addbeh.2006.06.032

Verdejo-Garcia, A.J., Perez-Garcia, M., 2007. Profile of executive deficits in cocaine
and heroin polysubstance users: Common and differential effects on separate

executive components. Psychopharmacol. 190, 517-530. doi: 10.1007/s00213-006-0632-8

Viechtbauer, W., Cheung, M.W.L., 2010. Outlier and influence diagnostics for meta-analysis. Research Synthesis Methods 1, 112-125. doi: 10.1002/jrsm.11

Wallis, J.D., 2007. Orbitofrontal cortex and its contribution to decision-making. Annu. Rev. Neurosci. 30, 31-56. doi: 10.1146/annurev.neuro.30.051606.094334

Wang, G.Y., Wouldes, T.A., Russell, B.R., 2013. Methadone Maintenance Treatment and Cognitive Function: A Systematic Review. Curr. Drug Abuse Rev. 6. doi: 10.2174/18744737112059990020

Wilson, M.J., Vassileva, J., 2016. Neurocognitive and psychiatric dimensions of hot, but not cool, impulsivity predict HIV sexual risk behaviors among drug users in protracted abstinence. Am. J. Drug Alcohol Abuse 42, 231-241. doi: 10.3109/00952990.2015.1121269

Yan, W.S., Li, Y.H., Xiao, L., Zhu, N., Bechara, A., Sui, N., 2014. Working memory and affective decision-making in addiction: A neurocognitive comparison between heroin addicts, pathological gamblers and healthy controls. Drug Alcohol Depend. 134, 194-200. doi: 10.1016/j.drugalcdep.2013.09.027

Yeh, T.L., Chen, K.C., Lin, S.H., Lee, I.H., Chen, P.S., Yao, W.J., Lee, S.Y., Yang, Y.K., Lu, R.B., Liao, M.H., Chiu, N.T., 2012. Availability of dopamine and serotonin transporters in opioid-dependent users--a two-isotope SPECT study. Psychopharmacol. 220, 55-64. doi: 10.1007/s00213-011-2454-6

Yuan, K., Qin, W., Dong, M., Liu, J., Sun, J., Liu, P., Zhang, Y., Wang, W., Wang, Y.L., Li, Q., 2010. Gray matter deficits and resting-state abnormalities in abstinent heroin-dependent individuals. Neurosci. Lett. 482, 101-105. doi: 10.1016/j.neulet.2010.07.005

Yuan, Y., Zhu, Z., Shi, J., Zou, Z., Yuan, F., Liu, Y.P., Lee, T.M.C., Weng, X., 2009. Gray matter density negatively correlates with duration of heroin use in young lifetime heroin-dependent individuals. Brain Cogn. 71, 223-228. doi: 10.1016/j.bandc.2009.08.014

Zaaijer, E.R., van Dijk, L., de Bruin, K., Goudriaan, A.E., Lammers, L.A., Koeter, M.W.J., van den Brink, W., Booij, J., 2015. Effect of extended-release

naltrexone on striatal dopamine transporter availability, depression and anhedonia in heroin-dependent patients. Psychopharmacol. 232, 2597-2607. doi: 10.1007/s00213-015-3891-4

Zakzanis, K.K., 2001. Statistics to tell the truth, the whole truth, and nothing but the truth: Formulae, illustrative numerical examples, and heuristic interpretation of effect size analyses for neuropsychological researchers. Arch. Clin. Neuropsychol. 16, 653-667. doi: 10.1016/S0887-6177(00)00076-7

Zeng, H., Lee, T.M., Waters, J., So, K.F., Sham, P.C., Schottenfeld, R., Marienfeld, C., Chawarski, M.C., 2013. Impulsivity, cognitive function, and their relationship in heroin-dependent individuals. J. Clin. Exp. Neuropsychol. 35, 897-905. doi: 10.1080/13803395.2013.828022

Zhang, X.L., Shi, J., Zhao, L.Y., Sun, L.L., Wang, J., Wang, G.B., Epstein, D.H., Lu, L., 2011. Effects of stress on decision-making deficits in formerly heroin-dependent patients after different durations of abstinence. Am. J. Psychiatry 168, 610-616. doi: 10.1176/appi.ajp.2010.10040499

Zhang, X.L., Wang, G.B., Zhao, L.Y., Sun, L.L., Wang, J., Wu, P., Lu, L., Shi, J., 2012. Clonidine improved laboratory-measured decision-making performance in abstinent heroin addicts. PLoS ONE 7, e29084-e29084. doi: 10.1371/journal.pone.0029084

DECISION-MAKING AND OPIATE USE

CHAPTER 4: Methodology for the Empirical Studies

4.1 Preamble

The previous chapter demonstrated that opiate users have relatively severe decision-making deficits, which were not accounted for by common co-morbidities such as head injury and poly drug dependence (see meta-analysis in Study 1). The next part of the thesis focuses on the empirical studies which analysed the emotion processing capacity of opiate users and how this relates to decision-making ability (Study 2), as well as opiate users' decision-making capacity under conditions of predictable risk (Study 3). More specifically, Study 2 measured the subjective and objective emotional response of opiate users and controls, and their ability to produce somatic markers when making decisions on the Iowa Gambling Task via physiological responsiveness (the skin conductance response). Study 3 measured decision-making under conditions of predictable risk using the Balloon Analogue Risk Task, in addition to measuring personality in both groups. The current chapter outlines the methodology adopted to test the aims of Studies 2 and 3. The results of these studies are then presented in Chapters 5 and 6.

DECISION-MAKING AND OPIATE USE

4.2 Research and Study Design

Two empirical studies were conducted (Studies 2 and 3). Both studies adopted a group-comparison, cross-sectional design that involved between-group comparisons comparing opiate users to healthy controls. Due to the difficulty of recruiting opiate-using participants willing to attend two separate testing sessions, the data for both studies was collected in a single session. This allowed for the recruitment of a sample larger than would have otherwise been likely for this population.

4.3 Participant Groups

Two participant groups were included. The first was composed of long-term opiate users enrolled in an opiate substitution program. The second was a group of healthy adult controls. All participants were screened for a number of inclusion and exclusion criteria. These are outlined below.

4.3.1 Eligibility criteria for opiate users

To be eligible for the studies, long-term opiate users had to meet the following inclusion criteria:

a) be at least 18 years of age;

b) have a history of heroin dependence;

c) be currently enrolled in an opiate substitution treatment program (methadone, buprenorphine or suboxone)[b];

d) be stable on their opiate substitute dose for at least two weeks; and

e) have English as a first language.

They were excluded if they had any of the following conditions:

f) a diagnosis of traumatic or acquired brain injury;

g) a history of stroke or epileptic seizures; and

h) current diagnosis of a psychiatric disorder (participants reporting diagnoses of anxiety and/or depression were not excluded, given the prevalence of these

---

[b] One opiate-using participant had recently stopped taking his opiate substitute dose, and so at the time of testing was only using street heroin.

diagnoses in this population, however other Axis I disorders such as schizophrenia or bipolar were excluded).

4.3.2 Eligibility criteria for healthy adults

Healthy adults had to meet the following criteria to be included in the study:

a) be at least 18 years of age; and

b) have English as a first language.

They were excluded if they had:

c) a history of alcohol or drug dependence (however, past experimental use of illicit drugs was tolerated);

d) a history of traumatic or acquired brain injury;

e) a history of stroke or epileptic seizures;

f) current or past periods of heavy drinking (i.e., regularly drinking to intoxication, or exceeding 28 standard drinks for a male per week, or 14 standard drinks for a female per week, as per the guidelines set out by the Australian National Health and Medical Research Council (2001)); and

g) a formal psychiatric diagnosis (including depression or anxiety).

4.3.3 Participant recruitment

Healthy control participants were recruited through personal networks, social media, classified advertisements (e.g., Gumtree), and via flyers posted in public spaces that healthy adults attended (such as gyms, libraries and community centres; see Appendix B 3.1 for a copy of the flyer). Opiate users were recruited from pharmacies that dispensed opiate substitute treatments (e.g., methadone) via flyers (see Appendix B 3.2 for a copy of the flyer). It was at the discretion of the opiate-dispensing pharmacist where these flyers were placed, however most left them in the dispensing room. Flyers encouraged all potential participants to call or send a text message to the dedicated research phone used by the PhD candidate. Potential participants were then contacted and screened over the phone and booked for testing.

DECISION-MAKING AND OPIATE USE

4.3.4 Protocols for the day of testing

Participants who met criteria for inclusion were informed of further inclusion criteria for the day of testing that they were required to adhere to. For all participants these were:

a) Not to use any illicit drugs for 24 hours before the testing session.

For opiate users, additional inclusion criteria for the day of testing were:

b) Not to take their opiate substitute dose for 3 hours before the session to ensure peak concentration of the opiate substitute in the body did not occur during the session. Participants were generally encouraged to take their dose early in the morning if they were booked for testing in the afternoon, or to wait to take their dose until after the testing session if they had a morning testing session.

Participants who did not meet these criteria on the day of testing completed whole or part of the testing protocols but were excluded from further analyses.

4.3.5 Participants included in the empirical studies

Figure 3 presents a flow chart describing the recruitment process and the final number of participants included in each study. In total, 31 opiate users and 43 controls provided valid data for studies 2 and 3.

DECISION-MAKING AND OPIATE USE

INCLUDED   **EXCLUDED**

Number of potential participants who contacted the researcher expressing interest in the study:

Opiate n = 104
Control n = 76

Controls excluded for not meeting inclusion/exclusion criteria (via telephone interview):
- History of substance use = 3
- Psychiatric diagnosis (e.g. depression) = 4
- Younger than 35 years old = 15
- Other issues (e.g. did not think $30 reimbursement was adequate, did not want to travel to Fitzroy) = 4
Control n = 26

Opiate users excluded for not meeting inclusion/exclusion criteria (via telephone interview):
- Current diagnosis of severe psychiatric disorder (e.g. schizophrenia, bipolar) = 10
- Diagnosis of a neurological condition (ABI, stroke, epilepsy) = 13
- Not current opiate user (i.e. only using amphetamines) = 1
- Could not re-contact after initial call/text = 11
- Refused participation after contact = 2
Opiate n = 37

Number of participants who met inclusion/exclusion criteria and were booked in for a testing session:

Opiate n = 67
Control n = 50

Participants who were booked in for a testing session but did not attend:
- Opiate users who did not attend without prior notice (no-show) = 17
- Opiate users who cancelled but did not re-book = 12
- Controls who cancelled but did not re-book = 6
Total n = 35

Number of participants who attended a testing session:

Opiate n = 38
Control n = 44

Participants excluded from analyses:
- Opiate users not included in any analyses due to having used illicit drugs in the 24 hours prior = 3
- Opiate users not included in analyses due to neurological or psychiatric diagnosis = 4
- Controls not included in any analyses due significant history of drug use (i.e. found out after completion of demographics questionnaire) = 1
Total n = 8

Number of participants with valid data for study 2 and/or 3:

Opiate n = 31
Control n = 43

Figure 3. Flowchart of participant inclusion and exclusion process.

4.4 Procedure

Figure 4 provides an overview of the assessment procedures during each testing session. At the start of each testing session, participants were given an information letter to read which outlined the details of the study (see Appendix B-1). Once the participants had read this, they were given a consent form to sign (see Appendix B-2) which confirmed their agreement to participate. Following consent, participants were asked to verbally complete a background questionnaire to confirm they met all eligibility criteria (e.g., that they had not taken illicit substances 24 hours prior to testing, and had not taken an opiate substitute less than 3 hours prior to testing), and to gather demographic information and drug use history. Following this, participants completed a measure of general (premorbid) intelligence (the National Adult Reading Task (NART); Nelson, 1982), a questionnaire assessing personality (the Behavioural Activation/Behavioural Inhibition scale (BAS/BIS); Carver & White, 1994) and a measure of anxiety and depression symptoms (the Hospital Anxiety and Depression Scale (HADS); Zigmond & Snaith, 1983).

Following completion of the background questionnaire, NART, BAS/BIS and HADS, participants were prepared for the physiological recordings of skin conductance (SCR) and heart beat (see section 4.6.1 below: 'Equipment set-up and preparation of electrode sites'). After this, participants completed an interoceptive accuracy test while heart beats were recorded. Participants then completed a measure of ambiguous decision-making (i.e., the IGT) while the skin conductance response was recorded. Following this, participants rated subjective emotional experience in response to a series of emotion-eliciting videos while skin conductance was recorded. Once these tasks were completed, electrodes were removed. Next, participants completed a measure of risky decision-making (i.e., the BART). Following this, participants were given a break and then returned to the testing room, and measurement of cognitive functioning (using the CogState battery of tests) was completed. Participants were then thanked and paid $30AUD for participating. Details of the measures administered are described next.
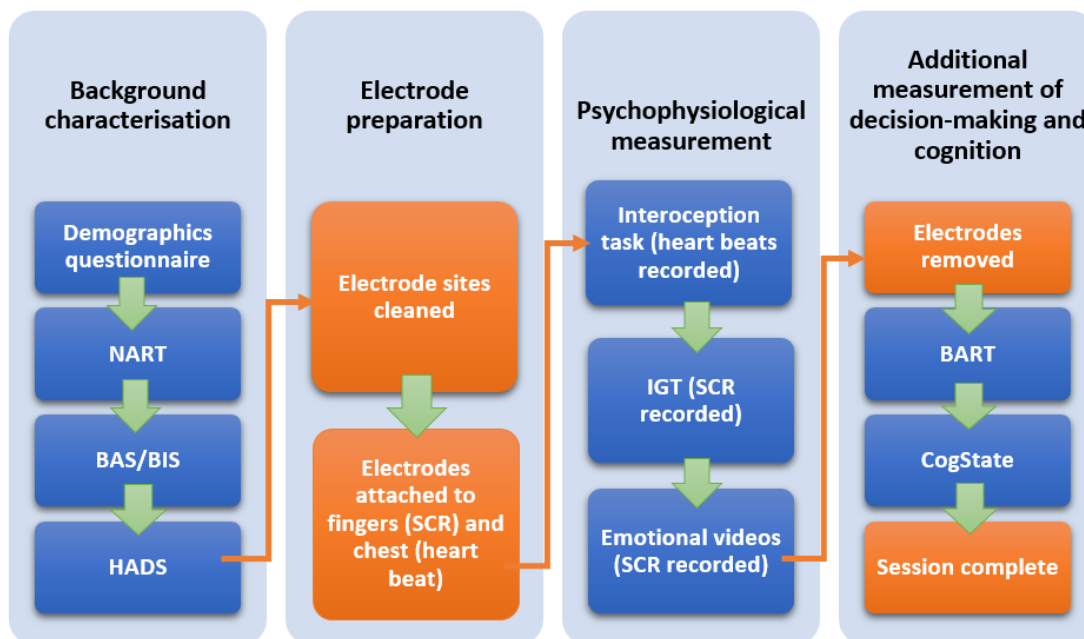
Figure 4. Measures administered at each stage of the assessment.

4.5 Background Characterisation Measures (Studies 2 and 3)

4.5.1 Demographics and drug-use questionnaire

A questionnaire was designed to collect background information for opiate users and controls across both empirical studies. This questionnaire collected data regarding demographics, such as age, sex and years of education. This questionnaire also collected detailed drug use history for all participants, and opiate substitute treatment history for opiate users. It also included a set of questions addressing eligibility criteria for the study (including questions about drug use in the 24 hours prior to testing). This set of eligibility questions was modified for each group. Appendix C-1 provides the questionnaire for opiate users and controls.

4.5.2 General intelligence

General (premorbid) intelligence was assessed using the *National Adult Reading Test* (NART; Nelson, 1982). It is a highly reliable word-recognition test that provides an estimate of pre-morbid IQ (Crawford, Deary, Starr, & Whalley, 2001; Crawford, Stewart, Cochrane, Parker, & Besson, 1989). Participants must read 50 English words with phonetically atypical pronunciation (e.g., cellist) and are scored on pronunciation. The number of words correctly pronounced was converted to an estimate of full-scale

IQ using formulas provided in the test manual. Higher scores indicate better performance.

4.5.3 General cognitive function

The following measures of cognitive function were used to characterise opiate users and controls.

Response initiation and suppression. Initiation and suppression of cognitive responses, which is an aspect of executive function, was measured using the *Hayling Sentence Completion Task* (Burgess & Shallice, 1996). In this task, participants were read a series of sentences by the examiner with the last word omitted, and were instructed to complete each sentence. Participants were required to give a connected answer (initiation) in part A (e.g., He posted a letter without a STAMP), and an unconnected response (suppression) in part B (e.g., The captain wanted to stay with the sinking BANANA). The time taken to respond was recorded. Scores for Part A and B and the total number of errors were summed to give an overall efficiency score, with higher scores indicating greater efficiency. The Hayling task has demonstrated modest ecological validity and reliability (Burgess & Shallice, 1996; Odhuba, Broek, & Johns, 2005).

Cognitive flexibility and working memory. Two additional aspects of cognitive function were assessed using the CogState battery of measures (Cogstate Research™, Cogstate Ltd 2009). This computerized battery is tailored to suit individual study needs, and researchers select specific tasks to be included in their study battery. The CogState measures of cognitive function have been shown to have good construct validity in clinical and healthy populations (Maruff et al., 2009; Pietrzak et al., 2009). For the current study, the Set Shift and Two-Back tasks were used.

Set Shift was used to assess cognitive flexibility, i.e., the ability to adapt to changing rules. In this task, participants must determine whether a series of cards contains a target stimulus according to one of two dimensions (a colour or a number). A single playing card was presented in the middle of the screen, and the participant was asked to guess whether the presented card was the 'correct' card. Above the card, either "Colour" or "Number" was written, indicating to the participant which dimension was being assessed (i.e., numbers on the card, or red vs black). Participants made choices using the 'Yes' (K) or 'No' (D) keys. As participants made their choices, the program

signalled whether the choice was correct (flip over to the next card) or incorrect (error sound). As trials continued, the dimensions being assessed changed, so that there were changes in target colour (e.g., red to black) or number (e.g., 2 to 7; intra-dimensional shift) or between dimensions (e.g., from colour to number; extra-dimensional shift). The participant was not told when these dimension shifts occurred, and had to re-learn new 'rules' as the task continued. The main index of performance was number of errors, with less errors indicating better performance.

Working memory was assessed using the *Two-Back Task*. In this task, a series of playing cards was presented, one at a time, face up in the centre of the screen. The participant had to decide whether the card currently presented was identical to the one presented two cards before. Participants made selections using the 'Yes' (K) or 'No' (D) keys and correct choices were signalled by cards flipping over, while incorrect choices were signalled by an error sound. A higher accuracy score indicated better performance.

4.5.4 Anxiety and depression

Anxiety and depression symptoms were measured using the *Hospital Anxiety and Depression Scale* (HADS; Zigmond & Snaith, 1983). This is a widely used self-report measure of anxiety and depression in adults. Participants respond to a series of 14 statements such as "I can laugh and see the funny side of things" on a 4-point scale from "very often" to "not at all". Given that opiate users tend to have concurrent psychiatric disorders, the most common of which are depression and anxiety (Astals et al., 2008), this measure was used to characterise the opiate-using sample. The HADS has been shown to be a valid and sensitive indicator of depression and anxiety in both clinical and healthy samples (Bjelland, Dahl, Haug, & Neckelmann, 2002).

4.6 Characteristics of Included Participants

Table 3 presents the demographic information, anxiety and depression symptoms, and scores on tasks of neuropsychological function for the opiate users and controls who were included in studies 2 and 3 of this thesis. Opiate users had significantly fewer years of education and lower estimated IQ than controls, and significantly higher depression and anxiety symptoms. Opiate users' cognitive ability did not differ from controls' in terms of initiation/suppression and cognitive flexibility, but opiate users did demonstrate significantly worse working memory than controls. Given this, performance on the two back task and performance on the IGT and BART were

DECISION-MAKING AND OPIATE USE

correlated separately for opiate users and controls. Results indicated no significant correlation between working memory and decision-making performance for either group (all p's $\geq$ .152). Thus, working memory was not included as a co-variate in the group-comparison analyses of decision-making performance (Tabachnick & Fidell, 2013).

Table 2.

Background Characteristics of All Included Participants for Studies 2 and 3

	Opiate Group $n = 31$		Control Group $n = 43$			
Proportion of men (%)	84%		53%			
	M	*SD*	*M*	*SD*	*t*	*d*
Age (years)	41.94	7.67	39.05	8.20	1.54	0.36
Education (years)	12.58	2.22	16.65	2.66	6.95[***]	1.66
Premorbid IQ[a]	101.40	9.19	105.71	8.73	2.04[*]	0.48
Anxiety and Depression Symptoms						
Depression[b]	6.63	3.48	2.93	2.38	5.43[***]	1.24
Anxiety[b]	9.58	3.41	6.49	3.48	3.85[***]	0.90
Cognitive function						
Initiation and suppression[c]	5.63	1.50	5.66	1.14	0.07	0.02
Cognitive flexibility[d]	27.38	16.38	24.77	15.60	0.65	0.16
Working memory[e]	0.85	0.26	1.15	0.80	5.39[***]	0.50

[a] Pre-morbid IQ score as predicted from the number of errors made on the NART

[b] Hospital Anxiety and Depression Scale subscale scores for anxiety and depression—range of scores was 0–21 for each subscale, 0–7 normal, 8–10 possible disorder and 11–21 presence of disorder

[c] Hayling Sentence Completion Task overall scaled score

[d] Set shift task number of errors

[e] Two-back task accuracy score

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

DECISION-MAKING AND OPIATE USE

4.7 Measures for Study 2

4.7.1 Iowa Gambling Task

In Study 2, ambiguous decision-making ability was assessed using the IGT (Bechara et al., 1994). The objective of this task is to earn as much money as possible over a series of trials. In the original version of this task, participants are told they have a balance of $2000 to play with in the game (note: they are told that the money is not real). They are instructed to maximize the amount of money that they win over the course of 100 trials by selecting cards from four decks (labelled A, B, C and D). Each card has a reward value, and some of the cards also have a punishment value. For decks A and B, the reward value is $100. For decks C and D, the reward value is $50. However, punishments vary across decks and also vary in frequency. For deck A, punishments are frequent, but not large ($150 to $350). For deck B, punishments are infrequent but large ($1250). Similarly, for deck C, punishments are frequent and small ($25 to $75) whereas punishments in deck D are infrequent and large ($250). The schedule of punishment and rewards leads to decks being deemed "advantageous" (C and D) or "disadvantageous" (A and B), as repeated selection from "advantageous" decks leads to a net gain whereas repeated selection from "disadvantageous" decks leads to a net loss.

A computerised version of the IGT was used, with the same schedule of rewards and punishments as described in Table 3 (for the first 20 choices), in order to replicate the methods originally used by Bechara and colleagues as closely as possible. This schedule was chosen to ensure that the outcome of decisions remained ambiguous, thereby allowing for the development of anticipatory somatic markers (Bechara & Damasio, 2005; Bechara et al., 2001; Bechara, Tranel, & Damasio, 2000). However, decks were labelled 1, 2, 3 and 4, and each of these decks corresponded with a lettered deck as in the original version (1=A, 2=C, 3=B, 4=D). Participants' wins and losses along with the running total were displayed for the entire 12 second inter-trial interval (see Figure 5). This interval was necessary in order to allow for an adequate amount of time to collect skin conductance data before and after choices (see section 4.9.2 below). Participants selected decks using keys 1,2,3, and ENTER (decks 1,2,3, and 4 respectively) on the right-hand side of the keyboard. This was to minimize movement throughout the game, thus allowing for cleaner recording of physiological signals.
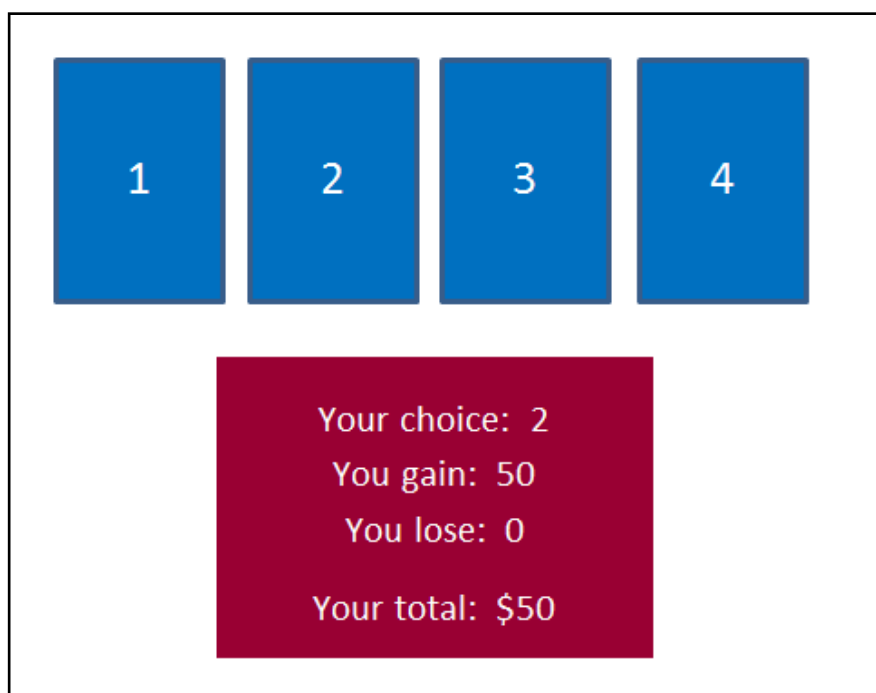
Figure 5. Iowa Gambling Task as presented to participants via Presentation 18.0.

Decision-making ability was indexed using the net score. This is the number of selections from advantageous minus the number of selections from disadvantageous decks [(C+D) – (A+B)]. Higher values indicate better decision-making. Participants who select more often from disadvantageous than advantageous decks receive net scores below 0 and are considered to have poor or impaired decision-making skills. Selecting from more advantageous than disadvantages decks results in a net score above 0, and participants with positive scores are considered to perform in the "normal" or unimpaired range. The IGT is sensitive to decision-making impairment in populations with impaired frontal lobe function (Dunn, Dalgleish, & Lawrence, 2006), including in opiate users (e.g., Barry & Petry, 2008; Li, Li, et al., 2013; Ma et al., 2015), and has been found to measure a unique aspect of decision-making relative to other decision-making measures (Buelow & Blaine, 2015).

DECISION-MAKING AND OPIATE USE

Table 3.

Schedule of Rewards and Punishments for the First 20 Selections from Each Deck of the IGT (adapted from Bechara et al., 1994; Chiu et al., 2008)

Deck	A		B		C		D	
Selection	Rew	Pun	Rew	Pun	Rew	Pun	Rew	Pun
1	100		100		50		50	
2	100		100		50		50	
3	100	-150	100		50	-50	50	
4	100		100		50		50	
5	100	-300	100		50	-50	50	
6	100		100		50		50	
7	100	-200	100		50	-50	50	
8	100		100		50		50	
9	100	-250	100	-1250	50	-50	50	
10	100	-350	100		50	-50	50	-250
Net outcome after 10 cards		-250		-250		250		250
11	100		100		50		50	
12	100	-350	100		50	-25	50	
13	100		100		50	-75	50	
14	100	-250	100	-1250	50		50	
15	100	-200	100		50		50	
16	100		100		50		50	
17	100	-300	100		50	-25	50	
18	100	-150	100		50	-75	50	
19	100		100		50		50	
20	100		100		50	-50	50	-250
Net outcome after 10 cards		-250		-250		250		250

4.7.2 Emotional experience measure

Study 2 assessed the emotional responses of opiate users and controls in response to dynamic stimuli. Eight short video clips were presented to participants, which were designed to elicit positive, negative and neutral emotions. Emotional responses to these video clips were measured both subjectively, using a self-report rating scale involving the Self-Assessment Manikin (see Figure 6), and objectively, using the skin conductance response (see section 4.9.2 below). The video clips were obtained from movies, TV shows and YouTube, and were 30-120 minutes in duration, with some clips (e.g., The Champ, Mr Bean) used in prior published studies (Mergl, Mavrogiorgou, Hegerl, & Juckel, 2005; Nasoz, Alvarez, Lisetti, & Finkelstein, 2004). Videos were presented using Presentation 18.0 software and were presented in a set order so that a

DECISION-MAKING AND OPIATE USE

neutral video always preceded and followed a positive or negative clip. All of the videos were piloted on a separate group of 8 healthy control participants within our laboratory. The videos successfully elicited the target emotions in the pilot participants (i.e., the positive videos were rated as more pleasant and arousing than neutral videos, and negative videos were rated as less pleasant and more arousing than neutral videos).
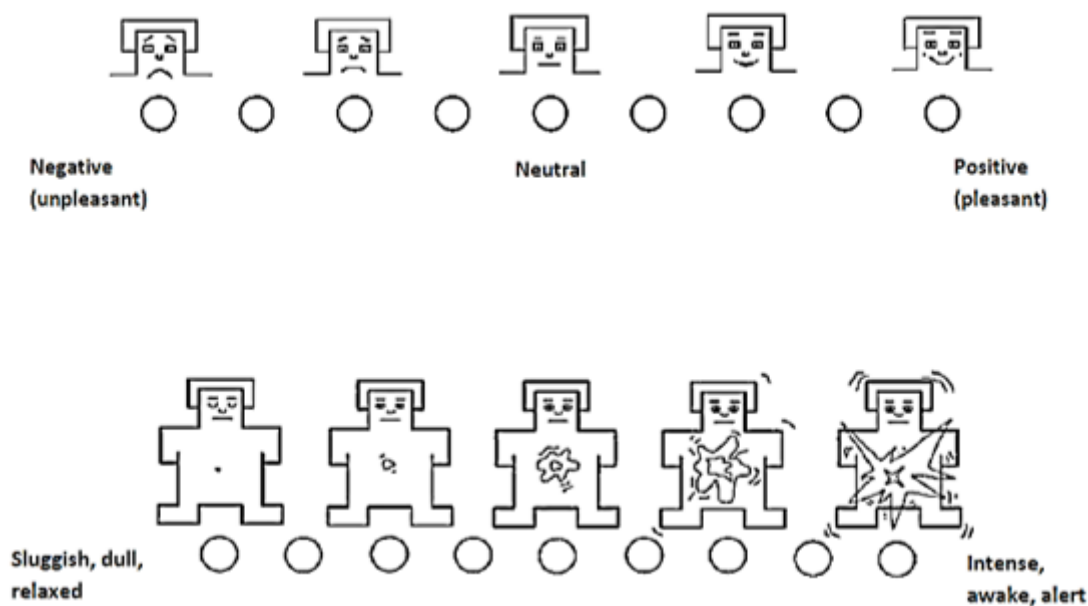
Figure 6. Self-Assessment Manikin used for the subjective emotional rating task (adapted from Bradley & Lang, 1994).

4.7.3 Interoceptive accuracy task

In Study 2, interoceptive accuracy was measured using the heartbeat detection task as described in Schandry, Bestler, and Montoya (1993) and Werner et al. (2009). Participants were instructed to silently count their heart beats when the experimenter gave the signal to begin, and to stop counting when the experimenter told them to stop. Participants were instructed to only concentrate on their heartbeat, and were not allowed to take their pulse or use any other manipulations (such as touching the chest) to help detect their heartbeats. There were three periods of measurement, lasting 25, 35 and 45 seconds respectively, with a 30 second break between each period of measurement. Heartbeat was measured continuously throughout each of these periods via electrodes attached to the chest and recorded in AcqKnowledge (see section 4.9 below). The

DECISION-MAKING AND OPIATE USE

number of heart beats recorded in AcqKnowledge for each period was counted. Using the method outlined in Werner et al. (2009) and Pollatos and Schandry (2008), interoceptive accuracy was calculated using the following equation:

$$Interoceptive\ accuracy = \frac{1}{3}\sum\left(1 - \frac{|actual\ heartbearts - reported\ heartbeats|}{actual\ heartbeats}\right)$$

Higher scores indicated better interoceptive accuracy. Results regarding these data are presented at the end of Chapter 5 (section 5.8).

4.8 Measures for Study 3

4.8.1 Balloon Analogue Risk Task

In Study 3, decision-making under conditions of risk was measured using the BART (Lejuez et al., 2002), which is a reliable measure of decision-making under conditions of calculable risk (Hunt, Hopko, Bare, Lejuez, & Robinson, 2005). The BART was presented on Inquisit 4.0 software. Participants were shown images of 30 balloons, presented individually a computer screen. Participants 'pumped' each balloon by clicking on a button (*Pump Balloon*) below it. Each pump inflated the balloon 1 degree (0.3cm in all directions) and earnt the participant 5 cents of imaginary money, which was placed in a temporary bank. The more the participant inflated the balloon, the more money they received. This money was held in the temporary bank until the person decided to 'collect' that money (by pressing the '*Collect $$$*' button shown in Figure 7) and transfer it to a permanent bank (see Figure 7). However, for each trial, the balloon was randomly allocated a certain number of pumps after which the balloon would explode. If the participant reached this explosion point, the balloon exploded and the participant lost the money accrued in their temporary bank for that trial. The probably of the balloon exploding was randomly set for each trial (so the balloon could pop anywhere from 1 to 128 pumps), and the probability of the balloon exploding increased with each additional pump. In other words, the probability that the balloon would explode on the first pump was 1/128, but if the balloon did not explode, the probability of exploding would be 1/127 on the second pump, 1/126 on the third pump etc., until the 128th pump where the probability of an explosion was 1/1 (i.e., 100%). Consequently, a higher numbers of pumps indicated more risky decision-making. Because the number of pumps is constrained on trials where the balloon explodes, the

developers of the task recommend the use of the *adjusted score* to index risky decision-making – that is, the average number of pumps across unexploded balloons. Therefore, the current study used the adjusted score as the measure of decision-making under conditions of risk. The BART has demonstrated good incremental and construct validity in healthy and clinical populations (Hunt et al., 2005; Lejuez et al., 2002).

Potential earnings: $2.30
Number of pumps: 46
Total Winnings: $3.70

Pump up the balloon

Collect $$$
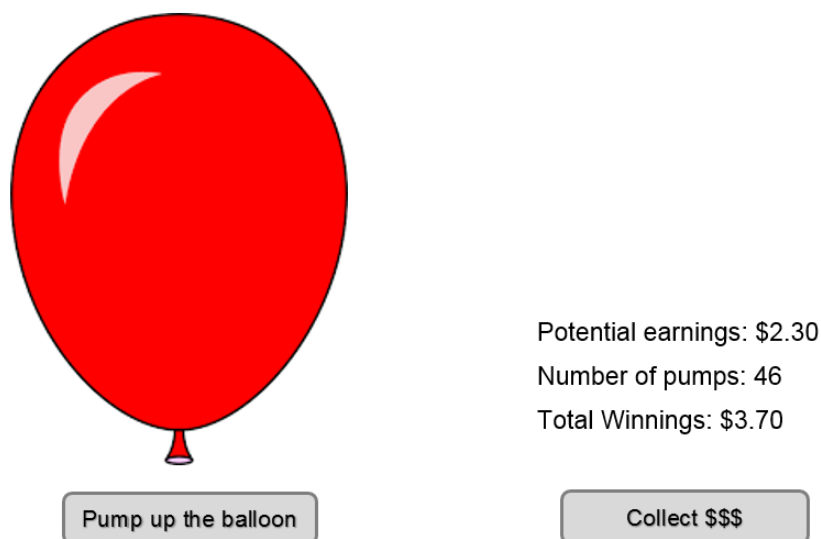
Figure 7. BART presentation screen as presented via Inquisit 4.0.

4.8.2 Behavioural Activation and Inhibition System scale.

In Study 3, sensitivity to punishment and reward was measured using the BAS/BIS scale (Carver & White, 1994), which is a frequently used personality measure. The 24-item scale measures sensitivity to reward on 3 subscales: *Reward Response* (BAS-RR), which focuses on positive responses to the occurrence or anticipation of reward, *Fun Seeking* (BAS-FS), which measures willingness to approach rewarding events on the spur of the moment, and *Drive* (BAS-D), which measures persistent pursuit of goals. The BIS measures sensitivity to punishment. Participants rate answers to each item on a four point Likert scale, ranging from 1 ('strongly disagree') to 4 ('strongly agree'). For example, "I'm always willing to try something new if I think it will be fun". The purpose of including this measure was to provide a personality-based measure of impulsivity, as reward responsiveness may lead to drug dependence (Dawe, Gullo, & Loxton, 2004; Dawe & Loxton, 2004) and opiate users have been shown to be

DECISION-MAKING AND OPIATE USE

more responsive to reward than controls (Dissabandara, Loxton, Dias, Daglish, & Stadlin, 2012; Dissabandara et al., 2014). The BAS/BIS scale has demonstrated good reliability (Cronbach's alpha for BIS = 0.78 and for BAS =0.81) and validity as a measure of personality traits (Cooper, Gomez, & Aucote, 2007; Jorm et al., 1998).

4.9 Psychophysiological Measurement and Analysis

In Study 2, the aims were to determine whether opiate users displayed abnormal emotional responses to emotional stimuli (videos), abnormal emotional responses to reward and punishment (during the IGT), and reduced anticipatory somatic markers (during the IGT). An additional aim was to analyse whether opiate users demonstrated reduced interoceptive accuracy. Objective emotional response and anticipatory somatic markers were measured through psychophysiological arousal, specifically the skin conductance response (SCR), while interoceptive accuracy was measured using heart beat tracking. The methods for collecting, extracting, cleaning and analysing this data, are detailed in the following sections (sections 4.6.1 to 4.6.3).

4.9.1 Equipment set-up and preparation of electrode sites.

All psychophysiological data was collected using the Biopac MP150 data acquisition system (Biopac, Goleta, GA). Skin conductance data was acquired via one GSR100C amplifier and heart beat data was acquired via one ECG100C amplifier. Shielded Ag/Ag-CL reusable electrodes were used for all recordings. Large (8mm) electrodes were used to acquire heart beat data, and finger electrodes with a plastic plate and Velcro straps were used for skin conductance acquisition. The skin conductance electrodes acted as ground for all participants. Ground electrodes are necessary in physiological data acquisition in order to reduce unwanted signals (Türker, Miles, & Le, 1988). Data was acquired at 1000Hz for all physiological measures. For the ECG100C amplifier, GAIN was set to 1000, HP to 0.5Hz and MODE to NORM (according to the recommendations of Biopac Application Note 233). The GSR100C amplifier low pass filter was set to 1.0Hz and no high pass filters were applied (i.e. all HP filters were set to DC) (Figner & Murphy, 2011).

Before electrodes were attached, each participant had their skin prepared in a specific manner, to ensure that the contact between skin and electrode was sufficient. Specifically:

DECISION-MAKING AND OPIATE USE

1) Skin was cleansed using a cleansing wipe (i.e., make-up wipe) to remove any grease and/or make-up from the skin,

2) Skin was exfoliated using a small piece of mildly abrasive sponge to remove dead skin cells. This step is critical in ensuring a clear signal is received from the skin,

3) Skin was cleansed again with NuPrep skin preparation gel (Weaver and Company),

4) Electrodes were filled with a conductive electrolyte gel to allow conductance of electrical signals between electrode plate and the skin and a double-sided adhesive collar was attached to the electrode. This was then used to attach the electrode to the participant's skin,

5) The electrodes were allowed to sit on the participant's skin for up to 5 minutes before recording began, to allow the gel to soak into the skin and become more conductive.

Skin conductance electrodes were attached to the distal phalanges of the first and second finger of the left hand, as these areas are more sensitive and produce higher SCR signals than other areas of the hand (Boucsein, 2012). The use of the left hand was necessary so that participants could use their right hand to select keys (make choices) during the IGT. Electrodes to measure heart beats were placed in a modified lead-II position, with one electrode place underneath the middle of the right collar bone (over the right carotid artery), and the other electrode placed on the second intercostal space on the ribs of the left side (Dellacherie, Roy, Hugueville, Peretz, & Samson, 2011). All electrodes were fixed in place using a double-sided adhesive collar.

4.9.2 Skin conductance response: data cleaning, extraction and analysis.

Skin conductance data was collected continuously throughout the IGT (to index both emotional response to reward and punishment as well as anticipatory somatic marking) and emotional videos tasks (to index objective emotional response to general emotional stimuli). The raw data recorded during these tasks was filtered and cleaned prior to analysis. The sections below outline the filtering of the raw SCR data and the methods of extraction and analysis for each task.

DECISION-MAKING AND OPIATE USE

Cleaning of raw SCR data

First, the raw skin conductance data for both tasks was filtered with a smoothing transformation to remove high-frequency noise. Second, the smoothed data was run through a moving-difference function to eliminate down-drift in the skin conductance signal (as outlined in Fernie & Tunney, 2013; Naqvi & Bechara, 2006). More specifically, the difference function converted every point of the raw skin conductance wave into a point representing the difference between its value and the value of a point located at a given interval before it (in this case 50msec, calculated based on a 200Hz sampling rate). This step was carried out to remove the drift in baseline skin conductance level that occurs over any period of time the SCR is recorded. Thus, a separate baseline is not needed when using this method of data extraction for the SCR (i.e., the SCR acts as its own baseline).

SCR data extraction and analysis for the IGT

Filtered skin conductance data was extracted for the 5 seconds preceding a choice and the 5 seconds following a choice on the IGT using the Area function in the AcqKnowledge software. Area values were then divided by 5 to calculate an area under the curve value in μS/sec (see Fernie & Tunney, 2006; Naqvi & Bechara, 2006). Consistent with previous studies (Bechara & Damasio, 2002; Bechara et al., 1999; Cavedini et al., 2012; Elvemo, Nilsen, Landrø, Borchgrevink, & Håberg, 2014; Fernie & Tunney, 2013; Guillaume et al., 2009; Miu, Heilman, & Houser, 2008; Wagar & Dixon, 2006), *anticipatory SCR* was calculated separately for advantageous and disadvantageous deck selections for the 5 seconds preceding a choice on the IGT. *Post-choice SCR* was calculated separately for deck selections resulting in gaining money without penalty (reward SCR) and selections resulting in gaining money followed by a loss (punishment SCR), also for the 5 seconds following a choice. In addition to this, a *relative difference score* was calculated for the anticipatory SCR. This was done in order to determine the magnitude of the difference between the anticipatory SCR before disadvantageous decisions, relative to the anticipatory SCR before advantageous decisions, using the following equation:

$$Relative\ difference = \frac{\text{Disadvantageous anticipatory SCR} - \text{Advantageous anticipatory SCR}}{\text{Advantageous anticipatory SCR}}$$

SCR data extraction and analysis for the emotional videos task

Each video was divided into 5 second epochs and the area of the SCR was extracted for each of these epochs. Area values were then divided by 5 to calculate an area under the curve value in μS/sec for each epoch. Epochs were excluded from analysis if movement artefacts were present. After cleaning the data, remaining epochs were used to calculate an *average* area under the curve value for each emotional video. These values were then used to calculate an average SCR for each category of emotional video (positive, negative and neutral).

4.9.3 Heart beat: data extraction and analysis.

Heart beat data was recorded continuously throughout the interoception task. Markers were set manually in the heart beat wave to signal the beginning and ending of each time period. Heart beats were manually counted for each time period and interoceptive accuracy was calculated using the formula described in section 4.7.3: 'Interoceptive accuracy task'.

4.10 General Statistical Analyses

Details of all statistical analyses are included within the methods section of each experimental papers in Chapters 5 and 6. The Statistical Package for the Social Sciences (SPSS), version 23.0 for Windows (IBM Corp), was used to conduct all statistical analyses for behavioural and physiological data.

CHAPTER 5: Study 2 - Investigation of Somatic Markers and Emotion Activation in Opiate Use

5.1 Preamble

As previously outlined in Chapter 2, the somatic marker hypothesis may be used to help explain the decision-making impairment in opiate users. While the meta-analysis presented in Chapter 3 clarified the magnitude of the decision-making impairment in opiate users, the mechanism for this impairment has not been thoroughly explored. The somatic marker hypothesis may be a good candidate to explain the mechanism underlying the decision-making impairment in opiate users. Opiate users are known to have structural and functional abnormalities in the areas of the brain responsible for responding to emotional stimuli (i.e., the orbitofrontal cortex), which in turn could lead to deficits in emotional processing. The somatic marker hypothesis contends that emotional responses to punishments and rewards are critical to the development of anticipatory warning signals or "somatic markers" which then inform choices during decision-making. Thus, the decision-making impairment in opiate users may be due to a reduced capacity to respond to emotion-inducing stimuli, such as punishments and rewards, thereby leading to an inability to produce somatic makers which should steer decision-making away from disadvantageous choices. Alternatively, opiate users may develop normal anticipatory somatic markers but, due to poor interoceptive ability, may be less able to "hear" or tune into these physiological changes, which may lead to impaired decision-making ability. The study presented in this chapter had two aims. The first aim was to assess whether deficient emotional responding and somatic marking (as indexed by the skin conductance response) contributed to the decision-making impairment in opiate users relative to a group of healthy controls. The second aim was to assess whether poor interoceptive abilities contributed to the decision-making impairment in opiate users relative to a group of healthy controls. It should be noted that the data presented in this chapter has fewer participants than described in the methods chapter, as not all participants completed both the Iowa Gambling Task for Study 2 and Balloon Analogue Risk Task for Study 3.

This chapter is presented in two parts. The first part (sections 5.3 to 5.8), which assessed the first aim, has been published in the journal *Psychopharmacology*:

DECISION-MAKING AND OPIATE USE

Biernacki, K., Terrett, G., McLennan, S. N., Labuschagne, I., Morton, P., Rendell, P. G. (2018). Decision-making, somatic markers and emotion processing in opiate users. *Psychopharmacology, 235*(1), 223-232. doi: 10.1007/s00213-017-4760-0

The second part (section 5.9) addresses the second aim regarding interoception. This second set of results was not included in the published manuscript, and is presented after the discussion for the published paper.

DECISION-MAKING AND OPIATE USE

5.2 Statement of Contribution for Publication 2

I acknowledge that my contribution to the paper is 50%

Name: Kathryn Biernacki

Signature:

I acknowledge that my contribution to the paper is 20%

Name: Gill Terrett

Signature:

I acknowledge that my contribution to the paper is 10%

Name: Skye N. McLennan
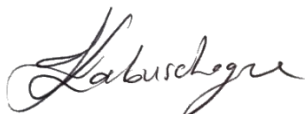
Signature:

I acknowledge that my contribution to the paper is 10%

Name: Izelle Labuschagne

Signature:

DECISION-MAKING AND OPIATE USE
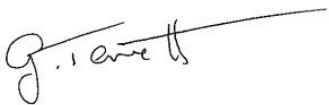
I acknowledge that my contribution to the paper is 5%

Name: Phoebe Morton
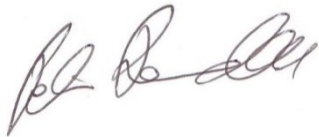
Signature:

I acknowledge that my contribution to the paper is 5%

Name: Peter G. Rendell

Signature:

DECISION-MAKING AND OPIATE USE

5.3 Abstract

Rationale Opiate use is associated with deficits in decision-making. A possible explanation for these deficits is provided by the somatic marker hypothesis, which suggests that substance users may experience abnormal emotional responses during decision-making involving reward and punishment. This in turn may interfere with the brief physiological arousal, i.e., somatic markers that normally occurs in anticipation of risky decisions. To date, the applicability of the somatic marker hypothesis to explain decision-making deficits has not been investigated in opiate users.

Objectives This study assessed whether decision-making deficits in opiate users were related to abnormal emotional responses and reduced somatic markers.

Methods Opiate users enrolled in an opiate substitute treatment program ($n = 28$) and healthy controls ($n = 32$) completed the Iowa Gambling Task (IGT) while their skin conductance responses (SCRs) were recorded. Participants' emotional responses to emotion-eliciting videos were also recorded using SCRs and subjective ratings.

Results Opiate users displayed poorer decision-making on the IGT than did controls. However, there were no differences between the groups in SCRs; both groups displayed stronger SCRs following punishment than following reward, and both groups displayed stronger anticipatory SCRs prior to disadvantageous decisions than advantageous decisions. There were no group differences in objective or subjective measures of emotional responses to the videos.

Conclusions The results suggest that deficits in emotional responsiveness are not apparent in opiate users who are receiving pharmacological treatment. Thus, the somatic marker hypothesis does not provide a good explanation for the decision-making deficits in this group.

Keywords: Opiate, heroin, decision-making, somatic marker, skin conductance, emotion experience

DECISION-MAKING AND OPIATE USE

5.4 Introduction

Opiates belong to one of the most addictive classes of drugs (Dacher and Nugent 2011). In addition to numerous health issues (Pillari and Narus 1973; Ryan and White 1996; Webster et al. 1979), opiate use has been associated with abnormalities in the structure and function of the frontal lobe of the brain (Pandria et al. 2016; Wollman et al. 2016; Wollman et al. 2015), and with a range of cognitive deficits (Baldacchino et al. 2017; Baldacchino et al. 2012). Of these cognitive deficits, impaired decision-making is the most consistently reported (Baldacchino et al. 2012). In opiate users, poor decision-making can manifest as problematic real life behaviours such as risky sexual practices, leading to increased risk of HIV (Wilson and Vassileva 2016), and to a reduced ability to maintain abstinence (Passetti et al. 2008). A better understanding of the factors that contribute to decision-making impairments is needed to provide more targeted support and better outcomes for opiate users.

The somatic marker hypothesis (Damasio 1994) is a theoretical model that was developed to explain decision-making impairment in people with orbitofrontal cortex injuries, but has recently been argued to also have utility in explaining poor decision-making in substance users (Bechara and Damasio 2002; Verdejo-Garcia and Bechara 2009; Verdejo-Garcia et al. 2006; Verdejo-Garcia et al. 2007). The somatic marker hypothesis contends that orbitofrontal cortex dysfunction leads to abnormalities in emotional responding which, in turn, disrupts decision-making (Bechara 2004; Bechara et al. 2000). The somatic marker hypothesis outlines two distinct stages in the decision-making process. First, it proposes that when decisions are followed by positive (rewarding) or negative (punishing) outcomes, these outcomes trigger emotional responses. These responses can be measured objectively via physiological indicators of autonomic arousal such as skin conductance responses (SCRs). The somatic marker hypothesis asserts that, in the second stage, after repeated exposure to similar decision-making scenarios, emotional responses and their associated physiological arousal begin to emerge in anticipation of decisions. These brief periods of anticipatory physiological arousal are referred to as somatic markers (Damasio 2009). Somatic markers that occur in anticipation of disadvantageous decisions are believed to bias decision-making away from such choices (Damasio et al. 1991).

DECISION-MAKING AND OPIATE USE

Research in healthy adults, largely using the Iowa Gambling Task (IGT; Bechara et al. 1994), has provided support for both of the stages described by the somatic marker hypothesis. First, a number of studies have demonstrated that SCRs following punishments are stronger than SCRs following rewards (Bechara et al. 1999; Crone et al. 2004; Mardaga and Hansenne 2012; Suzuki et al. 2003). Furthermore, several studies have reported that SCRs occur in anticipation of decisions, and have crucially shown that anticipatory SCRs are higher before high-risk decisions (i.e., disadvantageous decisions) compared to low-risk decisions (i.e., advantageous decisions) (Bechara et al. 1999; Guillaume et al. 2009; Jenkinson et al. 2008; Suzuki et al. 2003). Furthermore, larger differences in anticipatory SCRs prior to disadvantageous, relative to advantageous, decisions have been associated with better decision-making ability (Carter and Smith Pasqualini 2004; Guillaume et al. 2009; Mardaga and Hansenne 2012; Miu et al. 2012).

Consistent with the somatic marker hypothesis, people with injuries to the orbitofrontal cortex lack the capacity to produce distinct anticipatory somatic markers when contemplating disadvantageous decisions, and they also demonstrate impaired decision-making performance (Bechara et al. 1999; Bechara et al. 1996). Only one study has assessed the applicability of the somatic marker hypothesis to substance users, and it focused on a mixed group of users of cocaine, alcohol, and methamphetamines (Bechara and Damasio 2002). The results of that study were consistent with the somatic marker hypothesis, showing that the substance users demonstrated lower anticipatory SCRs before disadvantageous decisions relative to controls and impaired decision-making performance (Bechara and Damasio 2002). However, because opiate users were not included in this study, the relevance of the somatic marker hypothesis for this specific group is as yet unclear.

If opiate users do indeed display abnormal responses to reward and punishment, and/or disrupted somatic marker production, it is possible that this may stem from abnormalities in their emotional responses more generally (Verdejo-Garcia and Bechara 2009; Verdejo-Garcia et al. 2006). A neurological basis for this argument is provided by well documented findings of abnormalities in the orbitofrontal cortex in opiate users (Cheng et al. 2013; Lyoo et al. 2006; Ma et al. 2010; Qiu et al. 2016; Qiu et al. 2013), which is an area implicated in both emotional responding (Murphy et al. 2003) and sensitivity to reward and punishment consequences (Kringelbach and Rolls 2004;

O'Doherty et al. 2001). For example, patients with injuries to the orbitofrontal cortex display unusual patterns of emotional responding, such as decreased intensity of positive emotions and increased intensity of negative emotions (Anderson et al. 2006; Berlin et al. 2004). Currently, research into emotional responding in opiate users is limited, and the findings somewhat inconsistent. For example, there is some evidence suggesting that this group shows reduced pleasure in response to positive images and heightened ratings of unpleasantness in response to negative images relative to controls (Aguilar de Arcos et al. 2008; Gerra et al. 2003), but other studies have failed to identify differences between opiate users and controls on subjective emotional ratings (Carcoba et al. 2011; Smoski et al. 2011; Wang et al. 2010). Methodological issues, however, may to some extent account for the inconsistent findings. For instance, studies reporting null findings (Carcoba et al. 2011; Smoski et al. 2011; Wang et al. 2010) presented participants with static emotional stimuli for less than five seconds, while those reporting group differences presented emotional stimuli for longer (unlimited time or more than 30 seconds). Increasing the duration of stimuli presentation, and incorporating dynamic stimuli which may induce more intense emotional states than static stimuli (Rottenberg et al. 2007), would help clarify this issue, as would the use of more objective measurements, such as SCR, to assess emotional responses (Cheetham et al. 2010; Fernández et al. 2012).

The aim of the current study was to assess whether the somatic marker hypothesis can explain decision-making deficits in opiate users. First, we tested the prediction that opiate users would demonstrate poorer decision-making on the IGT relative to controls. Second, we tested the prediction that opiate users would demonstrate abnormal emotional responses to dynamic stimuli (relative to controls) outside of the decision-making context. We assessed subjective (self-ratings) as well as objective (SCRs) emotional responses to address this question. Third, we tested the prediction that opiate users would demonstrate reduced SCRs following punishments and rewards on the IGT, relative to controls. Fourth, we tested the prediction that opiate users would show reduced anticipatory SCRs prior to disadvantageous decisions on the IGT relative to controls. Finally, we sought to clarify the nature of the relationship between anticipatory SCR and decision-making performance in both opiate users and controls. Previous research suggests that a larger difference between SCRs prior to disadvantageous versus advantageous decisions is associated with better decision-making performance in

DECISION-MAKING AND OPIATE USE

healthy controls (Carter and Smith Pasqualini 2004; Guillaume et al. 2009; Mardaga and Hansenne 2012; Miu et al. 2012). Therefore, we expected a positive correlation in the current control group. However, given that the opiate users were expected to exhibit abnormal somatic markers, a weaker or absent correlation was anticipated in this group.

5.5 Method

5.5.1 Participants

Twenty-eight long-term opiate users with a history of heroin dependence were recruited (years of heroin use $M = 16.88$, $SD = 8.09$), as were 34 controls with no history of alcohol or drug dependence. All but one of the opiate users were currently participating in an opiate substitution program (methadone $n = 18$, suboxone $n = 7$, buprenorphine $n = 2$). The average dose was 55.39 mg ($SD = 31.02$) for methadone; 10 mg ($SD = 8.41$) for suboxone; and 9 mg ($SD = 1.41$) for buprenorphine. As is typical, the opiate users had a history of poly-drug abuse and some were still currently using other licit and illicit substances (see Table 4). All participants included in the study, except for one opiate user, reported that they were HIV negative.

Opiate users were recruited using fliers distributed to pharmacies, needle exchange sites, and drop-in clinics for drug users. Control participants were recruited using personal networks, advertisements on volunteer job sites, and by placing flyers in local community settings such as gyms and sports clubs. Opiate users had to have been stable on an opiate agonist for at least 2 weeks prior to testing and to have abstained from opiate agonist use for a minimum of 3 hours prior to testing. Opiate users were excluded if they had a severe psychiatric diagnosis (e.g., schizophrenia or bipolar disorder), however current diagnoses of depression and anxiety did not lead to exclusion, as these are common co-morbid disorders in this population. Controls were excluded if they were heavy users of alcohol (defined as 28 standard drinks per week for men and 14 for women; Australian National Health and Medical Research Council 2001), if they reported a history of drug dependence, or if they were diagnosed with a severe psychiatric disorder. Exclusion criteria for both groups were a history of neurological illness, and diagnosis of a traumatic or acquired brain injury.

The opiate user and control groups were matched on age and did not differ on gender distribution, $\chi^2(1) = 3.10$, $p = .079$. Groups differed on premorbid IQ as measured by the National Adult Reading Test (NART; Nelson 1982); opiate users had a

DECISION-MAKING AND OPIATE USE

slightly lower IQ than controls (see Table 4). Groups also differed in years of education; opiate users had fewer years of education than controls (see Table 4). Levels of depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith 1983). The HADS has been shown to be a valid and sensitive indicator of depression and anxiety in both clinical and healthy samples (Bjelland et al. 2002). Opiate users scores for depression indicated a possible mood disorder, based on the standard HADS cut-offs (see Table 4).

Informed consent was obtained from participants, and they were tested individually in one session. Participants were asked not to use illicit drugs in the 24 hours before testing and were reminded of this requirement via text message at least a day in advance of their testing time. Abstinence was confirmed via self-report on the day of testing. Regular breaks were provided. After completing the brief background questionnaire and the NART, all participants were prepared for SCR measurement then completed the IGT and the subjective emotional videos task. All participants were reimbursed up to AU$30 (~USD$25) for their time. This study was approved by the Australian Catholic University ethics committee and conformed to the ethical standards set out in the 1964 Declaration of Helsinki.

DECISION-MAKING AND OPIATE USE

Table 4.

Group Characteristics of Opiate Users and Controls included in the Study

	Opiate Group n = 28		Control Group n = 34			
Proportion of men (%)	82%		62%			
	M	*SD*	*M*	*SD*	*t*(60)	*d*
Age (years)	41.71	7.79	39.91	8.53	0.86	0.22
Education (years)	12.57	2.33	16.00	2.36	5.72***	1.46
Estimated IQ[a]	101.15	9.56	106.57	8.17	2.38*	0.61
Mental Health						
Depression[b]	6.59	3.47	2.91	2.09	5.15***	1.28
Anxiety[b]	9.68	3.54	6.06	3.23	4.21***	1.07
Substance use						
Nicotine[c]	25	-	1	-		
Alcohol[c]	13	-	27	-		
Cannabis[c]	13	-	-	-		
Heroin[c]	19	-	-	-		
Amphetamines[c]	5	-	-	-		
Cocaine[c]	1	-	-	-		

[a] Pre-morbid IQ score as predicted from the number of errors made on the NART. NART data was not available for two control participants.

[b] Hospital Anxiety and Depression Scale subscale scores for anxiety and depression—range of scores was 0–21 for each subscale, 0–7 normal, 8–10 possible disorder and 11–21 presence of disorder

[c] Number of participants reporting "at least once a month" or more current use of the substance

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

DECISION-MAKING AND OPIATE USE

5.5.2 Material and apparatus

Iowa Gambling Task

Decision-making was assessed using a computerised version of the IGT (Bechara et al. 1994), presented via Presentation Version 18.0 (Neurobehavioral Systems, Inc.). Participants were instructed to maximize the amount of imaginary money won by selecting from 4 decks of cards (A, B, C, D) over 100 trials. Continuous selection from disadvantageous decks (A and B) resulted in high wins ($100), but also high losses, leading to an overall net loss. Conversely, continuous selection from advantageous decks (C and D) led to small wins ($50) and small losses, but a net gain. The schedule of wins and losses replicated that used by Bechara et al. (1994). Following selection from each deck, a message appeared on the computer screen that detailed the amount of money won and/or lost, and participants' cumulative total. Trial duration was set at 12 seconds, and participants could not move on to the next trial until this time had elapsed. The relatively long interval between trials ensured that there was no overlap in post-choice and anticipatory SCR recordings between trials (Dawson et al. 2011). Decision-making ability was indexed using the net score, calculated by subtracting the number of choices from disadvantageous decks from the number of choices from advantageous decks (i.e., net score = [C+D]-[A+B]) (Lemenager et al. 2011; Wang et al. 2012; Wilson and Vassileva 2016). Possible net scores ranged from -100 to 100, with higher scores indicating better decision-making performance.

Emotional Videos Task

Subjective and objective responses to general emotional stimuli were measured using an emotional videos task. Participants were presented with eight short video clips designed to elicit pleasant, unpleasant and neutral emotions (two positive, two negative, four neutral) using Presentation 18.0 software. The video clips were obtained from movies, TV shows and YouTube, and were 30-120 seconds in duration. Three of the clips (from "The Champ", "Mr Bean" and "I Love Lucy") had been used in previous research to elicit emotions (Gross and Levenson 1995; Mergl et al. 2005; Nasoz et al. 2004; Smith et al. 1996). All of the videos were piloted on a separate group of 8 healthy control participants within our laboratory and were shown to elicit the target emotions. Video clips were presented in a set order such that a neutral video always preceded and followed positive and negative videos. Following the viewing of each video clip,

DECISION-MAKING AND OPIATE USE

participants were given two 9-point Self-Assessment Manikin (SAM) scales to rate how pleasant they felt and their level of emotional arousal.

Skin conductance response (SCR)

The Biopac MP150 data acquisition system (Biopac Systems, Inc, Goleta, CA) was used to record skin conductance via Ag/Ag-Cl GSR reusable electrodes attached to the distal phalanges of the index and middle fingers of the left hand. AcqKnowledge software package version 4.2 (Biopac Systems, Inc, Goleta, CA.) was used to collect skin conductance raw data while the participants completed the IGT, and while they watched the emotional video clips. This raw data was filtered with a smoothing transformation to remove high-frequency noise, and was then run through a moving-difference function to eliminate down-drift in the skin conductance signal (Naqvi and Bechara 2006). Filtered skin conductance data was then extracted via the Area function in the AcqKnowledge software. This data cleaning procedure followed that of Fernie and Tunney (2013) and Naqvi and Bechara (2006).

For the IGT, filtered skin conductance data was used to generate anticipatory and post-decision SCRs. Data was extracted for the 5 seconds preceding each choice and the 5 seconds following each choice. These values were then divided by 5 to calculate an area under the curve value in amplitude units per second ($\mu S/sec$). Markers were set automatically during data collection so that whenever a decision was made (i.e., button pressed), a marker was set in the SCR wave. Trials with artefacts due to movement or deep breathing were excluded from analyses. Anticipatory SCRs (used to index somatic markers) were calculated separately for advantageous and disadvantageous deck selections for the 5 seconds preceding a choice on the IGT. Post-decision SCRs (used to index emotional response to reward and punishment) were calculated separately for deck selections resulting in gaining money (reward SCRs), and deck selections resulting in losing money (punishment SCRs) for the 5 seconds following a choice. The relative difference in anticipatory SCR before choosing from advantageous versus disadvantageous decks was indexed by subtracting the mean anticipatory SCR before choices from disadvantageous decks from the mean anticipatory SCR before choices from advantageous decks. This value was then divided by the mean anticipatory SCR before choices from advantageous decks to take into account individual differences in skin conductance reactivity (Dawson et al. 2000).

DECISION-MAKING AND OPIATE USE

The objective measure of emotional response was operationalized as autonomic arousal (i.e., SCRs) during the emotional videos task. Filtered skin conductance data was extracted for 5 second epochs during each video. The area of each epoch was divided by 5 to calculate an area under the curve value in μS/sec for each epoch. These values were used to calculate an average area under the curve value for each video, and the values were then averaged across each type of stimuli valence (positive, negative, and neutral). Epochs with artefacts due to movement or deep breathing were excluded from analyses.

5.5.3 Data analysis

All statistical tests were two-tailed and were conducted using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp). An alpha level of $p < 0.05$ was considered statistically significant, and effect sizes were estimated using partial eta squared (η^2) and Cohen's d. Expectation maximisation was used to replace missing values. Outliers were replaced with scores + or -2 SD of the mean as appropriate. Greenhouse-Geisser adjustments were applied in analyses where the assumption of sphericity was violated. Due to a technical error, data from the emotional videos task was lost for one control and three opiate users.

5.6 Results

5.6.1 Decision-making ability (performance on the Iowa Gambling Task)

Due to group differences in IQ and education, correlations between these variables and IGT net scores were examined separately for each group. All correlations were non-significant (all p's $> .05$). Therefore, these variables were not included as co-variates in further analyses (Tabachnick and Fidell 2013). Performance on the IGT was significantly different between the two groups, with opiate users' decision-making ability ($M = -9.43$, SD = 15.00) significantly worse than controls' ($M = 6.67$, SD = 30.66; $t (60) = 2.54$, $p = 0.014$, Cohen's $d = 0.67$)[c].

---

[c] We replicated this analysis comparing decision-making performance in opiate users who were using heroin concurrently with opiate substitutes (current users, $n = 19$) with opiate users not concurrently taking heroin (past users, $n = 9$). There was no significant group difference in decision-making performance: $t (26) = 0.30$, $p = 0.976$, $d = 0.01$.

DECISION-MAKING AND OPIATE USE

5.6.2 Subjective emotional responses to emotional videos

Ratings of pleasantness were analysed using a mixed ANOVA, with the between-subjects factor of *group* (opiate, control) and within-subjects factor of *stimuli valence* (positive, negative, neutral). The main effect of group was not significant, $F(1, 56) = 0.03$, $p = 0.875$, $\eta_p^2 < 0.01$, but there was a significant main effect of stimuli valence, $F(1.64, 91.84) = 150.80$, $p < 0.001$, $\eta_p^2 = 0.73$, where the pleasantness ratings of positive ($M = 7.03$, SD $= 1.43$), negative ($M = 2.98$, SD $= 1.34$) and neutral videos ($M = 5.82$, SD $= 1.07$) all significantly differed from each other (all p's < 0.01). There was no significant interaction between stimuli valence and group, $F(1.64, 91.84) = 2.57$, $p = 0.092$, $\eta_p^2 = 0.04$.

Ratings of emotional arousal were analysed using a mixed ANOVA, with the between-subjects factor of *group* (opiate, control) and within-subjects factor of *stimuli valence* (positive, negative, neutral). The main effect of group was not significant, $F(1, 56) = 2.21$, $p = 0.143$, $\eta_p^2 = 0.04$, but there was a significant main effect of stimuli valence, $F(2, 112) = 27.37$, $p < 0.001$, $\eta_p^2 = 0.33$, where the arousal ratings of positive ($M = 6.41$, SD $= 1.41$), negative ($M = 5.84$, SD $= 1.55$) and neutral videos ($M = 4.86$, SD $= 1.39$) all significantly differed from each other (all p's < 0.05). There was no significant interaction between arousal and group, $F(2, 112) = 0.02$, $p = 0.982$, $\eta_p^2 < 0.01$.

5.6.3 Objective emotional response to emotional videos (SCRs)

The level of physiological arousal (SCR area under the curve) in response to the emotional videos was analysed using a mixed ANOVA, with the between subjects factor of *group* (opiate, control) and the within-subjects factor of *stimuli valence* (positive, negative, neutral). The main effect of stimuli valence was significant [$F(1.75, 97.84) = 8.22$, $p < 0.001$, $\eta_p^2 = 0.13$] where the SCR associated with positive videos ($M = 0.09$, SD $= 0.08$) significantly differed from the SCR associated with negative videos ($M = 0.07$, SD $= 0.07$, $p = 0.002$, Cohen's $d = 0.30$). The SCR associated with neutral videos ($M = 0.08$, SD $= 0.06$) did not significantly differ from that of positive ($p = 0.080$) or negative videos ($p = 0.161$). The main effect of group [$F(1, 56) = 1.12$, $p = 0.295$, $\eta_p^2 = 0.02$] and the interaction of group and stimuli valence [$F(1.75, 97.84) = 1.99$, $p = 0.142$, $\eta_p^2 = 0.03$] were not significant.

DECISION-MAKING AND OPIATE USE

5.6.4 Objective emotional response to reward and punishment during the IGT (Post-decision SCRs)

Emotional response to reward and punishment during the IGT was analysed using post-decision SCRs in a mixed ANOVA, with the between-subjects factor of *group* (opiate, control) and within-subjects factors of *outcome* (reward, punishment). Results indicated no significant main effect of group [$F(1, 60) = 0.20$, $p = 0.653$, $\eta_p^2 < 0.01$), but there was a significant main effect of outcome [$F(1, 60) = 8.42$, $p = 0.005$, $\eta_p^2 = 0.12$], where the SCRs in response to punishment ($M = 0.12$, SD $= 0.14$) were higher than the SCRs in response to reward ($M = 0.10$, SD $= 0.10$, $p = 0.005$, Cohen's $d = 0.14$). There was no significant interaction between group and outcome [$F(1, 60) < 0.01$, $p = 0.923$, $\eta_p^2 < 0.01$].

5.6.5 Somatic markers production during the IGT (Anticipatory SCR)

Anticipatory SCRs were analysed using a mixed ANOVA, with the between-subjects factor of *group* (opiate, control) and within-subjects factor of *decision* (advantageous, disadvantageous). The results showed that the main effect of group was not significant, $F(1, 60) = 1.55$, $p = 0.218$, $\eta_p^2 = 0.03$, but there was a significant main effect of decision [$F(1, 60) = 7.28$, $p = 0.009$, $\eta_p^2 = 0.11$], where the SCRs were higher before disadvantageous decisions compared to advantageous decisions (see Figure 1). There was no significant interaction between choice and group, $F(1, 60) = 0.07$, $p = 0.790$, $\eta_p^2 < 0.01$[de].

5.6.6 Relationship between IGT performance and anticipatory SCRs

The relationship between decision-making ability and the relative difference between anticipatory SCRs for advantageous compared to disadvantageous choices (as indexed by first calculating the difference between the mean SCR prior to choices from

---

[d] We replicated the SCR analyses comparing opiate users who were using heroin concurrently with opiate substitutes (current users, n = 19) with opiate users not concurrently taking heroin (past users, n = 9). There were no group differences in SCR (all p's ≥ 0.587, all F's ≤ 0.30) and the Cohen's d effect sizes for the group differences were small ($0.12 \leq d \leq 0.22$).

[e] It is possible that participants may not produce anticipatory somatic markers in the early stages of the IGT due to a lack of repeated exposure to the rewards and punishments associated with each deck. We therefore re-ran the analyses of anticipatory SCR while excluding the first 20 trials of the IGT. The results replicated of the original analyses. Specifically, we found that there was no main effect of group and no interaction between group and decision (all F's ≤ 1.76, all p's ≥ 0.190). There was a main effect of decision, with the anticipatory SCR prior to disadvantageous decisions ($M = 0.08$, SD $= 0.09$) significantly higher than the SCR prior to advantageous decisions ($M = 0.07$, SD $= 0.07$; $F(1, 60) = 8.09$, $p = 0.006$).

DECISION-MAKING AND OPIATE USE

disadvantageous decks and mean SCR prior to choices from advantageous decks, then dividing by the mean SCR prior to choices from advantageous decks) was analysed using Pearson correlations. The relative difference in anticipatory SCRs for opiate users ($M = 0.14$, $SD = 0.32$) did not differ significantly from that of controls ($M = 0.09$, $SD = 0.29$; $t(60) = 0.59$, $p = .559$, Cohen's $d = 0.15$). The correlation between the relative difference in anticipatory SCRs and IGT net score in controls was positive, but not significant ($r = .23$, $p = .191$). For opiate users this correlation was negative and significant ($r = -.43$, $p = .023$).
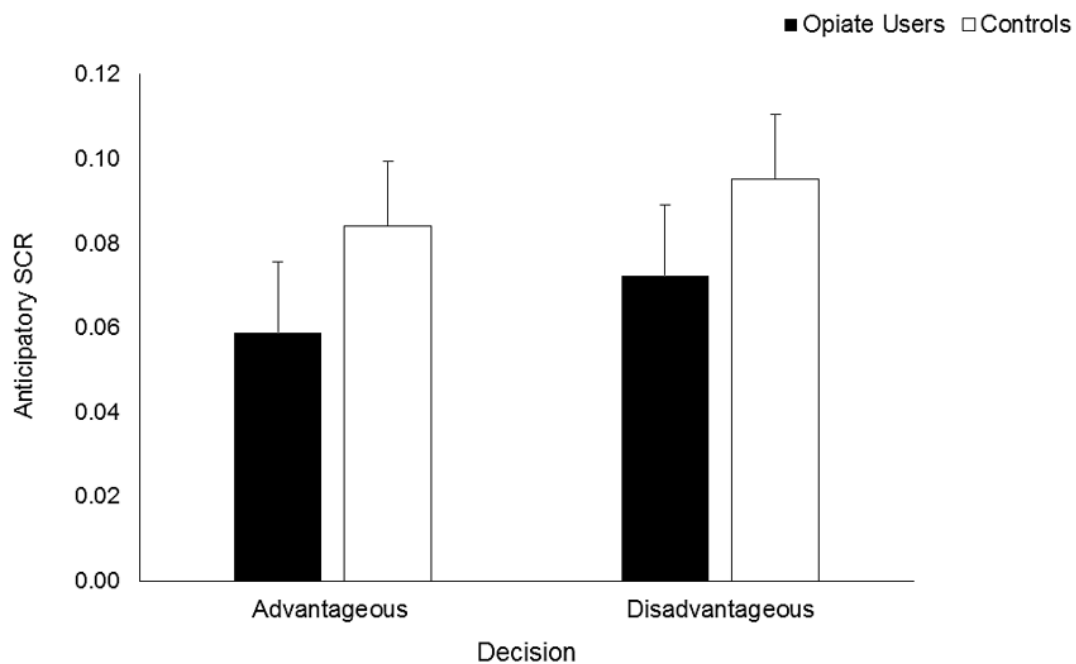
Figure 8. Anticipatory SCR for opiate users and controls prior to different decision types on the IGT.

5.7 Discussion

We assessed whether the decision-making deficit observed in opiate users could be explained by abnormalities in emotional responses (in a decision-making context or more broadly) and/or by difficulties generating somatic markers. Although opiate users demonstrated significantly poorer decision-making ability than controls, they did not demonstrate the hypothesised differences in emotional responses to reward and punishment, nor did they respond differently to emotional videos. Furthermore, the two groups displayed a similar pattern of anticipatory SCRs during the IGT which distinguished disadvantageous from advantageous decisions, thus indicating that opiate

users did not have difficulties generating somatic makers. These results suggest that abnormal emotional responding and impaired somatic marker production cannot explain the decision-making deficit in opiate users.

As predicted, opiate users demonstrated impaired decision-making on the IGT. That is, they chose more often from decks that appeared to provide short term gains but ultimately led to long term losses. These results align with previous research indicating that opiate users display poorer decision-making ability than healthy controls (Biernacki et al. 2016), with the magnitude of the deficit in opiate users in the current study ($d =$ 0.67) similar to that seen in prior research ($d = 0.70$; Biernacki et al. 2016).

In relation to somatic markers, contrary to predictions, opiate users produced larger anticipatory SCRs (i.e., relatively stronger somatic markers) before disadvantageous decisions than before advantageous decisions which, as noted, mirrored the pattern seen in the controls. Thus, opiate users' autonomic activation was no different from controls' and they were able to produce distinct somatic markers before disadvantageous decisions. The current results set opiate users apart from other groups with reduced decision-making capacity (e.g., pathological gamblers, people with orbitofrontal cortex injuries, and in some cases people with obsessive compulsive disorder) who do not appear to produce prominent somatic markers before disadvantageous decisions (Bechara et al. 1999; Cavedini et al. 2012; Elvemo et al. 2014; Goudriaan et al. 2006). The current results also contrast with those of Bechara and Damasio (2002) who found that the SCRs before disadvantageous decisions in a mixed group of substance users were significantly lower than those seen in healthy controls. Interestingly, however, that study did identify a subgroup of substance users who demonstrated SCRs that were no different from controls, suggesting that at least some substance users generate normal somatic markers.

The results of the current study also showed no differences in emotional responses between the opiate users and the control group either in the context of, or separate from, decision-making. More specifically, during the IGT, emotional responses to rewards and punishments as indexed by SCRs were similar, with both groups exhibiting relatively small changes in SCRs after receiving imaginary monetary rewards, and relatively larger changes in SCRs after punishments involving imaginary monetary losses. Outside of the decision-making context, when opiate users watched emotionally

DECISION-MAKING AND OPIATE USE

evocative videos, their emotional responses again mirrored those of the controls when measured objectively using SCR. This was also the case when emotional responses were measured using subjective ratings. Importantly, both the objective and subjective measures were sensitive to differences in the valence of the stimuli (particularly happy versus sad stimuli), indicating that the stimuli successfully evoked different emotional states. The findings suggest that the opiate users in the current study did not experience blunted positive or heightened negative emotional responses as observed in some other studies of opiate users (Aguilar de Arcos et al. 2008; Gerra et al. 2003). Taken together, the current findings are more consistent with those demonstrating that opiate users' emotional responsiveness is comparable to that of controls (Carcoba et al. 2011; Smoski et al. 2011; Wang et al. 2010) and as such, do not support the claim that the decision-making impairment often observed in opiate users is due to abnormalities in emotional responding (Verdejo-Garcia and Bechara 2009; Verdejo-Garcia et al. 2006).

After examining group differences, the final analyses focused on the relationship between decision-making ability and the relative difference between anticipatory SCRs before advantageous compared to disadvantageous decisions in each group. Specifically, we were interested in whether people who produced much larger SCRs before disadvantageous decisions than before advantageous decisions (i.e., more distinct somatic markers), displayed better decision-making overall. Contrary to prior research (Carter and Smith Pasqualini 2004; Guillaume et al. 2009; Miu et al. 2012), this relationship was not observed in the control group. However, in opiate users the correlation was negative, indicating that those with relatively large anticipatory SCRs prior to disadvantageous decisions compared to advantageous decisions (i.e., more distinctive somatic markers) displayed worse decision-making performance. This result is not consistent with the predictions of the somatic marker hypothesis, which argues that relatively larger somatic markers prior to disadvantageous decisions should lead to better decision-making. This finding therefore suggests that a different relationship between somatic marker production and decision-making may exist in opiate users. For example, one possibility is that while opiate users may produce normal somatic markers when a decision is being contemplated, they may be less able to "tune in" to those markers (i.e., display a lack of interoceptive awareness; Craig 2002) leading to reduced decision-making capacity. However, given that there was a moderate negative relationship (rather than an absence of a relationship) between somatic marker

distinctiveness and decision-making ability, this explanation seems unlikely. Instead, it may be that opiate users are aware of the somatic markers that occur prior to disadvantageous decisions, but respond to them by choosing riskier options, rather than the 'safer' options that the somatic marker hypothesis would predict. If this is the case, the question is then raised as to whether this tendency to choose 'riskier options' in response to somatic marker production is a consequence of long-term opiate use, or may in fact have been apparent prior to opiate use. In keeping with this latter possibility, previous research has identified a group of healthy controls with normal somatic markers who behave disadvantageously on the IGT, classifying them as "risky" decision-makers (Bechara and Damasio 2002; Crone et al. 2004). Taken together, the current results indicate that additional research should be conducted to further explore the nature of the relationship between somatic marker production and risky decisions in opiate users. Future research should also consider adopting other approaches such as computational modelling to provide insight into other cognitive and emotional factors that may contribute to impaired decision-making in this group, especially given recent findings using this approach showing that impaired decision-making in ex-opiate users was characterised by reduced loss aversion (Ahn et al. 2014).

It should be noted that the current sample of opiate users was relatively high-functioning, with higher levels of education (12.56 years) than in other studies of decision-making in this group (8.37 years to 12.25 years; Ma et al. 2015; Mintzer et al. 2005; Pirastu et al. 2006; Upton et al. 2012). In addition, the opiate users were enrolled in a treatment program and were living independently in the community. As such, the generalisability of the results to a broader sample of opiate users is currently unclear, and the possibility that the somatic marker hypothesis may be more applicable to other subgroups of opiate users cannot be ruled out. Furthermore, it should be noted that although screened for, no formal assessment of psychiatric disorders was conducted. Therefore, it is possible that externalising traits and disorders, such as antisocial personality disorder or ADHD, which are highly co-morbid in substance using populations, and are independently associated with deficits on the IGT (Bowden-Jones et al. 2004; Mazas et al. 2000; Mowinckel et al. 2015; Ruiz et al. 2008), may also have contributed to impaired decision-making in the opiate-using group.

In conclusion, the current study supports previous findings that opiate use is associated with relatively severe decision-making impairment. However, the

DECISION-MAKING AND OPIATE USE

impairment seen in the current sample does not appear to be driven by reduced emotional responding or by an inability to form somatic markers in anticipation of poor choices. Interestingly, more distinct somatic markers were associated with worse decision-making in this group. This suggests other cognitive processes may intervene between the activation of a somatic marker and the selection of a choice, leading opiate users to make more risky decisions. Future research should focus on how these cognitive processes interact with somatic markers.

5.8 Additional Analyses of Interoceptive Accuracy and its Relationship to Decision-Making in Opiate Users and Controls

The following results were not included in the submission to *Psychopharmacology,* but follow on from the data presented in the published manuscript.

The ability to perceive changes in bodily states (i.e., interoception) may play a role in the ability to perceive somatic markers (Craig, 2009; Dunn et al., 2010). Indeed, at least one study has shown that more accurate perception of heartbeats in healthy adults is associated with better decision-making ability (Werner et al., 2009). In the case of opiate users, it may be suggested that reduced ability to perceive changes in physiology (i.e., somatic markers) may contribute to impaired decision-making in this group. To date, only one study has analysed interoceptive accuracy in substance users (including opiate users), and found that substance users were impaired in their ability to perceive heartbeat, relative to controls (Sönmez et al., 2016). However, the relationship between interoception and decision-making capacity in substance users was not assessed. Therefore, the additional analyses of interoceptive accuracy presented in this section aimed to determine whether the ability to "tune in" to physiological signals (as measured by the heart beat counting task) was related to decision-making ability in both opiate users and controls. Based on previous research, we expected to see reduced interoceptive accuracy in opiate users, relative to controls, and a positive correlation between interoception accuracy and decision-making ability in both groups. The methods for measuring interoceptive accuracy are detailed in the Methods Chapter (section 4.7.3). The results of these analyses are detailed below.

Contrary to expectation, opiate users ($M = 0.69$, SD $= 0.18$) were able to perceive heartbeat more accurately on the interoceptive accuracy task than controls ($M = 0.56$, SD $= 0.26$; $t(58) = 2.05$, $p = .045$, Cohen's $d = 0.58$). However, there was no significant correlation between decision-making ability and interoceptive accuracy in controls ($r = .28$, $p = .111$) or opiate users ($r = .07$, $p = .728$).

The results showing that opiate users were more accurate than controls in their ability to "tune in to" physiological signal, contrast with those of Sönmez et al. (2016), who used the same interoceptive accuracy task as was used in the current study. Although it has been argued that better interoceptive accuracy is correlated with better

DECISION-MAKING AND OPIATE USE

decision-making ability, only one study has found that more accurate perception of heartbeats in healthy adults is associated with better decision-making ability (Werner et al., 2009), while two other studies have found no correlation between interoceptive accuracy and decision-making capacity in healthy adults (Werner et al., 2013). The results of the current analyses support the latter, as interoceptive accuracy was unrelated to decision-making ability in both opiate users and controls. These results, in addition to the findings that anticipatory somatic markers were negatively correlated with decision-making in opiate users (in the submitted manuscript), suggest that interoceptive awareness is not important in the decision-making process in opiate users. However, given that relatively few studies have analysed the relationship between interoceptive accuracy and decision-making capacity, and this is the first to conduct such analyses in a clinical group with known decision-making impairment, further research is warranted.

DECISION-MAKING AND OPIATE USE

5.9 References for Chapter 5 (formatted for *Psychopharmacology*)

Aguilar de Arcos F, Verdejo-García A, Ceverino A, Montañez-Pareja M, López-Juárez E, Sánchez-Barrera M, López-Jiménez Á, Pérez-García M (2008) Dysregulation of emotional response in current and abstinent heroin users: Negative heightening and positive blunting. Psychopharmacology (Berl) 198: 159-166.

Anderson SW, Barrash J, Bechara A, Tranel D (2006) Impairments of emotion and real-world complex behavior following childhood-or adult-onset damage to ventromedial prefrontal cortex. J Int Neuropsychol Soc 12: 224-235.

Australian National Health and Medical Research Council (2001) Australian alcohol guidelines: Health risks and benefits, Commonwealth of Australia, Canberra

Baldacchino A, Armanyous M, Balfour DJK, Humphris G, Matthews K (2017) Neuropsychological functioning and chronic methadone use: A systematic review and meta-analysis. Neurosci Biobehav Rev 73: 23-38.

Baldacchino A, Balfour DJK, Passetti F, Humphris G, Matthews K (2012) Neuropsychological consequences of chronic opioid use: A quantitative review and meta-analysis. Neurosci Biobehav Rev 36: 2056-2068.

Bechara A (2004) The role of emotion in decision-making: Evidence from neurological patients with orbitofrontal damage. Brain Cogn 55: 30-40.

Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50: 7-15.

Bechara A, Damasio H (2002) Decision-making and addiction (part I): Impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. Neuropsychologia 40: 1675-1689.

Bechara A, Damasio H, Damasio AR (2000) Emotion, decision making and the orbitofrontal cortex. Cereb Cortex 10: 295-307.

Bechara A, Damasio H, Damasio AR, Lee GP (1999) Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. J Neurosci 19: 5473-5481.

DECISION-MAKING AND OPIATE USE

Bechara A, Tranel D, Damasio H, Damasio AR (1996) Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. Cereb Cortex 6: 215-225.

Berlin HA, Rolls ET, Kischka U (2004) Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions. Brain 127: 1108-1126.

Biernacki K, McLennan SN, Terrett G, Labuschagne I, Rendell PG (2016) Decision-making ability in current and past users of opiates: A meta-analysis. Neurosci Biobehav Rev 71: 342-351.

Carcoba LM, Contreras AE, Cepeda-Benito A, Meagher MW (2011) Negative affect heightens opiate withdrawal-induced hyperalgesia in heroin dependent individuals. J Addict Dis 30: 258-270.

Carter S, Smith Pasqualini M (2004) Stronger autonomic response accompanies better learning: A test of damasio's somatic marker hypothesis. Cogn Emot 18: 901-911.

Cavedini P, Zorzi C, Baraldi C, Patrini S, Salomoni G, Bellodi L, Freire RC, Perna G (2012) The somatic marker affecting decisional processes in obsessive-compulsive disorder. Cognit Neuropsychiatry 17: 177-190.

Cheetham A, Allen NB, Yücel M, Lubman DI (2010) The role of affective dysregulation in drug addiction. Clin Psychol Rev 30: 621-634.

Cheng GLF, Zeng H, Leung MK, Zhang HJ, Lau BWM, Liu YP, Liu GX, Sham PC, Chan CCH, So KF (2013) Heroin abuse accelerates biological aging: A novel insight from telomerase and brain imaging interaction. Transl Psychiatry 3: e260.

Craig AD (2002) How do you feel? Interoception: The sense of the physiological condition of the body. Nat Rev Neurosci 3: 655-666.

Crone EA, Somsen RJM, Beek BV, Van Der Molen MW (2004) Heart rate and skin conductance analysis of antecendents and consequences of decision making. Psychophysiol 41: 531-540.

DECISION-MAKING AND OPIATE USE

Dacher M, Nugent FS (2011) Opiates and plasticity. Neuropharmacology 61: 1088-1096.

Damasio AR (1994) Descartes' error: Emotion, reason and the human brain. Grosset/Putnam, New York

Damasio AR (2009) Neuroscience and the emergence of neuroeconomics. In: Glimcher PW, Fehr E, Camerer C, Poldrack RA (eds) Neuroeconomics: Decision making and the brain. Elsevier Science, Burlington, pp 209-214

Damasio AR, Tranel D, Damasio H (1991) Somatic markers and the guidance of behavior: Theory and preliminary testing. In: Levin HS, Eisenberg HM, Benton AL (eds) Frontal lobe function and dysfunction. Oxford Univerity Press, New York, NY, pp 217-229

Dawson ME, Schell AM, Courtney CG (2011) The skin conductance response, anticipation, and decision-making. J Neurosci Psychol Econ 4: 111-116.

Dawson ME, Schell AM, Filion DL (2000) The electrodermal system. In: Cacioppo JT, Tassinary LG, Berntson GG (eds) Handbook of psychophysiology. Cambridge University Press, Cambridge, UK, pp 200-223

Dunn, B. D., Galton, H. C., Morgan, R., Evans, D., Oliver, C., Meyer, M., . . . Dalgleish, T. (2010). Listening to your heart: How interoception shapes emotion experience and intuitive decision making. Psych Sci 21, 1835-1844.

Elvemo NA, Nilsen KB, Landrø NI, Borchgrevink PC, Håberg AK (2014) Patients with chronic pain lack somatic markers during decision-making. J Pain Res 7: 425-437.

Fernández C, Pascual JC, Soler J, Elices M, Portella MJ, Fernández-Abascal E (2012) Physiological Responses Induced by Emotion-Eliciting Films. Appl Psychophysiol Biofeedback 37: 73-79.

Fernie G, Tunney RJ (2013) Learning on the IGT follows emergence of knowledge but not differential somatic activity. Frontiers in Psychology 4: 697.

Gerra G, Baldaro B, Zaimovic A, Moi G, Bussandri M, Raggi MA, Brambilla F (2003) Neuroendocrine responses to experimentally-induced emotions among abstinent opioid-dependent subjects. Drug Alcohol Depend 71: 25-35.

DECISION-MAKING AND OPIATE USE

Goudriaan AE, Oosterlaan J, de Beurs E, van den Brink W (2006) Psychophysiological determinants and concomitants of deficient decision making in pathological gamblers. Drug Alcohol Depend 84: 231-239.

Gross JJ, Levenson RW (1995) Emotion elicitation using films. Cogn Emot 9: 87-108.

Guillaume S, Jollant F, Jaussent I, Lawrence N, Malafosse A, Courtet P (2009) Somatic markers and explicit knowledge are both involved in decision-making. Neuropsychologia 47: 2120-2124.

Jenkinson PM, Baker SR, Edelstyn NMJ, Ellis SJ (2008) Does autonomic arousal distinguish good and bad decisions? Healthy individuals' skin conductance reactivity during the Iowa Gambling Task. J Psychophysiol 22: 141-149.

Kringelbach ML, Rolls ET (2004) The functional neuroanatomy of the human orbitofrontal cortex: Evidence from neuroimaging and neuropsychology. Prog Neurobiol 72: 341-372.

Lemenager T, Richter A, Reinhard I, Gelbke J, Beckmann B, Heinrich M, Kniest A, Mann K, Hermann D (2011) Impaired decision making in opiate addiction correlates with anxiety and self-directedness but not substance use parameters. J Addict Med 5: 203-213.

Lyoo IK, Pollack MH, Silveri MM, Ahn KH, Diaz CI, Hwang J, Kim SJ, Yurgelun-Todd DA, Kaufman MJ, Renshaw PF (2006) Prefrontal and temporal gray matter density decreases in opiate dependence. Psychopharmacology (Berl) 184: 139-144.

Ma N, Liu YP, Li N, Wang CX, Zhang H, Jiang XF, Xu HS, Fu XM, Hu X, Zhang DR (2010) Addiction related alteration in resting-state brain connectivity. Neuroimage 49: 738-744.

Ma XF, Qiu YW, Tian JZ, Wang JH, Li SM, Zhan WF, Wang TY, Zeng SQ, Jiang GH, Xu YK (2015) Aberrant default-mode functional and structural connectivity in heroin-dependent individuals. PLoS ONE 10.

Mardaga S, Hansenne M (2012) Personality and skin conductance responses to reward and punishment. J Individ Differ 33: 17-23.

DECISION-MAKING AND OPIATE USE

Mergl R, Mavrogiorgou P, Hegerl U, Juckel G (2005) Kinematical analysis of emotionally induced facial expressions: A novel tool to investigate hypomimia in patients suffering from depression. J Neurol Neurosurg Psychiatry 76: 138-140.

Mintzer MZ, Copersino ML, Stitzer ML (2005) Opioid abuse and cognitive performance. Drug Alcohol Depend 78: 225-230.

Miu AC, Crişan LG, Chiş A, Ungureanu L, Drugă B, Vulturar R (2012) Somatic markers mediate the effect of serotonin transporter gene polymorphisms on Iowa Gambling Task. Genes Brain Behav 11: 398-403.

Murphy FC, Nimmo-Smith I, Lawrence AD (2003) Functional neuroanatomy of emotions: A meta-analysis. Cogn Affect Behav Neurosci 3: 207-233.

Naqvi NH, Bechara A (2006) Skin conductance: A psychophysiological approach to the study of decision making. In: Senior C, Russell T, Gazzaniga MS (eds) Methods in Mind. The MIT Press, pp 103-122

Nasoz F, Alvarez K, Lisetti CL, Finkelstein N (2004) Emotion recognition from physiological signals using wireless sensors for presence technologies. Cognition, Technology and Work 6: 4-14.

Nelson HE (1982) National adult reading test (NART): Test manual, Windsor: NFER

O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C (2001) Abstract reward and punishment representations in the human orbitofrontal cortex. Nat Neurosci 4: 95-102.

Pandria N, Kovatsi L, Vivas AB, Bamidis PD (2016) Resting-state abnormalities in heroin-dependent individuals. Neuroscience. doi: 10.1016/j.neuroscience.2016.11.018.

Passetti F, Clark L, Mehta MA, Joyce E, King M (2008) Neuropsychological predictors of clinical outcome in opiate addiction. Drug Alcohol Depend 94: 82-91.

Pillari G, Narus J (1973) Physical effects of heroin addiction. Am J Nurs 73: 2105-2108.

DECISION-MAKING AND OPIATE USE

Pirastu R, Fais R, Messina M, Bini V, Spiga S, Falconieri D, Diana M (2006) Impaired decision-making in opiate-dependent subjects: Effect of pharmacological therapies. Drug Alcohol Depend 83: 163-168.

Qiu YW, Jiang GH, Ma XF, Su HH, Lv XF, Zhuo FZ (2016) Aberrant interhemispheric functional and structural connectivity in heroin-dependent individuals. Addict Biol. doi: 10.1111/adb.12387.

Qiu YW, Jiang GH, Su HH, Lv XF, Zhang XL, Tian JZ, Zhuo FZ (2013) Progressive white matter microstructure damage in male chronic heroin dependent individuals: A DTI and TBSS study. PLoS ONE 8: e63212-e63212.

Rottenberg J, Ray RD, Gross JJ (2007) Emotion elicitation using films. In: Coan JA, Allen JJB (eds) Handbook of emotion elicitation and assessment. Oxford University Press, New York, NY, pp 9-28

Ryan CF, White JM (1996) Health status at entry to methadone maintenance treatment using the SF-36 health survey questionnaire. Addiction 91: 39-46.

Smith MC, Smith MK, Ellgring H (1996) Spontaneous and posed facial expression in Parkinson's disease. J Int Neuropsychol Soc 2: 383-391.

Smoski MJ, Salsman N, Wang L, Smith V, Lynch TR, Dager SR, LaBar KS, Linehan MM (2011) Functional imaging of emotion reactivity in opiate-dependent borderline personality disorder. Personal Disord Theory Res Treat 2: 230-241.

Sönmez, M. B., Kahyacı Kılıç, E., Ateş Çöl, I., Görgülü, Y., & Köse Çınar, R. (2016). Decreased interoceptive awareness in patients with substance use disorders. J Substance Use, Published online 25 May 2016: 1-6. doi:10.3109/14659891.2016.1143048

Suzuki A, Hirota A, Takasawa N, Shigemasu K (2003) Application of the somatic marker hypothesis to individual differences in decision making. Biol Psychol 65: 81-88.

Tabachnick BG, Fidell LS (2013) Using multivariate statistics, 6th edn. Pearson, Boston

Upton DJ, Kerestes R, Stout JC (2012) Comparing the Iowa and Soochow gambling tasks in opiate users. Front Neurosci 6: 34.

DECISION-MAKING AND OPIATE USE

Verdejo-Garcia A, Bechara A (2009) A somatic marker theory of addiction. Neuropharmacology 56: 48-62.

Verdejo-Garcia A, Perez-Garcia M, Bechara A (2006) Emotion, decision-making and substance dependence: A somatic-marker model of addiction. Current Neuropharmacol 4: 17-31.

Verdejo-Garcia A, Rivas-Perez C, Vilar-Lopez R, Perez-Garcia M (2007) Strategic self-regulation, decision-making and emotion processing in poly-substance abusers in their first year of abstinence. Drug Alcohol Depend 86: 139-146.

Wang GB, Zhang XL, Zhao LY, Sun LL, Wu P, Lu L, Shi J (2012) Drug-related cues exacerbate decision making and increase craving in heroin addicts at different abstinence times. Psychopharmacology (Berl) 221: 701-708.

Wang ZX, Zhang JX, Wu QL, Liu N, Hu XP, Chan RCK, Xiao ZW (2010) Alterations in the processing of non-drug-related affective stimuli in abstinent heroin addicts. Neuroimage 49: 971-976.

Webster IW, Waddy N, Jenkins LV, Lai LYC (1979) Health status of a group of narcotic addicts in a methadone treatment programme. Int J Rehabil Res 2: 399.

Werner, N. S., Jung, K., Duschek, S., & Schandry, R. (2009). Enhanced cardiac perception is associated with benefits in decision-making. Psychophysiology 46: 1123-1129.

Werner, N. S., Schweitzer, N., Meindl, T., Duschek, S., Kambeitz, J., & Schandry, R. (2013). Interoceptive awareness moderates neural activity during decision-making. Bio Psych 94: 498-506.

Wilson MJ, Vassileva J (2016) Neurocognitive and psychiatric dimensions of hot, but not cool, impulsivity predict HIV sexual risk behaviors among drug users in protracted abstinence. Am J Drug Alcohol Abuse 42: 231-241.

Wollman SC, Alhassoon OM, Hall MG, Stern MJ, Connors EJ, Kimmel CL, Allen KE, Stephan RA, Radua J (2016) Gray matter abnormalities in opioid-dependent patients: A neuroimaging meta-analysis. Am J Drug Alcohol Abuse. doi: 10.1080/00952990.2016.1245312.

Wollman SC, Alhassoon OM, Stern MJ, Hall MG, Rompogren J, Kimmel CL, Perez-Figueroa AM (2015) White matter abnormalities in long-term heroin users: a preliminary neuroimaging meta-analysis. Am J Drug Alcohol Abuse 41: 133-138.

Zigmond AS, Snaith RP (1983) The hospital and anxiety depression scale. Acta Psychiatr Scand 67: 361-370.

CHAPTER 6: Study 3 - Risky Decision-Making in Opiate Use

6.1 Preamble

Study 1 demonstrated that both current and ex-users of opiates have relatively severe decision-making impairments. Study 2 demonstrated that this decision-making impairment is not underpinned by reduced emotional responsiveness, or by an inability to form anticipatory warning signals prior to poor decisions. However Study 2, which used the IGT, focused on decision-making under conditions of ambiguity, which is the most commonly investigated type of decision-making. Given that decision-making is a multi-faceted construct, it remains to be seen whether opiate users also make poor decisions under other circumstances, in particular under conditions of calculable risk. Poorer decision-making in opiate users relative to controls under conditions of calculable risk might, at least in part, be due to underlying differences in the personality of opiate users, which drives behaviour towards risky, but rewarding, options. The aim of Study 3 was therefore to assess decision-making under conditions of calculable risk in opiate users and controls, using a relatively new measure of decision-making that involves choosing between risky or safe options. An additional aim of Study 3 was to analyse whether decision-making under conditions of calculable risk in opiate users is related to underlying personality differences in reward responsiveness.

DECISION-MAKING AND OPIATE USE

6.2 Introduction

Opiate use is associated with a propensity for high risk behaviours, often leading to negative consequences such as imprisonment for drug-related crime (Degenhardt et al., 2014) and HIV infection due to needle-sharing and high risk sexual practices (Gossop, Griffiths, Powis, & Strang, 1993; Gyarmathy, Neaigus, Miller, Friedman, & Des Jarlais, 2002). The tendency to display such behaviours in daily life may reflect impairment in higher-order cognitive functions, in particular decision-making (Bechara et al., 1999; Kohno, Morales, Ghahremani, Hellemann, & London, 2014; Waters-Wood, Xiao, Denburg, Hernandez, & Bechara, 2012), which, as previously noted, appears to be the most consistently impaired cognitive function in opiate users (Baldacchino, Balfour, Passetti, Humphris, & Matthews, 2012).

Decision-making occurs in a number of different situations and theorists have differentiated these decision-making situations based on the probability of outcomes (Bechara, 2004; Einhorn & Hogarth, 1985; Ellsberg, 1961). Specifically, in situations of ambiguity, decision-makers do not have explicit knowledge of the probability of receiving a reward or a punishment. On the other hand, in situations of risk, the probability of a punishment or reward can be predicted. That is, in situations of risk, decision-makers must choose between a safe option, where the probability of reward is high but the value of that reward is relatively low, or a risky option, where the probability of reward is low but the value of the reward is relatively high (Bechara, 2004; Euteneuer et al., 2009; Krain, Wilson, Arbuckle, Castellanos, & Milham, 2006). Given that decision-making is not a unitary construct, it has been suggested that decision-making performance under conditions of ambiguity and decision-making under conditions of calculable risk could vary (Brand, Labudda, & Markowitsch, 2006; Euteneuer et al., 2009).

One of the most commonly used measures to investigate decision-making impairment in clinical populations is the Iowa Gambling Task (IGT; Bechara et al., 1994; Steingroever, Wetzels, Horstmann, Neumann, & Wagenmakers, 2013). The IGT claims to measure decision-making under conditions of ambiguity (Bechara & Damasio, 2005; Brand et al., 2006) as it is presumed that participants never fully acquire knowledge about the probabilities of punishment and reward for choices made on this task (Bechara & Damasio, 2005). Specifically, participants are presented with four

decks of cards that are associated with both reward and punishment. Two of these decks present the decision-maker with a high reward for each choice ($100), but over the course of the task, choices from these decks also occasionally lead to larger punishments (-$150 to -$1250), and these decks are therefore deemed "disadvantageous". The other two decks present the decision-maker with a lower reward for each choice ($50), but also occasionally lead to smaller punishments (-$25 to -$250) over the course of the task, and are therefore deemed "advantageous" decks (see Chapter 4 for a breakdown of the schedule of reward and punishment). Thus, good decision-making on the IGT is exemplified by more choices from advantageous relative to disadvantageous decks, while impaired decision-making is characterised by a tendency to choose more often from disadvantageous decks. The IGT has been shown to be a valid indicator of decision-making impairment, with poorer decision-making on the IGT associated with more unsafe sexual practices (Golub, Thompson, & Kowalczyk, 2016), as well as with increased rates of relapse (Stevens et al., 2013; Stevens et al., 2015) and more medical, legal, and alcohol and drug related problems in substance users (Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2006). The IGT has also been used to demonstrate poor decision-making in a range of clinical populations, including people with injuries to the frontal lobe, schizophrenia, obsessive compulsive disorder, ADHD, as well as pathological gamblers (e.g. Brevers, Bechara, Cleeremans, & Noel, 2013; Cavedini et al., 2012; Lee et al., 2007; Malloy-Diniz, Fuentes, Leite, Correa, & Bechara, 2007; Waters-Wood et al., 2012), and is now one of the most widely used tools in decision-making research (Bull, Tippett, & Addis, 2015; Dunn et al., 2006). Although an often-used measure, the IGT has received some criticism regarding its validity. In particular, it has been argued that deck B may appear the more advantageous deck given the frequency with which punishment is delivered (Lin, Chiu, Lee, & Hsieh, 2007), and the deck contingencies may be more cognitively penetrable than first thought, leading to substantial variation in control performance on the task (Dunn et al., 2006). Nevertheless, the IGT is a sensitive measure of decision-making impairment and is a useful approach in a range of clinical populations.

Given the ubiquity of the IGT, it is not surprising that a substantial number of studies have used this instrument to measure decision-making impairment in opiate users (e.g., Barry & Petry, 2008; Lemenager et al., 2011; Ma et al., 2015; Pirastu et al., 2006; Rotheram-Fuller et al., 2004; Upton et al., 2012; Verdejo-Garcia, Perales, et al.,

DECISION-MAKING AND OPIATE USE

2007). The vast majority of these studies (see Biernacki et al., 2016 for a review) have demonstrated that opiate users performed significantly worse than controls on this measure, with opiate users tending to select more often from disadvantageous, compared to advantageous decks. Thus, the widely held belief that decision-making is impaired in opiate users is largely based on studies analysing decision-making under conditions of ambiguity.

An alternative situation in which decision-making impairment may manifest is under conditions of predictable risk. In such a decision-making scenario, such as during the Balloon Analogue Risk Task (BART; Lejuez et al., 2002), outcomes can be predicted to some degree (Leigh, 1999; Rao, Dunn, Zhou, & Li, 2015; Tversky & Fox, 1995). The BART presents decision-makers with a visual representation of a balloon, which needs to be "pumped" in order to gain imaginary money. Participants receive a small reward (5 cents) for each pump, which is stored in a temporary bank. Each balloon is randomly allocated an "explosion point" when the balloon will explode. If a participant chooses to "collect" the money stored in the temporary bank before the balloon explodes, this money is transferred to a permanent bank. If, however, the balloon pops before the money is safely stored, the participant loses the money in the temporary bank. As such, the BART places decision-makers in a situation of calculable risk, as continued pumping increases the value of the potential reward but simultaneously reduces the probability of winning that reward. While the external validity of other measures of risky decision-making such as the Cambridge Gambling Task and the Game of Dice Task has not been established, the BART has been shown to be a valid indicator of risky decision-making in real life, with higher propensity for risk-taking on the BART correlating with real life risky behaviours in healthy adults and adolescents, such as smoking, poly-drug use, gambling, and risky sexual behaviours (Aklin, Lejuez, Zvolensky, Kahler, & Gwadz, 2005; Lejuez et al., 2003; Lejuez et al., 2002). More risky decisions during the BART have also been correlated with more risky real life behaviours in poly-substance users (Aklin et al., 2005; Hopko et al., 2006; Lejuez, Simmons, Aklin, Daughters, & Dvir, 2004). Furthermore, studies have found that performance on the BART does not correlate with performance on the IGT in healthy adults (Aklin et al., 2005; Buelow & Blaine, 2015; Skeel, Neudecker, Pilarski, & Pytlak, 2007) or in substance using populations (Bishara et al., 2009; Lejuez et al.,

2003), leading to the suggestion that the BART taps a unique aspect of decision-making.

In contrast to the large number of studies that have assessed opiate users' decision-making abilities under conditions of ambiguity on the IGT, only two studies have analysed their decision-making abilities under conditions of predictable risk on the BART. In the first study, illicit opiate users ($n = 25$) demonstrated more risky decision-making behaviour than a group of matched controls on the BART (Khodadadi et al., 2010). However, a subset of opiate users from this group who were subsequently assessed after completing 6 months of methadone treatment ($n = 19$), no longer showed impairment on the BART relative to controls. This suggests that there may be some improvement in this type of decision-making ability when illicit opiates are substituted by methadone. However, the possibility that the observed reduction in risky behaviour may have been due to risky decision-makers dropping out before completing 6 months of treatment was not assessed by the authors. Additionally, a lack of characterisation of the opiate-using sample (e.g., education, opiate use duration and dose) also makes it difficult to rule out whether other factors influenced the pattern of results observed after 6 months of treatment. In the second study, ex-opiate users (who had stopped using all forms of opiates, including methadone) were compared to controls on the BART and performance did not differ between the groups (Ahn & Vassileva, 2016). Overall, however, given the paucity of studies, further research is necessary to develop a clearer picture of opiate users' decision-making ability under conditions of calculable risk.

The possibility that opiate users may display a propensity to make riskier decisions could be linked to underlying personality traits such as reward responsiveness (i.e., the experience of pleasure in anticipation or in the presence of reward-related stimuli; Taubitz, Pedersen, & Larson, 2015). It has been proposed that higher responsiveness to reward may precipitate drug use (Dawe & Loxton, 2004; Dissabandara et al., 2014). Consistent with this idea, opiate users have been found to be more reward responsive than controls (Dissabandara et al., 2012; Dissabandara et al., 2014; Khosravani, Mehdizadeh, Dortaj, Alvani, & Amirinezhad, 2017) and differences in this aspect of personality are associated with earlier onset of opiate users' drug use (Dissabandara et al., 2014). In the context of decision-making under conditions of calculable risk, higher reward responsiveness may drive opiate users to choose options which may lead to high reward, regardless of the known probability of punishment. In a

study that used computational modelling to identify the cognitive processes underlying the pattern of choices that opiate users made on the BART, it was found that opiate users valued gaining a reward, regardless of the actual anticipated outcome, thus arguably leading to impaired performance on this task (Khodadadi et al., 2010). This suggests that increased reward responsiveness in opiate users may be related to more risky decision-making on the BART. However, to date, only three studies have examined the relationship between reward responsiveness and risk-taking propensity on the BART in any group. While these studies of adolescents (Braams, van Duijvenvoorde, Peper, & Crone, 2015), people with ADHD (Barnhart & Buelow, 2017), and those vulnerable to bipolar disorder (Collett, 2016) found no significant relationship between this personality trait and risky decision-making in these groups, no research has yet analysed whether a relationship exists in opiate users.

The current study had two aims. The first was to assess whether opiate users' decision-making impairment extended to decision-making in a situation where risk was predictable. While previous evidence is limited and somewhat inconsistent, it was anticipated that opiate users in the current study would make riskier choices on the BART. The second aim was to investigate whether opiate users were more reward responsive than controls, and to analyse the extent to which opiate users' performance on the BART was related to reward responsiveness. It was anticipated that opiate users would demonstrate higher reward responsiveness, relative to controls, and that there would be a positive correlation between performance on the BART and reward responsiveness in both groups.

6.3 Method

6.3.1 Participants included in Study 3

Thirty long-term opiate users with a history of heroin dependence were recruited (years of heroin use $M = 16.70$, $SD = 7.98$), as were a group of 43 controls with no history of alcohol or drug dependence. Twenty-nine of the opiate users were currently participating in an opiate substitution program (methadone $n = 19$, suboxone $n = 8$, buprenorphine $n = 2$), and had been using their opiate substitute for an average of 5.97 years ($SD = 4.93$). One opiate user had recently stopped taking their opiate substitute and was only using street heroin. Groups did not differ significantly in age (opiate users $M = 42.10$, $SD = 7.75$; controls $M = 39.05$, $SD = 8.20$; $t(71) = 1.60$, $p = .114$, Cohen's d

= 0.38). Groups differed in years of education (opiate $M = 12.57$, $SD = 2.25$; control $M = 16.65$, $SD = 2.66$; $t(71) = 6.86$, $p < .001$, Cohen's $d = 1.66$) and on premorbid IQ, as measured by the NART (Nelson, 1982) (opiate $M = 101.34$, $SD = 9.34$; control $M = 107.21$, $SD = 7.95$; $t(65) = 2.78$, $p = .007$, Cohen's $d = 0.68$). Participants were recruited in the same manner as presented in Study 2 (see Chapter 5). The participants included all of those who participated in Study 2 (28 opiate users, 34 controls) plus an additional 11 participants (2 opiate users, 9 controls) who completed the measures for Study 3 but did not complete the IGT for Study 2.

6.3.2 Measures

Balloon Analogue Risk Task (BART)

Risky decision-making was measured using the BART (Lejuez et al., 2002). The current study used the 30-trial BART, where participants were presented with 30 balloon trials. For each trial, participants 'pumped' a balloon by clicking on a button (*Pump Balloon*), with each pump earning the participant 5 cents of imaginary money. This money was held in the temporary 'bank', indicated on the screen. For each balloon, a random point of explosion was allocated. If the participant decided to 'collect' that money (by clicking on the *Collect $$$* button below the balloon) before the balloon exploded, the money earned for that balloon was transferred to a permanent bank where it was stored until the end of the task. If the participant reached the explosion point, however, the balloon exploded and the participant lost the money accrued in their temporary bank for that balloon. The average number of pumps across unexploded balloons (i.e., the *adjusted score*) was used as the measure of risky decision-making, with a higher number of pumps indicating riskier decision-making. The BART has demonstrated good incremental and construct validity in healthy and clinical populations (Hunt et al., 2005; Lejuez et al., 2002).

Behavioural Activation System and Behavioural Inhibition System (BAS/BIS) Scale

Sensitivity to reward and punishment was measured using the 24-item BAS/BIS scale (Carver & White, 1994), using three subscales of reward sensitivity: *Reward Response* (BAS-RR), *Fun Seeking* (BAS-FS) and *Drive* (BAS-D). The BIS subscale measured sensitivity to punishment. Higher scores on each subscale indicated greater

DECISION-MAKING AND OPIATE USE

levels of reward or punishment sensitivity. The BAS/BIS scale has demonstrated good reliability and validity as a measure of personality traits (Cooper et al., 2007; Jorm et al., 1998).

6.3.3 Procedures

Informed consent was obtained from participants, and they were tested individually in one session lasting approximately three hours. Regular breaks were provided. After completing the brief background questionnaire, NART and BAS/BIS, participants were administered the protocols specific to Study 2 (IGT and emotional video task) and Study 3 (the BART).

6.3.4 Data analysis

All statistical tests were two-tailed and were conducted using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp). All statistical tests were two-tailed. An alpha level of $p < 0.05$ was considered statistically significant, and effect sizes were estimated using Cohen's d. Outliers were replaced with scores + or - 2SD of the mean where appropriate.

6.4 Results

6.4.1 Decision-making ability under conditions of calculable risk (BART)

Due to group differences in IQ and education, correlations between these variables and BART adjusted pumps scores were examined separately for each group. All correlations were non-significant (all p's >.05). Therefore, these variables were not included as co-variates in further analyses (Tabachnick & Fidell, 2013). There was no significant difference in performance on the BART between opiate users ($M = 26.34$, $SD = 12.64$) and controls ($M = 27.33$, $SD = 11.32$), $t(71) = 0.35$, $p = .728$, Cohen's $d = 0.08$.

When the sample was restricted to the same opiate-using participants who completed the IGT in Study 2 (where they showed deficits relative to controls; opiate $n = 27$, control $n = 34$), the group comparison again revealed no group differences on the BART: opiate users $M = 26.34$, $SD = 13.31$; controls $M = 27.67$, $SD = 11.38$; $t(59) = 0.42$, $p = .676$, Cohen's $d = 0.11$.

DECISION-MAKING AND OPIATE USE

6.4.2 Reward and punishment sensitivity (BAS/BIS)

There were no significant differences between opiate users and controls on the Drive and Fun Seeking subscales of the BAS, or on the BIS (see Table 5). However, controls reported significantly higher reward responsiveness than opiate users on the Reward Responsiveness subscale of the BAS (see Table 5).

6.4.3 Relationship between decision-making under conditions of risk and reward and punishment sensitivity

There were no significant correlations between performance the BART and any of the subscales of the BAS or the BIS, in either group (see Table 6).

Table 5.

Mean Scores and Group Differences on the BAS/BIS Subscales

	Opiate Group $n = 30$		Control Group $n = 43$			
	M	*SD*	*M*	*SD*	*t*	*d*
BAS-D	11.24	1.94	11.28	2.57	0.07	0.02
BAS-RR	16.06	2.50	17.22	1.96	2.21[*]	0.52
BAS-FS	12.55	2.07	12.00	2.22	1.08	0.26
BIS	20.88	3.66	21.04	3.64	0.18	0.04

Note. * $p > .05$; BAS = Behavioural Activation System; BAS-D = BAS Drive subscale; BAS-RR = BAS Reward Responsiveness subscale; BAS-FS = BAS Fun Seeking subscale; BIS = Behavioural Inhibition System.

Table 6.

Correlations Between BART Scores and Subscales of the BAS/BIS

	BART	BAS-D	BAS-RR	BAS-FS	BIS	
BART	-	.21	-.11	.33	.02	
BAS-D	-.03	-	.40*	.50**	-.19	
BAS-RR	-.02	.44*	-	.31	.25	
BAS-FS	-.04	.24	.55***	-	-.05	
BIS	.16	.04	.41*	.18	-	

(Controls below diagonal; Opiate users above diagonal)

Note. * *p* > .05, ** *p* > .01, *** *p* > .001; BAS = Behavioural Activation System; BAS-D = BAS Drive subscale; BAS-RR = BAS Reward Responsiveness subscale; BAS-FS = BAS Fun Seeking subscale; BART = Balloon Analogue Risk Task; BIS = Behavioural Inhibition System. *Opiate users above diagonal, controls below diagonal*

6.5 Discussion

The current study aimed to determine whether the decision-making impairment under conditions of ambiguity observed in opiate users in Study 2, extended to decision-making under conditions of calculable risk. Contrary to expectations, the results indicated that the opiate users in the current study did not show impairment in decision-making under these conditions, as measured by the BART. Furthermore, contrary to expectations, opiate users in the current study were not more reward responsive than controls, and there was no relationship between reward responsiveness and decision-making under conditions of calculable risk in either group.

Based on the results of the current study, it appears that the decision-making impairment of opiate users is not apparent under conditions of calculable risk, as measured by performance on the BART. When the analysis was restricted to the subgroup that completed both the IGT and the BART, performance on the BART again did not differ between groups, suggesting that opiate users are specifically impaired in decision-making under conditions of ambiguity, but not risk. The failure to detect a group difference on the BART does not appear to be the result of low power; the effect size was very small, whereas the effect size for group differences on the IGT (see Study

2) was moderate to large. These results are consistent with those of Khodadadi et al. (2010), who found no difference on the BART between opiate users who had received methadone maintenance treatment for 6 months, and controls. The opiate users in the current study, although not totally abstinent from heroin, had also been receiving methadone and other pharmacological treatment, albeit over a longer period (5.97 years). The fact that Khodadadi et al. (2010), however, did report a difference on the BART between opiate users and controls prior to commencing treatment, raises the possibility that decision-making under conditions of calculable risk may be impaired when people are using street heroin, but this impairment may be attenuated when they receive pharmacological treatment (i.e., methadone). Khodadadi et al. (2010) suggest that methadone treatment "normalises" opiate-users' valuation of reward. Methadone given as a stable dose acts to stabilize the plasma levels of opiates, which has follow-on stabilizing effects for other neurological and hormonal functions (Bart, 2012). While the exact mechanism is unclear, it seems possible that the stabilizing effects of methadone may reduce risky behaviour by reducing the fluctuations in brain chemistry (and withdrawal symptoms) associated with short-acting opiates such as street heroin. Alternative explanations however, are also possible. For example, considering the findings of both the current study and the Khodadadi et al. (2010) study, it may instead be that opiate users who chose to enter (and remain in treatment) are less prone to making risky decisions than those who do not enter or drop-out of treatment. These possibilities require further empirical investigation.

The second aim of the current study was to investigate the role of reward responsiveness in decision-making under conditions of risk. More specifically, the study aimed to investigate whether opiate users were more reward responsive than controls, and to determine whether the level of reward responsiveness was related to the level of decision-making performance in a risky scenario. Contrary to expectations, the opiate users in the current study were not more reward responsive than controls. These results deviate from previous findings, where opiate users have been found to be more reward responsive than controls on the BAS (Dissabandara et al., 2012; Dissabandara et al., 2014; Khosravani et al., 2017). In fact, in the current study, controls' ratings of reward responsiveness were higher than opiate users', suggesting that the controls may have been more sensitive to rewards than the opiate users. If reward responsiveness underpins decision-making under conditions of risk, the higher level of reward

DECISION-MAKING AND OPIATE USE

responsiveness shown by the control group might have been expected to lead to more risky decision-making on the BART in controls, relative to the opiate users. This was not the case, however, with no group differences found. Thus, the current findings are not consistent with the claim that reward responsiveness is a major contributor to performance on a decision-making task involving calculable risk.

The finding that sensitivity to reward was not correlated with BART performance in either group further reinforces the argument that reward responsiveness does not play a major role when making decisions under conditions of predictable risk. The suggestion that decision-making ability under conditions of calculable risk may be associated with sensitivity to reward has been the subject of limited empirical investigation to date. Indeed, only three studies have examined the relationship between the two measures (Barnhart & Buelow, 2017; Braams et al., 2015; Collett, 2016), and each reported no relationship. The current results are consistent with these findings. However, because of the small sample included in this (and the previous) studies, these results should be considered exploratory and require further replication. Further research may also consider the possibility that aspects of personality, other than reward-sensitivity, may be more important predictors of poor decision-making in risky situations. For example, sensation seeking has been found to be related to BART performance (Lauriola, Panno, Levin, & Lejuez, 2014). Given that a previous study (Dissabandara et al., 2014) has reported that opiate users scored higher on a measure of sensation seeking than controls, future research may investigate whether personality traits such as sensation seeking have stronger relationships with decision-making under risk in this group.

Overall, although the number of studies is small, available evidence suggests that the decision-making impairment in opiate user appears to manifest mostly in situations of ambiguity, and not under conditions of predictable risk (Ahn & Vassileva, 2016; Khodadadi et al., 2010). This pattern differentiates opiate users from people dependent on other substances, such as amphetamines, cocaine or cannabis, who demonstrate impaired performance on both the IGT and the BART (Bechara et al., 2001; Bishara et al., 2009; Bolla, Eldreth, Matochik, & Cadet, 2005; Bornovalova, Daughters, Hernandez, Richards, & Lejuez, 2005; Gonzalez, Schuster, Mermelstein, & Diviak, 2015; Hopko et al., 2006; Kohno et al., 2014). However, the reason that opiate users show impaired decision-making in ambiguous, but not risky conditions is not well

understood. It could be argued that task complexity may differentiate performance on the IGT and BART in opiate users. Specifically, the IGT is a more complex task requiring a learning component (Dunn et al., 2006; Dymond, Cella, Cooper, & Turnbull, 2010), whereas the BART does not involve this element of complexity, which has been shown to be impaired in opiate users (Myers et al., 2016). Thus, reward-based learning on the IGT may be more impaired than the simple decision-making process required on the BART. In order to better understand the cognitive (or personality) factors driving particular patterns of behaviour (i.e., impaired decision-making) in this group, a computational modelling approach may be applied (Ahn, Dai, Vassileva, Busemeyer, & Stout, 2016). More specifically, computational modelling may be used to analyse the pattern of responses made on the IGT and BART to better understand why opiate users are particularly impaired when making decisions in conditions of ambiguity, but not risk. This may help to determine the underlying cognitive processes, and how they are impaired, in each of these decision-making contexts.

While it is important to investigate decision-making in opiate users under conditions of calculable risk and conditions of ambiguity, given that problems in each of these may translate to significant problems for an opiate user in everyday life (e.g., Wilson & Vassileva, 2016), it should be noted that these situations represent only two aspects of decision-making ability that can be measured. Further investigation of additional types of decision-making, ideally within a single sample of opiate users, would provide a better understanding of the conditions under which decision-making is impaired in this group. For example, the Ultimatum Game measures decision-making in a social context, where decisions must be made to "split" monetary rewards with a hypothetical other player under fair and unfair conditions (Van't Wout, Kahn, Sanfey, & Aleman, 2006). To date, only one study has analysed this type of decision-making in opiate users. The findings indicated that opiate users were more willing to accept unfair offers when the value of the reward was relatively high, but not when the value of the reward was low, highlighting how decision-making changes depending on reward value and social context (Hou, Zhao, Yao, & Ding, 2016). Similarly, moral decision-making has been explored in users of other substances, with results indicating that substance users tend to choose more utilitarian options in personal moral dilemmas (Carmona-Perera, Verdejo-García, Young, Molina-Fernández, & Pérez-García, 2012; Khemiri, Guterstam, Franck, & Jayaram-Lindström, 2012; Kornreich et al., 2013). This type of

decision-making has not been investigated in opiate users, and presents an additional line of research for future studies.

Overall, the results of this study do not align with previous suggestions that opiate users may be prone to making risky decisions (Baldacchino et al., 2015; Brand et al., 2008; Ersche et al., 2005). In conditions where risk can be calculated, opiate users who are receiving pharmacological treatment made choices in the same way as controls. Future research should, however, continue to investigate the profile of decision-making impairment across the spectrum of decision-making situations and amongst opiate users who are not in treatment. By understanding where specific impairments in decision-making ability lie, therapy may be tailored to provide the most appropriate support to opiate users.

DECISION-MAKING AND OPIATE USE

CHAPTER 7: General Discussion

7.1 Summary of the main findings

From the literature review presented in Chapter 2, it was apparent that opiate use was associated with decision-making impairment. However, the consistency of this impairment, and whether any other factors contributed to the impairment, was unclear. Therefore, the aim of Study 1 was to quantify the decision-making impairment in opiate users via meta-analytic techniques, and to analyse whether other factors may have some impact on the magnitude of this impairment. Consistent with the hypotheses, Study 1 showed that current opiate users demonstrated a significant decision-making impairment ($d = -0.70$) across a range of neuropsychological decision-making tasks, relative to healthy controls. Contrary to expectation, however, longer duration of opiate use was not associated with more severe decision-making impairment. Furthermore, other co-morbid factors thought to impair decision-making over and above opiate use, namely poly-substance dependence and head injury, did not significantly alter the severity of the deficit. It was also hypothesised that studies that analysed decision-making in ex-users of opiates would demonstrate a reduced impairment compared to studies that included current users of opiates. However, results indicated that abstinence was not associated with a significant reduction in the decision-making impairment. Furthermore, longer duration of abstinence was not associated with better decision-making capacity. Overall then, the decision-making impairment in opiate users appears to be relatively severe, and is not mitigated or worsened by other factors common in opiate users.

Study 2 aimed to determine whether reduced emotional responding provided an explanation for impaired decision-making in opiate users, as suggested by the somatic marker hypothesis model of decision-making. This model contends that abnormal emotional processing may lead to an inability to respond normally to the outcomes of choices (i.e., rewards and punishments), thereby leading to an inability to form anticipatory somatic markers which would otherwise guide decision-making. The results of Study 2 demonstrated that, although opiate users were impaired in their decision-making capacity relative to controls ($d = -0.67$), they did not demonstrate blunted emotional responses outside of a decision-making context relative to controls, either in subjective ratings or through objective measures of emotional arousal (see

DECISION-MAKING AND OPIATE USE

Chapter 5, sections 5.6.2 and 5.6.3). Furthermore, opiate users did not differ in their capacity to respond to punishment and rewards in a decision-making context. Most notably, opiate users demonstrated normal anticipatory somatic marking. However, stronger marking prior to disadvantageous decisions (relative to advantageous decisions) was associated with worse decision-making performance in this group (see Chapter 5, section 5.6.6). In an extension to this study, it was also found that opiate users were no less accurate than controls in their ability to perceive physiological changes (i.e., they did not have reduced interoceptive accuracy). Overall, the findings of Study 2 confirm a decision-making impairment in opiate users, and suggest that they may make disadvantageous decisions.

The results of Study 2 demonstrated that decision-making was impaired under conditions of ambiguity, but could not clarify whether opiate users also made poor decisions in other contexts. Therefore, the aim of Study 3 was to analyse whether opiate users made poor decisions under conditions of calculable risk as opposed to ambiguous situations, and whether this behaviour was associated with underlying differences in personality, namely increased responsiveness to reward. The results of Study 3 demonstrated that opiate users did not differ from controls in their capacity to make decisions under conditions of calculable risk and that they were no more responsive to reward than controls. Furthermore, reward responsiveness was not associated with more risky decision-making in opiate users or controls.

Taken together, the results of this thesis suggest that opiate users demonstrate impaired decision-making in situations of ambiguity, but not risk, and that this impairment is not driven by an inability to emotionally respond to the consequences of their choices.

7.2 Contributions and implications of the research

The results of this PhD thesis contribute to the literature surrounding opiate use, both in terms of decision-making and emotional processing capacity. In addition, the results of these studies also have important implications for the treatment of opiate dependence and provide at least some explanation for opiate users' continued engagement in the addiction cycle and therefore their poor quality of life. The sections below outline the contributions and implications of this research.

7.2.1 Cognitive and emotional processing in opiate users

Opiate use has been associated with a range of cognitive deficits (Baldacchino et al., 2012; Ersche & Sahakian, 2007) which may stem from neurological abnormalities of the frontal lobes (Wollman et al., 2016). However, previous research suggests that decision-making is the most consistently and severely impaired cognitive function, with less consistent impairment demonstrated in other cognitive functions (Baldacchino et al., 2012). This pattern is supported by the results of the meta-analysis in Study 1 as well as the results regarding executive function in the current sample, presented in Chapter 4 (see section 4.6). In the meta-analysis, both current (d = -0.70) and ex-users of opiates (d = -0.43) demonstrated significant decision-making impairment relative to healthy controls while, as reported in in Chapter 4, opiate users performed no differently to controls in two of three measures of executive function, with only a moderate difference between groups on a measure of working memory. Furthermore, opiate users also demonstrated impaired decision-making on the Iowa Gambling Task (IGT) in Study 2, relative to controls. Thus, the pattern of results of the empirical studies presented in this thesis extends, and is consistent with, the literature regarding cognitive function and decision-making in opiate users.

The current research also adds to the relatively small body of literature surrounding emotion processing capacity in opiate users. While some previous research has found that opiate users demonstrate reduced emotion processing capacity (Aguilar de Arcos et al., 2008; Gerra et al., 2003), others have not found an impairment (Carcoba et al., 2011; Lubman et al., 2009; Smoski et al., 2011; Wang et al., 2010). The results of Study 2 are consistent with the latter. Therefore, this research adds to the sparse literature regarding the emotion processing capacity of opiate users and adds weight to the argument that opiate use is not associated with reduced emotion processing capacity. However, some caution must be applied to these conclusions, given that the opiate users included in this study were treated with opiate substitutes. Indeed, in the previous studies of opiate users' emotional responsiveness, almost all opiate users were also receiving pharmacological treatment. Thus, these results may only apply to this group and not to untreated users of illicit opiates. Nevertheless, these results shed some light on the emotion processing capacity and decision-making ability of opiate users currently in treatment.

DECISION-MAKING AND OPIATE USE

While the current research contributes to the literature regarding cognitive and emotional processing in opiate users, this and most other studies of addicted populations cannot address the key issue of causality. That is, cross-sectional studies of people with substance dependence and cognitive impairment cannot tease out whether cognitive impairment pre-dated drug dependence (placing this group of people at risk of making poor decisions, ultimately leading to drug dependence), or whether neural and cognitive change occurred after the initiation of opiate use. Indeed, a third pathway also seems possible, whereby a pre-existing impairment may be exacerbated by heavy drug use. Ideally, this question could be answered by longitudinal research, which would track the cognitive abilities of at-risk populations prior to initiating heavy drug use, during dependence, and then after abstinence. For example, populations at risk of developing opiate dependence may be identified by psychosocial markers in childhood and adolescence (Darke, 2011; Verdejo-Garcia et al., 2008), and then cognitive abilities may be monitored continuously throughout adulthood. Alternatively, the cognitive function of clinical groups who may be at higher risk of developing substance dependence, such as people with schizophrenia (Chambers, Krystal, & Self, 2001) or ADHD (Chilcoat & Breslau, 1999), could be assessed at the onset of the disorder and monitored over time. However, longitudinal research is difficult, given the expense of recruiting and then following drug-using populations for long periods of time, the high likelihood of dropouts, and the fact that heroin-using participants are often lost from research due to death (up to 50% after 30 years; Grella & Lovinger, 2011; Hser et al., 2007). Thus, cross-sectional research is the norm, but is nevertheless valuable in that it can be pooled and meta-analysed, as in Study 1, to systematically examine a number of factors and analyse their impact on cognitive functioning.

7.2.2 Implications of the current findings for the treatment of opiate dependence

Impaired decision-making in everyday life outside the laboratory may contribute to the poorer quality of life and the cycle of addiction that opiate users are often engaged in. More specifically, impaired decision-making may lead to reduced compliance with treatment programs, possibly leading to relapse, and therefore to the negative outcomes that are often experienced by this group, such as disease and death. The research presented in this thesis provides some insight into the factors that may (or may not) contribute to impaired decision-making in this group, and can be used to

understand what forms of support opiate users need in order to manage and/or overcome this addiction.

As outlined in Chapter 2 (see section 2.2: 'Cycle of addiction in opiate users'), opiate users who enter treatment often cycle through phases of heavy use, treatment, abstinence, and relapse (Darke, 2011; Darke et al., 2009). For example, studies have shown that, on average, heroin users entering treatment have done so at least 5 times previously (Hser et al., 2007; Substance Abuse and Mental Health Services Administration, 2017). Many (67.7%) of the opiate users included in Studies 2 and 3 also reported having been through multiple treatment cycles, and reflect the general population of opiate users who go through multiple treatment and relapse episodes over the course of their "career". This suggests that while many opiate users are able to engage positively with treatment services, they may struggle with continuing to make good decisions that will help maintain their engagement in treatment, and may ultimately relapse. Indeed, poor performance on laboratory-based measures of decision-making has been shown to predict relapse during treatment (Passetti et al., 2011; Passetti et al., 2008), and may therefore undermine the successful maintenance of abstinence.

Pharmacological treatment of opiate dependence is often supplemented with psychological intervention (Gowing, Farrell, Bornemann, Sullivan, & Ali, 2011) and research demonstrates that psychological interventions such as cognitive behavioural therapy (CBT), motivational interviewing, and contingency management can reduce drug taking in opiate users (Bernstein et al., 2005; Carroll, Ball, Nich, & et al., 2001; Scherbaum et al., 2005; Schottenfeld et al., 2005). However, given that opiate users in treatment often continue using heroin (Bloor, McIntosh, McKeganey, & Robertson, 2008) and often relapse into heavy use (Darke et al., 2016; Jimenez-Trevino et al., 2011), psychological therapies may not provide the support that opiate users need to continue making good decisions in particular situations, which may contribute to the continued cycle of addiction. For example, CBT aims to teach opiate users to avoid high-risk situations where they may be vulnerable to drug use, and to use cognitive and behavioural strategies to cope effectively when these risky situations occur (Carroll & Onken, 2005). However, the results of Study 3 suggest that opiate users may be able to recognise and avoid making poor choices in these risky situations. Instead, relapse may stem from an inability to make adaptive choices in *ambiguous* situations. For example,

an opiate user who chooses to use heroin for the first time since commencing treatment may not know how this will interfere with their prescribed pharmacological treatment. Thus, failure to make good decisions in these ambiguous situations could lead to poor choices which may consequently lead to relapse. Indeed, most decision-making scenarios are ambiguous in real-life situations. Therefore, successful treatment of opiate dependence may require a focus on strategies for ambiguous situations. For example, CBT may be modified to help opiate users identify *any* decision-making scenario where they may be likely to make a poor decision (ambiguous or risky), with therapists role-playing likely scenarios so that these situations may become less ambiguous through experience.

The results of Study 2 demonstrated that opiate users are able to produce physiological warning signals prior to bad decisions, and are aware of these changes in physiology, i.e., opiate users had good interoceptive accuracy. Therefore, these results suggest that a greater focus on helping opiate users to tune into their physiology may be helpful. Mindfulness therapy teaches people to be more aware of their feelings and bodily sensations (Marcus & Zgierska, 2009). Thus, mindfulness therapy may help opiate users better interpret physiological signals and more effectively factor their emotional state into decision-making. Research has shown that mindfulness meditation on its own can reduce substance use and cravings in substance users (Bowen et al., 2014; Grow, Collins, Harrop, & Marlatt, 2015; Witkiewitz, Bowen, Douglas, & Hsu, 2013), and when used in conjunction with Goal Management Therapy, a cognitive remediation therapy which trains cognitive control processes, mindfulness can improve decision-making capacity in poly-substance abusers (Alfonso, Caracuel, Delgado-Pastor, & Verdejo-García, 2011). Mindfulness has been shown to effectively reduce opiate craving and misuse in chronic pain patients (Garland, Froeliger, Zeidan, Partin, & Howard, 2013). However, future research could analyse the use of mindfulness in long-term users of heroin to determine whether this may be an effective alternative modality for psychological intervention. Specifically, mindfulness may be used to help opiate users recognise the heightened physical and emotional reactions that follow making a disadvantageous decision. They may then better understand what an anticipatory somatic marker before a disadvantageous decision "feels" like and use this to avoid making a disadvantageous decision again in the future.

It should be noted, however, that the success of any treatment, whether pharmacological or psychological in nature, is dependent on the motivation of the opiate user to reduce or terminate illicit opiate use. Although enrolment in a treatment program may suggest some level of motivation to become abstinent, maintaining that motivation can create another barrier to treatment. Specifically, the drug user must shift their motivation away from seeking drugs (and their rewarding properties) towards new activities such as seeking support and other more adaptive behaviours (Verdejo-Garcia, Chong, Stout, Yücel, & London, 2017). Indeed, lack of motivation to perform well on decision-making tasks in the laboratory may negatively skew results in opiate users. Future studies may therefore benefit from the inclusion of a test of motivation or even the use of real money incentives for decision-making tasks. Previous research has demonstrated real money incentives can remediate cognitive control deficits in other populations such as aging and Parkinson's disease (e.g., Harsay, Buitenweg, Wijnen, Guerreiro, & Ridderinkhof, 2010). Studies of contingency management in opiate users, where users are rewarded for adaptive behaviours with incentives such as vouchers, have also demonstrated this is an effective therapeutic technique. Thus, more research needs to focus on the motivational drives of opiate users and target these in conjunction with decision-making processes (Verdejo-Garcia, Chong, et al., 2017).

7.3 Limitations of the current research

While the current research provides novel information regarding decision-making and emotion processing in opiate users, it is not without its limitations. One limitation was that self-report was used to collect information regarding abstinence from drug use in the 24 hours prior to testing. Self-report was also used to report psychiatric co-morbidities. This may have led to the unwitting inclusion of participants who were intoxicated at the time of testing or who did not meet the exclusion criteria relating to psychiatric diagnoses. The presence of co-morbid psychiatric conditions may cloud the interpretability of the decision-making capacity of opiate users, given that psychiatric conditions such as schizophrenia are independently associated with deficits on the IGT (e.g., Lee et al., 2007; Shurman, Horan, & Nuechterlein, 2005). Similarly, acute intoxication with illicit opiates or other drugs may have impeded cognitive function throughout the testing session. While steps were taken to minimise the inclusion of participants who had significant co-morbid psychiatric conditions or who were acutely intoxicated, it would have been preferable to conduct a drug-screen analysis using a

DECISION-MAKING AND OPIATE USE

urine test or similar, to confirm abstinence from drug use on the day of testing, and to have access to psychiatric reports of all opiate users, given the common co-morbidity of drug and psychiatric issues in this population. However, opiate users were recruited from the community, so verified psychiatric diagnoses were not available. Similarly, it would have been valuable to collect time since prescription-opiate dose to disentangle the acute effect of opiates from those that are longer term. It may therefore be valuable for future studies to collect this information to better understand the acute effect of opiates on cognition.

A second limitation is the exclusion of the control group based on a clinical diagnosis of depression or anxiety. While opiate users were only excluded for severe psychiatric diagnoses, controls were excluded if they reported depression and anxiety, which may have biased the sample distribution. However, control participants were not excluded based on scores on the HADS (a commonly-used measure of depressive and anxiety symptoms, Bjelland et al., 2002), with scores on this measure indicating a wide variability in mood states in controls (depression range: 0-11; anxiety range: 0-17) that was not correlated with decision-making performance.

The final limitation is the nature of the tools used to assess decision-making in the laboratory. Although decision-making tasks such as the IGT and the BART aim to simulate decision-making in real life conditions of ambiguity and risk, the consequences of actions on these measures are necessarily artificial. In other words, these tasks do not provide an opportunity to experience 'real' consequences (i.e., lose large sums of money), given the ethical requirement not to cause harm to participants. Thus, decision-making tasks conducted in the laboratory can only provide an indication of how decision-makers might behave in a real-life situation (Collett, 2016). Research into the ecological validity of the IGT and other decision-making tools is limited but generally supported (Buelow & Suhr, 2009; Dunn et al., 2006), with performance on the BART and IGT correlating with real life risk taking behaviour (Aklin et al., 2005; Golub et al., 2016; Hopko et al., 2006; Lejuez et al., 2003; Lejuez et al., 2002; Lejuez et al., 2004). To better understand decision-making in real life, future research may adopt ecological momentary assessment methods to track decisions made in real-time via a mobile app, with previous research demonstrating relatively high compliance in opiate users (Serre et al., 2012).

7.4 Strengths of the current research

In addition to the contribution to the literature regarding decision-making in opiate users, there are a number of other strengths of the current research. Firstly, this study expands on previous studies of emotional experience in opiate users by incorporating dynamic emotion-eliciting stimuli (i.e., films), which may elicit a stronger and longer lasting emotional response than static images (Bos, Jentgens, Beckers, & Kindt, 2013). Secondly, given that emotional response goes beyond subjective awareness (Fernández et al., 2012), the inclusion of skin conductance arousal provides an additional line of evidence that supports the idea that opiate users experience emotions in a similar way to controls. In addition, including an objective measure of emotional arousal (i.e., the SCR) during decision-making provides an additional source of evidence regarding emotional arousal during-decision-making. The involvement of emotional arousal in decision-making is often ignored in studies of cognition. Thus, by incorporating an objective measure of emotional arousal, this study expands knowledge of how emotion is linked (or not linked) to decision-making in a group with severe decision-making impairment.

A third strength of the current research is that the current opiate-using sample was representative of typical opiate users functioning independently in the community who enter treatment. Opiate users were recruited from the community via pharmacies that dispensed opiate substitutes and from organisations that provided support to opiate users living in the community. Participation in these studies was reliant on study participants' motivation and ability to attend testing sessions. Therefore, the opiate users recruited represented a high-functioning and motivated subset of the wider clinical group. The nature of the sample means that the results of Studies 2 and 3 are directly relevant to the real life functioning and decision-making capacity of treatment-maintained opiate users living in the community.

7.5 Directions for future research

The findings presented in this thesis highlights new avenues for future research. More specifically, as outlined below, future research should explore decision-making in ex-opiate users in more detail; use computational modelling to better understand cognitive processes that may be involved in decision-making; and investigate other types of decision-making in opiate users. By better understanding the scope of the

decision-making impairment and other factors which may contribute to this deficit, existing treatment options for addiction may be adapted, or new treatment modalities may be implemented, to further support opiate users through treatment and abstinence.

7.5.1 Further investigation of decision-making in ex-users

The first key avenue for research is further study of decision-making in ex-users of opiates. The meta-analysis from Study 1 demonstrated that, although ex-users had a significant decision-making impairment relative to controls, there was a trend for improved decision-making capacity following a mean of 0.89 years of abstinence. However, it is possible that those people included in the studies of ex-users were made up of a combination of opiate users who had previously been abstinent on multiple occasions, and "first timers" who had not previously reached abstinence. Ex-users who had been abstinent on multiple occasions may be able to draw on skills learnt in previous treatment episodes to inform decision-making, while "first timers" may have more impaired decision-making capacity. Thus, more research is necessary in ex-users, investigating the impact of the number of times opiate users have achieved abstinence, as well as the impact of longer periods of abstinence on decision-making capacity, especially as a study by Zhang, Shi, et al. (2011) found that, after two years of abstinence, decision-making in opiate users was comparable to that of controls. Given that the average abstinence duration of ex-users included in the meta-analysis in Study 1 was relatively short, the ability to draw conclusions regarding the issue of length of abstinence is somewhat limited. Thus, future research should undertake further cross-sectional and longitudinal research in people who become completely abstinent to determine how decision-making capacity changes over time, and whether any meaningful recovery in this cognitive process occurs. Furthermore, very few studies have analysed risky decision-making in ex-users of opiates. As demonstrated in the meta-analysis in Study 1, the majority of studies analysing decision-making in ex-users focus on decision-making under conditions of ambiguity (via the IGT), with only one study analysing risky decision-making via performance on the Cambridge Gambling Task and the BART. Future research therefore also needs to further analyse the decision-making capacity of ex-users in risky situations, which may help determine whether poor decision-making in these situations contributes to relapse in this population.

7.5.2 Cognitive processes involved in the decision-making capacity of opiate users

The results of Study 2 demonstrated that the decision-making impairment in opiate users was not due to reduced emotional responding. This suggests that other cognitive processes may intervene between the activation of a somatic marker and the selection of a decision. Thus, future research may investigate what cognitive processes occur between the activation of a somatic state, and the choice to pick disadvantageous options.

To address this, computational modelling methods may be adopted to mathematically model the cognitive processes underlying decision-making in opiate users. Computational modelling allows researchers to analyse the pattern of choices that people make during decision-making tasks and break down the complex cognitive processes involved in making decisions. These processes may include learning from experience and what value an individual places on a particular outcome (Ahn et al., 2016; Verdejo-Garcia, Chong, et al., 2017). Researchers have started to adopt this analysis technique to better understand the cognitive processes that contribute to impaired decision-making substance users (Bishara et al., 2009; Fridberg et al., 2010; Vassileva et al., 2013), including opiate users (Ahn et al., 2014; Khodadadi et al., 2010). The only study to date that has conducted computational modelling of performance on the BART in opiate users suggests that people under the acute influence of illicit opiates place more intrinsic value on rewards (Khodadadi et al., 2010), while modelling of choices on the IGT suggests that ex-users pay less attention to losses (Ahn et al., 2014). However, further research is required using computational modelling to better understand cognitive processes underlying decision-making in opiate users across the spectrum of the addiction cycle.

In addition, future research may look at other fields of cognition to understand how deficiencies in decision-making may relate to other aspects of impaired cognition. For example, previous research has found that opiate users are impaired in their ability to mentally travel forward in time, referred to as episodic foresight or future thinking (Mercuri et al., 2015). Similarly, opiate users are impaired in their ability to remember to perform intended actions in the future (prospective memory; Terrett et al., 2014). Both of these capacities may be important for making decisions which will have long-

DECISION-MAKING AND OPIATE USE

term consequences. In other words, if opiate users are unable to "see into the future", this may have some impact on their decision-making capacity. Research to date has not analysed the relationship between future thinking, prospective memory, and decision-making in opiate users. Thus, this represents another area for further research into the cognitive processes underlying decision-making in opiate users.

7.5.3 Alternative types of decision-making in opiate users

Future research may also start investigating other types of decision-making in opiate users. For example, as noted in Study 3, only one study has analysed the decision-making capacity of opiate users in more social situations, using the Ultimatum Game. It found that opiate users were more willing than controls to accept unfair offers when the value of the reward was relatively high (Van't Wout et al., 2006). More recent research has shown that substance users' willingness to accept unfair offers may be related to reduced emotional responding via neural abnormalities in the orbitofrontal cortex (Verdejo-Garcia, Verdejo-Roman, Albein-Urios, Martinez-Gonzalez, & Soriano-Mas, 2017). Future research could analyse whether poor decision-making in social situations is underpinned by the same neural abnormalities which arguably contribute to poor decision-making in ambiguous situations.

Opiate users' performance on measures of moral decision-making may also help to clarify the role of emotion in decision-making. So far, no research has analysed decision-making in moral situations in opiate users. However, research has shown that substance users tend to make more utilitarian decisions than controls (Carmona-Perera, Reyes del Paso, Pérez-García, & Verdejo-García, 2013; Carmona-Perera et al., 2012; Khemiri et al., 2012; Kornreich et al., 2013). More utilitarian decision-making in moral contexts may be indicative of reduced emotional responsiveness (Moretto, Làdavas, Mattioli, & Di Pellegrino, 2010). Given that the results of Study 2 demonstrated that opiate users' emotional responsiveness was no different to controls, future research should investigate whether opiate users also demonstrate a pattern of moral decision-making comparable to that of controls.

7.6 Conclusions

This research project is the first to systematically analyse the decision-making impairment in opiate users. Prior to this research, it was unknown whether co-morbid factors such as head injury and polysubstance dependence had a significant impact on

DECISION-MAKING AND OPIATE USE

the decision-making capacity of opiate users, and it was assumed that abstinence from opiates would lead to better decision-making capacity. The findings from the meta-analysis in the first study clarified that the decision-making impairment in opiate users is not significantly mitigated by abstinence, at least in the short term, nor is it significantly worsened by head injury or poly-substance dependence. The second study was the first to analyse the applicability of the somatic marker hypothesis to opiate users, with results demonstrating that the decision-making impairment in opiate users was not due to impaired emotion processing capacity. These results also demonstrated that opiate users were able to produce somatic warning signals which should steer decision-making away from poor long-term outcomes, but were unable to appropriately use this information. Finally, the third study demonstrated that poor decision-making in opiate users was not due to more risky behaviour on the part of opiate users, suggesting a specific impairment in situations of ambiguity. This research makes a significant contribution to the literature relating to the decision-making capacity of opiate users, and provides a platform for future investigation into the cognitive processes underlying impaired decision-making in opiate users. Ultimately, these results may contribute to tailored treatment options in a drug-using population highly vulnerable to relapse.

References

Aguilar de Arcos, F., Verdejo-García, A., Ceverino, A., Montañez-Pareja, M., López-Juárez, E., Sánchez-Barrera, M., . . . Pérez-García, M. (2008). Dysregulation of emotional response in current and abstinent heroin users: Negative heightening and positive blunting. *Psychopharmacology, 198*(2), 159-166. doi: 10.1007/s00213-008-1110-2

Ahn, W. Y., Dai, J., Vassileva, J., Busemeyer, J. R., & Stout, J. C. (2016). Computational modeling for addiction medicine: From cognitive models to clinical applications. *Progress in Brain Research, 224*, 53-65. doi: 10.1016/bs.pbr.2015.07.032

Ahn, W. Y., Vasilev, G., Lee, S. H., Busemeyer, J. R., Kruschke, J. K., Bechara, A., & Vassileva, J. (2014). Decision-making in stimulant and opiate addicts in protracted abstinence: Evidence from computational modeling with pure users. *Decision Neuroscience, 5*, 849. doi: 10.3389/fpsyg.2014.00849

Ahn, W. Y., & Vassileva, J. (2016). Machine-learning identifies substance-specific behavioral markers for opiate and stimulant dependence. *Drug and Alcohol Dependence, 161*, 247-257. doi: 10.1016/j.drugalcdep.2016.02.008

Aklin, W. M., Lejuez, C. W., Zvolensky, M. J., Kahler, C. W., & Gwadz, M. (2005). Evaluation of behavioral measures of risk taking propensity with inner city adolescents. *Behaviour Research and Therapy, 43*(2), 215-228. doi: 10.1016/j.brat.2003.12.007

Alfonso, J. P., Caracuel, A., Delgado-Pastor, L. C., & Verdejo-García, A. (2011). Combined goal management training and mindfulness meditation improve executive functions and decision-making performance in abstinent polysubstance abusers. *Drug and Alcohol Dependence, 117*(1), 78-81. doi: 10.1016/j.drugalcdep.2010.12.025

Areias, G., Paixao, R., & Figueira, A. P. C. (2016). Decision-making in opioid-dependent individuals using the Iowa Gambling Task. *Cuadernos de medicina psicosomática y psiquiatria de enlace, 118*, 59-70.

Astals, M., Domingo-Salvany, A., Buenaventura, C. C., Tato, J., Vazquez, J. M., Martín-Santos, R., & Torrens, M. (2008). Impact of substance dependence and dual diagnosis on the quality of life of heroin users seeking treatment. *Substance Use and Misuse, 43*(5), 612-632. doi: 10.1080/10826080701204813

Australian Catholic University. (2015). Guidelines on the Preparation and Presentation of a Research or Doctoral Thesis for Examination.

Australian National Health and Medical Research Council. (2001). Australian alcohol guidelines: Health risks and benefits. Commonwealth of Australia, Canberra.

Baldacchino, A., Balfour, D. J. K., & Matthews, K. (2015). Impulsivity and opioid drugs: Differential effects of heroin, methadone and prescribed analgesic medication. *Psychological Medicine, 45*(6), 1167-1179. doi: 10.1017/S0033291714002189

Baldacchino, A., Balfour, D. J. K., Passetti, F., Humphris, G., & Matthews, K. (2012). Neuropsychological consequences of chronic opioid use: A quantitative review and meta-analysis. *Neuroscience and Biobehavioral Reviews, 36*, 2056-2068. doi: 10.1016/j.neubiorev.2012.06.006

Barnhart, W. R., & Buelow, M. T. (2017). Assessing impulsivity: Relationships between behavioral and self-report measures in individuals with and without

self-reported ADHD. *Personality and Individual Differences, 106*, 41-45. doi: 10.1016/j.paid.2016.10.034

Barry, D., & Petry, N. M. (2008). Predictors of decision-making on the iowa gambling task: Independent effects of lifetime history of substance use disorders and performance on the trail making test. *Brain and Cognition, 66*(3), 243-252. doi: 10.1016/j.bandc.2007.09.001

Bart, G. (2012). Maintenance medication for opiate addiction: The foundation of recovery. *Journal of Addictive Diseases, 31*(3), 207-225. doi: 10.1080/10550887.2012.694598

Bechara, A. (2004). The role of emotion in decision-making: Evidence from neurological patients with orbitofrontal damage. *Brain and Cognition, 55*(1), 30-40. doi: 10.1016/j.bandc.2003.04.001

Bechara, A., & Damasio, A. R. (2005). The somatic marker hypothesis: A neural theory of economic decision. *Games and Economic Behavior, 52*(2), 336-372. doi: 10.1016/j.geb.2004.06.010

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50*(1), 7-15. doi: 10.1016/0010-0277(94)90018-3

Bechara, A., & Damasio, H. (2002). Decision-making and addiction (part I): Impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. *Neuropsychologia, 40*(10), 1675-1689. doi: 10.1016/S0028-3932(02)00015-5

Bechara, A., Damasio, H., & Damasio, A. R. (2000). Emotion, decision making and the orbitofrontal cortex. *Cerebral Cortex, 10*(3), 295-307. doi: 10.1093/cercor/10.3.295

Bechara, A., Damasio, H., Damasio, A. R., & Lee, G. P. (1999). Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *Journal of Neuroscience, 19*(13), 5473-5481.

Bechara, A., Damasio, H., Tranel, D., & Anderson, S. W. (1998). Dissociation of working memory from decision making within the human prefrontal cortex. *Journal of Neuroscience, 18*(1), 428-437.

Bechara, A., Dolan, S., Denburg, N., Hindes, A., Anderson, S. W., & Nathan, P. E. (2001). Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia, 39*(4), 376-389. doi: 10.1016/S0028-3932(00)00136-6

Bechara, A., Tranel, D., & Damasio, H. (2000). Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain, 123*(11), 2189-2202. doi: 10.1093/brain/123.11.2189

Bechara, A., Tranel, D., Damasio, H., & Damasio, A. R. (1996). Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. *Cerebral Cortex, 6*(2), 215-225. doi: 10.1093/cercor/6.2.215

Bernstein, J., Bernstein, E., Tassiopoulos, K., Heeren, T., Levenson, S., & Hingson, R. (2005). Brief motivational intervention at a clinic visit reduces cocaine and heroin use. *Drug and Alcohol Dependence, 77*(1), 49-59. doi: 10.1016/j.drugalcdep.2004.07.006

Biernacki, K., McLennan, S. N., Terrett, G., Labuschagne, I., & Rendell, P. G. (2016). Decision-making ability in current and past users of opiates: A meta-analysis. *Neuroscience and Biobehavioral Reviews, 71*, 342-351. doi: 10.1016/j.neubiorev.2016.09.011

DECISION-MAKING AND OPIATE USE

Bishara, A. J., Pleskac, T. J., Fridberg, D. J., Yechiam, E., Lucas, J., Busemeyer, J. R., . . . Stout, J. C. (2009). Similar processes despite divergent behavior in two commonly used measures of risky decision making. *Journal of Behavioral Decision Making, 22*(4), 435-454. doi: 10.1002/bdm.641

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the hospital anxiety and depression scale: An updated literature review. *Journal of Psychosomatic Research, 52*(2), 69– 77. doi: 10.1016/S0022-3999(01)00296-3

Bloor, M., McIntosh, J., McKeganey, N., & Robertson, M. (2008). 'Topping up'methadone: An analysis of patterns of heroin use among a treatment sample of scottish drug users. *Public Health, 122*(10), 1013-1019. doi: 10.1016/j.puhe.2008.01.007

Bolla, K. I., Eldreth, D. A., Matochik, J. A., & Cadet, J. L. (2005). Neural substrates of faulty decision-making in abstinent marijuana users. *Neuroimage, 26*(2), 480-492. doi: 10.1016/j.neuroimage.2005.02.012

Bornovalova, M. A., Daughters, S. B., Hernandez, G. D., Richards, J. B., & Lejuez, C. W. (2005). Differences in impulsivity and risk-taking propensity between primary users of crack cocaine and primary users of heroin in a residential substance-use program. *Experimental and Clinical Psychopharmacology, 13*(4), 311-318. doi: 10.1037/1064-1297.13.4.311

Bos, M. G. N., Jentgens, P., Beckers, T., & Kindt, M. (2013). Psychophysiological response patterns to affective film stimuli. *PLoS ONE, 8*(4), e62661. doi: 10.1371/journal.pone.0062661

Boucsein, W. (2012). *Electrodermal activity* (2nd ed.). New York, NY: Springer Science & Business Media.

Bowen, S., Witkiewitz, K., Clifasefi, S. L., Grow, J. C., Chawla, N., Hsu, S. H., . . . Lustyk, M. K. (2014). Relative efficacy of mindfulness-based relapse prevention, standard relapse prevention, and treatment as usual for substance use disorders: a randomized clinical trial. *JAMA Psychiatry, 71*(5), 547-556. doi: 10.1001/jamapsychiatry.2013.4546

Braams, B. R., van Duijvenvoorde, A. C. K., Peper, J. S., & Crone, E. A. (2015). Longitudinal changes in adolescent risk-taking: A comprehensive study of neural responses to rewards, pubertal development, and risk-taking behavior. *Journal of Neuroscience, 35*(18), 7226-7238. doi: 10.1523/jneurosci.4764-14.2015

Bradley, M. M., & Lang, P. J. (1994). Measuring emotion: The self-assessment manikin and the semantic differential. *Journal of Behavior Therapy and Experimental Psychiatry, 25*(1), 49-59. doi: 10.1016/0005-7916(94)90063-9

Brand, M., Labudda, K., & Markowitsch, H. J. (2006). Neuropsychological correlates of decision-making in ambiguous and risky situations. *Neural Networks, 19*(8), 1266-1276. doi: 10.1016/j.neunet.2006.03.001

Brand, M., Recknor, E. C., Grabenhorst, F., & Bechara, A. (2007). Decisions under ambiguity and decisions under risk: Correlations with executive functions and comparisons of two different gambling tasks with implicit and explicit rules. *Journal of Clinical and Experimental Neuropsychology, 29*(1), 86-99. doi: 10.1080/13803390500507196

Brand, M., Roth-Bauer, M., Driessen, M., & Markowitsch, H. J. (2008). Executive functions and risky decision-making in patients with opiate dependence. *Drug and Alcohol Dependence, 97*(1), 64-72. doi: 10.1016/j.drugalcdep.2008.03.017

Brevers, D., Bechara, A., Cleeremans, A., & Noel, X. (2013). Iowa Gambling Task (IGT): twenty years after – gambling disorder and IGT. *Frontiers in Psychology, 4*(665). doi: 10.3389/fpsyg.2013.00665

Britton, J. C., Taylor, S. F., Sudheimer, K. D., & Liberzon, I. (2006). Facial expressions and complex IAPS pictures: Common and differential networks. *Neuroimage, 31*(2), 906-919. doi: 10.1016/j.neuroimage.2005.12.050

Buelow, M. T., & Blaine, A. L. (2015). The assessment of risky decision making: A factor analysis of performance on the Iowa Gambling Task, Balloon Analogue Risk Task, and Columbia Card Task. *Psychological Assessment, 27*(3), 777-785. doi: 10.1037/a0038622

Buelow, M. T., & Suhr, J. A. (2009). Construct validity of the Iowa Gambling Task. *Neuropsychology Review, 19*(1), 102-114. doi: 10.1007/s11065-009-9083-4

Bull, P. N., Tippett, L. J., & Addis, D. R. (2015). Decision making in healthy participants on the Iowa Gambling Task: New insights from an operant approach. *Frontiers in Psychology, 6*(391). doi: 10.3389/fpsyg.2015.00391

Burgess, P. W., & Shallice, T. (1996). The Hayling and Brixton tests. Bury St Edmonds, England: Thames Valley Test Company.

Carcoba, L. M., Contreras, A. E., Cepeda-Benito, A., & Meagher, M. W. (2011). Negative affect heightens opiate withdrawal-induced hyperalgesia in heroin dependent individuals. *Journal of Addictive Diseases, 30*(3), 258-270. doi: 10.1080/10550887.2011.581985

Carmona-Perera, M., Reyes del Paso, G. A., Pérez-García, M., & Verdejo-García, A. (2013). Heart rate correlates of utilitarian moral decision-making in alcoholism. *Drug and Alcohol Dependence, 133*(2), 413-419. doi: 10.1016/j.drugalcdep.2013.06.023

Carmona-Perera, M., Verdejo-García, A., Young, L., Molina-Fernández, A., & Pérez-García, M. (2012). Moral decision-making in polysubstance dependent individuals. *Drug and Alcohol Dependence, 126*(3), 389-392. doi: 10.1016/j.drugalcdep.2012.05.038

Carroll, K. M., Ball, S. A., Nich, C., & et al. (2001). Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: Efficacy of contingency management and significant other involvement. *Archives of General Psychiatry, 58*(8), 755-761. doi: 10.1001/archpsyc.58.8.755

Carroll, K. M., & Onken, L. S. (2005). Behavioral therapies for drug abuse. *American Journal of Psychiatry, 162*(8), 1452-1460. doi: 10.1176/appi.ajp.162.8.1452

Carter, S., & Smith Pasqualini, M. (2004). Stronger autonomic response accompanies better learning: A test of damasio's somatic marker hypothesis. *Cognition and Emotion, 18*(7), 901-911. doi: 10.1080/02699930341000338

Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The bis/bas scales. *Journal of Personality and Social Psychology, 67*(2), 319-333. doi: 10.1037/0022-3514.67.2.319

Cavedini, P., Zorzi, C., Baraldi, C., Patrini, S., Salomoni, G., Bellodi, L., . . . Perna, G. (2012). The somatic marker affecting decisional processes in obsessive-compulsive disorder. *Cognitive Neuropsychiatry, 17*(2), 177-190. doi: 10.1080/13546805.2011.614152

Chambers, R. A., Krystal, J. H., & Self, D. W. (2001). A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biological Psychiatry, 50*(2), 71-83. doi: 10.1016/S0006-3223(01)01134-9

Chan, R. C. K., Shum, D., Toulopoulou, T., & Chen, E. Y. H. (2008). Assessment of executive functions: Review of instruments and identification of critical issues. *Archives of Clinical Neuropsychology, 23*(2), 201-216. doi: 10.1016/j.acn.2007.08.010

Cheng, G. L. F., Zeng, H., Leung, M. K., Zhang, H. J., Lau, B. W. M., Liu, Y. P., . . . So, K. F. (2013). Heroin abuse accelerates biological aging: A novel insight from telomerase and brain imaging interaction. *Translational Psychiatry, 3*(5), e260. doi: 10.1038/tp.2013.36

Cheng, J., Lu, Y., Han, X., Gonzalez-Vallejo, & Sui, N. (2012). Temporal discounting in heroin-dependent patients: No sign effect, weaker magnitude effect, and the relationship with inhibitory control. *Experimental and Clinical Psychopharmacology, 20*(5), 400-409. doi: 10.1037/a0029657

Chilcoat, H. D., & Breslau, N. (1999). Pathways From ADHD to Early Drug Use. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(11), 1347-1354. doi: 10.1097/00004583-199911000-00008

Chiu, Y. C., Lin, C. H., Huang, J. T., Lin, S., Lee, P. L., & Hsieh, J. C. (2008). Immediate gain is long-term loss: Are there foresighted decision makers in the Iowa Gambling Task. *Behavioural and Brain Functions, 4*(13), 10.1186. doi: 10.1186/1744-9081-4-13

Collett, J. (2016). *It's not all about that BAS: Trait bipolar disorder vulnerability weakly correlated with trait BAS and not predictive of risky decision-making.* (Doctoral Thesis), Swinburne University of Technology, Melbourne, Australia. Retrieved from https://researchbank.swinburne.edu.au/file/3f4a86e1-ee4e-4447-92a8-75d9550dbb7d/1/James%20Daniel%20Collett%20Thesis.pdf

Compton, W. M., Boyle, M., & Wargo, E. (2015). Prescription opioid abuse: Problems and responses. *Preventive Medicine, 80*, 5-9. doi: 10.1016/j.ypmed.2015.04.003

Cooper, A., Gomez, R., & Aucote, H. (2007). The behavioural inhibition system and behavioural approach system (BIS/BAS) scales: Measurement and structural invariance across adults and adolescents. *Personality and Individual Differences, 43*(2), 295-305. doi: 10.1016/j.paid.2006.11.023

Craig, A. D. (2002). How do you feel? Interoception: The sense of the physiological condition of the body. *Nature Reviews Neuroscience, 3*(8), 655-666. doi: 10.1038/nrn894

Craig, A. D. (2009). How do you feel—now? The anterior insula and human awareness. *Nature Reviews Neuroscience, 10*(1), 59-70. doi: 10.1038/nrn2555

Crawford, J. R., Deary, I. J., Starr, J., & Whalley, L. J. (2001). The nart as an index of prior intellectual functioning: A retrospective validity study covering a 66-year interval. *Psychological Medicine, 31*(3), 451-458. doi: 10.1017/S0033291701003634

Crawford, J. R., Stewart, L. E., Cochrane, R. H. B., Parker, D. M., & Besson, J. A. O. (1989). Construct validity of the National Adult Reading Test: A factor analytic study. *Personality and Individual Differences, 10*, 585-587. doi: 10.1016/0191-8869(89)90043-3

Critchley, H. D. (2005). Neural mechanisms of autonomic, affective, and cognitive integration. *Journal of Comparative Neurology, 493*(1), 154-166. doi: 10.1002/cne.20749

Critchley, H. D., Wiens, S., Rotshtein, P., Öhman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience, 7*(2), 189-195. doi: 10.1038/nn1176

Crone, E. A., Somsen, R. J. M., Beek, B. V., & Van Der Molen, M. W. (2004). Heart rate and skin conductance analysis of antecendents and consequences of decision making. *Psychophysiology, 41*(4), 531-540. doi: 10.1111/j.1469-8986.2004.00197.x

Daglish, M. R. C., Weinstein, A., Malizia, A. L., Wilson, S., Melichar, J. K., Britten, S., . . . Grasby, P. (2001). Changes in regional cerebral blood flow elicited by craving memories in abstinent opiate-dependent subjects. *American Journal of Psychiatry, 158*(10), 1680-1686. doi: 10.1176/appi.ajp.158.10.1680

Damasio, A. R. (1994). *Descartes' error: Emotion, reason and the human brain*. New York: Grosset/Putnam.

Damasio, A. R. (2009). Neuroscience and the emergence of neuroeconomics. In P. W. Glimcher, E. Fehr, C. Camerer & R. A. Poldrack (Eds.), *Neuroeconomics: Decision making and the Brain* (pp. 209-214). Burlington: Elsevier Science.

Darke, S. (2011). *The life of the heroin user: Typical beginnings, trajectories and outcomes*. New York, NY: Cambridge University Press.

Darke, S., McDonald, S., Kaye, S., & Torok, M. (2012a). Comparative patterns of cognitive performance amongst opioid maintenance patients, abstinent opioid users and non-opioid users. *Drug and Alcohol Dependence, 126*(3), 309-315. doi: 10.1016/j.drugalcdep.2012.05.032

Darke, S., McDonald, S., Kaye, S., & Torok, M. (2012b). Prevalence and correlates of traumatic brain injury amongst heroin users. *Addiction Research and Theory, 20*(6), 522-528. doi: 10.3109/16066359.2012.672600

Darke, S., Mills, K. L., Ross, J., & Teesson, M. (2011). Rates and correlates of mortality amongst heroin users: findings from the Australian Treatment Outcome Study (ATOS), 2001–2009. *Drug and Alcohol Dependence, 115*(3), 190-195. doi: 10.1016/j.drugalcdep.2010.10.021

Darke, S., Mills, K. L., Ross, J., Williamson, A., Havard, A., & Teesson, M. (2009). The ageing heroin user: Career length, clinical profile and outcomes across 36 months. *Drug and Alcohol Review, 28*(3), 243-249. doi: 10.1111/j.1465-3362.2008.00024.x

Darke, S., Sims, J., McDonald, S., & Wickes, W. (2000). Cognitive impairment among methadone maintenance patients. *Addiction, 95*(5), 687-695. doi: 10.1046/j.1360-0443.2000.9556874.x

Darke, S., Slade, T., Ross, J., Marel, C., Mills, K. L., & Tessson, M. (2016). Patterns and correlates of injecting among heroin users: A 11-Year follow-up of the Australian Treatment Outcome Study Cohort. *Addictive Disorders and Their Treatment, 15*(3), 111-119. doi: 10.1097/ADT.0000000000000082

Dawe, S., Gullo, M. J., & Loxton, N. J. (2004). Reward drive and rash impulsiveness as dimensions of impulsivity: Implications for substance misuse. *Addictive Behaviors, 29*(7), 1389-1405. doi: 10.1016/j.addbeh.2004.06.004

Dawe, S., & Loxton, N. J. (2004). The role of impulsivity in the development of substance use and eating disorders. *Neuroscience and Biobehavioral Reviews, 28*(3), 343-351. doi: 10.1016/j.neubiorev.2004.03.007

De Maeyer, J., Vanderplasschen, W., & Broekaert, E. (2010). Quality of life among opiate-dependent individuals: A review of the literature. *International Journal of Drug Policy, 21*(5), 364-380. doi: 10.1016/j.drugpo.2010.01.010

De Maeyer, J., Vanderplasschen, W., Lammertyn, J., van Nieuwenhuizen, C., Sabbe, B., & Broekaert, E. (2011). Current quality of life and its determinants among opiate-dependent individuals five years after starting methadone treatment. *Quality of Life Research, 20*(1), 139-150. doi: 10.1007/s11136-010-9732-3

Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M., & McLaren, J. (2011). Mortality among regular or dependent users of heroin and other opioids: A systematic review and meta-analysis of cohort studies. *Addiction, 106*(1), 32-51. doi: 10.1111/j.1360-0443.2010.03140.x

Degenhardt, L., Charlson, F., Mathers, B., Hall, W. D., Flaxman, A. D., Johns, N., & Vos, T. (2014). The global epidemiology and burden of opioid dependence: results from the global burden of disease 2010 study. *Addiction, 109*(8), 1320-1333. doi: 10.1111/add.12551

Dellacherie, D., Roy, M., Hugueville, L., Peretz, I., & Samson, S. (2011). The effect of musical experience on emotional self-reports and psychophysiological responses to dissonance. *Psychophysiology, 48*(3), 337-349. doi: 10.1111/j.1469-8986.2010.01075.x

Di Chiara, G., & North, A. R. (1992). Neurobiology of opiate abuse. *Trends in Pharmacological Sciences, 13*, 185-193. doi: 10.1016/0165-6147(92)90062-B

Dissabandara, L. O., Loxton, N. J., Dias, S. R., Daglish, M. R. C., & Stadlin, A. (2012). Testing the fear and anxiety distinction in the BIS/BAS scales in community and heroin-dependent samples. *Personality and Individual Differences, 52*(8), 888-892. doi: 10.1016/j.paid.2012.01.023

Dissabandara, L. O., Loxton, N. J., Dias, S. R., Dodd, P. R., Daglish, M. R. C., & Stadlin, A. (2014). Dependent heroin use and associated risky behaviour: The role of rash impulsiveness and reward sensitivity. *Addictive Behaviors, 39*(1), 71-76. doi: 10.1016/j.addbeh.2013.06.009

Dube, S. R., Felitti, V. J., Dong, M., Chapman, D. P., Giles, W. H., & Anda, R. F. (2003). Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. *Pediatrics, 111*(3), 564-572. doi: 10.1542/peds.111.3.564

Dunn, B. D., Dalgleish, T., & Lawrence, A. D. (2006). The somatic marker hypothesis: A critical evaluation. *Neuroscience and Biobehavioral Reviews, 30*(2), 239-271. doi: 10.1016/j.neubiorev.2005.07.001

Dunn, B. D., Galton, H. C., Morgan, R., Evans, D., Oliver, C., Meyer, M., . . . Dalgleish, T. (2010). Listening to your heart: How interoception shapes emotion experience and intuitive decision making. *Psychological Science, 21*(1), 1835-1844. doi: 10.1177/0956797610389191

Dymond, S., Cella, M., Cooper, A., & Turnbull, O. H. (2010). The contingency-shifting variant Iowa Gambling Task: An investigation with young adults. *Journal of Clinical and Experimental Neuropsychology, 32*(3), 239-248. doi: 10.1080/13803390902971115

Edalati, H., & Krank, M. D. (2016). Childhood maltreatment and development of substance use disorders: a review and a model of cognitive pathways. *Trauma, Violence, and Abuse, 17*(5), 454-467. doi: 10.1177/1524838015584370

Einhorn, H. J., & Hogarth, R. M. (1985). Ambiguity and uncertainty in probabilistic inference. *Psychological Review, 92*(4), 433-461. doi: 10.1037/0033-295X.92.4.433

Ellsberg, D. (1961). Risk, ambiguity, and the savage axioms. *The Quarterly Journal of Economics, 75*(4), 643-669. doi: 10.2307/1884324

Elvemo, N. A., Nilsen, K. B., Landrø, N. I., Borchgrevink, P. C., & Håberg, A. K. (2014). Patients with chronic pain lack somatic markers during decision-making. *Journal of Pain Research, 7*, 425-437. doi: 10.2147/JPR.S62492

Ersche, K. D., Clark, L., London, M., Robbins, T. W., & Sahakian, B. J. (2006). Profile of executive and memory function associated with amphetamine and opiate

dependence. *Neuropsychopharmacology, 31*(5), 1036-1047. doi: 10.1038/sj.npp.1300889

Ersche, K. D., Roiser, J. P., Clark, L., London, M., Robbins, T. W., & Sahakian, B. J. (2005). Punishment induces risky decision-making in methadone-maintained opiate users but not in heroin users or healthy volunteers. *Neuropsychopharmacology, 30*(11), 2115-2124. doi: 10.1038/sj.npp.1300812

Ersche, K. D., & Sahakian, B. J. (2007). The neuropsychology of amphetamine and opiate dependence: Implications for treatment. *Neuropsychology Review, 17*(3), 317-336. doi: 10.1007/s11065-007-9033-y

Euteneuer, F., Schaefer, F., Stuermer, R., Boucsein, W., Timmermann, L., Barbe, M. T., . . . Kalbe, E. (2009). Dissociation of decision-making under ambiguity and decision-making under risk in patients with Parkinson's disease: A neuropsychological and psychophysiological study. *Neuropsychologia, 47*(13), 2882-2890. doi: 10.1016/j.neuropsychologia.2009.06.014

Fernández, C., Pascual, J. C., Soler, J., Elices, M., Portella, M. J., & Fernández-Abascal, E. (2012). Physiological responses induced by emotion-eliciting films. *Applied Psychophysiology and Biofeedback, 37*(2), 73-79. doi: 10.1007/s10484-012-9180-7

Fernie, G., & Tunney, R. J. (2006). Some decks are better than others: The effect of reinforcer type and task instructions on learning in the iowa gambling task. *Brain and Cognition, 60*(1), 94-102. doi: 10.1016/j.bandc.2005.09.011

Fernie, G., & Tunney, R. J. (2013). Learning on the igt follows emergence of knowledge but not differential somatic activity. *Frontiers in Psychology, 4*, 697. doi: 10.3389/fpsyg.2013.00687

Figner, B., & Murphy, R. O. (2011). Using skin conductance in judgment and decision making research. In M. Schulte-Mecklenbeck, A. Kuehberger & R. Ranyard (Eds.), *A handbook of process tracing methods for decision research* (pp. 163-184). Hove, Great Britain: Psychology Press.

Fishbein, D. H., Krupitsky, E., Flannery, B. A., Langevin, D. J., Bobashev, G., Verbitskaya, E., . . . Schech, B. (2007). Neurocognitive characterizations of russian heroin addicts without a significant history of other drug use. *Drug and Alcohol Dependence, 90*(1), 25-38. doi: 10.1016/j.drugalcdep.2007.02.015

Fridberg, D. J., Queller, S., Ahn, W. Y., Kim, W., Bishara, A. J., Busemeyer, J. R., . . . Stout, J. C. (2010). Cognitive mechanisms underlying risky decision-making in chronic cannabis users. *Journal of Mathematical Psychology, 54*(1), 28-38. doi: 10.1016/j.jmp.2009.10.002

Gardini, S., & Venneri, A. (2012). Reduced grey matter in the posterior insula as a structural vulnerability or diathesis to addiction. *Brain Research Bulletin, 87*(2–3), 205-211. doi: 10.1016/j.brainresbull.2011.11.021

Garland, E. L., Froeliger, B., Zeidan, F., Partin, K., & Howard, M. O. (2013). The downward spiral of chronic pain, prescription opioid misuse, and addiction: Cognitive, affective, and neuropsychopharmacologic pathways. *Neuroscience and Biobehavioral Reviews, 37*(10), 2597-2607. doi: 10.1016/j.neubiorev.2013.08.006

Gerra, G., Baldaro, B., Zaimovic, A., Moi, G., Bussandri, M., Raggi, M. A., & Brambilla, F. (2003). Neuroendocrine responses to experimentally-induced emotions among abstinent opioid-dependent subjects. *Drug and Alcohol Dependence, 71*(1), 25-35. doi: 10.1016/S0376-8716(03)00065-6

Gerra, G., Calbiani, B., Zaimovic, A., Sartori, R., Ugolotti, G., Ippolito, L., . . . Fontanesi, B. (1998). Regional cerebral blood flow and comorbid diagnosis in

abstinent opioid addicts. *Psychiatry Research: Neuroimaging, 83*(2), 117-126. doi: 10.1016/S0925-4927(98)00030-4

Goldstein, W. M., & Hogarth, R. M. (1997). Judgment and decision research: Some historical context. In W. M. Goldstein & R. M. Hogarth (Eds.), *Research on judgment and decision making: Currents, connections, and controversies* (pp. 3-65). Cambridge, NY: Cambridge University Press.

Golub, S. A., Thompson, L. I., & Kowalczyk, W. J. (2016). Affective differences in Iowa Gambling Task performance associated with sexual risk taking and substance use among HIV-positive and HIV-negative men who have sex with men. *Journal of Clinical and Experimental Neuropsychology, 38*(2), 141-157. doi: 10.1080/13803395.2015.1085495

Gonzalez, R., Schuster, R. M., Mermelstein, R. M., & Diviak, K. R. (2015). The role of decision-making in cannabis-related problems among young adults. *Drug and Alcohol Dependence, 154*, 214-221. doi: 10.1016/j.drugalcdep.2015.06.046

Gossop, M., Griffiths, P., Powis, B., & Strang, J. (1993). Severity of heroin dependence and HIV risk. II. Sharing injecting equipment. *AIDS Care, 5*(2), 159-168. doi: 10.1080/09540129308258596

Gossop, M., Marsden, J., Stewart, D., & Rolfe, A. (2000). Reductions in acquisitive crime and drug use after treatment of addiction problems: 1-year follow-up outcomes. *Drug and Alcohol Dependence, 58*(1–2), 165-172. doi: 10.1016/S0376-8716(99)00077-0

Goudriaan, A. E., Oosterlaan, J., de Beurs, E., & van den Brink, W. (2006). Psychophysiological determinants and concomitants of deficient decision making in pathological gamblers. *Drug and Alcohol Dependence, 84*(3), 231-239. doi: 10.1016/j.drugalcdep.2006.02.007

Gowing, L., Farrell, M., Bornemann, R., & Ali, R. (2008). Substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database of Systematic Reviews, 2*, CD004145. doi: 10.1002/14651858.CD004145.pub2

Gowing, L., Farrell, M. F., Bornemann, R., Sullivan, L. E., & Ali, R. (2011). Oral substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database of Systematic Reviews, 8*, CD004145. doi: 10.1002/14651858.CD004145.pub4

Grafman, J., & Litvan, I. (1999). Importance of deficits in executive functions. *The Lancet, 354*(9194), 1921-1923.

Grella, C. E., & Lovinger, K. (2011). 30-Year trajectories of heroin and other drug use among men and women sampled from methadone treatment in California. *Drug and Alcohol Dependence, 118*(2), 251-258. doi: 10.1016/j.drugalcdep.2011.04.004

Grow, J. C., Collins, S. E., Harrop, E. N., & Marlatt, G. A. (2015). Enactment of home practice following mindfulness-based relapse prevention and its association with substance-use outcomes. *Addictive Behaviors, 40*, 16-20. doi: 10.1016/j.addbeh.2014.07.030

Guillaume, S., Jollant, F., Jaussent, I., Lawrence, N., Malafosse, A., & Courtet, P. (2009). Somatic markers and explicit knowledge are both involved in decision-making. *Neuropsychologia, 47*(10), 2120-2124. doi: 10.1016/j.neuropsychologia.2009.04.003

Gupta, S., Iudicello, J. E., Shi, C., Letendre, S., Knight, A., Li, J., . . . Heaton, R. K. (2014). Absence of neurocognitive impairment in a large Chinese sample of HCV-infected injection drug users receiving methadone treatment. *Drug and Alcohol Dependence, 137*, 29-35. doi: 10.1016/j.drugalcdep.2013.12.021

Gyarmathy, A. V., Neaigus, A., Miller, M. A., Friedman, S. R., & Des Jarlais, D. C. (2002). Risk correlates of prevalent HIV, Hepatitis B virus, and Hepatitis C virus infections among noninjecting heroin users. *Journal of Acquired Immune Deficiency Syndromes, 30*(4), 448-456. doi: 10.1097/01.qai.0000018880.78058.98

Harsay, H. A., Buitenweg, J. I., Wijnen, J. G., Guerreiro, M. J., & Ridderinkhof, K. R. (2010). Remedial effects of motivational incentive on declining cognitive control in healthy aging and Parkinson's disease. *Frontiers in Aging Neuroscience, 2*, 144.

Hastie, R. (2001). Problems for judgment and decision making. *Annual Review of Psychology, 52*(1), 653-683. doi: 10.1146/annurev.psych.52.1.653

Henry, P. K., Umbricht, A., Kleykamp, B. A., Vandrey, R., Strain, E. C., Bigelow, G. E., & Mintzer, M. Z. (2012). Comparison of cognitive performance in methadone maintenance patients with and without current cocaine dependence. *Drug and Alcohol Dependence, 124*(1–2), 167-171. doi: 10.1016/j.drugalcdep.2011.12.009

Hopko, D. R., Lejuez, C. W., Daughters, S. B., Aklin, W. M., Osborne, A., Simmons, B. L., & Strong, D. R. (2006). Construct validity of the Balloon Analogue Risk Task (BART): Relationship with MDMA use by inner-city drug users in residential treatment. *Journal of Psychopathology and Behavioral Assessment, 28*(2), 95-101. doi: 10.1007/s10862-006-7487-5

Hou, Y., Zhao, L. Y., Yao, Q., & Ding, L. (2016). Altered economic decision-making in abstinent heroin addicts: Evidence from the Ultimatum Game. *Neuroscience Letters, 627*, 148-154. doi: 10.1016/j.neulet.2016.06.002

Hser, Y. I., Huang, D., Brecht, M. L., Li, L., & Evans, E. (2008). Contrasting trajectories of heroin, cocaine, and methamphetamine use. *Journal of Addictive Diseases, 27*(3), 13-21. doi: 10.1080/10550880802122554

Hser, Y. I., Huang, D., Chou, C. P., & Anglin, M. D. (2007). Trajectories of heroin addiction. *Evaluation Review, 31*(6), 548-563. doi: doi:10.1177/0193841X07307315

Hunt, M. K., Hopko, D. R., Bare, R., Lejuez, C. W., & Robinson, E. V. (2005). Construct validity of the balloon analog risk task (bart) associations with psychopathy and impulsivity. *Assessment, 12*(4), 416-428. doi: 10.1177/1073191105278740

Hunter, S. J., & Sparrow, E. P. (2012). Models of executive functioning. In S. J. Hunter & E. P. Sparrow (Eds.), *Executive function and dysfunction: Identification, assessment, and treatment*. New York, NY: Cambridge University Press.

IBM Corp. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY.

Jiang, G. H., Qiu, Y. W., Zhang, X. L., Han, L. J., Lv, X. F., Li, L. M., . . . Tian, J. Z. (2011). Amplitude low-frequency oscillation abnormalities in the heroin users: A resting state fMRI study. *Neuroimage, 57*(1), 149-154. doi: 10.1016/j.neuroimage.2011.04.004

Jimenez-Trevino, L., Saiz, P. A., Garcia-Portilla, M. P., Díaz-Mesa, E. M., Sanchez-Lasheras, F., Buron, P., . . . Bobes, J. (2011). A 25-year follow-up of patients admitted to methadone treatment for the first time: Mortality and gender differences. *Addictive Behaviors, 36*(12), 1184-1190. doi: 10.1016/j.addbeh.2011.07.019

Jones, C. M., Logan, J., Gladden, R. M., & Bohm, M. K. (2015). Vital Signs: Demographic and substance use trends among heroin users - United States, 2002-2013. *Morbidity and Mortality Weekly Report, 64*(26), 719-725.

Jorm, A. F., Christensen, H., Henderson, A. S., Jacomb, P. A., Korten, A. E., & Rodgers, B. (1998). Using the BIS/BAS scales to measure behavioural inhibition and behavioural activation: Factor structure, validity and norms in a large community sample. *Personality and Individual Differences, 26*(1), 49-58. doi: 10.1016/S0191-8869(98)00143-3

Kahneman, D., & Tversky, A. (1979). Prospect theory: An analysis of decision under risk. *Econometrica: Journal of the Econometric Society, 47*(2), 263-291.

Khemiri, L., Guterstam, J., Franck, J., & Jayaram-Lindström, N. (2012). Alcohol dependence associated with increased utilitarian moral judgment: A case control study. *PLoS ONE, 7*(6), e39882. doi: 10.1371/journal.pone.0039882

Khodadadi, A., Dezfouli, A., Fakhari, P., & Ekhtiari, H. (2010). Effects of methadone maintenance treatment on decision-making processes in heroin abusers: A cognitive modeling analysis. *Basic and Clinical Neuroscience, 1*(3), 44-49.

Khosravani, V., Mehdizadeh, A., Dortaj, A., Alvani, A., & Amirinezhad, A. (2017). Early maladaptive schemas, behavioral inhibition/approach systems, and defense styles in the abusers of opiate, stimulant, and cannabis drugs and healthy subjects. *Journal of Substance Use, 22*(3), 317-323. doi: 10.1080/14659891.2016.1208776

Kirby, K. N., & Petry, N. M. (2004). Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. *Addiction, 99*(4), 461-471. doi: 10.1111/j.1360-0443.2004.00669.x

Kirby, K. N., Petry, N. M., & Bickel, W. K. (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *Journal of Experimental Psychology: General, 128*(1), 78-87. doi: 10.1037/0096-3445.128.1.78

Klee, H., & Morris, J. (1994). Crime and drug misuse: Economic and psychological aspects of the criminal activities of heroin and amphetamine injectors. *Addiction Research and Theory, 1*(4), 377-386. doi: 10.3109/16066359409005204

Kohno, M., Morales, A. M., Ghahremani, D. G., Hellemann, G., & London, E. D. (2014). Risky decision making, prefrontal cortex, and mesocorticolimbic functional connectivity in methamphetamine dependence. *JAMA Psychiatry, 71*(7), 812-820. doi: 10.1001/jamapsychiatry.2014.399

Koob, G. F., & Le Moal, M. (2005). Opioids *Neurobiology of Addiction* (pp. 121-171). London, UK: Academic Press.

Kornreich, C., Brevers, D., Ermer, E., Hanak, C., Verbanck, P., Campanella, S., & Noël, X. (2013). Polysubstance dependent patients display a more utilitarian profile in moral decision-making than alcohol-dependent patients, depressive patients and controls. *Drug and Alcohol Dependence, 132*(3), 434-440. doi: 10.1016/j.drugalcdep.2013.03.005

Kosten, T. R., & George, T. P. (2002). The neurobiology of opioid dependence: Implications for treatment. *Science and Practice Perspectives, 1*(1), 13-20.

Krain, A. L., Wilson, A. M., Arbuckle, R., Castellanos, F. X., & Milham, M. P. (2006). Distinct neural mechanisms of risk and ambiguity: A meta-analysis of decision-making. *Neuroimage, 32*(1), 477-484. doi: 10.1016/j.neuroimage.2006.02.047

Lauriola, M., Panno, A., Levin, I. P., & Lejuez, C. W. (2014). Individual differences in risky decision making: A meta-analysis of sensation seeking and impulsivity with the Balloon Analogue Risk Task. *Journal of Behavioral Decision Making, 27*(1), 20-36. doi: 10.1002/bdm.1784

Lee, Y., Kim, Y. T., Seo, E., Park, O., Jeong, S. H., Kim, S. H., & Lee, S. J. (2007). Dissociation of emotional decision-making from cognitive decision-making in

chronic schizophrenia. *Psychiatry Research, 152*(2–3), 113-120. doi: 10.1016/j.psychres.2006.02.001

Leigh, B. C. (1999). Peril, chance, adventure: concepts of risk, alcohol use and risky behavior in young adults. *Addiction, 94*(3), 371-383. doi: 10.1046/j.1360-0443.1999.9433717.x

Lejuez, C. W., Aklin, W. M., Jones, H. A., Richards, J. B., Strong, D. R., Kahler, C. W., & Read, J. P. (2003). The balloon analogue risk task (BART) differentiates smokers and nonsmokers. *Experimental and Clinical Psychopharmacology, 11*(1), 26-33. doi: 10.1037/1064-1297.11.1.26

Lejuez, C. W., Read, J. P., Kahler, C. W., Richards, J. B., Ramsey, S. E., Stuart, G. L., . . . Brown, R. A. (2002). Evaluation of a behavioral measure of risk taking: The balloon analogue risk task (BART). *Journal of Experimental Psychology: Applied, 8*(2), 75. doi: 10.1037/1076-898X.8.2.75

Lejuez, C. W., Simmons, B. L., Aklin, W. M., Daughters, S. B., & Dvir, S. (2004). Risk-taking propensity and risky sexual behavior of individuals in residential substance use treatment. *Addictive Behaviors, 29*(8), 1643-1647. doi: 10.1016/j.addbeh.2004.02.035

Lemenager, T., Richter, A., Reinhard, I., Gelbke, J., Beckmann, B., Heinrich, M., . . . Hermann, D. (2011). Impaired decision making in opiate addiction correlates with anxiety and self-directedness but not substance use parameters. *Journal of Addiction Medicine, 5*(3), 203-213. doi: 10.1097/ADM.0b013e31820b3e3d

Li, W., Li, Q., Wang, Y., Zhu, J., Ye, J., Yan, X., . . . Liu, Y. (2016). Methadone-induced Damage to White Matter Integrity in Methadone Maintenance Patients: A Longitudinal Self-control DTI Study. *Scientific Reports, 6*, 19662-19662. doi: 10.1038/srep19662

Li, W., Li, Q., Zhu, J., Qin, Y., Zheng, Y., Chang, H., . . . Wang, W. (2013). White matter impairment in chronic heroin dependence: A quantitative DTI study. *Brain Research, 1531*, 58-64. doi: 10.1016/j.brainres.2013.07.036

Li, X., Zhang, F., Zhou, Y., Zhang, M., Wang, X., & Shen, M. (2013). Decision-making deficits are still present in heroin abusers after short-to long-term abstinence. *Drug and Alcohol Dependence, 130*(1), 61-67. doi: 10.1016/j.drugalcdep.2012.10.012

Liang, C. S., Ho, P. S., Yen, C. H., Yeh, Y. W., Kuo, S. C., Huang, C. C., . . . Huang, S. Y. (2016). Reduced striatal dopamine transporter density associated with working memory deficits in opioid-dependent male subjects: a SPECT study. *Addiction Biology, 21*(1), 196-204. doi: 10.1111/adb.12203

Lin, C. H., Chiu, Y. C., Lee, P. L., & Hsieh, J. C. (2007). Is deck B a disadvantageous deck in the Iowa Gambling Task? *Behavioral and Brain Functions, 3*(1), 16. doi: 10.1186/1744-9081-3-16

Lin, W. C., Chou, K. H., Chen, C. C., Huang, C. C., Chen, H. L., Lu, C. H., . . . Lin, C. P. (2012). White matter abnormalities correlating with memory and depression in heroin users under methadone maintenance treatment. *PLoS ONE, 7*(4), e33809. doi: 10.1371/journal.pone.0033809

Lin, W. C., Chou, K. H., Chen, H. L., Huang, C. C., Lu, C. H., Li, S. H., . . . Chen, C. C. (2012). Structural deficits in the emotion circuit and cerebellum are associated with depression, anxiety and cognitive dysfunction in methadone maintenance patients: A voxel-based morphometric study. *Psychiatry Research: Neuroimaging, 201*(2), 89-97. doi: 10.1016/j.pscychresns.2011.05.009

Liu, H., Hao, Y., Kaneko, Y., Ouyang, X., Zhang, Y., Xu, L., . . . Liu, Z. (2009). Frontal and cingulate gray matter volume reduction in heroin dependence: Optimized

voxel-based morphometry. *Psychiatry and Clinical Neurosciences, 63*(4), 563-568. doi: 10.1111/j.1440-1819.2009.01989.x

Liu, H., Li, L., Hao, Y., Cao, D., Xu, L., Rohrbaugh, R., . . . Liu, Z. (2008). Disrupted white matter integrity in heroin dependence: A controlled study utilizing diffusion tensor imaging. *American Journal of Drug and Alcohol Abuse, 34*(5), 562-575. doi: 10.1080/00952990802295238

Liu, J., Liang, J. Y., Qin, W., Tian, J., Yuan, K., Bai, L., . . . Gold, M. S. (2009). Dysfunctional connectivity patterns in chronic heroin users: An fMRI study. *Neuroscience Letters, 460*(1), 72-77. doi: 10.1016/j.neulet.2009.05.038

Liu, Y. P., Han, M., Liu, X., Deng, Y., Li, Y. H., Yuan, J., . . . Gao, J. (2013). Dopamine transporter availability in heroin-dependent subjects and controls: longitudinal changes during abstinence and the effects of Jitai tablets treatment. *Psychopharmacology, 230*(2), 235-244. doi: 10.1007/s00213-013-3148-z

Loeber, S., Nakovics, H., Kniest, A., Kiefer, F., Mann, K., & Croissant, B. (2012). Factors affecting cognitive function of opiate-dependent patients. *Drug and Alcohol Dependence, 120*(1), 81-87. doi: 10.1016/j.drugalcdep.2011.07.001

Lubman, D. I., Allen, N. B., Peters, L. A., & Deakin, J. F. W. (2008). Electrophysiological evidence that drug cues have greater salience than other affective stimuli in opiate addiction. *Journal of Psychopharmacology, 22*(8), 836-842. doi: 10.1177/0269881107083846

Lubman, D. I., Yücel, M., Kettle, J. W. L., Scaffidi, A., MacKenzie, T., Simmons, J. G., & Allen, N. B. (2009). Responsiveness to drug cues and natural rewards in opiate addiction: Associations with later heroin use. *Archives of General Psychiatry, 66*(2), 205-212. doi: 10.1001/archgenpsychiatry.2008.522

Lyoo, I. K., Pollack, M. H., Silveri, M. M., Ahn, K. H., Diaz, C. I., Hwang, J., . . . Renshaw, P. F. (2006). Prefrontal and temporal gray matter density decreases in opiate dependence. *Psychopharmacology, 184*(2), 139-144. doi: 10.1007/s00213-005-0198-x

Lyoo, I. K., Streeter, C. C., Ahn, K. H., Lee, H. K., Pollack, M. H., Silveri, M. M., . . . Ciraulo, D. A. (2004). White matter hyperintensities in subjects with cocaine and opiate dependence and healthy comparison subjects. *Psychiatry Research: Neuroimaging, 131*(2), 135-145. doi: 10.1016/j.pscychresns.2004.04.001

Ma, N., Liu, Y. P., Li, N., Wang, C. X., Zhang, H., Jiang, X. F., . . . Zhang, D. R. (2010). Addiction related alteration in resting-state brain connectivity. *Neuroimage, 49*(1), 738-744. doi: 10.1016/j.neuroimage.2009.08.037

Ma, X. F., Qiu, Y. W., Tian, J. Z., Wang, J. H., Li, S. M., Zhan, W. F., . . . Xu, Y. K. (2015). Aberrant default-mode functional and structural connectivity in heroin-dependent individuals. *PLoS ONE, 10*(4), e0120861. doi: 10.1371/journal.pone.0120861

MacDonald, A. W., Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science, 288*(5472), 1835-1838. doi: 10.1126/science.288.5472.1835

Madden, G. J., Petry, N. M., Badger, G. J., & Bickel, W. K. (1997). Impulsive and self-control choices in opioid-dependent patients and non-drug-using control patients: Drug and monetary rewards. *Experimental and Clinical Psychopharmacology, 5*(3), 256-262. doi: 10.1037/1064-1297.5.3.256

Malloy-Diniz, L., Fuentes, D., Leite, W. B., Correa, H., & Bechara, A. (2007). Impulsive behavior in adults with attention deficit/hyperactivity disorder: characterization of attentional, motor and cognitive impulsiveness. *Journal of*

the International Neuropsychological Society, 13(04), 693-698. doi: 10.10170S1355617707070889

Maradiaga, J. A., Nahvi, S., Cunningham, C. O., Sanchez, J., & Fox, A. D. (2016). "I Kicked the Hard Way. I Got Incarcerated." Withdrawal from Methadone During Incarceration and Subsequent Aversion to Medication Assisted Treatments. *Journal of Substance Abuse Treatment, 62*, 49-54. doi: 10.1016/j.jsat.2015.11.004

Marcus, M. T., & Zgierska, A. (2009). Mindfulness-based therapies for substance use disorders: Part 1 (Editorial). *Substance Abuse, 30*(4), 263. doi: 10.1080/08897070903250027

Maruff, P., Thomas, E., Cysique, L., Brew, B., Collie, A., Snyder, P., & Pietrzak, R. H. (2009). Validity of the CogState brief battery: Relationship to standardized tetsts and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. *Archives of Clinical Neuropsychology, 24*(2), 165-178. doi: 10.1093/arclin/acp010

Mercuri, K., Terrett, G., Henry, J. D., Bailey, P. E., Curran, H. V., & Rendell, P. G. (2015). Episodic foresight deficits in long-term opiate users. *Psychopharmacology, 232*(7), 1337-1345. doi: 10.1007/s00213-014-3772-2

Mergl, R., Mavrogiorgou, P., Hegerl, U., & Juckel, G. (2005). Kinematical analysis of emotionally induced facial expressions: A novel tool to investigate hypomimia in patients suffering from depression. *Journal of Neurology, Neurosurgery and Psychiatry, 76*(1), 138-140. doi: 10.1136/jnnp.2004.037127

Messinis, L., Lyros, E., Andrian, V., Katsakiori, P., Panagis, G., Georgiou, V., & Papathanasopoulos, P. (2009). Neuropsychological functioning in buprenorphine maintained patients versus abstinent heroin abusers on naltrexone hydrochloride therapy. *Human Psychopharmacology: Clinical and Experimental, 24*(7), 524-531. doi: 10.1002/hup.1050

Meulenbeek, P. A. M. (2000). Addiction problems and methadone treatment. *Journal of Substance Abuse Treatment, 19*(2), 171-174. doi: 10.1016/S0740-5472(00)00116-1

Mintzer, M. Z., Copersino, M. L., & Stitzer, M. L. (2005). Opioid abuse and cognitive performance. *Drug and Alcohol Dependence, 78*(2), 225-230. doi: 10.1016/j.drugalcdep.2004.10.008

Mintzer, M. Z., & Stitzer, M. L. (2002). Cognitive impairment in methadone maintenance patients. *Drug and Alcohol Dependence, 67*(1), 41-51. doi: 10.1016/S0376-8716(02)00013-3

Miu, A. C., Crişan, L. G., Chiş, A., Ungureanu, L., Drugă, B., & Vulturar, R. (2012). Somatic markers mediate the effect of serotonin transporter gene polymorphisms on Iowa Gambling Task. *Genes, Brain and Behavior, 11*(4), 398-403. doi: 10.1111/j.1601-183X.2012.00774.x

Miu, A. C., Heilman, R. M., & Houser, D. (2008). Anxiety impairs decision-making: Psychophysiological evidence from an Iowa Gambling Task. *Biological Psychology, 77*(3), 353-358. doi: 10.1016/j.biopsycho.2007.11.010

Moretto, G., Làdavas, E., Mattioli, F., & Di Pellegrino, G. (2010). A psychophysiological investigation of moral judgment after ventromedial prefrontal damage. *Journal of Cognitive Neuroscience, 22*(8), 1888-1899. doi: 10.1162/jocn.2009.21367

Myers, C. E., Sheynin, J., Balsdon, T., Luzardo, A., Beck, K. D., Hogarth, L., . . . Moustafa, A. A. (2016). Probabilistic reward- and punishment-based learning in

opioid addiction: Experimental and computational data. *Behavioural Brain Research, 296*, 240-248. doi: 10.1016/j.bbr.2015.09.018

Naqvi, N. H., & Bechara, A. (2006). Skin conductance: A psychophysiological approach to the study of decision making. In C. Senior, T. Russell & M. S. Gazzaniga (Eds.), *Methods in mind* (pp. 103-122): The MIT Press.

Naqvi, N. H., Shiv, B., & Bechara, A. (2006). The role of emotion in decision making a cognitive neuroscience perspective. *Current Directions in Psychological Science, 15*(5), 260-264. doi: 10.1111/j.1467-8721.2006.00448.x

Nasoz, F., Alvarez, K., Lisetti, C. L., & Finkelstein, N. (2004). Emotion recognition from physiological signals using wireless sensors for presence technologies. *Cognition, Technology, and Work, 6*(1), 4-14. doi: 10.1007/s10111-003-0143-x

Nelson, H. E. (1982). *National adult reading test (NART): Test manual*. Windsor: NFER.

Norman, D. A., & Shallice, T. (1986). Attention to action: Willed and automatic control of behaviour. In R. J. Davidson, G. E. Schwartz & D. Shapiro (Eds.), *Consciousness and self-regulation: Advances in research and theory* (pp. 1-18). New York: Springer.

Odhuba, R. A., Broek, M. D., & Johns, L. C. (2005). Ecological validity of measures of executive functioning. *British Journal of Clinical Psychology, 44*(2), 269-278. doi: 10.1348/014466505X29431

Pandria, N., Kovatsi, L., Vivas, A. B., & Bamidis, P. D. (2016). Resting-state abnormalities in heroin-dependent individuals. *Neuroscience, Available online ahead of print, 21 November 2016*. doi: 10.1016/j.neuroscience.2016.11.018

Passetti, F., Clark, L., Davis, P. E., Mehta, M. A., White, S., Checinski, K., . . . Abou-Saleh, M. (2011). Risky decision-making predicts short-term outcome of community but not residential treatment for opiate addiction. Implications for case management. *Drug and Alcohol Dependence, 118*(1), 12-18. doi: 10.1016/j.drugalcdep.2011.02.015

Passetti, F., Clark, L., Mehta, M. A., Joyce, E., & King, M. (2008). Neuropsychological predictors of clinical outcome in opiate addiction. *Drug and Alcohol Dependence, 94*(1), 82-91. doi: 10.1016/j.drugalcdep.2007.10.008

Pau, C. W. H., Lee, T., & Chan, S. F. (2002). The impact of heroin on frontal executive functions. *Archives of Clinical Neuropsychology, 17*(7), 663-670. doi: 10.1016/S0887-6177(01)00169-X

Paulus, M. P., & Stewart, J. L. (2014). Interoception and drug addiction. *Neuropharmacology, 76*, 342-350. doi: 10.1016/j.neuropharm.2013.07.002

Pezawas, L., Fischer, G., Podreka, I., Schindler, S., Brücke, T., Jagsch, R., . . . Kasper, S. M. (2002). Opioid addiction changes cerebral blood flow symmetry. *Neuropsychobiology, 45*(2), 67-73.

Pietrzak, R. H., Olver, J., Norman, T., Piskulic, D., Maruff, P., & Snyder, P. J. (2009). A comparison of the CogState Schizophrenia Battery and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Battery in assessing cognitive impairment in chronic schizophrenia. *Journal of Clinical and Experimental Neuropsychology, 31*(7), 848-859. doi: 10.1080/13803390802592458

Pirastu, R., Fais, R., Messina, M., Bini, V., Spiga, S., Falconieri, D., & Diana, M. (2006). Impaired decision-making in opiate-dependent subjects: Effect of pharmacological therapies. *Drug and Alcohol Dependence, 83*(2), 163-168. doi: 10.1016/j.drugalcdep.2005.11.008

Plous, S. (1993). *The psychology of judgment and decision making*: McGraw-Hill Book Company.

Pollatos, O., & Schandry, R. (2008). Emotional processing and emotional memory are modulated by interoceptive awareness. *Cognition and Emotion, 22*(2), 272-287. doi: 10.1080/02699930701357535

Qiu, Y. W., Han, L., Lv, X., Jiang, G., Tian, J., Zhuo, F., . . . Zhang, X. L. (2011). Regional homogeneity changes in heroin-dependent individuals: Resting-state functional mr imaging study. *Radiology, 261*(2), 551-559. doi: 10.1148/radiol.11102466

Qiu, Y. W., Jiang, G., Su, H., Lv, X., Zhang, X. L., Tian, J., & Zhuo, F. (2013). Progressive white matter microstructure damage in male chronic heroin dependent individuals: A dti and tbss study. *PLoS ONE, 8*(5), e63212. doi: 10.1371/journal.pone.0063212

Qiu, Y. W., Jiang, G., Su, H. H., Lv, X. F., Tian, J. Z., Li, L. M., & Zhuo, F. Z. (2013). The impulsivity behavior is correlated with prefrontal cortex gray matter volume reduction in heroin-dependent individuals. *Neuroscience Letters, 538*, 43-48. doi: 10.1016/j.neulet.2013.01.019

Rao, L. L., Dunn, J. C., Zhou, Y., & Li, S. H. (2015). The neural correlates of risky decision making across short and long runs. *Scientific Reports, 5*, 15831. doi: 10.1038/srep15831

Roiser, J. P., & Sahakian, B. J. (2013). Hot and cold cognition in depression. *CNS Spectrums, 18*(3), 139-149. doi: 10.1017/S1092852913000072

Rolls, E. T. (2000). The orbitofrontal cortex and reward. *Cerebral Cortex, 10*(3), 284-294. doi: 10.1093/cercor/10.3.284

Rolls, E. T. (2004). The functions of the orbitofrontal cortex. *Brain and Cognition, 55*(1), 11-29. doi: 10.1016/S0278-2626(03)00277-X

Rotheram-Fuller, E., Shoptaw, S., Berman, S. M., & London, E. D. (2004). Impaired performance in a test of decision-making by opiate-dependent tobacco smokers. *Drug and Alcohol Dependence, 73*(1), 79-86. doi: 10.1016/j.drugalcdep.2003.10.003

Savage, L. J. (1954). *The foundations of statistics*. New York: Wiley & Sons.

Schandry, R., Bestler, M., & Montoya, P. (1993). On the relation between cardiodynamics and heartbeat perception. *Psychophysiology, 30*, 467-474. doi: 10.1111/j.1469-8986.1993.tb02070.x

Scherbaum, N., Kluwig, J., Specka, M., Krause, D., Merget, B., Finkbeiner, T., & Gastpar, M. (2005). Group psychotherapy for opiate addicts in methadone maintenance treatment – A controlled trial. *European Addiction Research, 11*(4), 163-171. doi: 10.1159/000086397

Schlaepfer, T. E., Lancaster, E., Heidbreder, R., Strain, E. C., Kosel, M., Fisch, H. U., & Pearlson, G. D. (2006). Decreased frontal white-matter volume in chronic substance abuse. *The International Journal of Neuropsychopharmacology, 9*(02), 147-153. doi: 10.1017/S1461145705005705

Schmidt, A., Borgwardt, S., Gerber, H., Wiesbeck, G. A., Schmid, O., Riecher-Rössler, A., . . . Walter, M. (2014). Acute effects of heroin on negative emotional processing: Relation of amygdala activity and stress-related responses. *Biological Psychiatry, 76*(4), 289–296. doi: 10.1016/j.biopsych.2013.10.019

Schoemaker, P. J. H. (1982). The expected utility model: Its variants, purposes, evidence and limitations. *Journal of Economic Literature, 20*(2), 529-563.

Schottenfeld, R. S., Chawarski, M. C., Pakes, J. R., Pantalon, M. V., Carroll, K. M., & Kosten, T. R. (2005). Methadone versus buprenorphine with contingency

management or performance feedback for cocaine and opioid dependence. *American Journal of Psychiatry, 162*(2), 340-349. doi: 10.1176/appi.ajp.162.2.340

Serre, F., Fatseas, M., Debrabant, R., Alexandre, J. M., Auriacombe, M., & Swendsen, J. (2012). Ecological momentary assessment in alcohol, tobacco, cannabis and opiate dependence: A comparison of feasibility and validity. *Drug and Alcohol Dependence, 126*(1), 118-123. doi: 10.1016/j.drugalcdep.2012.04.025

Shi, J., Zhao, L. Y., Copersino, M. L., Fang, Y. X., Chen, Y. Y., Tian, J., . . . Lu, L. (2008). PET imaging of dopamine transporter and drug craving during methadone maintenance treatment and after prolonged abstinence in heroin users. *European Journal of Pharmacology, 579*(1-3), 160-166. doi: 10.1016/j.ejphar.2007.09.042

Shurman, B., Horan, W. P., & Nuechterlein, K. H. (2005). Schizophrenia patients demonstrate a distinctive pattern of decision-making impairment on the Iowa Gambling Task. *Schizophrenia Research, 72*(2–3), 215-224. doi: 10.1016/j.schres.2004.03.020

Skeel, R. L., Neudecker, J., Pilarski, C., & Pytlak, K. (2007). The utility of personality variables and behaviorally-based measures in the prediction of risk-taking behavior. *Personality and Individual Differences, 43*(1), 203-214. doi: 10.1016/j.paid.2006.11.025

Smoski, M. J., Salsman, N., Wang, L., Smith, V., Lynch, T. R., Dager, S. R., . . . Linehan, M. M. (2011). Functional imaging of emotion reactivity in opiate-dependent borderline personality disorder. *Personality Disorders: Theory, Research, and Treatment, 2*(3), 230-241. doi: 10.1037/a0022228

Sönmez, M. B., Kahyacı Kılıç, E., Ateş Çöl, I., Görgülü, Y., & Köse Çınar, R. (2016). Decreased interoceptive awareness in patients with substance use disorders. *Journal of Substance Use, Published online 25 May 2016*, 1-6. doi: 10.3109/14659891.2016.1143048

Steingroever, H., Wetzels, R., Horstmann, A., Neumann, J., & Wagenmakers, E. J. (2013). Performance of healthy participants on the iowa gambling task. *Psychological Assessment, 25*(1), 180–193. doi: 10.1037/a0029929

Stevens, L., Betanzos-Espinosa, P., Crunelle, C. L., Vergara-Moragues, E., Roeyers, H., Lozano, O., . . . Verdejo-García, A. (2013). Disadvantageous decision-making as a predictor of drop-out among cocaine-dependent individuals in long-term residential treatment. *Frontiers in Psychiatry, 4*, 149. doi: 10.3389/fpsyt.2013.00149

Stevens, L., Goudriaan, A. E., Verdejo-Garcia, A. J., Dom, G., Roeyers, H., & Vanderplasschen, W. (2015). Impulsive choice predicts short-term relapse in substance-dependent individuals attending an in-patient detoxification programme. *Psychological Medicine, 45*(10), 2083-2093. doi: 10.1017/S003329171500001X

Stewart, D., Gossop, M., Marsden, J., & Rolfe, A. (2000). Drug misuse and acquisitive crime among clients recruited to the National Treatment Outcome Research Study (NTORS). *Criminal Behaviour and Mental Health, 10*(1), 10-20. doi: 10.1002/cbm.339

Substance Abuse and Mental Health Services Administration. (2017). Treatment Episode Data Set (TEDS): 2005-2015. https://www.samhsa.gov/data/sites/default/files/2015%20TEDS%20National%20Admissions.pdf: Center for Behavioral Health Statistics and Quality, Rockville, MD.

Sun, Y., Wang, G. B., Lin, Q. X., Lu, L., Shu, N., Meng, S. Q., . . . Shi, J. (2015). Disrupted white matter structural connectivity in heroin abusers. *Addiction Biology*. doi: 10.1111/adb.12285

Sun, Y., Zhao, L. Y., Wang, G. B., Yue, W. H., He, Y., Shu, N., . . . Shi, J. (2015). ZNF804A variants confer risk for heroin addiction and affect decision making and gray matter volume in heroin abusers. *Addiction Biology*. doi: 10.1111/adb.12233

Tabachnick, B. G., & Fidell, L. S. (2013). *Using multivariate statistics* (6th ed.). Boston: Pearson.

Taubitz, L. E., Pedersen, W. S., & Larson, C. L. (2015). BAS Reward Responsiveness: A unique predictor of positive psychological functioning. *Personality and Individual Differences, 80*, 107-112. doi: 10.1016/j.paid.2015.02.029

Terrett, G., McLennan, S. N., Henry, J. D., Biernacki, K., Mercuri, K., Curran, H. V., & Rendell, P. G. (2014). Prospective memory impairment in long-term opiate users. *Psychopharmacology*, 1-10. doi: 10.1007/s00213-014-3432-6

Tolomeo, S., Gray, S., Matthews, K., Steele, J., & Baldacchino, A. (2016). Multifaceted impairments in impulsivity and brain structural abnormalities in opioid dependence and abstinence. *Psychological Medicine, 46*(13), 2841-2853. doi: 10.1017/S0033291716001513

Türker, K. S., Miles, T. S., & Le, H. T. (1988). The lip-clip:A simple, low-impedance ground electrode for use in human electrophysiology. *Brain Research Bulletin, 21*(1), 139-141. doi: 10.1016/0361-9230(88)90130-X

Tversky, A., & Fox, C. R. (1995). Weighing risk and uncertainty. *Psychological Review, 102*(2), 269-283. doi: 10.1037/0033-295X.102.2.269

United Nations Office on Drugs and Crime. (2010). World drug report: United Nations Publications,.

United Nations Office on Drugs and Crime. (2012). World Drug Report

United Nations Office on Drugs and Crime. (2016). World Drug Report.

Upton, D. J., Kerestes, R., & Stout, J. C. (2012). Comparing the iowa and soochow gambling tasks in opiate users. *Frontiers in Neuroscience, 6*, 34. doi: 10.3389/fnins.2012.00034

Van't Wout, M., Kahn, R. S., Sanfey, A. G., & Aleman, A. (2006). Affective state and decision-making in the ultimatum game. *Experimental Brain Research, 169*(4), 564-568. doi: 10.1007/s00221-006-0346-5

Vassileva, J., Ahn, W. Y., Weber, K. M., Busemeyer, J. R., Stout, J. C., Gonzalez, R. G., & Cohen, M. H. (2013). Computational modeling reveals distinct effects of hiv and history of drug use on decision-making processes in women. *PLoS ONE, 8*(8), e68962. doi: 10.1371/journal.pone.0068962

Veilleux, J. C., Colvin, P. J., Anderson, J., York, C., & Heinz, A. J. (2010). A review of opioid dependence treatment: Pharmacological and psychosocial interventions to treat opioid addiction. *Clinical Psychology Review, 30*(2), 155-166. doi: 10.1016/j.cpr.2009.10.006

Verdejo-Garcia, A., Bechara, A., Recknor, E. C., & Perez-Garcia, M. (2006). Decision-making and the iowa gambling task: Ecological validity in individuals with substance dependence. *Psychologica Belgica, 46*(1-2), 1-2.

Verdejo-Garcia, A., Chong, T. T. J., Stout, J. C., Yücel, M., & London, E. D. (2017). Stages of dysfunctional decision-making in addiction. *Pharmacology Biochemistry and Behavior*. doi: 10.1016/j.pbb.2017.02.003

DECISION-MAKING AND OPIATE USE

Verdejo-Garcia, A., Clark, L., & Dunn, B. D. (2012). The role of interoception in addiction: A critical review. *Neuroscience and Biobehavioral Reviews, 36*(8), 1857-1869. doi: 10.1016/j.neubiorev.2012.05.007

Verdejo-Garcia, A., Lawrence, A. J., & Clark, L. (2008). Impulsivity as a vulnerability marker for substance-use disorders: Review of findings from high-risk research, problem gamblers and genetic association studies. *Neuroscience and Biobehavioral Reviews, 32*(4), 777-810. doi: 10.1016/j.neubiorev.2007.11.003

Verdejo-Garcia, A., Perales, J. C., & Perez-Garcia, M. (2007). Cognitive impulsivity in cocaine and heroin polysubstance abusers. *Addictive Behaviors, 32*(5), 950-966. doi: 10.1016/j.addbeh.2006.06.032

Verdejo-Garcia, A., & Perez-Garcia, M. (2007). Profile of executive deficits in cocaine and heroin polysubstance users: Common and differential effects on separate executive components. *Psychopharmacology, 190*(4), 517-530. doi: 10.1007/s00213-006-0632-8

Verdejo-Garcia, A., Perez-Garcia, M., & Bechara, A. (2006). Emotion, decision-making and substance dependence: A somatic-marker model of addiction. *Current Neuropharmacology, 4*(1), 17-31.

Verdejo-Garcia, A., Rivas-Perez, C., Vilar-Lopez, R., & Perez-Garcia, M. (2007). Strategic self-regulation, decision-making and emotion processing in poly-substance abusers in their first year of abstinence. *Drug and Alcohol Dependence, 86*(2), 139-146. doi: 10.1016/j.drugalcdep.2006.05.024

Verdejo-Garcia, A., Verdejo-Roman, J., Albein-Urios, N., Martinez-Gonzalez, M., & Soriano-Mas, C. (2017). Brain substrates of social decision-making in dual diagnosis: Cocaine dependence and personality disorders. *Addiction Biology, 22*(2), 457-467. doi: 10.1111/adb.12318

Von Neumann, J., & Morgenstern, O. (1947). *Theory of games and economic behavior*. Princeton, NJ: Princeton University Press.

Wagar, B. M., & Dixon, M. (2006). Affective guidance in the Iowa Gambling Task. *Cognitive, Affective, and Behavioral Neuroscience, 6*(4), 277-290. doi: 10.3758/CABN.6.4.277

Walter, M., Degen, B., Treugut, C., Albrich, J., Oppel, M., Schulz, A., . . . Wiesbeck, G. A. (2011). Affective reactivity in heroin-dependent patients with antisocial personality disorder. *Psychiatry Research, 187*(1-2), 210-213. doi: 10.1016/j.psychres.2010.10.017

Wang, P. W., Lin, H. C., Liu, G. C., Yang, Y. H. C., Ko, C. H., & Yen, C. F. (2016). Abnormal interhemispheric resting state functional connectivity of the insula in heroin users under methadone maintenance treatment. *Psychiatry Research: Neuroimaging, 255*, 9-14. doi: 10.1016/j.pscychresns.2016.07.009

Wang, X., Li, B., Zhou, X., Liao, Y., Tang, J., Liu, T., . . . Hao, W. (2012). Changes in brain gray matter in abstinent heroin addicts. *Drug and Alcohol Dependence, 126*(3), 304-308. doi: 10.1016/j.drugalcdep.2012.05.030

Wang, Y. H., Li, W., Li, Q., Yang, W., Zhu, J., & Wang, W. (2011). White matter impairment in heroin addicts undergoing methadone maintenance treatment and prolonged abstinence: A preliminary DTI study. *Neuroscience Letters, 494*(1), 49-53. doi: 10.1016/j.neulet.2011.02.053

Wang, Z. X., Zhang, J. X., Wu, Q. L., Liu, N., Hu, X. P., Chan, R. C. K., & Xiao, Z. W. (2010). Alterations in the processing of non-drug-related affective stimuli in abstinent heroin addicts. *Neuroimage, 49*(1), 971-976. doi: 10.1016/j.neuroimage.2009.08.020

Waters-Wood, S. M., Xiao, L., Denburg, N. L., Hernandez, M., & Bechara, A. (2012). Failure to learn from repeated mistakes: Persistent decision-making impairment as measured by the Iowa Gambling Task in patients with ventromedial prefrontal cortex lesions. *Journal of the International Neuropsychological Society, 18*(5), 927-930. doi: 10.1017/S135561771200063X

Werner, N. S., Jung, K., Duschek, S., & Schandry, R. (2009). Enhanced cardiac perception is associated with benefits in decision-making. *Psychophysiology, 46*(6), 1123-1129. doi: 10.1111/j.1469-8986.2009.00855.x

Werner, N. S., Schweitzer, N., Meindl, T., Duschek, S., Kambeitz, J., & Schandry, R. (2013). Interoceptive awareness moderates neural activity during decision-making. *Biological Psychology, 94*(3), 498-506. doi: 10.1016/j.biopsycho.2013.09.002

Wilson, M. J., & Vassileva, J. (2016). Neurocognitive and psychiatric dimensions of hot, but not cool, impulsivity predict HIV sexual risk behaviors among drug users in protracted abstinence. *American Journal of Drug and Alcohol Abuse, 42*(2), 231-241. doi: 10.3109/00952990.2015.1121269

Witkiewitz, K., Bowen, S., Douglas, H., & Hsu, S. H. (2013). Mindfulness-based relapse prevention for substance craving. *Addictive Behaviors, 38*(2), 1563-1571. doi: 10.1016/j.addbeh.2012.04.001

Wollman, S. C., Alhassoon, O. M., Hall, M. G., Stern, M. J., Connors, E. J., Kimmel, C. L., . . . Radua, J. (2016). Gray matter abnormalities in opioid-dependent patients: A neuroimaging meta-analysis. *American Journal of Drug and Alcohol Abuse, Published online 3 Nov 2016*, 1-13. doi: 10.1080/00952990.2016.1245312

Wollman, S. C., Alhassoon, O. M., Stern, M. J., Hall, M. G., Rompogren, J., Kimmel, C. L., & Perez-Figueroa, A. M. (2015). White matter abnormalities in long-term heroin users: a preliminary neuroimaging meta-analysis. *American Journal of Drug and Alcohol Abuse, 41*(2), 133-138. doi: 10.3109/00952990.2014.985829

World Health Organization. (2004). *Neuroscience of psychoactive substance use and dependence*. Geneva, Switzerland: World Health Organisation.

Xie, C., Li, S. J., Shao, Y., Fu, L., Goveas, J., Ye, E., . . . Yang, Z. (2011). Identification of hyperactive intrinsic amygdala network connectivity associated with impulsivity in abstinent heroin addicts. *Behavioural Brain Research, 216*(2), 639-646. doi: 10.1016/j.bbr.2010.09.004

Yan, W. S., Li, Y. H., Xiao, L., Zhu, N., Bechara, A., & Sui, N. (2014). Working memory and affective decision-making in addiction: A neurocognitive comparison between heroin addicts, pathological gamblers and healthy controls. *Drug and Alcohol Dependence, 134*, 194-200. doi: 10.1016/j.drugalcdep.2013.09.027

Yeh, T. L., Chen, K. C., Lin, S. H., Lee, I. H., Chen, P. S., Yao, W. J., . . . Chiu, N. T. (2012). Availability of dopamine and serotonin transporters in opioid-dependent users--a two-isotope SPECT study. *Psychopharmacology, 220*(1), 55-64. doi: 10.1007/s00213-011-2454-6

Yuan, J., Liu, X. D., Han, M., Lv, R. B., Wang, Y. K., Zhang, G. M., & Li, Y. H. (2015). Comparison of striatal dopamine transporter levels in chronic heroin-dependent and methamphetamine-dependent subjects. *Addiction Biology*. doi: 10.1111/adb.12271

Yuan, K., Qin, W., Dong, M., Liu, J., Sun, J., Liu, P., . . . Li, Q. (2010). Gray matter deficits and resting-state abnormalities in abstinent heroin-dependent individuals. *Neuroscience Letters, 482*(2), 101-105. doi: 10.1016/j.neulet.2010.07.005

Yuan, Y., Zhu, Z., Shi, J., Zou, Z., Yuan, F., Liu, Y. P., . . . Weng, X. (2009). Gray matter density negatively correlates with duration of heroin use in young lifetime heroin-dependent individuals. *Brain and Cognition, 71*(3), 223-228. doi: 10.1016/j.bandc.2009.08.014

Zeelenberg, M., Nelissen, R. M. A., Breugelmans, S. M., & Pieters, R. (2008). On emotion specificity in decision making: Why feeling is for doing. *Judgment and Decision Making, 3*(1), 18-27.

Zeng, H., Lee, T. M. C., Waters, J. H., So, K. F., Sham, P. C., Schottenfeld, R. S., . . . Chawarski, M. C. (2013). Impulsivity, cognitive function, and their relationship in heroin-dependent individuals. *Journal of Clinical and Experimental Neuropsychology, 35*(9), 897-905. doi: 10.1080/13803395.2013.828022

Zeng, H., Su, D., Jiang, X. F., Zhu, L., & Ye, H. (2016). The similarities and differences in impulsivity and cognitive ability among ketamine, methadone, and non-drug users. *Psychiatry Research, 243*, 109-114. doi: 10.1016/j.psychres.2016.04.095

Zhang, X. L., Shi, J., Zhao, L. Y., Sun, L. L., Wang, J., Wang, G. B., . . . Lu, L. (2011). Effects of stress on decision-making deficits in formerly heroin-dependent patients after different durations of abstinence. *American Journal of Psychiatry, 168*(6), 610-616. doi: 10.1176/appi.ajp.2010.10040499

Zhang, X. L., Wang, G. B., Zhao, L. Y., Sun, L. L., Wang, J., Wu, P., . . . Shi, J. (2012). Clonidine improved laboratory-measured decision-making performance in abstinent heroin addicts. *PLoS ONE, 7*(1), e29084. doi: 10.1371/journal.pone.0029084

Zhang, Y., Tian, J., Yuan, K., Liu, P., Zhuo, L., Qin, W., . . . Liu, Y. (2011). Distinct resting-state brain activities in heroin-dependent individuals. *Brain Research, 1402*, 46-53. doi: 10.1016/j.brainres.2011.05.054

Zigmond, A. S., & Snaith, R. P. (1983). The hospital and anxiety depression scale. *Acta Psychiatrica Scandinavica, 67*, 361-370. doi: 10.1111/j.1600-0447.1983.tb09716.x

DECISION-MAKING AND OPIATE USE

Appendices.

Appendix A   Human Research Ethics Committee Study Approval

Human Research Ethics Committee
Approval Form

Principal Investigator/Supervisor: Dr Gill Terrett

Co-Investigators:

Student Researcher: Kathryn Biernacki, Lauren McKeogh, Phoebe Morton

Ethics approval has been granted for the following project:
  Psychophysiological correlates of decision making in long term opiate users and healthy adults

for the period: 30/06/2018

Human Research Ethics Committee (HREC) Register Number: 2014 306V

This is to certify that the above application has been reviewed by the Australian Catholic University Human Research Ethics Committee (ACU HREC). The application has been approved for the period given above.

Researchers are responsible for ensuring that all conditions of approval are adhered to, that they seek prior approval for any modifications and that they notify the HREC of any incidents or unexpected issues impacting on participants that arise in the course of their research. Researchers are also responsible for ensuring that they adhere to the requirements of the *National Statement on Ethical Conduct in Human Research*, the *Australian Code for the Responsible Conduct of Research* and the University's *Code of Conduct*.

Any queries relating to this application should be directed to the Research Ethics Manager (resethics.manager@acu.edu.au).

Kind regards

  Date 10/08/2017
Research Ethics Manager

Research Ethics | Office of the Deputy Vice-Chancellor (Research)
Australian Catholic University
T: +61 2 9739 2646
E: Res.Ethics@acu.edu.au
W: ACU Research Ethics

DECISION-MAKING AND OPIATE USE

Appendix B Participant Recruitment and Informed Consent

Appendix B – 1   Information Letter.

PARTICIPANT INFORMATION LETTER

PROJECT TITLE: Physical responses to decision making

PRINCIPAL SUPERVISOR: Dr Skye McLennan

STUDENT RESEARCHERS: Ms Kathryn Biernacki, Ms Phoebe Morton

STUDENT'S DEGREE: Doctor of Philosophy (Psychology); Bachelor of Psychological Science (Honours)

Dear Participant,

You are invited to participate in the research project described below.

What is the project about?
This research project investigates how the body reacts when making decisions. In particular, this study aims to test whether people who have used opiates (e.g. heroin) have different physical reactions to people who have not used drugs, while making decisions.

Who is undertaking the project?
This project is being conducted by Kathryn Biernacki and Phoebe Morton and will form the basis for the degree of Doctor of Philosophy (Psychology) and Bachelor of Psychological Science (Honours) at Australian Catholic University under the supervision of Dr Skye McLennan.

Are there any risks associated with participating in this project?
There are no foreseeable risks in participating in this study.

What will I be asked to do?
A mutually convenient time will be arranged for you to complete a single testing session. All testing will be conducted at the Melbourne campus of ACU, in the Daniel Mannix building.
Body measurements and decision making: You will be asked to complete a computerised test of decision-making (a gambling-type game), while being monitored for changes in skin responses. This will involve placing a number of non-invasive sensors on the skin, in particular to the cheek, brow, fingers, chest and left abdomen (just above your waist). The researcher will place the sensors on your cheek, brow and fingers. However, you will be instructed to place the sensors on your chest and left abdomen yourself. You will need to wear a shirt or top that allows you to put the sensors on your chest (e.g. a button-down shirt or singlet top). These tasks will also be recorded on videotape to provide a backup check of the accuracy of the measures.
Background questionnaire: You will also be asked to complete a background questionnaire, which asks you about your education, general health and drug use.

1

Background tests: You will also complete several background tests. These will require you to fill out questionnaires, pronounce words, complete sentences, and complete some tasks on a computer. There will also be a small role-play activity. Any verbal responses will require audio recording of answers to provide a check of the accuracy of the measure.

Saliva swab: You will be asked to provide samples of saliva, to test levels of hormones in the body during the testing session. The samples will be placed into a small container and samples will be stored at the University for testing.

Hair sample: You will be asked to provide a small sample of hair to test levels of hormones in the body during testing. The researcher will cut a small sample of hair from the back of your head (no bigger than half a pencil-width).

How much time will the project take?

The project will consist of one testing session, with the option to participate in a further testing session at a later date. The initial testing session will last approximately 3 hours.

What are the benefits of the research project?

There are no immediate benefits to the participant. General benefits include greater understanding of the different processes that aid decision-making.

Can I withdraw from the study?

Participation in this study is completely voluntary. You are not under any obligation to participate. If you agree to participate, you can withdraw from the study at any time without adverse consequences.

Will anyone else know the results of the project?

Participants will be given a code, and names will be stored separately to the data. Aggregate results of the study will be reported at a conference and/or in a scientific journal. It is emphasized that individual participants will not be able to be identified in any report of the study, as only group data will be reported. Also, given that illicit substance use is unlawful, the researchers cannot guarantee that a third party could not use some legal process to gain access to the data. It is stressed that identifying information will not be kept with the data in order to make re-identifying data difficult.

Will I be able to find out the results of the project?

Findings of the study will be made available to participants upon request.

Who do I contact if I have questions about the project?

Any questions regarding this project can be directed to the student investigators: Ms Kathryn Biernacki and Ms Phoebe Morton in the School of Psychology, St. Patrick's Campus (Australian Catholic University, Level 5, The Daniel Mannix Building, Young Street, Fitzroy 3065).

What if I have a complaint or any concerns?
The study has been reviewed by the Human Research Ethics Committee at Australian Catholic University (approval number 2014 306V). If you have any complaints or concerns about the conduct of the project, you may write to the Chair of the Human Research Ethics Committee care of the Office of the Deputy Vice Chancellor (Research).

Research Ethics Manager (ResEthics.Manager@acu.edu.au)

Office of the Deputy Vice-Chancellor (Research)

Australian Catholic University

North Sydney Campus

PO Box 968

North Sydney NSW 2059.

Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

I want to participate! How do I sign up?
If you are willing to participate please sign the attached informed consent forms. You should sign both copies of the consent form and keep one copy for your records and return the other copy to the staff supervisor. Your support for the research project will be most appreciated.

Yours sincerely,

Ms Kathryn Biernacki   **Dr Skye McLennan**
Student Researcher   Supervisor

Ms Phoebe Morton
Student researcher

DECISION-MAKING AND OPIATE USE

Appendix B - 2   Consent Form.

ACU | health sciences

CONSENT FORM
Copy for Researcher to Keep

TITLE OF PROJECT: Physical responses to decision making

SUPERVISOR: Dr Skye McLennan

STUDENT RESEARCHERS: Ms Kathryn Biernacki and Ms Phoebe Morton

I .... *(the participant)* have read *(or, where appropriate, have had read to me)* and understood the information provided in the Letter to Participants. Any questions I have asked have been answered to my satisfaction. I agree to participate in a testing session taking up to three hours, comprising of: answering a background questionnaire, completing several pen-and-paper and computerised tests, and playing a computerised game while being monitored by sensors attached to my face, fingers and chest. I realise that I can withdraw my consent at any time (without adverse consequences). I agree that research data collected for the study may be published or may be provided to other researchers in a form that does not identify me in any way. I agree to participate in this activity realising that information gathered will remain confidential and secure except when it is required by law, and/or failure to disclose the information would place myself or another person at risk. In addition:

☐ I agree to have a small sample of hair cut from the back of my head to be used for measuring the hormone cortisol (please tick the box if you agree).

☐ I agree to provide saliva samples throughout the testing session to be used for measuring the hormones oxytocin and vasopressin (please tick the box if you agree).

☐ I agree to be contacted about participation in later studies, understanding that I can refuse participation without adverse consequences (please tick the box if you agree). Please fill out the form on the next page if you tick this box.

NAME OF PARTICIPANT: ....

SIGNATURE ....   DATE ....

SIGNATURE OF PRINCIPAL INVESTIGATOR (or SUPERVISOR):..
                                                            DATE:.............................…..

SIGNATURE OF STUDENT RESEARCHER:...
                                                            DATE:.......................………..

DECISION-MAKING AND OPIATE USE

Appendix B - 3   Recruitment Flyer

Appendix B - 3.1   Recruitment flyer for opiate users

DECISION-MAKING AND OPIATE USE

Appendix B – 3.2   *Recruitment flyer for controls*

DECISION-MAKING AND OPIATE USE

Appendix C   Experimental materials

Appendix C – 1   Demographic Questionnaire

ID: Date

Background Questionnaire (methadone sample cover)

To participate in this study you need to confirm all of the following statements. If you are unable to confirm ALL of the statements, unfortunately you are not eligible to participate in this study.

1. Are you over 18 years old?

2. Do you have a history of heroin dependence?

3. Are you currently participating in a methadone (buprenorphine) maintenance program for heroin dependence?

4. Have you been to hospital for surgery? What surgery?

5. Have you lost consciousness for 5 minutes or more?

6. Have you ever overdosed?

7. Do you have a history of head injury that led to hospitalization?

8. Do you have any formal diagnosis of Traumatic Brain Injury (TBI) or Acquired Brain injury (ABI)?

9. Have you ever had a stroke or epileptic fit?

10. Have you been stable on methadone (buprenorphine) for at least 2 weeks?

11. Have you consumed any methadone (buprenorphine) in the last 5 hours?

12. Have you used heroin or other illicit drugs within the last 24 hours?

13. Have you ever been a heavy drinker of alcohol? This is regularly drinking to intoxication or having more than 28 standard drinks per week if you are male, or more than 14 standard drinks per week if you are female.

14. Is English is your first language?

15. Have you been diagnosed as HIV+?

16. Do you have any formal psychiatric diagnoses (e.g. schizophrenia)?

DECISION-MAKING AND OPIATE USE

ID: _____   Date

Background Questionnaire (control sample cover)

To participate in this study you need to confirm all of the following statements. If you are unable to confirm ALL of the statements, unfortunately you are not eligible to participate in this study.

1. Are you over 18 years old?

2. Do you have a history of alcohol or drug dependence?

3. Do you have a history of head injury that led to hospitalization

4. Do you have any formal diagnosis of Traumatic Brain Injury (TBI) or Acquired Brain injury (ABI)?

5. Have you ever had a stroke or epileptic fit?

6. Have you used alcohol or any other illicit drug within the last 24 hours?

7. Have you taken any other medications in the last 24 hours (e.g. cold and flu, antihistamine, sleeping pills)? Please specify: _____

8. Have you ever been a heavy drinker of alcohol? This is regularly drinking to intoxication or having more than 28 standard drinks per week if you are male, or more than 14 standard drinks per week if you are female.

9. Is English is your first language?

10. Do you have any formal psychiatric diagnoses (e.g. schizophrenia)?

DECISION-MAKING AND OPIATE USE

ID: _____   Date

Section 1: Demographics

Age: _____ years   **Gender** *(please tick)*: Male ☐ Female ☐ Other*(please specify)*_____

Relationship Status:

☐ Married

☐ Living together/defacto

☐ Partnered but not living together

☐ Separated/divorced

☐ Single

Number of children:

☐ 0

☐ 1

☐ 2

☐ 3

☐ More than 3

Employment Status:

☐ Full-time

☐ Part-time

☐ Casual

☐ Unemployed

Occupation: _____

Years of education:

Number of years: _____

Type of education completed/attempted (select one or more):

☐ Up to Year 10   ☐ Up to Year 12   ☐ TAFE   ☐ Undergraduate degree

☐ Postgraduate degree   ☐ Other, please specify _____

Section 2: English Language Skills

Is English your first language: ☐Yes   ☐No

If NO, how many years have you spoken English? _____ years

How do you rate your level of English?

Excellent ☐   Very good ☐   Not very good ☐   Poor ☐

DECISION-MAKING AND OPIATE USE

ID: _____   **Date**

_____

Section 3: Health

Using the following as a guide please answer the questions below. Please tick the box that
best describes you.

    Excellent: No problems
    Very good: no major problems
    Good: occasional bad days
    Not very good: a number of problems
    Poor: Persistent serious problems

How would you describe your state of health over the last month or so?

Excellent ☐   Very good ☐   Good☐   Not very good ☐   Poor ☐

How would you describe your state of health today?

Excellent ☐   Very good ☐   Good☐   Not very good ☐   Poor ☐

How would you describe how you have been sleeping over the last few weeks?

Excellent ☐   Very good ☐   Good☐   Not very good ☐   Poor ☐

Have you been diagnosed as HIV+?

Yes ☐   No ☐

Are you taking any medications for a medical condition? (e.g. heart condition)

Yes ☐   No ☐

Please specify: _____

_____

Section 4: Psychiatric History

Are you aware of any formal psychiatric diagnoses? Yes ☐   No ☐

If **YES**, please specify:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

ID: Date

Section 5a: Substance use

The following section asks about current and past use of **alcohol, cigarettes and illicit substances** (such as amphetamines or heroin).

For each substance please indicate whether you are a *current user, have used in the past,* or *have never used* the substance.

If you are a <u>current user</u> or <u>have used any substances in the past (including alcohol and cigarettes),</u> please indicate for each type of substance:
- The age of first use
- The age of regular use (if applicable)
- How often you use
- How much of the drug you would use
- How long you used the drug

(Fill out tables on the next page)

For any substance you have *not* used please tick NEVER, and continue to the next substance.

If you have <u>never used any type of illicit substance, cigarettes or alcohol</u> you do not have to complete this section.

ID: Date

Alcohol
Current use ☐   Past use ☐   Never ☐
Age of first use: _____ years   Age of regular use: _____ years

Frequency	Dosage	Duration
☐ Daily	☐ 1-6 standard drinks each week	☐ less than 6 months
☐ At least once a week	☐ 7-14 standard drinks each week	☐ 6 months – 1year
☐ At least once a fortnight	☐ 15-21 standard drinks each week	☐ 1-3 years
☐ At least once a month	☐ 22-27 standard drinks each week	☐ 3-5 years
☐ Less than once a month	☐ 28 or more standard drinks each week	☐ 5-10 years
☐ Never/once or twice	☐ Other:	☐ More than 10 years

Cigarettes
Current use ☐   Past use ☐   Never ☐
Age of first use: _____ years   Age of regular use: _____ years

Frequency	Dosage	Duration
☐ Daily	☐ few cigarettes a day	☐ less than 6 months
☐ At least once a week	☐ less than a packet a day	☐ 6 months – 1year
☐ At least once a fortnight	☐ a packet a day	☐ 1-3 years
☐ At least once a month	☐ more than a packet a day	☐ 3-5 years
☐ Less than once a month	☐ Other:	☐ 5-10 years
☐ Never/once or twice		☐ More than 10 years

Cannabis
Current use ☐   Past use ☐   Never ☐
Age of first use: _____ years   Age of regular use: _____ years

Frequency	Dosage	Duration
☐ Daily	☐ 1g to 3g per session	☐ less than 6 months
☐ At least once a week	☐ 4g to 6g per session	☐ 6 months – 1year
☐ At least once a fortnight	☐ 7g or more per session	☐ 1-3 years
☐ At least once a month	☐ Other:	☐ 3-5 years
☐ Less than once a month		☐ 5-10 years
☐ Never/once or twice		☐ More than 10 years

DECISION-MAKING AND OPIATE USE

ID: Date

Amphetamines (e.g. speed, ecstasy, ice, MDMA)
Current use ☐   Past use ☐   Never ☐
Age of first use: ____ years   Age of regular use: ____ years

Frequency	Dosage	Duration
☐ Daily	☐ 0.1g to 0.5g per session	☐ less than 6 months
☐ At least once a week	☐ 0.6 to 1.0g per session	☐ 6 months – 1year
☐ At least once a fortnight	☐ More than 1.0g per session	☐ 1-3 years
☐ At least once a month	☐ Other:	☐ 3-5 years
☐ Less than once a month	Specify:	☐ 5-10 years
☐ Never/once or twice		☐ More than 10 years

Heroin
Current use ☐   Past use ☐   Never ☐
Age of first use: ____ years   Age of regular use: ____ years   Total years heroin use:_____

Frequency	Dosage	Duration
☐ Daily	☐ 1 hit at a time	☐ less than 6 months
☐ At least once a week	☐ 2-3 hits at a time	☐ 6 months – 1year
☐ At least once a fortnight	☐ 4 or more hits at a time	☐ 1-3 years
☐ At least once a month	☐ Other:	☐ 3-5 years
☐ Less than once a month		☐ 5-10 years
☐ Never/once or twice	1 hit = 0.3g heroin	☐ More than 10 years

Cocaine
Current use ☐   Past use ☐   Never ☐
Age of first use: ____ years   Age of regular use: ____ years

Frequency	Dosage	Duration
☐ Daily	☐ 1 line at a time	☐ less than 6 months
☐ At least once a week	☐ 2-3 lines at a time	☐ 6 months – 1year
☐ At least once a fortnight	☐ 4 or more lines at a time	☐ 1-3 years
☐ At least once a month	☐ Other:	☐ 3-5 years
☐ Less than once a month		☐ 5-10 years
☐ Never/once or twice		☐ More than 10 years

ID: Date

LSD/Acid
Current use ☐   Past use ☐   Never ☐
Age of first use: _____ years   Age of regular use: _____ years

Frequency	Dosage	Duration
☐ Daily	☐ 1-2 tabs at a time	☐ less than 6 months
☐ At least once a week	☐ 2-3 tabs at a time	☐ 6 months – 1year
☐ At least once a fortnight	☐ 4 or more tabs at a time	☐ 1-3 years
☐ At least once a month	☐ Other:	☐ 3-5 years
☐ Less than once a month		☐ 5-10 years
☐ Never/once or twice		☐ More than 10 years

Prescription medications (e.g. Vallium, Xanax, Seroquel)
Current use ☐   Past use ☐   Never ☐
Age of first use: _____ years   Age of regular use: _____ years

Frequency	Dosage	Duration
☐ Daily	☐ 1 pill at a time	☐ less than 6 months
☐ At least once a week	☐ 2-3 pills at a time	☐ 6 months – 1year
☐ At least once a fortnight	☐ more than 3 pills at a time	☐ 1-3 years
☐ At least once a month	☐ Other:	☐ 3-5 years
☐ Less than once a month	Specify:	☐ 5-10 years
☐ Never/once or twice		☐ More than 10 years

Section 5b: Substance use
If there drug/s you have used have not already been specified, please provide details in the space provided below.

Other _____
Current use ☐   Past use ☐   Never ☐
Age of regular use: _____ years

Frequency	Dosage	Duration
☐ Daily		
☐ At least once a week		☐ less than 6 months
☐ At least once a fortnight		☐ 6 months – 1year
☐ At least once a month		☐ 1-3 years
☐ Less than once a month		☐ 3-5 years
☐ Never/once or twice		☐ More than 5 years

ID: _____   **Date**

Section 6a: Opiate substitute (Current)

DO NOT complete this section if you are an abstinent user

What opiate substitute are you currently taking? _____

Have you taken others in the past? Please specify: _____

What is your current dose: _____

How long have you been on this dose: _____

How long have you been stable on this dose: _____

What has been your highest dose of this substitute? _____

How long have you been on this substitute overall? _____

_____

Appendix D   Proof of publication or acceptance to journal

Appendix D – 1 Proof of publication of Study 1

Review article

Decision-making ability in current and past users of opiates: A meta-analysis

Kathryn Biernacki [*,1], Skye N. McLennan, Gill Terrett, Izelle Labuschagne, Peter G. Rendell

Cognition and Emotion Research Centre, School of Psychology, Australian Catholic University, Melbourne, Australia

A R T I C L E   I N F O

A B S T R A C T

Opiate use is associated with deficits in decision-making. However, the impact of abstinence and co-morbid factors, like head injury and poly-substance abuse, on this ability, is currently unclear. This meta-analysis aimed to assess 1) the magnitude of decision-making deficits in opiate users; 2) whether co-morbid factors moderate the severity of these deficits; 3) whether ex-opiate users demonstrate smaller decision-making deficits than current users; and 4) whether the length of abstinence is related to the magnitude of decision-making deficits. We analysed 22 studies that compared the performance of current and ex-opiate users to healthy controls on decision-making measures such as the Iowa Gambling Task. Current users demonstrated a moderately strong impairment in decision-making relative to controls, which was not significantly moderated by co-morbid factors. The magnitude of the impairment did not significantly differ between studies assessing current or ex-users, and this impairment was not related to length of abstinence. Thus, it appears that opiate users have relatively severe decision-making deficits that persist at least 1.5 years after cessation of use.

Contents

1. Introduction

* Corresponding author at: Cognition and Emotion Research Centre, School of Psychology, Australian Catholic University, Melbourne, Australia.
   E-mail address: Kathryn.Biernacki@acu.edu.au (K. Biernacki).
[1] Locked Bag 4115, Fitzroy MDC, Victoria, 3065, Australia.

Long term opiate use is associated with a range of problems in everyday life, including poor physical and mental health, impaired social functioning, and high unemployment rates (De Maeyer et al., 2010, 2011; Meulenbeek, 2000). These difficulties may be linked

Appendix D – 2 Proof of publication of Study 2

CrossMark

ORIGINAL INVESTIGATION

Decision-making, somatic markers and emotion processing in opiate users

Kathryn Biernacki[1] [iD] · **Gill Terrett**[1] · **Skye N. McLennan**[1] · **Izelle Labuschagne**[1] · **Phoebe Morton**[1] · **Peter G. Rendell**[1]

Abstract

Rationale Opiate use is associated with deficits in decision-making. A possible explanation for these deficits is provided by the somatic marker hypothesis, which suggests that substance users may experience abnormal emotional responses during decision-making involving reward and punishment. This in turn may interfere with the brief physiological arousal, i.e. somatic markers that normally occur in anticipation of risky decisions. To date, the applicability of the somatic marker hypothesis to explain decision-making deficits has not been investigated in opiate users.

Objectives This study assessed whether decision-making deficits in opiate users were related to abnormal emotional responses and reduced somatic markers.

Methods Opiate users enrolled in an opiate substitute treatment program ($n = 28$) and healthy controls ($n = 32$) completed the Iowa Gambling Task (IGT) while their skin conductance responses (SCRs) were recorded. Participants' emotional responses to emotion-eliciting videos were also recorded using SCRs and subjective ratings.

Results Opiate users displayed poorer decision-making on the IGT than did controls. However, there were no differences between the groups in SCRs; both groups displayed stronger SCRs following punishment than following reward, and both groups displayed stronger anticipatory SCRs prior to disadvantageous decisions than advantageous decisions. There were no group differences in objective or subjective measures of emotional responses to the videos.

Conclusions The results suggest that deficits in emotional responsiveness are not apparent in opiate users who are receiving pharmacological treatment. Thus, the somatic marker hypothesis does not provide a good explanation for the decision-making deficits in this group.

Keywords Opiate · Heroin · Decision-making · Somatic marker · Skin conductance · Emotion experience

Introduction

Opiates belong to one of the most addictive classes of drugs (Dacher and Nugent 2011). In addition to numerous health issues (Pillari and Narus 1973; Ryan and White 1996; Webster et al. 1979), opiate use has been associated with abnormalities in the structure and function of the frontal lobe of the brain (Pandria et al. 2016; Wollman et al. 2016; Wollman et al. 2015) and with a range of cognitive deficits (Baldacchino et al. 2017; Baldacchino et al. 2012). Of these cognitive deficits, impaired decision-making is the most consistently reported (Baldacchino et al. 2012). In opiate users, poor decision-making can manifest as problematic real-life behaviours such as risky sexual practices, leading to increased risk of HIV (Wilson and Vassileva 2016) and to a reduced ability to maintain abstinence (Passetti et al. 2008). A better understanding of the factors that contribute to decision-making impairments is needed to provide more targeted support and better outcomes for opiate users.

The somatic marker hypothesis (Damasio 1994) is a theoretical model that was developed to explain decision-making impairment in people with orbitofrontal cortex injuries but has recently been argued to also have utility in explaining poor decision-making in substance users (Bechara and Damasio 2002; Verdejo-Garcia and Bechara 2009; Verdejo-Garcia

✉ Kathryn Biernacki
   Kathryn.Biernacki@acu.edu.au

[1] Cognition and Emotion Research Centre, School of Psychology, Australian Catholic University, Melbourne, Australia