Drug and non-drug reward processing in cigarette and cannabis users

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I, Will Lawn, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Most people who try psychoactive drugs never become addicted. Theoretically, hypersensitivity to drug rewards and hyposensitivity to non-drug rewards may contribute to the development of drug addiction. In **chapter 1**, I review this literature, focusing on the psychology and neuroscience of reward processing, in nicotine and cannabis addictions. In **chapter 2**, using a novel task (the DReaM-Choice), I demonstrate that dependent (n=20), compared with occasional smokers (n=20), had greater motivation for and liking of cigarettes, but displayed little evidence of a difference in non-drug reward processing. Surprisingly, I also show the effects of 12 hour abstinence on reward processing were similar in dependent and occasional smokers. I then report a functional magnetic-resonance-imaging (fMRI) experiment (**chapter 3**), in which dependent smokers (n=22) had greater behavioural motivation for cigarettes and a stronger neural response to winning cigarettes than occasional smokers (n=20). However, there were no differences between the groups in behavioural or neural processing of the non-drug reward (music). I attempted to lessen the motivation to smoke cigarettes in the study reported in **chapter 4**, by administering a dopamine D2/3 receptor agonist (0.5mg pramipexole) to both dependent (n=20) and occasional (n=20) smokers. Pramipexole had no impact on motivation to smoke cigarettes, though it did impair reward learning and effort-related decision-making for monetary reward. In **chapter 5**, I found that, in non-dependent cannabis users (n=17), acutely administered cannabis reduced motivation for monetary reward; an effect which was moderated by the presence of cannabidiol in the cannabis. In a separate study, I demonstrate that dependent cannabis users (n=20) had impaired reward learning, but were not amotivated, relative to non-dependent, drug-using controls (n=20). Finally, in **chapter 6**, I summarise my findings, discuss their theoretical and clinical implications, consider their limitations and suggest future research directions for the field of reward processing in addiction.

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The work presented in this thesis has given rise to the following publications:

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Contents

List of Tables

List of Figures

Chapter 1: Drug and non-drug reward processing in addiction

Use of licit and illicit drugs is common and widespread. In the U.K., 19% of adults currently smoke cigarettes (Health and Social Care Information Centre, 2014) and 69% of adults drink alcohol once per week or more (ONS, 2013). In the European Union, 23.3% of adults have tried cannabis and 4.6% have tried cocaine at least once in their lifetime (European Monitoring Centre for Drugs and Drug Addiction, 2015). However, the majority of licit and illicit drug users will never become addicted. The percentages of those who have tried a drug and go on to become dependent are approximately: 32% for tobacco, 23% for heroin, 17% for cocaine, 15% for alcohol and 9% for cannabis (Anthony, Warner, & Kessler, 1994). One particularly eye-opening study, conducted after the Vietnam War, showed that only 5% of soldiers who regularly used heroin in Vietnam were addicted to the drug after returning to the U.S.A. (Robins, 1993). The reasons why most people are able to use drugs occasionally without becoming addicted while the minority end up in a decidedly difficult situation are mostly unknown, but they likely range from the sociological (Anthony et al., 1994) to the psychological (Lopez-Quintero et al., 2011) and neurobiological (Dalley et al., 2007). Gaining a better understanding of these reasons will improve the development of effective prevention and treatment strategies.

1.1 Introduction

Most of this thesis will focus on nicotine dependence, which, according to the epidemiological statistics described above, is the most likely addiction experienced after initial use. Despite substantial reductions in tobacco smoking, from a peak of around 80% in men during the late 1940s, it still embodies the leading cause of preventable death in the U.K., with approximately 100,000 people dying each year as a result of tobacco (Action on Smoking and Health, 2014). Of those over 35 years of age, 17% of all deaths in England were estimated to be caused by smoking (Health and Social Care Information Centre, 2014). Therefore, helping dependent cigarette smokers quit and remain abstinent is one of the primary ways we can improve the public health of our nation and the world at large.

Given the demonstrably unpleasant consequences of chronic tobacco smoking, it is unsurprising that around 70% of smokers in Great Britain want to quit (Lader & Goddard, 2004). In spite of this common desire, of those making an unaided quit only 3-5% remain abstinent one year later (Hughes, Keely, & Naud, 2004). Currently, the best form of treatment for nicotine dependence is a combination of the partial nicotinic receptor agonist varenicline and specialised behavioural therapy, which leads to a 31% abstinence rate after one year (West & Owen, 2012). Even highly motivated dependent smokers are more likely to fail than succeed (Zhou et al., 2009).

Cannabis dependence, although rare compared with nicotine dependence, is the most common illicit drug addiction: an estimated 13 million people are addicted worldwide (Degenhardt et al., 2013) including 1% of European adults (European Monitoring Centre for Drugs and Drug Addiction, 2015). Demand for treatment is increasing, especially among young people (Public Health England, 2013). However, current psychological treatments are limited (Cooper, Chatters, Kaltenthaler, & Wong, 2015) and there are no pharmacological treatments yet available.

Hence, important questions within the field of addiction include: what are the mechanisms that underlie the start, continuation and end of addictive behaviours? Research into what separates dependent drug users from non-dependent, occasional users should help us answer these questions. Such knowledge is hoped to help those dependent drug users who want to stop using drugs but find it difficult. One factor that is thought to drive addiction and relapse is the disruption of reward processing associated with chronic drug use (Goldstein & Volkow, 2011; Kelley & Berridge, 2002).

In this chapter, I will first introduce the broad concept of reward processing, the underlying neurobiological and pharmacological systems, and how recreational drugs interact with these systems. Subsequently, I will review the literature concerning whether nicotine and cannabis dependence are associated with alterations to the reward system and, crucially, whether they are associated with a hypersensitivity to drug rewards and a hyposensitivity to non-drug rewards. I will argue that the results are inconclusive and more research must be carried out before concluding that

nicotine and cannabis dependence are associated with clear reward processing alterations. I will propose that research which investigates drug and non-drug reward processing concurrently and which measures different aspects of reward processing is needed.

1.1.1 Addiction, dependence and substance use disorder

In this thesis I will use the terms 'drug dependence' and 'drug addiction' interchangeably. These terms refer to harmful drug use that is driven by strong motivations (West & Brown, 2013). Specifically, addiction is defined as 'a chronic condition involving a repeated powerful motivation to engage in a rewarding behaviour, acquired as a result of engaging in that behaviour, that has significant potential for unintended harm. Someone is addicted to something to the extent that they experience this repeated powerful motivation' (West & Brown, 2013, page 18).

Drug addiction/dependence/use disorders are often diagnosed using the diagnostic and statistical manual of mental disorders (DSM). In the previous edition (DSM-IV), diagnoses of either 'drug abuse' or 'drug dependence' were given, depending on the type and number of symptoms reported by the person (DSM-IV American Psychiatric Association, 2000). However, in the current edition (DSM-5), diagnoses are given, using similar symptoms to those used in DSM-IV, on a continuum of mild to severe 'substance use disorder' (SUD) (DSM-5 American Psychiatric Association, 2013) (see table 1.1). A mild SUD requires two-three symptoms, a moderate SUD requires four-five symptoms and a severe SUD requires six or more symptoms, to be present with a 12 month period. Surprisingly, the words 'addiction' and 'dependence' are never used to describe the disorder in DSM-5, although I believe the severity of the DSM-5 SUD can be approximated to the severity of drug addiction or dependence.

A variety of other questionnaires and clinical tools are also available to determine dependence level, such as the severity of dependence scale (SDS) (Gossop et al., 1995), and addiction-specific assessments, such as the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). Although there are many tools to assess the level of drug dependence,

they all tap similar constructs. In essence, drug addiction is characterised by repeated, powerful motivations to take drugs despite the potential for harmful consequences.

Table 1.1 The DSM-5 diagnostic criteria for substance use disorders. Severity of the disorder: 2-3 symptoms = mild; 3-4 symptoms = moderate; 6+ symptoms = severe.

Diagnostic Criteria
1. The substance is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control use of the substance.
3. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
4. Craving, or a strong desire or urge to use the substance.
5. Recurrent use of the substance resulting in a failure to fulfil major role obligations at work, school or home.
6. Continued use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use.
7. Important social, occupational or recreational activities are given up or reduced because of use of the substance.
8. Recurrent use of the substance in situations in which it is physically hazardous.
9. Use of the substance is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following: a) A need for markedly increased amounts of the substance to achieve the desired effect b) A markedly diminished effect with continued use of the same amount of the substance.
11. Withdrawal, as manifested by either of the following: a) The characteristic withdrawal syndrome for the substance b) The substance is taken to relieve or avoid withdrawal symptoms.

1.2 Reward processing

1.2.1 What is a reward and what is reward processing?

In this thesis, I will define a 'reward' as an appetitive stimulus that reinforces behaviour (Skinner, 1938) and/or provides pleasure to the recipient. A reward can be something that, when received, increases the likelihood of the preceding behaviour, i.e. a reinforcer. However a reward can also be something that provokes pleasure in the recipient without necessarily reinforcing the preceding behaviour. Very often, though, these two features of a reward exist together. Primary rewards have rewarding properties without the need for learning, for example food, water and sex. Contrastingly, secondary rewards require learning, for example money (Sescousse, Redouté, & Dreher, 2010). Other rewards,

such as humour and music, are more difficult to categorise as primary or secondary; however they may be thought of as 'higher level', in that non-human animals may not find them rewarding.

A reward process is therefore any distinct psychological process that involves engaging with a reward. Hence, there are many types of reward process, including motivation (e.g. being motivated to earn money) and pleasure (e.g. taking pleasure from eating a delicious slice of pizza). The processing of rewards is critical for the survival of all organisms. Salient, appetitive events must be successfully encoded so that animals learn about and are motivated to engage with stimuli which enhance the likelihood of effective gene transmission, such as the consumption of food and sexual reproduction. Furthermore, the experience of pleasure is important in our concept of human well-being (Deci & Ryan, 2008). Hence, reward processing is key to our continued existence and the quality of our existence.

The overarching term 'reward processing' refers to many distinct psychological concepts. Berridge and Robinson (1998) described 'wanting', 'learning' and 'liking' as separate components. However, I would argue that many other psychological processes fall under the 'reward processing' umbrella. Decision-making about rewards, including gambling, has become a burgeoning field (Bechara, Dolan, & Hindes, 2002), as has the closely related topic of valuation (Kable & Glimcher, 2009). Furthermore, the pleasure associated with rewards has recently been split into anticipatory and consummatory pleasure (Gard, Gard, Kring, & John, 2006). Moreover, the concepts of conscious, self-reported liking and wanting appear, on the face of it, somewhat different from the behavioural assays which assess potentially less conscious liking and wanting (or motivation), which often use face movements and button-presses, respectively (Berridge & Robinson, 1998).

I will introduce each relevant component of reward processing in more detail at appropriate stages in the thesis. However, in order to provide clear examples of what I mean by the different *components* of reward processing and to introduce four major components, which are frequently discussed in this thesis, I have briefly described: motivation, learning, liking and decision-making in table 1.2.

Furthermore, I have listed the ways in which these reward processes have been assessed in the work described in this thesis. This table is in no way exhaustive and should just be used to illustrate how reward processing can be broken up into distinct components.

Table 1.2 Four major reward processing components; descriptions of what they are; and ways that they are assessed within this thesis.

Reward processing component	Description	Ways it is assessed in this thesis
Motivational processing	The way in which organisms regulate the proximity and availability of stimuli (Salamone & Correa, 2002). Motivation has a directional component, in that organisms are directed towards some stimuli and not others, e.g. towards a tasty chocolate bar but not an empty plate. Motivation also has an activational component, in that organisms can work for a reward with a large amount of vigor or a small amount of vigor. Therefore, to have strong motivation for a reward involves directing behaviour towards it and working with a large amount of vigor. It has been suggested that motivation can be split up into conscious wanting (i.e. explicit desire) and non-conscious motivation, which is more closely associated with the attribution of 'incentive salience' to stimuli and rewards (Berridge & Robinson, 2003). At a more conceptual level, motivation has recently been considered a consequence of five interacting processes: plans, responses, impulses/inhibitory forces, motives and evaluations (West & Brown, 2013). This theory of motivation synthesises both complicated, conscious plans and simpler, potentially automatic impulses and responses, which provides a more comprehensive view of motivation.	(1) the DReaM-Choice task (2) the adapted Monetary Incentive Delay task (Knutson et al., 2001) (3) the Effort Expenditure for Rewards Task (Treadway et al., 2009) (4) self-reported wanting.
Learning about rewards	The formation of associations between two events, which can be between a neutral stimulus and a reward (in the case of Pavlovian learning) or between an action and a reward (in the case of instrumental learning). It is thought that some aspects of learning can happen implicitly, without conscious awareness, and explicitly, with conscious awareness (Destrebecqz & Cleeremans, 2001). Although most studies investigating implicit learning have focused on procedural, motor skills, it is feasible that reward learning could occur both explicitly and implicitly.	(1) the Probabilistic Reward Task (Pizagalli et al., 2005)
Liking (or hedonic processing)	The pleasure which one experiences when engaging with certain stimuli. Researchers have postulated that liking can be both conscious, expressed via self-report, and non-conscious, sometimes expressed via facial movements (Berridge and Robinson, 1998). However, I suggest in section 1.5.2.2 that the only way to measure pleasure in humans may be to ask them about their experiences.	(1) reward consumption followed by self-reported liking
Decision-making about rewards	The series of steps which allow an organism to choose between two reward options, including valuation and action selection (Rangel, 2008). Often these decisions involve cost-benefit analyses, like pitting the magnitude of the reward against the amount of effort required to receive the reward.	(1) the Effort Expenditure for Rewards Task (Treadway et al., 2009)

Given rewards are so inherently critical to our survival, it isn't surprising that there are many different ways we, and other animals, engage with them. The structure and taxonomy of reward processing, to my mind, is not yet clear. Some processes seem, by common sense, very related to one-another, for example valuation and decision-making, while others seem less closely related, for example learning about what predicts a reward and the pleasure taken from consuming a reward. The last few decades have seen a proliferation in the amount of research investigating this topic and the tasks used to assess different aspects of 'reward processing'. Over 30,000 articles have been published about 'reward', with the numbers of articles increasing each year (PubMed search 14/10/15). Clearly, this is a blossoming research area and reward processing studies are being carried out in many sub-disciplines of psychology, from behavioural neuroscience to clinical psychology. However, I believe we are still some way off understanding how the different components of reward processing relate to one another. More research that investigates performance across a wide range of tasks and questionnaires within the same individuals will be required to more thoroughly understand the separate and related aspects of reward processing.

In this thesis, I will argue that it is unhelpful to claim that clinical populations, such as 'drug addicts', are, *in general*, deficient in reward processing. Given the large number of reward processes, we must be specific about which components we are investigating and talking about. Examining various processes will allow us to determine *which* reward processes are disrupted within clinical populations, and even better, which of these can be targeted to help treat different clinical disorders.

1.2.2 The emergence of reward processing neurobiology

The demonstration that rats work for electrical stimulation in specific brain regions (Olds & Milner, 1954), opened up a new field of research into the neurobiology of reward and reinforcement. The powerful behavioural effects of operant reinforcement had been established previously by B.F. Skinner (Skinner, 1938). However, the basic neurobiological underpinnings of this motivated behaviour were elucidated by the work in a wide range of animals (Olds, 1962) demonstrating that

intracranial self-stimulation (ICSS) occurred when electrodes were placed in only specific brain areas, such as the lateral hypothalamus, medial forebrain bundle and tegmentum, across different species. This was extended to humans, who also exhibited ICSS and reported great pleasure when stimulated in certain regions, such as the septal area (Heath, 1963). This research strongly suggested that there is a phylogenetically older network of brain regions which encode reinforcement learning, motivated behaviour and even the subjective feelings of pleasure.

Subsequently, 6-hydroxydopamine lesion studies confirmed the role of mesocorticolimbic dopamine pathways, originating in the ventral tegmental area, in motivated responding for food and drugs of abuse (Fibiger, Zis, & McGeer, 1973; Roberts & Koob, 1982). Furthermore, the role of dopamine, while remaining controversial (Berridge & Robinson, 1998; Robbins & Everitt, 2007), became more strongly linked with reward processing, as electrophysiological (Di Chiara & Imperato, 1988; Hernandez & Hoebel, 1988) and positron emission tomography (PET) studies (Leyton et al., 2002; Small, Jones-Gotman, & Dagher, 2003) demonstrated that both food and psychostimulant drugs trigger increases in extracellular dopamine levels at cell terminals. The role of dopamine is discussed in more detail in section 1.3.1.

1.2.3 Neuroanatomy of reward processing (Figure 1.1)

Over the past few decades, more focused animal and neuroimaging work has delineated the specific roles of different components of the reward circuitry. Several brain regions have appeared as critical units of the reward system, including the ventral and dorsal striatum, orbitofrontal cortex, amygdala and thalamus.

The ventral striatum, including the nucleus accumbens, is thought to be involved with stimulus-outcome learning, and therefore goal-directed behaviour (Everitt & Robbins, 2005). Functional magnetic resonance (fMRI) studies have demonstrated its importance in the anticipation of rewards (Knutson, Adams, Fong, & Hommer, 2001) and choices between reward options (Knutson & Greer, 2008). The nucleus accumbens receives its dopaminergic input from the ventral tegmental area,

making up part of the mesocorticolimbic dopamine pathway (Haber & Knutson, 2010). Dopaminergic afferents from the ventral striatum innervate the ventral pallidum, where opioid transmission appears to be critical in hedonic processing (Peciña, Smith, & Berridge, 2006).

The dorsal striatum appears to be important in preparing and guiding actions, which are informed by the anticipation of rewards (Hikosaka, Bromberg-Martin, Hong, & Matsumoto, 2008), as well as habitual, stimulus-response behaviour, which occurs after long periods of training with the same reward in the same context (Everitt & Robbins, 2005). The dorsal striatum receives most of its dopaminergic innervation from the substantia nigra (Haber & Knutson, 2010).

The orbitofrontal cortex, which receives dopaminergic innervation and is reciprocally connected with the ventral and dorsal striatum, is thought to underlie the valuation of many kinds of reward (Chib, Rangel, Shimojo, & O'Doherty, 2009) and is important in decision-making. Moreover, its activation tracks the subjective pleasure assigned to rewards during consumption (Kringelbach, O'Doherty, Rolls, & Andrews, 2003)

The amygdala and the thalamus have been implicated in the processing of reward outcomes (Sescousse, Caldú, Segura, & Dreher, 2013). Furthermore, the basolateral amygdala has been found to play a critical role in assigning value to rewarding options during goal-directed behaviour while the central amygdala is more strongly associated with simple Pavlovian conditioning (Parkinson, Robbins, & Everitt, 2000).

Thus, the cortico-basal ganglia network, including the structures described above and the mesocorticolimbic and nigrostriatal dopamine pathways, is a reward-to-action interface (Haber & Knutson, 2010), which underpins various components of the overarching theme of reward processing. This network is shown diagrammatically in figure 1.1.

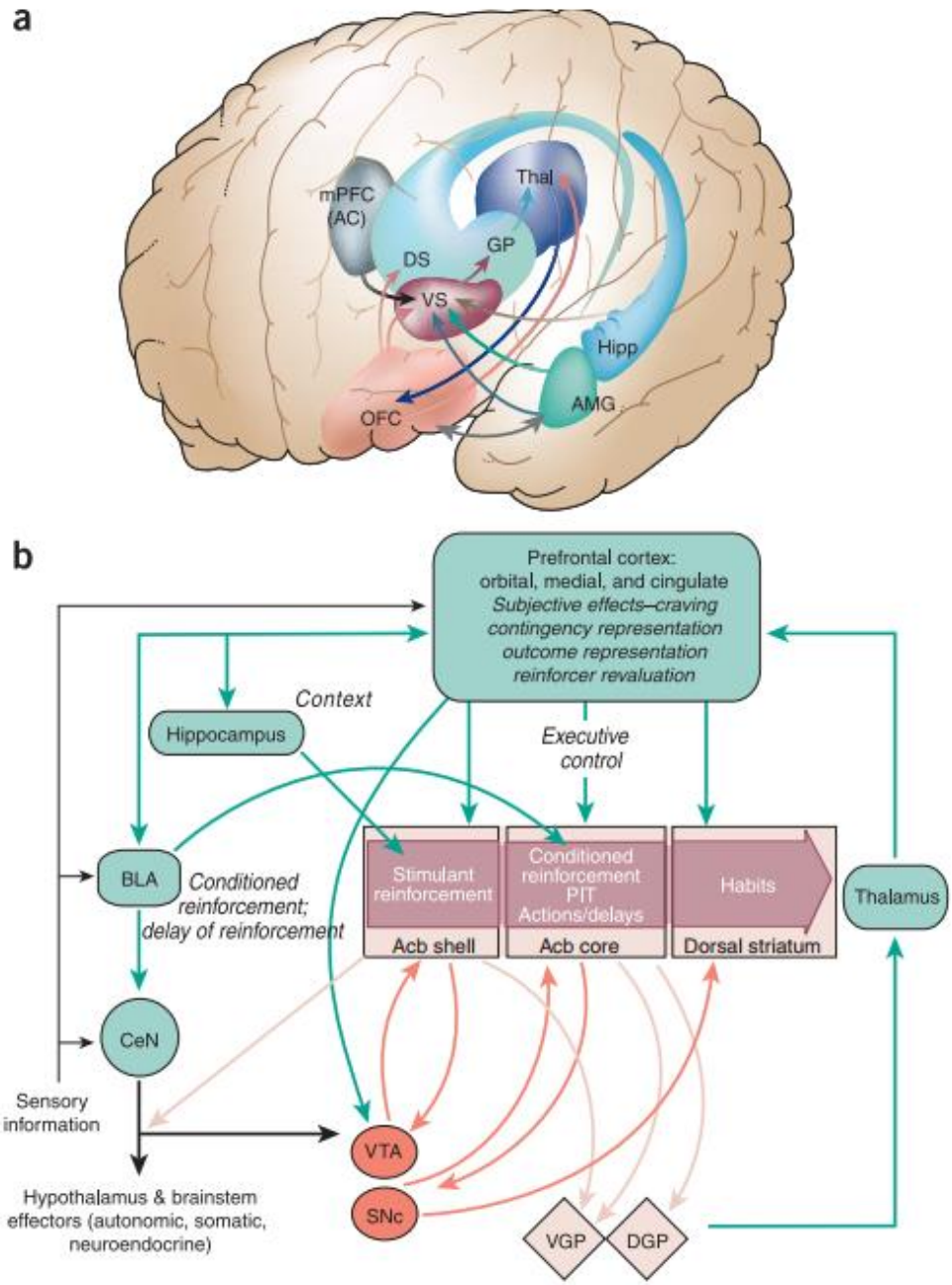


Figure 1.1 The neuroanatomy of the reward system (taken from Everitt & Robbins, 2005). a) The physical locations and connections of important reward processing regions, b) A diagrammatic representation of the functions and connections of important reward processing regions. Green/blue arrows, glutamatergic projections; orange arrows, dopaminergic projections; pink arrows, GABAergic projections; Acb, nucleus accumbens; AMG, amygdala; BLA, basolateral amygdala; CeN, central nucleus of the amygdala; VTA, ventral tegmental area; SNc, substantia nigra pars compacta. GP, globus pallidus (D, dorsal; V, ventral); Hipp, hippocampus; mPFC, medial prefrontal cortex; AC, anterior cingulate cortex; OFC, orbitofrontal cortex; VS, ventral striatum; DS, dorsal striatum; Thal, thalamus.

1.3 Dopamine

1.3.1 Dopamine and reward processing

Dopamine clearly plays a very important role in reward processing and this role has seen many interesting historical developments. In the 1970s and 80s, dopamine was viewed by researchers as a 'pleasure neurotransmitter', which made people feel good and like things (Wise, 1980). However, later research demonstrated the specific importance of dopamine in anticipatory and motivation-related behaviour, rather than consummatory processes. Dopamine antagonists administered to rodents substantially reduced their motivated responses for both food and drugs of abuse (Woolverton & Virus, 1989), but did not affect the consumption of food (Berridge & Robinson, 1998). The pleasure hypothesis was further discredited by work showing that dopaminergic cell lesions and dopamine agonists do not alter hedonic reactions (measured by tongue protrusions and mouth gapes) to pleasant and unpleasant tastes in animals (Berridge & Robinson, 1998). Despite this, associations between dopaminergic release and subjective pleasure associated with rewards are frequently (Barrett, Boileau, Okker, Pihl, & Dagher, 2004; Small et al., 2003; Volkow et al., 1997), but not always (Stokes, Mehta, Curran, Breen, & Grasby, 2009), reported. Departing from pleasure, two major theories of dopamine's role in reward processing are the incentive-salience theory (Berridge & Robinson, 1998) and the reinforcement learning theory (Schultz, Dayan, & Montague, 1997).

The incentive-salience theory posits that mesocorticolimbic dopamine signals imbue stimuli with incentive-salience such that they are 'wanted' and become 'motivational magnets', driving approach and appetitive responses. Evidence for this theory includes observations that dopaminergic lesions of mesocorticolimbic brain regions do not affect learning about sucrose rewards, but they do affect motivated responding for rewards (Berridge & Robinson, 1998). Additionally, rats that attribute large amounts of incentive-salience and orient behaviour towards reward predictive cues, so called 'sign-trackers', have stronger cue-induced dopaminergic responses in the nucleus accumbens compared with rats that orient behaviour towards reward outcomes, so called 'goal-trackers' (Flagel et al., 2011).

Furthermore, only the acquisition of sign-tracking, and not goal-tracking, is influenced by dopamine antagonism (Flagel et al., 2011).

The reinforcement learning theory posits that phasic dopamine release, in neurons originating the ventral tegmental area and the substantia nigra, encode a prediction error between expected reward and experienced reward (Schultz et al., 1997). If an unforeseen reward is presented, dopamine neurons will fire in response, because the error between the prediction (zero) and the outcome (a reward) was positive (figure 1.2). If a stimulus repeatedly precedes the reward, the dopamine neurons will no longer fire in response to the reward because it is entirely predicted by the presence of the stimulus. Instead, the dopamine neurons will fire on presentation of the stimulus. Evidence for the role of dopamine in reinforcement learning comes from data such as this dovetailing with formal theories of reinforcement learning (Schultz et al., 1997). Furthermore, human neuroimaging experiments have shown that levo-dopa, a precursor to dopamine, enhances learning and the associated prediction error BOLD responses (Cools, Lewis, Clark, Barker, & Robbins, 2007; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006).

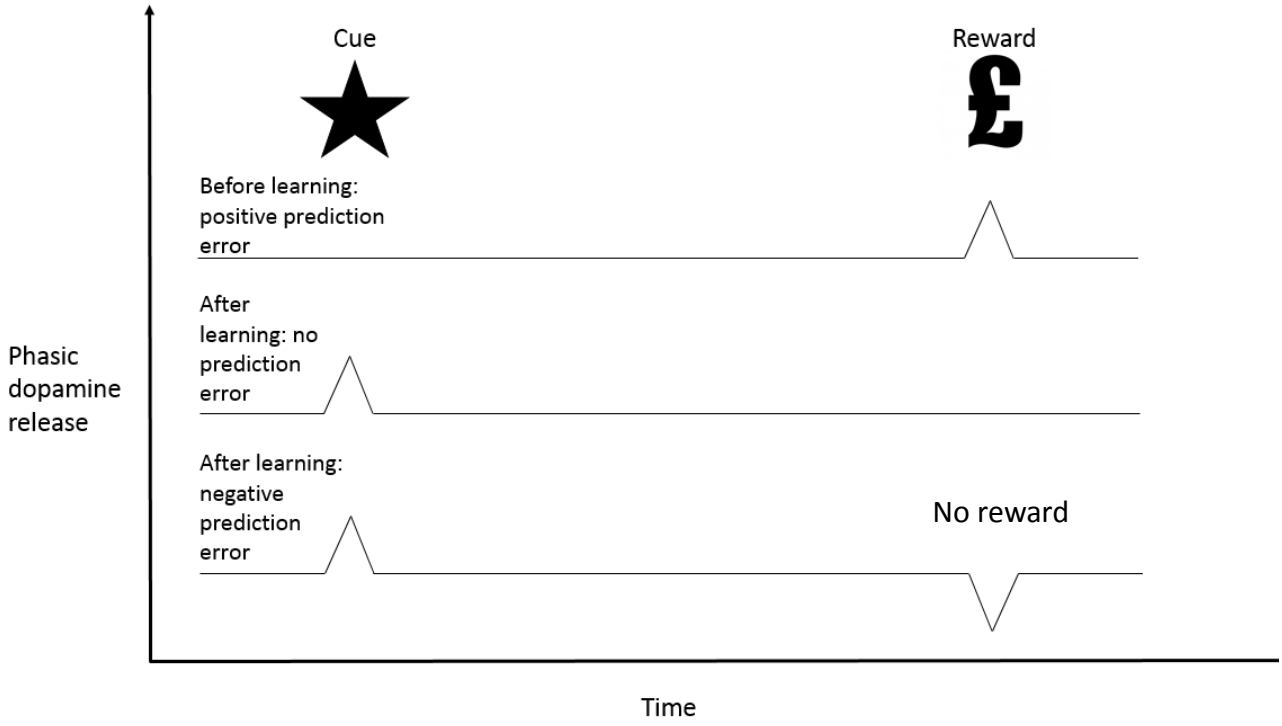


Figure 1.2 A diagrammatic representation of how phasic dopamine firing underpins prediction error learning. The unexpected delivery of a reward produces phasic dopamine release as there is a positive prediction error: the reward was not expected (top). After successfully learning that the cue predicts the reward, phasic dopamine release occurs on the presentation of the cue, but there is no change in firing on presentation of the reward, as there is no error in the prediction (middle). If the reward is not presented following the cue, a negative prediction error occurs and so phasic dopamine firing is reduced, relative to baseline (bottom).

Two distinct mechanisms underlying dopamine release have been proposed: phasic and tonic (Grace, 1991). Phasic dopamine release is caused by neuronal firing and leads to a large, fast burst of dopamine into the synapse, which is quickly removed by re-uptake systems. It is thought to be caused by salient, external events, such as an unpredicted reward or a highly novel stimulus and is therefore thought to be involved in reinforcement learning and the attribution of incentive-salience. On the other hand, the sustained, background dopamine level, referred to as 'tonic' dopamine, is thought to be controlled by prefrontal, glutamatergic afferents. This tonic dopamine level changes more slowly than the phasic bursts and plays a putatively different role in reward processing: underpinning behavioural vigour and protracted motivation (Niv, Daw, Joel, & Dayan, 2007; Salamone, Correa, Farrar, & Mingote, 2007).

1.3.2 Cannabinoids and reward processing

It should be noted that although dopamine is very closely related to many aspects of reward processing, other neurotransmitters are critically involved too. The endocannabinoid system is a neuromodulatory system comprising cannabinoid receptors, their endogenous ligands, including anandamide and 2-arachidonoylglycerol, and the enzymes that break these ligands down (Maldonado, Valverde, & Berrendero, 2006). The main psychoactive component of cannabis, Δ^9-tetrahydrocannabinol (THC), is a partial agonist of the cannabinoid 1 (CB1) receptor (Pertwee, 2008). Cannabinoid receptors act in a pre-synaptic, retrograde fashion, such that their stimulation reduces the likelihood of neurotransmitter release from the neuron they are bound to (Ohno-Shosaku, Maejima, & Kano, 2001).

The endocannabinoid system is also closely connected to the mesocorticolimbic dopamine system (see figure 1.3) and other brain regions which are pivotal in reward processing, as described in section 1.2.3. There are pre-synaptic CB1 receptors on both GABAergic and glutamatergic neurons that innervate the ventral tegmental area. These receptors play a critical role in tweaking the mesolimbic projections from the ventral tegmental area to the nucleus accumbens, which govern reward-seeking (Parsons & Hurd, 2015). Indeed, administration of anandamide (Solinas, Justinova, Goldberg, & Tanda, 2006) and THC (Chen et al., 1990) in rodents can augment extracellular dopamine levels in the nucleus accumbens. Furthermore, there is a high density of CB1 receptors in the globus pallidus, hippocampus, dorsal striatum, prefrontal cortex and basolateral amygdala (Parsons & Hurd, 2015). Thus, the endocannabinoid system contributes importantly to the processing of natural rewards, including food (Mahler, Smith, & Berridge, 2007) and sex (Klein, Hill, Chang, Hillard, & Gorzalka, 2012). These contributions are thought to be made via interactions with the hypothalamus and opioid neurotransmission, as well as the mesocorticolimbic dopamine system (Parsons & Hurd, 2015).

The role of the endocannabinoid system in reward processing has been further elucidated using experiments with rodents and a range of non-cannabinoid drugs of abuse. For instance, in rodents,

CB1 receptor agonists enhance self-administration of and conditioned place preference for alcohol, nicotine and opiates, while CB1 receptor antagonists do the opposite. Similarly, CB1 knockout mice have reduced self-administration of these drugs (Parsons & Hurd, 2015).

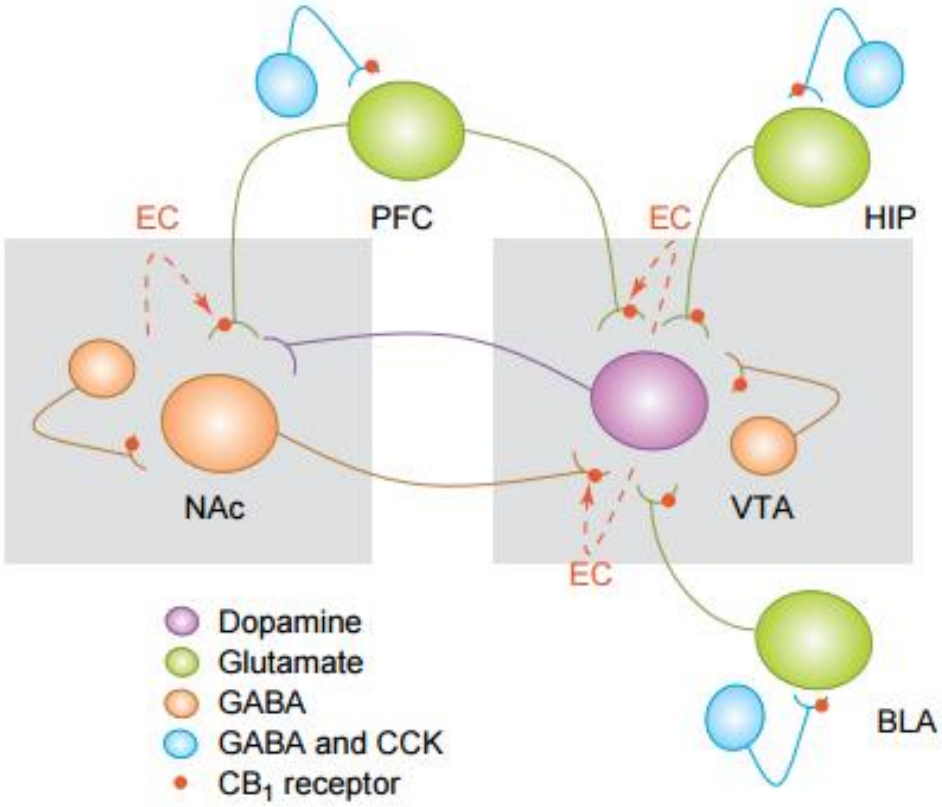


Figure 1.3 Diagrammatic representation of the way that the endocannabinoid system is associated with the mesolimbic dopamine system and other neurotransmitters (taken from Maldonado et al., 2006). In the ventral tegmental area (VTA), CB1 receptors are expressed on the pre-synaptic glutamatergic and GABAergic neurons. Activation of the CB1 receptors by endocannabinoids (EC; broken red arrows) inhibits GABA release, thus stimulating dopaminergic neuron activity. CB1 receptors are also expressed on the axon terminals of glutamatergic and GABAergic neurons, which project to the nucleus accumbens (NAc), hippocampus (HIP), basolateral amygdala (BLA) and prefrontal cortex (PFC).

1.3.3 Dopamine and recreational drugs

Many recreational drugs acutely increase extracellular dopamine levels in the nucleus accumbens; this has been demonstrated in animals using in vivo microdialysis (Di Chiara & Imperato, 1988) and in humans using PET (Boileau et al., 2003; Brody et al., 2004; Leyton et al., 2002). This effect is, however, much more apparent in psychostimulant drugs than other classes of drugs, especially opiates and

cannabis (Nutt, Lingford-Hughes, Erritzoe, & Stokes, 2015). Despite some negative findings in the PET literature, including nicotine (Montgomery, Lingford-Hughes, Egerton, Nutt, & Grasby, 2007), and the importance of other neurotransmitter systems in addiction, the discovery that most recreational drugs can lead to increases in striatal dopamine release has been the foundation of a popular and unifying dopamine theory of addiction (Nutt et al., 2015). In essence, this theory argues that recreational drugs acutely increase dopamine release and chronic use leads to neuroadaptations in the mesocorticolimbic dopamine system, which underpins addiction.

Natural rewards produce downstream effects on dopamine receptors through the processing of incentive-salience and reinforcement learning. In contrast, drugs enter the brain and pharmacologically act on dopamine neurons, either directly through the stimulation of dopamine receptors, as is the case with psychostimulants, or indirectly through the modulation of dopaminergic cell firing, as is the case with drugs such as alcohol and nicotine. This pharmacological action on the dopaminergic system is thought to explain the strongly reinforcing nature of drugs. The drugs 'hijack' the brain's natural reward system (Redish, 2004), produce a much greater release of dopamine than normal and therefore provide an abnormally strong, positive teaching signal which encodes reinforcement. The systems that have evolved to encode learning, motivation and pleasure are powerfully stimulated by this artificially induced experience and so the likelihood of repeating this behaviour can be large.

The major addictive substance in tobacco is thought to be nicotine (Stolerman & Jarvis, 1995), which binds to various nicotinic acetylcholine receptors. The acetylcholine pathways are closely related to the mesocorticolimbic dopamine system (figure 1.4). The ventral tegmental area receives cholinergic innervation from the pedunculopontine tegmental nucleus and the laterodorsal tegmental nucleus (Changeux, 2010). In rodents, nicotine enhances extracellular dopamine levels in the ventral striatum (Di Chiara & Imperato, 1988), which is thought to be produced by nicotine binding to $\alpha_4\beta_2$ nicotinic acetylcholine receptors in the ventral tegmental area. This action appears to underlie the reinforcing

properties of nicotine as antagonism of these receptors in the ventral tegmental area eliminates nicotine self-administration in rats (Corrigall, Coen, & Adamson, 1994). However, the ability of nicotine to acutely provoke dopamine release in the human striatum is somewhat controversial (Nutt et al., 2015), with some studies showing significant release (Brody et al., 2009; Brody et al., 2004) and others reporting null results (Barrett et al., 2004; Montgomery et al., 2007). Despite this, the latter two studies did show a relationship between striatal dopamine release and the pleasure taken from smoking.

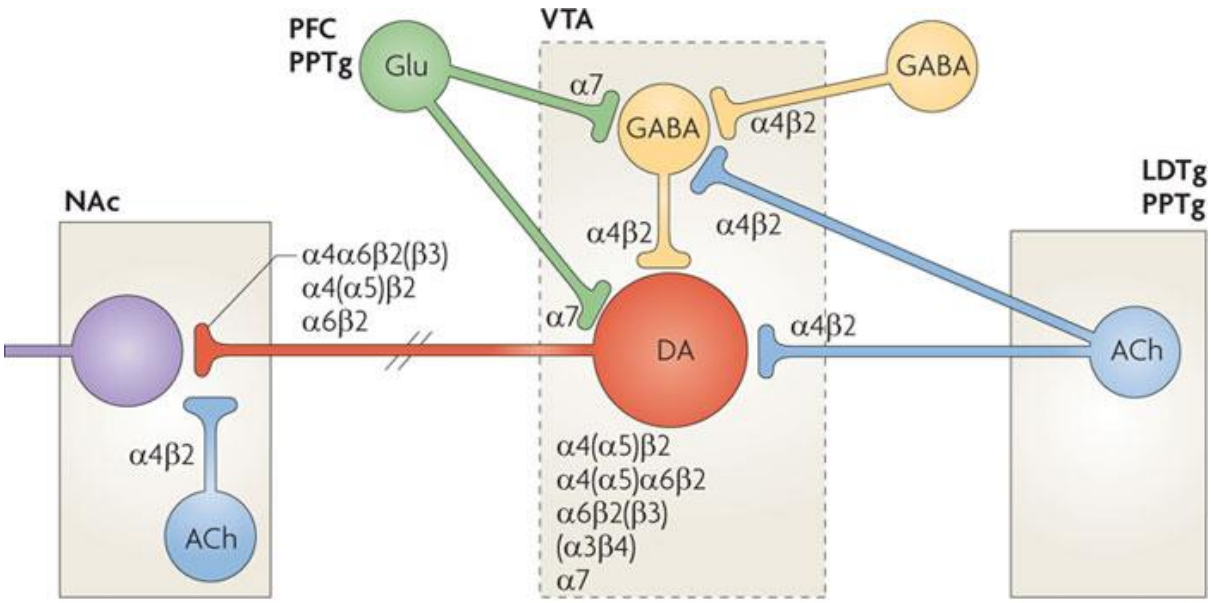


Figure 1.4 Nicotinic acetylcholine receptors involvement in the mesolimbic dopamine pathway (taken from Changeux, 2010). Dopaminergic neurons (red) in the ventral tegmental area (VTA) receive two main sources of excitatory input: from cholingergic neurons (blue) and from glutamatergic neurons (green). Dopaminergic neurons in the VTA also receive inhibitory input from GABAergic neurons (yellow). The VTA sends projections to the nucleus accumbens (NAc), which interact with inputs from cholinergic interneurons.

As described in section 1.3.2, the endocannabinoid system interacts with the mesocorticolimbic dopamine system. The pre-synaptic CB1 receptors on GABAergic and glutamatergic neurons, which innervate the ventral tegmental area, can enhance or reduce cell firing by inhibiting GABAergic input or glutamatergic input, respectively (figure 1.4) (Maldonado et al., 2006). Human PET studies investigating the acute effects of cannabis on striatal dopamine release have found both enhancing (Bossong et al., 2009) and null (Stokes et al., 2009) effects. Interestingly, a combination of those

studies still showed a small but significant effect (Bossong et al., 2015). Importantly, in rodents, CB1 receptor antagonists and knockout of the CB1 receptor gene lead to a reduction in nucleus accumbens dopamine release observed following alcohol and nicotine administration, as well as reduced self-administration (Parsons & Hurd, 2015). These results demonstrate the critical relationships between the endocannabinoid system, the mesolimbic dopamine system and the rewarding effects of alcohol and nicotine.

In summary, most drugs that are used recreationally by humans induce extracellular striatal dopamine release in rodents (Di Chiara & Imperato, 1988). However, these effects may be less pronounced in human PET studies and psychostimulants generally produce much greater dopamine release than other drugs, such as cannabis and heroin (Nutt et al., 2015). Having said that, the endocannabinoid system is closely connected with the mesocorticolimbic dopamine system and dopamine is demonstrably involved in numerous aspects of reward processing. Although the pharmacological effects of nicotine and cannabis are complex, and likely involve many interconnected neurotransmitter systems, the evidence described here suggests that they both affect dopamine levels to some extent.

1.3.4 Chronic neurobiological changes associated with drug use

Chronic use of recreational drugs may result in physiological changes to these aforementioned systems, which could then be associated with psychological changes. Addictions to various drugs, including alcohol (Volkow et al., 1996), opiates (Wang et al., 1997), methamphetamine (Volkow et al., 2014), cocaine (Martinez et al., 2004) and cigarettes (Fehr et al., 2008), have been associated with a low striatal dopamine D2/3 receptor density. This may be a product of chronic drug use or a pre-existing vulnerability factor that contributed to chronic drug use. Prolonged use of drugs which stimulate dopamine release putatively lead to downregulation of dopamine receptors. This is thought to play a contributory role to the maintenance of addiction and likelihood of future relapse, with low dopamine receptor levels requiring artificial stimulation from drugs to maintain hedonic homeostasis

(Koob & Le Moal, 1997). The low levels of dopamine receptors are also thought to lead to a concomitant reduction in natural reward processing (Volkow, Fowler, Wang, & Swanson, 2004). Although these findings appear robust in psychostimulant users, the reductions in D2/3 receptor density have sometimes not been found with dependent cigarette (Yang et al., 2006; Yang et al., 2008), opiate (Daglish et al., 2008) and cannabis (Albrecht et al., 2013; Sevy et al., 2008; Stokes et al., 2012; Urban et al., 2012) users. This questions the role of dopaminergic neuroadaptations in these addictions.

However, various other dopaminergic changes have been observed in nicotine dependent individuals. Nicotine dependence has been associated with reduced striatal D1 receptor levels (Dagher et al., 2001), reduced striatal dopamine transporter levels (Leroy et al., 2012) and increased utilization of L-DOPA (Salokangas et al., 2000), although this was not replicated (Bloomfield, Pepper, et al., 2014).

There is much less evidence to suggest that cannabis dependence is associated with changes to the dopaminergic systems. Four studies have failed to reveal a reduction in striatal D2/D3 receptor density in cannabis dependent people relative to matched controls (Albrecht et al., 2013; Sevy et al., 2008; Stokes et al., 2009; Urban et al., 2012). However, two of these demonstrated a relationship between the extent of cannabis use and reduced dopamine receptor density, within the cannabis group (Albrecht et al., 2013; Urban et al., 2012), and cannabis dependence has been associated with reduced dopamine synthesis (Bloomfield, Morgan, Egerton, et al., 2014). Furthermore, chronic cannabis use has been associated with reductions in volumetric size of the hippocampi and amygdalae (Batalla et al., 2013) and reductions in the number of CB1 receptors (D'Souza et al., 2015).

In a more general sense, chronic drug use is thought to be associated with changes to pleasure and motivation processing because of the opponent processes that respond to drug use in these psychological systems (Solomon & Corbit, 1974). Any rapid increase in pleasure or motivation should theoretically be followed by a slower, but more substantial, decline in those processes, regardless of dopaminergic neuroadaptations.

To briefly conclude, there is strong evidence that dopamine is critical in various aspects of reward processing, although it's specific role(s) is/are controversial. Striatal dopamine release and dopaminergic neuroadaptations are likely to be pivotal in psychostimulant addiction and are probably still important, but to a lesser degree, in nicotine and cannabis addiction. These neuroadaptations and opponent psychological processes are thought to underlie changes to reward processing which contribute to addictive behaviours. Importantly for this thesis, it has been hypothesised that these alterations lead to a hypersensitivity, or 'enhanced processing', of drug rewards and related stimuli (Robinson & Berridge, 1993) and a simultaneous hyposensitivity, or 'reduced processing', of non-drug rewards and related stimuli (Goldstein & Volkow, 2011; Koob & Le Moal, 2008; Volkow et al., 2004). I will now begin to review these theories, which propose alterations in drug and non-drug reward processing in addiction, and introduce the empirical work which supports and opposes these theories.

1.4 Theories of addiction

Positive reinforcement accounts of drug addiction suggest that drugs generate positive appetitive states that maintain drug-taking behaviour (Stewart, De Wit, & Eikelboom, 1984). According to the seminal incentive-sensitisation theory, long-term drug use leads to enhanced dopamine overflow in the nucleus accumbens on presentation of drugs and drug-related stimuli (Robinson & Berridge, 1993; Vezina, 2004). Subsequently this augments the likelihood of future drug-taking and underlies addiction.

On the contrary, negative reinforcement accounts of drug addiction, through a variety of proposed mechanisms, suggest that drug-taking is caused by the alleviation of negative states, such as withdrawal (Wikler, 1973) or long-term, allostatic adaptations to reward and stress processing (Koob & Le Moal, 1997). One of the most developed of these theories (Koob, 2013) states that the basic circuitry of reward processing ends up in a degraded state and cannot recover, while the hypothalamus-pituitary-adrenal stress system ends up being overactive, and this results in a hyposensitivity to reward, amongst other things, which contributes to compulsive drug use.

Over the past few years, various researchers have suggested that addiction is associated with both a hypersensitivity to drug rewards and a hyposensitivity to non-drug rewards (Anselme, 2009; Goldstein & Volkow, 2011; Sweitzer, 2013; Volkow et al., 2004). In Goldstein and Volkow's (2011) 'impaired response inhibition and salience attribution' (iRISA) theory, which informed many hypotheses in this thesis, drug addicts assign excessive salience to drugs and drug-related stimuli and are hyposensitive to non-drug rewards (figure 1.5). Furthermore, these issues are hypothesised to become accentuated during times of abstinence and craving. Recent studies have additionally suggested that it may not just be the absolute processing of drug and non-drug rewards that is important in addiction, but also *the balance between them* (Bühler et al., 2010; Versace et al., 2014; Versace et al., 2012). In other words, addiction may be more closely related to the difference in motivation for drug and non-drug rewards, rather than solely the motivation for drug rewards. This concept of reward processing *balance* will be investigated in this thesis using tasks that provide cigarette and non-drug rewards concurrently.

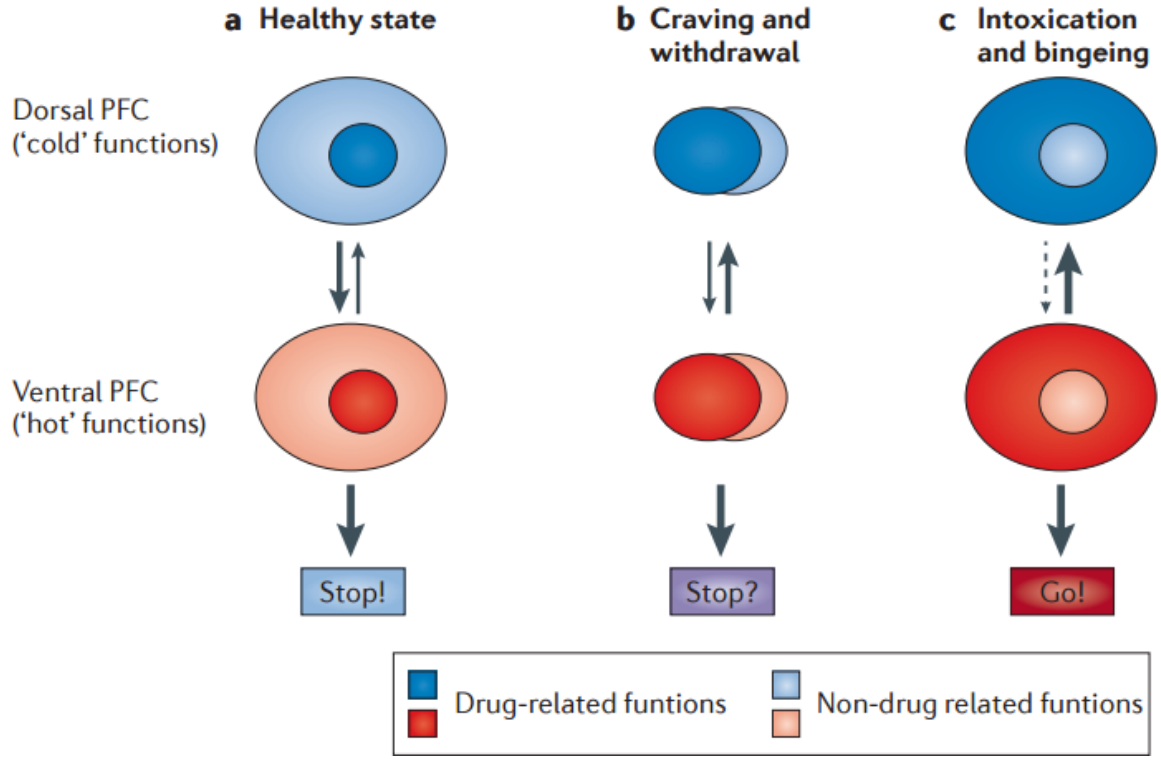


Figure 1.5 A diagrammatic representation of the 'impaired response inhibition and salience attribution' (iRISA) theory and the role of the prefrontal cortex (PFC) in addictive processes (taken from Goldstein & Volkow, 2011). In general, this diagram demonstrates that behaviour can be split into drug-related and non-drug related functions. When in a healthy state (a), the non-drug related functions (e.g. sustained motivation, pleasure from natural rewards) outweigh the drug-related functions (e.g. craving, attentional bias, drug-seeking). When in an unhealthy state like 'craving and withdrawal' or 'intoxication and bingeing' (b or c), the non-drug related functions are similar to or outweighed by drug-related functions, respectively. During 'craving and withdrawal' decreased attention and/or value is assigned to non-drug rewards and stimuli, and this is associated with reduced self-control and anhedonia. During 'intoxication and bingeing' behaviour is focused almost exclusively on drugs and compulsive drug-taking ensues. The blue ovals represent dorsal PFC and dorsal anterior cingulate cortex functions, which are related to non-affective, control-based processes. The red ovals represent orbitofrontal cortex and ventromedial prefrontal cortex functions, which are related to affective processes.

1.5 Changes to reward processing in addiction

I will now review the literature concerning possible changes to drug and non-drug reward processing in nicotine and cannabis dependence, while drawing attention to the effect of short-term nicotine deprivation when appropriate. I will review research covering a wide range of reward processing components, ranging from animal ICSS experiments to human self-report data. Hence, hyper/hypo-sensitivity to reward could come in the form of altered lever-pressing, self-reported craving, striatal BOLD response to certain cues, amongst others. This will demonstrate that general rules, such as

"addicts are hyposensitive to non-drug rewards", are inaccurate, as there are many ways of assessing reward processing. There is a great diversity in the type of participants (animals or humans), the type of drug addiction, the stage of drug addiction, whether the participants are acutely abstinent from their drug and the reward process under investigation, so it is unsurprising that there is a large variety in the outcomes that researchers report.

1.5.1 Hypersensitivity to drugs and drug-related stimuli

In section 1.1.1, I described addiction as a state in which there are repeated, powerful motivations to take drugs despite the potential for harmful consequences (West & Brown, 2013). Furthermore, addiction is often viewed as a chronic, relapsing disorder characterised by compulsive use (Leshner, 1997). Hence, an augmented motivation for the addict's drug is almost by definition part of addiction. However empirical research in this area with nicotine/tobacco and cannabis has produced some surprisingly counterintuitive results.

1.5.1.1 Animal research

In animal models, the effects of previous chronic drug use (thought to model dependence) on motivation for future drug use are examined by providing one group of animals with 'extended access' to the drug and providing another group of animals with 'limited access' to the drug. Subsequently, motivation for the drug is tested in a self-administration paradigm. Interestingly, rats with extended access (6 hours/day for 30 days) to nicotine did not increase their later self-administration of nicotine relative to those with limited access (1 hour/day) (Paterson & Markou, 2004). Thus, the rats in the extended access group did show greater dependence symptoms and yet did not demonstrate greater motivation for nicotine; this opposes the hypothesis that nicotine dependence is associated with motivational hypersensitivity to nicotine reward. However, following this study, it was shown that rats given intermittent, extended access (21 hours/day, with 24 or 48 hour abstinence breaks, for approximately 40 days) did subsequently have greater motivation for nicotine than rats given normal extended access (21 hours/day) and limited access (1 hour/day) (Cohen, Koob, & George, 2012).

Hence, it appears that a specific schedule of nicotine self-administration is needed to produce the stronger motivation for nicotine that is expected. To my knowledge, these kinds of experiments have not been conducted in animals with cannabinoid administration.

The incentive-sensitisation theory predicts that addicts should be hypersensitive to drug-related cues (Robinson & Berridge, 1993). One way of examining sensitivity to these cues in animals is with conditioned reinforcers, which are cues that have been presented alongside drug administration in the past, such that they become reinforcing in themselves. Nicotine-paired cues will elicit and maintain responding (Palmatier et al., 2007), however I could not find any research that investigated conditioned reinforcement by cannabis-paired cues. Furthermore, to my knowledge no studies have examined the relationship between previous drug use and the extent to which nicotine-paired cues can evoke conditioned reinforcement. Both nicotine (Risinger & Oakes, 1995) and THC (Lepore, Vorel, Lowinson, & Gardner, 1995), at appropriate doses, have been shown to elicit conditioned place preference. Furthermore, nicotine pre-treatment (7 days) increased the extent of subsequent nicotine-induced conditioned place preference in rats (Mohammed Shoaib, Stolerman, & Kumar, 1994), which suggests that previous drug exposure enhanced either the formation of the nicotine-place association or the motivation to return to that place. Thus, there was an increased sensitivity to this aspect of drug reward processing. Overall, there is good evidence that nicotine and THC are able to produce important addiction-related associations, but only some evidence that previous nicotine exposure enhances nicotine-related reward processes.

So far I have considered the motivational and learning aspects of drug reward processing in animal research. Another important aspect is the actual effects of the drugs themselves and how these vary following previous drug use. It is not possible to ask an animal how much they like a drug's effects. Rodent tongue protrusion has been used as a measurement of food 'liking' (Berridge & Robinson, 1998), but this is not possible when investigating drugs. Tolerance to simple behavioural and physiological effects following previous drug exposure may help us understand how dependence

could be associated with changes in reward-related responses to the drug. For instance, repeated administration of nicotine led to diminished nicotine-induced depression of movement (I. Stolerman, Fink, & Jarvik, 1973) and body temperature (McCallum, Collins, Paylor, & Marks, 2006). Similarly, repeated administration of THC lessened the effects of acutely administered THC on activity, catalepsy, hypothermia and hypotension (Compton, Dewey, & Martin, 1990).

As described above, dopamine release in the nucleus accumbens is putatively important in motivational processing and recreational drugs often stimulate dopamine release in this region. Previous chronic nicotine exposure appears to reduce the dopamine-releasing effects of acute nicotine when it is administered a few days after chronic nicotine administration has ceased, but it sensitizes the dopamine-releasing effects of acute nicotine when it is administered a few weeks after chronic administration has ceased (Vezina, McGehee, & Green, 2007). Hence, there is evidence of tolerance for some behavioural and physiological effects of nicotine and cannabis following previous chronic administration. However, the dopamine-releasing effects of acute nicotine, which theoretically contribute to its rewarding properties, seem to change depending on the time between chronic administration and the acute dose.

1.5.1.2 Human research

Human addicts self-administer nicotine (Harvey et al., 2004) and cannabis (Bedi, Lindquist, & Haney, 2015) in the laboratory. To my knowledge, there are very few studies that have investigated the relationships between dependence level (or previous drug exposure) and actual self-administration of nicotine/tobacco and cannabis. Low dependent (Fagerstrom Test for Nicotine Dependence (FTND) ≤ 2) and high dependent (FTND ≥ 5) smokers did not differ in terms of their motivation for their preferred brand of cigarettes on a progressive ratio task (Barrett, 2010). Similarly, there was a non-significant difference between low dependent (FTND = 0) and high dependent (FTND > 5) smokers on a fixed ratio button-pressing task for cigarettes (Buhler et al., 2010). Occasional (1-3 cannabis cigarettes/month), intermittent (1-3 cannabis cigarettes/week) and heavy (1-3 cannabis

cigarettes/day) chose and worked similarly hard for cannabis (Mendelson & Mello, 1984). These results are highly surprising because they suggest that nicotine and cannabis dependence (or frequency of use) are not associated with motivation for that drug. Alternatively, the tasks utilised may not have been sensitive enough or the studies not well powered enough to detect group differences. The context of the laboratory-based experiment, such as being allocated a set time to smoke or a reduction in the number of environmental smoking-related cues, could blunt the expected relationships between dependence and self-administration. Thus drug-seeking behaviour in the laboratory may not be as closely related to real world behaviour as researchers may hope. Further research is warranted to examine these perplexing results.

On the other hand, recent work using a *hypothetical* purchase task has demonstrated clear associations between nicotine and cannabis dependence and the willingness to buy cigarettes and cannabis at increasing prices (Aston, Metrik, & MacKillop, 2015; MacKillop et al., 2008; Murphy, MacKillop, Tidey, Brazil, & Colby, 2011). This discrepancy may result from the larger samples used in these studies, as they are much easier and cheaper to run, given no actual drugs are administered. However, this leaves open the question of: if the rewards were real rather than hypothetical, would the same results be observed? Evidence in favour of the validity of these hypothetical purchase tasks compared with real purchase tasks has been provided, at least for cigarettes (Amlung, Acker, Stojek, Murphy, & MacKillop, 2012).

In terms of subjective effects in humans, there is some evidence of changes to the responses to nicotine and cannabis following long-term use. Chronic cigarette smoking is associated with lower subjective effects of nicotine, for example 'head rush' and 'jittery' (Perkins, Grobe, et al., 1994). And in a group of dependent smokers, cigarette-elicited pleasure was positively associated with years of smoking, although not level of dependence (Pomerleau & Pomerleau, 1992). In another large group of dependent smokers, dependence was not associated with pleasantness of cigarette smoking, using ecological momentary assessment (Shiffman & Kirchner, 2009). Furthermore, the enjoyment taken

from smoking a cigarette predicted whether a quit attempt was made in a six month period, but not whether the quit attempt was successful (Fidler & West, 2011). Thus, the relationship between nicotine dependence and the pleasure associated with smoking is quite unclear. Interestingly, the striatal dopamine release to nicotine has been positively associated with nicotine dependence (Takahashi et al., 2008), dovetailing with the finding that, in rodents, chronic nicotine can sensitize the dopamine-releasing effects of nicotine, under some circumstances (Vezina et al., 2007).

Frequent cannabis users report 'feeling' THC more than infrequent users at a low dose (7.5mg) and also 'liking' THC more than infrequent users at a high dose (15mg), although that was due to infrequent users disliking it (Kirk & De Wit, 1999). Contrastingly, frequent cannabis users reported similar desirable effects of THC, such as 'high' and 'relaxed', compared with healthy controls, however the frequent users showed evidence of tolerance to negative effects of THC (D'Souza et al., 2008). Moreover, light and heavy cannabis users rated themselves similarly 'stoned' after a vaporized dose of THC (Hindocha, Freeman, Schafer, et al., 2015). This suggests that the subjective responses to drugs do vary with previous chronic use, but not necessarily in systematic ways.

It is surprising that the hedonic aspect of drug reward processing has been somewhat overlooked. Hedonic responses to drugs are theoretically important in future goal-directed behaviour (Dayan & Balleine, 2002) and initial responses to drugs are important in future drug use (De Wit, Uhlenhuth, & Johanson, 1986; Eissenberg & Balster, 2000; Fergusson, Horwood, Lynskey, & Madden, 2003). Furthermore, it may be fair to say that the pleasure associated with drug-taking has been the elephant in the room for psychopharmacology and addiction research. While the unpleasant consequences of drug-taking have been emphasised, the short-term pleasures may have been neglected by the research community. It seems reasonable to claim that many drug users are motivated to take drugs because of the pleasure provided by them, rather than a desire to alleviate a negative state. Investigation of the hedonic aspects of drug-taking (including cigarette and cannabis smoking) may well improve our knowledge of why people continue to take drugs and why some of those end up

addicted. Moreover, in a pure academic sense, there may be inherent worth in learning about the ways in which drugs, and other rewards, elicit pleasure and positive feelings (Kringelbach & Berridge, 2010).

Other research has examined the processing of drug rewards without administering drugs themselves by utilising drug-associated stimuli. In human drug addicts, attentional bias has often been used to investigate increased sensitivity to visual cues and has generally shown that addicts are biased towards drug-related relative to neutral cues. However, this effect appears to be moderated by the type of task used, length of abstinence and type of addiction (Field & Cox, 2008). Perhaps surprisingly, more dependent smokers have shown a weaker attentional bias than less dependent smokers (Mogg, Field, & Bradley, 2005). On the other hand, current smokers have a greater attentional bias to cigarette cues than non-smokers, while former smokers lie in an intermediate spot (Ehrman et al., 2002). Moreover, there is some evidence in cigarette smokers that a stronger attentional bias to cigarette cues predicts future relapse (Waters et al., 2003). Dependent cannabis users have been shown to have an attentional bias to cannabis-related words, while non-dependent users did not (M. Field, 2005).

The advent of neuroimaging produced another means of assessing sensitivity to drug-associated stimuli. Response to cigarette cues has been shown to activate a large range of reward-related brain regions in cigarette smokers (Engelmann et al., 2012). Greater nicotine dependence has been associated with greater orbitofrontal cortex and anterior cingulate BOLD response to cigarette cues (McClernon, Kozink, & Rose, 2008). This neural hypersensitivity to cigarette-cues predicted future cigarette smoking during a quit attempt (Janes et al., 2010). Furthermore, on presentation of cannabis cues, greater activation in reward-related brain regions has been shown in heavy cannabis users compared with less frequent and non-users (Cousijn et al., 2013).

Short-term nicotine deprivation theoretically disrupts both drug and non-drug reward processing (Goldstein & Volkow, 2011). Researchers have proposed that acute nicotine abstinence leads to a hypofunctioning mesocorticolimbic dopamine system (Powell, Dawkins, & Davis, 2002). This claim has

been somewhat borne out empirically. Monkeys that had been previously exposed to nicotine utilised less L-DOPA after short-term nicotine abstinence (Domino, Tsukada, & Harada, 2009) and reduced homovanillic acid levels have been found in abstaining smokers' cerebrospinal fluid (Geracioti Jr et al., 1999). On the other hand, human PET studies have not shown an effect of overnight abstinence on raclopride binding potential with D1 (Dagher et al., 2001) or D2 (Fehr et al., 2008) receptors.

Related to these possible changes in the mesocorticolimbic dopamine system, short-term nicotine deprivation theoretically disrupts both drug and non-drug reward processing (Goldstein & Volkow, 2011). Hence, acute nicotine abstinence may moderate some of the results concerning cigarette reward processing described above. In terms of behavioural effects, there is good evidence that acute (overnight or approximately 12 hours) abstinence enhances craving and self-administration of cigarettes (Barrett, 2010; Epstein, Bulik, Perkins, Caggiula, & Rodefer, 1991; Kollins et al., 2013; Perkins, Grobe, et al., 1994). Nicotine abstinence appears to boost hypersensitivity to cigarette-related cues in terms of augmentation of attentional bias to (Field, Mogg, & Bradley, 2004) and overshadowing in favour of cigarette cues relative to neutral cues (Freeman, Morgan, Beesley, & Curran, 2012). Furthermore, one fMRI cue reactivity study demonstrated an increased BOLD response to cigarette cues (McClernon, Kozink, Lutz, & Rose, 2009).

On the other hand, there is some surprising evidence for reduced cigarette reward processing during abstinence. Diminished cue-induced craving (Powell et al., 2002) and reduced fMRI cue reactivity to cigarette cues have been reported (David et al., 2005). Furthermore, motivation to work for cigarettes and the BOLD response during anticipation of cigarette points were not affected by 36 hours of abstinence in either occasional or dependent cigarette smokers (Bühler et al., 2010). These two sets of results appear contradictory and, to me, it is surprising to learn of *reduced* cigarette reward processing during acute abstinence. However, these studies demonstrate that it can be important to carefully examine relationships between drug use and reward processing that may, on the face of it, seem quite obvious.

In summary, the relationships between nicotine/cannabis dependence and cigarette/cannabis reward processing appear complex and poorly understood. In animals and humans there is good evidence that both drugs serve as reinforcers. However, there is mixed evidence concerning the relationships between previous drug use and subsequent self-administration of the drug, although positive associations between dependence and the willingness to buy cigarettes/cannabis have been shown in hypothetical purchase tasks. Furthermore, there is only a small amount of evidence to suggest that heavy cigarette or cannabis smoking is associated with the pleasure taken from acute administration of the respective drug, although this should be considered an under-researched area. Cigarette and cannabis users appear to have attentional biases towards their drug cues, but there may be a negative relationship between nicotine dependence and extent of attentional bias to cigarette images. There is better evidence for hypersensitivity to cigarette and cannabis images in respective addictions from fMRI studies. Finally, acute nicotine deprivation has frequently, but not always, been shown to augment various aspects of cigarette reward processing. Thus, in general, more work is warranted to clarify which aspects of drug reward processing are altered in nicotine and cannabis dependence.

1.5.2 Hyposensitivity to non-drug rewards and related stimuli

As described above, chronic drug use is associated with neuroadaptations to the mesocorticolimbic dopamine system and to opponent psychological processes in the reward system. These are hypothesised by some to contribute to a hyposensitivity to alternative, non-drug rewards (Blum et al., 2000; Goldstein & Volkow, 2011; Koob, 2013). In contrast, others have suggested that addicted individuals are generally impulsive and this is a result of hypersensitivity to all rewards (Hommer, Bjork, & Gilman, 2011). Moreover, chronic drug abuse may sensitize the reward system to all rewards, leading to 'spillover' effects where addicts desire non-drug rewards more than healthy controls (Robinson & Berridge, 2008). Hence researchers make divergent predictions about how addiction is related to the processing of non-drug rewards and the related literature appears distinctly mixed.

1.5.2.1 Animal research

Extended administration of nicotine has resulted in both a reduction (LeSage, Burroughs, & Pentel, 2006) and null effects (Der-Avakian & Markou, 2010) on responding for sucrose reward on the first day of nicotine deprivation in rats. Interestingly, motivation for the sucrose reward increased in the days following cessation of nicotine administration such that it became larger than baseline levels (LeSage et al., 2006). Rhesus monkeys given cannabis smoke daily, or just on weekends, worked less hard for a food reinforcer compared with those given placebo smoke (Paule et al., 1992), while chronic THC treatment reduced copulatory behaviour in rats (Fattore, Melis, Fadda, Pistis, & Fratta, 2010).

Another technique used to assess reward sensitivity in animals is the lowest electrical current that maintains ICSS. Nicotine, like other drugs of abuse (Ahmed, Kenny, Koob, & Markou, 2002), acutely lowers this threshold (Kenny & Markou, 2006), while short-term nicotine abstinence (up to 104 hours) substantially augments it (Epping-Jordan, Watkins, Koob, & Markou, 1998), demonstrating reduced reward circuitry sensitivity. Fascinatingly, and against all expectation, rats that self-administered nicotine for 20 consecutive days demonstrated *reduced* thresholds and therefore *enhanced* sensitivity for at least 36 days after administration ceased (Kenny & Markou, 2006), following the initial, short-term reduction in sensitivity. This potentially dovetails with the finding that motivation for sucrose reward was originally *reduced* after one day of nicotine abstinence but was *greater* after five days (LeSage et al., 2006). There has been little research using ICSS and THC. An acute dose of 1mg/kg THC lowered the ICSS threshold while withdrawal from the same dose augmented the threshold (Tanda & Goldberg, 2003). To my knowledge, the chronic effects of THC on ICSS thresholds have not been investigated.

In general, this line of research demonstrates the stimulating effects of acutely administered THC and nicotine on the reward circuitry, as well as the robust lowering of reward sensitivity during acute nicotine withdrawal. The long-term increase in sensitivity of the reward circuitry observed with nicotine is surprising and challenges the proposed allostatic reduction in hedonic set point (Koob & Le Moal, 1997), as does the reported increase in motivation for sucrose reward after five days of

abstinence (LeSage et al., 2006). These studies reveal several points: (1) in animal models, both chronic nicotine and THC/cannabis treatment have been, but are not always, associated with non-drug reward processing deficits; (2) different drugs of abuse can be associated with different effects on non-drug reward processing; (3) even with the same drug, different outcomes have been reported; (4) the length of abstinence post drug-administration is important; (5) the method in which non-drug reward processing is assessed is important.

1.5.2.2 Human behavioural research

There has been limited research investigating the behavioural aspects of non-drug reward processing in addicted individuals. This dearth potentially relates to the large amount of neuroimaging research in this area, which is introduced below. One notable exception is Powell's and Dawkins's research with the 'card arranging reward responsivity objective test' (CARROT), which has investigated motivation for monetary reward in smokers. In this task, participants sort cards into three different piles, depending on what numbers are shown on the card, as quickly as possible. In some rounds, participants receive no monetary reward for their sorting. In other rounds, participants receive 10 pence for every five cards sorted. The difference in the sorting speed is taken as a measure of motivation for monetary reward. They have consistently demonstrated deficits in motivation for monetary reward in cigarette smokers after overnight (Dawkins, Powell, West, Powell, & Pickering, 2006; Powell et al., 2002) and 10 days of nicotine abstinence (Al-Adawi & Powell, 1997). Furthermore, performance of the smokers only differed from non-smokers after abstinence (Al-Adawi & Powell, 1997; Powell et al., 2002). The authors argue that these results are a consequence of a hypodopaminergic state being unmasked only when the chronic nicotine administration is transiently removed. Despite this evidence, nicotine abstinence was not found to have the expected effect on motivation for monetary reward using a modified version of this task (Kalamboka, Remington, & Glautier, 2009), thus questioning the previous findings. Moreover, the same research group reported lower motivation for monetary reward between high and low dependent smokers, regardless of

abstinence (Kalamboka, 2008), although this result was not replicated in other parts of the thesis in which this result was reported. Using a separate task, button-pressing for monetary reward in occasional and dependent smokers was not affected by 36 hours of smoking (Bühler et al., 2010).

A recent series of studies has focused on the potential of acutely administered nicotine to enhance reinforcement by non-drug rewards (Perkins, Grottenthaler, & Wilson, 2009; Perkins & Karelitz, 2013a, 2013b; Perkins, Karelitz, Jao, & Stratton, 2012). These studies have also indirectly investigated the effects of nicotine dependence and abstinence on non-drug reward processing. Acute nicotine did not enhance reinforced responding for money, music or the termination of an aversive sound in non-smokers (Perkins et al., 2009). However, after overnight abstinence, in dependent and occasional smokers, nicotine enhanced reinforced responding for music reward (Perkins & Karelitz, 2013b). This suggests that motivation for music is greater during nicotine satiation compared with nicotine deprivation. However, dependent and occasional smokers did not differ from each other on motivation for any reward and the effect of abstinence/satiation was not moderated by dependence level. Importantly, responding was reinforced throughout the task, so one cannot determine if nicotine enhanced the pleasure associated with music reward and subsequently enhanced responding or if nicotine enhanced motivation for music reward without affecting the hedonic response to the reward. Overall, there is some evidence that dependent cigarette smokers differ from occasional smokers or healthy controls on motivation for non-drug reward, almost always following acute abstinence. However, other research has questioned the effects of nicotine deprivation on motivation for non-drug rewards.

Research into the chronic effects of cannabis on behavioural aspects of reward processing is lacking, despite the enduring, anecdotally-based claim that chronic cannabis use causes an ‘amotivational syndrome’. Poorly controlled, older studies found no evidence of a difference between heavy cannabis users and light cannabis users on tasks which assessed motivation to earn money or tickets to exchange for goods (Mello & Mendelson, 1985; Mendelson, Kuehnle, Greenberg, & Mello, 1976). A

more recent study, however, reported that adolescent cannabis users, compared with non-users were less willing to exert effort for a monetary reward (Lane, Cherek, Pietras, & Steinberg, 2005). Similarly, cannabis acutely reduced motivation for money (Cherek, Lane, & Dougherty, 2002), although they only had a sample of five, which limits the conclusions that can be drawn.

One task that has gained great popularity in assessing non-drug reward processing is the probabilistic reward task (PRT) (Pizzagalli, Jahn, & O'Shea, 2005) (figure 1.6). This task was used twice in the studies described in this thesis. The PRT involves two stimuli that are financially reinforced with an asymmetrical reinforcement schedule, such that a response bias towards the more reinforced stimulus usually develops. The stimuli are mouths of two lengths shown on a symbolic face; one mouth is defined as short and one mouth as long, though they only differ by approximately 1mm. These stimuli are shown for a very short amount of time (approximately 100ms). The participant is asked to identify which mouth is shown on a given trial and over the course of the task participants often start identifying the more reinforced mouth more frequently than the less reinforced mouth. The extent to which a participant forms a response bias towards the more reinforced mouth is termed 'reward responsiveness', which, in this task, is essentially reward learning. Reduced reward responsiveness has been shown to be associated with self-reported anhedonia (Pizzagalli et al., 2005) and depression (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008) and is affected by dopamine agonist treatment (Pizzagalli, Evins, et al., 2008). The PRT theoretically captures two processes: sensitivity to the experience of reward, i.e. the internal value assigned to reward, and learning rate, i.e. the speed at which prediction error affects behaviour (Huys, Pizzagalli, Bogdan, & Dayan, 2013).

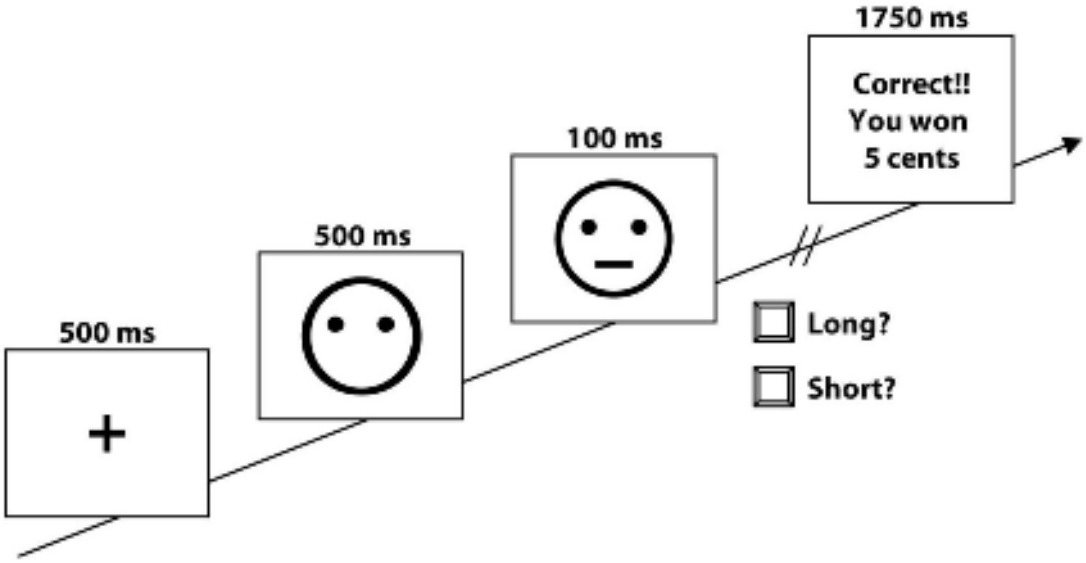


Figure 1.6 A diagrammatic representation of the Probabilistic Reward Task (taken from Pizzagalli et al., 2005). First a fixation cross is shown for 500ms, then a faceless mouth is shown for 500ms, then a long or short mouth (13mm and 11.5mm in the original version, respectively) is shown for 100ms, then the participant responds for either the long or the short mouth, then feedback is given for 1750ms. Unbeknownst to the participant, one of the mouths is reinforced three times more frequently than the other mouth, and so a response bias usually develops towards that mouth.

Importantly for this thesis, the PRT has been used to investigate reward processing in nicotine dependent individuals. Response bias does not differ between dependent smokers, who have been abstinent for 4 hours, and non-smokers (Peechatka, Whitton, Farmer, Pizzagalli, & Janes, 2015). This suggests that even after a short period of deprivation, which can provoke withdrawal symptoms (Hendricks, Ditre, Drobes, & Brandon, 2006), there may be no difference in this aspect of non-drug reward processing between dependent smokers and non-smokers. Within dependent smokers, 24 hours of abstinence produced marked reductions in response bias, while 9 hours did not (Audrain-McGovern, Wileyto, Ashare, Cuevas, & Strasser, 2014; Pergadia et al., 2014), although a longer and more sensitive version of the task was used in the former experiment. Acute nicotine, however, enhanced response bias (Barr, Pizzagalli, Culhane, Goff, & Evins, 2008) and cigarette smoking appears to normalise the reward hyposensitivity in depression (Janes et al., 2015; Liverant et al., 2014). Hence, there is some evidence for the enhancing effects of acute nicotine and the diminishing effects of acute

nicotine abstinence on reward learning, although smokers and non-smokers may not differ after a short period (4 hours) of deprivation.

One could argue that all of the reward processing studies I have described so far measure 'anhedonia'. In fact, Treadway et al. (2009), creators of the 'effort expenditure for rewards task' (EEfRT), define anhedonia as 'a decreased motivation for and sensitivity to rewarding experiences'. However, I would argue that decreased motivation is better referred to as 'amotivation'. Moreover, I believe that the PRT does not assess 'anhedonia', but a deficit in reward learning instead (Pizzagalli et al., 2005). In general, it seem as though it is now common to equate 'anhedonia' with 'reward processing deficits'. Indeed, the American Psychiatric Association (APA) define anhedonia as the loss of pleasure or interest in previously enjoyed activities (DSM-5 American Psychiatric Association, 2013), which makes it a multifaceted construct. This may be important clinically, however for research purposes I believe it is desirable to use specific language and not conflate different terms. Hence, I would define anhedonia as a deficiency in hedonic or pleasure processing: a difficulty in taking pleasure from usually pleasurable things (Hatzigiakoumis, Martinotti, Di Giannantonio, & Janiri, 2011; Janiri et al., 2005). Anhedonia then represents the ability to subjectively take pleasure from, or feel positively about, enjoyable experiences. In my opinion, anhedonia is just one problematic element of 'reward processing' as a whole, rather than being synonymous with 'impaired reward processing'.

Therefore, to my mind, the best ways to assess anhedonia are to administer questionnaires which ask about the capacity to take pleasure from things or for participants to consume rewards which are then rated in terms of producing a positive, subjective state (such as 'pleasure', 'liking', 'happiness', etc…). Hence, despite others referring to reward learning (Pizzagalli et al., 2005) and effort-related decision-making (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009) as 'anhedonia', and the APA emphasising the loss of pleasure *and* interest, I will keep to my definition of deficient subjective, pleasure processing.

Various anhedonia/pleasure scales have been developed (Chapman, Chapman, & Raulin, 1976; Fawcett, Clark, Scheftner, & Gibbons, 1983; Gard et al., 2006; Snaith et al., 1995). In the studies reported in this thesis, I frequently administered the temporal experiences of pleasure scale (TEPS) (Gard et al., 2006) and the Snaith-Hamilton pleasure scale (SHAPS) (Snaith et al., 1995). The TEPS assesses both consummatory (e.g. 'I really enjoy the feeling of a good yawn') and anticipatory (e.g. 'looking forward to a pleasurable experience is in itself pleasurable') pleasure at a trait level. Traditionally, the SHAPS assesses pleasure processing 'in the last few days'. However, based on previous research (Dawkins et al., 2006), I investigated state pleasure processing by asking participants how they felt 'at this moment in time'. These two questionnaires are popular in current research as they are not thought to be culturally biased (Gard et al., 2006; Snaith et al., 1995) and the TEPS taps two aspects of pleasure processing which are theoretically dissociable, with anticipatory pleasure putatively more associated with motivation than consummatory pleasure (Sherdell, Waugh, & Gotlib, 2012).

In terms of previous findings in cigarette smokers, anhedonia levels were found to be similar in satiated dependent cigarette smokers and non-smokers but were greater in smokers after overnight abstinence (Powell et al., 2002). Similarly, overnight nicotine abstinence in dependent cigarette smokers led to reduced 'happiness' ratings in response to 'positive' film clips (Dawkins et al., 2006). Anhedonia, measured using ecological momentary assessment, also follows the temporal profile of a standard withdrawal symptom pre and post quit (Cook et al., 2015), which demonstrates its close link with smoking and abstinence. The importance of self-reported anhedonia in future smoking is clear, with higher anhedonia predicting relapse over and above other depressive symptoms (Cook, Spring, McChargue, & Doran, 2010; Leventhal, Piper, Japuntich, Baker, & Cook, 2014). Low hedonic capacity also predicts the strength of craving for cigarettes following 24 hours of nicotine deprivation (Cook, Spring, McChargue, & Hedeker, 2004). Furthermore, successfully quitting cigarette smoking has been associated with reduced anhedonia after one (Dawkins, Powell, Pickering, Powell, & West, 2009; Snuggs & Hajek, 2013) and four weeks (Snuggs & Hajek, 2013)

To my knowledge, there has been less research into anhedonia and cannabis use. One study demonstrated that baseline cannabis abuse predicted later anhedonia (Bovasso, 2001) and another showed dependent adolescent cannabis users had greater anhedonia than non-drug using controls (Dorard, Berthoz, Phan, Corcos, & Bungener, 2008). Moreover, five days of abstinence substantially reduced anhedonia in quitting cannabis users (Dawes, Sitharthan, Conigrave, Phung, & Weltman, 2011). However, an additional study found no association between frequency of cannabis use and anhedonic symptoms within a sample of cannabis users (Johnson, Bonn-Miller, Leyro, & Zvolensky, 2009). The relationships between substance use and anhedonia are quite complicated (Garfield, Lubman, & Yücel, 2014). It may not be that dependent uses are necessarily more anhedonic than controls, but that within some drug user populations (including cigarette smokers), anhedonia may predispose people to future drug use or failed quit attempts. Furthermore, abstinence appears to play an important role in anhedonia severity, while anhedonia can moderate the effects of abstinence on cigarette cravings.

1.5.2.3 Neuroimaging research

The sensitivity of the human reward system has been probed in recent years by allowing participants to win real rewards in the scanner. As described above, electrophysiological studies in animals have shown that mesocorticolimbic dopamine neurons exhibit phasic firing when they receive unpredicted rewards or when cues predict anticipated reward (Schultz et al., 1997). In humans, the neurobiology underlying anticipation and receipt of reward has often been investigated using the monetary incentive delay task (MIDT) (Knutson, Westdorp, Kaiser, & Hommer, 2000). In this task, cues are presented that predict monetary wins, losses and neutral outcomes. After a cue is presented, participants wait for a few seconds (usually 2-3s) and are required to press a button in order to win money, not lose money or receive nothing (figure 1.7). The BOLD response is usually measured in the waiting stage, while participants anticipate the opportunity to press the button. Similar to the role of mesocorticolimbic dopamine neurons in animals, anticipation of winning money recruits striatal and

medial forebrain structures, e.g. the nucleus accumbens, caudate, putamen, medial prefrontal cortex (Knutson et al., 2000). The BOLD response is also often recorded during the feedback stage, when participants find out whether they have won money or not. Receipt of monetary reward recruits similar reward-related regions, including the nucleus accumbens, caudate, putamen and amygdala (Knutson & Greer, 2008).

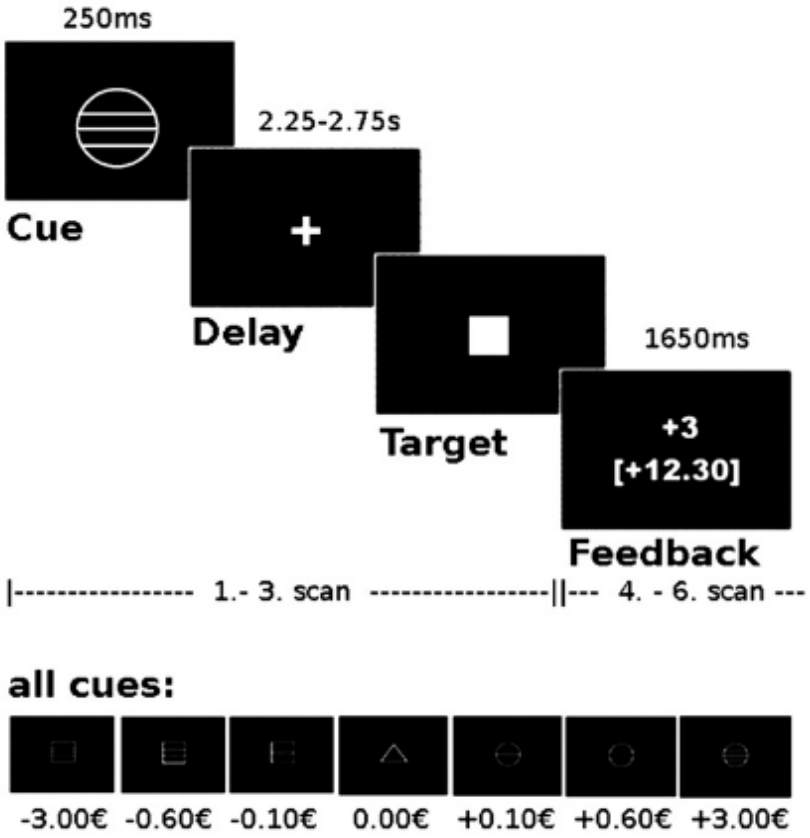


Figure 1.7 A diagrammatic representation of the monetary incentive delay task (MIDT) (taken from Wrase et al., 2007). In this traditional version of the task, a cue is first shown for 250ms which provides information about how much money can be won or lost, then there is a delay of 2.25-2.75s which is the anticipation phase, then a target is shown which must be responded to in a set time in order to win money or avoid losing money, finally feedback is presented for 1750ms.

Importantly, dopaminergic function, as measured by raclopride displacement in a PET study, in the ventral striatum correlated with BOLD response in both the ventral tegmental area and ventral striatum during anticipation of monetary reward in the MIDT (Schott et al., 2008). This provides good evidence that the anticipatory BOLD response in the MIDT is associated with dopaminergic function, similar to that observed in animals when they see a cue predictive of reward.

Despite some researchers arguing for either reduced (Goldstein & Volkow, 2011) or enhanced non-drug reward processing (Hommer et al., 2011) prevailing in addicted individuals, there is no simple pattern within the addiction MIDT literature (Bjork, Smith, & Hommer, 2008; Wrase et al., 2007). Differences in the stage of addiction, acute abstinence/drug effects, smoking status, comorbid disorders and task methodologies may account for some of these discrepancies (Balodis & Potenza, 2015).

There has been some research using the MIDT with cigarette smokers. Dependent smokers, who had smoked approximately 2 hours beforehand, showed reduced anticipatory BOLD responses to monetary gain and loss in the nucleus accumbens, compared with non-smokers (Rose et al., 2013). However, in the same study, it was shown that dependent smokers had enhanced sensitivity to *changes* in magnitude for anticipatory BOLD response and a greater response to positive feedback in the left cingulate (Rose et al., 2013). On the other hand, dependent smokers, compared with non-smokers, showed weaker sensitivity to monetary magnitude changes, but they had similar overall anticipatory responses (Jansma et al., 2013). Furthermore, nicotine-satiated dependent smokers, compared with non-smokers, showed weaker anticipatory striatal activation to delayed monetary reward and marginally weaker anticipatory striatal activation to immediate monetary reward (Luo, Ainslie, Giragosian, & Monterosso, 2011). Adolescent smokers, relative to never-smokers, also showed reduced anticipatory striatal response (Peters et al., 2011). These results imply that there is a trend for smokers to show a weaker BOLD response while anticipating money in reward-related brain regions compared with non-smokers. Furthermore, the weaker the striatal response while anticipating monetary reward, the more likely a person is to choose to smoke during a period in which abstinence is reinforced with financial payment (Sweitzer, 2013; Wilson et al., 2014), which demonstrates a putative relationship between non-drug reward processing and future cigarette smoking.

Research using radiolabelled water PET has found similar results. A visual discrimination task was used which provided monetary reinforcement for correct performance on some blocks but not others. In

one study, both smokers and non-smokers showed activation in various reward-related regions such as the orbitofrontal cortex and midbrain during the reinforced blocks, however no activation was seen in the striatum of smokers, but it was seen in non-smokers (Martin-Sölch et al., 2001). In a later study using the same task, there was a positive relationship between the amount of money available on each block and striatal activity in controls, but there was no such relationship in the smokers (Martin-Soelch, Missimer, Leenders, & Schultz, 2003).

There has been less research into impaired neurobiology underlying reward anticipation in cannabis dependence. Individuals with cannabis dependence have shown both reduced (van Hell et al., 2010) and enhanced (Nestor, Hester, & Garavan, 2010) anticipatory BOLD response to monetary reward.

1.5.3 The balance between drug and non-drug reward processing

In line with the proposed hypersensitivity to drug rewards and hyposensitivity to non-drug rewards, the reduction or termination of enjoyable activities not related to drugs is one of the criteria for the diagnosis of substance use disorders (DSM-5 American Psychiatric Association, 2013). This concept of sacrificing alternative activities in favour of drugs has been operationalised in experiments using choice-based tasks. Lee Hogarth has consistently demonstrated that the choice of cigarettes over chocolate is associated with nicotine dependence (Hogarth & Chase, 2011, 2012). Furthermore, overnight nicotine deprivation has been shown to bias responding in favour of cigarettes over money and food (Epstein et al., 1991; Perkins, Epstein, Grobe, & Fonte, 1994). However, in these deprivation studies the rewards were consumed throughout the experiment, so, as described in section 1.5.2.2, one cannot tell what process has been altered: pleasure and therefore motivation or just motivation. Furthermore, as these rewards were available simultaneously, one cannot assign a motivational value to each separately.

Interestingly, it has been shown in tobacco (Bisaga, Padilla, Garawi, Sullivan, & Haney, 2007) and cannabis addicts (Haney, Comer, Ward, Foltin, & Fischman, 1997) that the magnitude of an alternative

reinforcer affects drug-seeking. Drug addicted individuals reduce their drug-seeking when larger alternative reinforcers are available; however the extent to which their putative hyposensitivity to non-drug rewards alters the effect of alternative reinforcers on behaviour is not well understood. Behavioural economic research has reported both null and negative associations between elasticity of cigarette purchase and nicotine dependence (MacKillop et al., 2008; Murphy et al., 2011). These negative associations suggest that greater dependence may be associated with a weaker sensitivity to increases in cost, thus implying that nicotine dependent individuals may not alter their cigarette-seeking behaviour in response to external factors as much as non-dependent individuals.

Other experiments have investigated reward processing of cigarettes and non-drug rewards within the same paradigm without participants choosing between them. In an experiment which greatly informed this thesis, dependent and occasional smokers worked for both cigarettes and money on separate trials by pressing a button (Bühler et al., 2010). This experiment combined behavioural and fMRI outcomes. Occasional smokers worked harder for money than cigarettes, and had greater neural activity in reward-related brain regions while anticipating money compared with cigarettes. In contrast, within dependent smokers, there was no difference between the motivation for money and cigarettes or neural activity while they anticipated the rewards. This suggests that it may be the balance between cigarette and non-drug reward processing which is important in nicotine dependence, rather than one or the other. Surprisingly, 36 hours of nicotine abstinence had no effect on either the behavioural or fMRI outcomes in this experiment, which opposes the hypothesis that craving and abstinence should heighten differences in drug and non-drug reward processing (Goldstein & Volkow, 2011). However, a similar experiment which did not measure any behavioural response, found differential effects of acute abstinence on BOLD response during anticipation of cigarettes and money (Sweitzer et al., 2013).

This balance between drug and non-drug reward processing was also found to be important in studies predicting future smoking in dependent smokers making a quit attempt (Versace et al., 2014; Versace

et al., 2012). Before ceasing smoking, participants viewed pleasant and cigarette-related images. They were then grouped into two categories: (1) blunted response to pleasant images relative to cigarette images or (2) similar response to pleasant images relative to cigarette images, based on the late positive potential (Versace et al., 2012) and BOLD response (Versace et al., 2014). On both occasions, the first group was more likely to relapse than the second group.

In summary, tasks pitting a drug against an alternative, non-drug reward have good face validity (DSM-5 American Psychiatric Association, 2013) and show close associations between performance and dependence, however they do not provide separate measures of reward processing for each type of reward. Tasks that allow both types of reward to be earned within the same paradigm but on separate trials (Bühler et al., 2010; Sweitzer et al., 2013) permit the comparison of reward processing on the same scale. Therefore, conclusions can be made about the comparative value of drug and non-drug rewards. Hence, for the purposes of this thesis I specifically designed a task which had both of these qualities: (1) a choice stage and (2) a separate motivational stage.

1.5.4 Characteristics of reward

Most of the studies described above used money as a non-drug reward (Bühler et al., 2010) or investigated responses to pleasant and drug-related images (Versace et al., 2014; Versace et al., 2012). Although these are well-validated and useful ways of probing reward processing, and I have used monetary reward in parts of this thesis, I believe they may not be ideal for investigating drug and non-drug reward processing. In this work, I aimed to compare drug and non-drug reward processing while ensuring that: (1) the rewards were meaningful and tangible and (2) the nature of the drug and non-drug rewards were as similar as possible. I reasoned that the optimal way of studying motivation to smoke a cigarette is to provide participants with the opportunity to win and smoke real cigarettes, rather than, for example, presenting cigarette-related images.

Furthermore, given that I wanted to compare drug with non-drug reward processing, I wished to choose non-drug rewards that were similar to cigarettes in various reward characteristics. Monetary reward may not be similar to a cigarette reward because it cannot be consumed; it can only be exchanged for other goods. Moreover, it can be exchanged for cigarettes, and so money could represent cigarette reward in some smokers' minds. Whereas, music and chocolate, which have both been used as non-drug rewards in smoking research (Hogarth & Chase, 2011; Perkins & Karelitz, 2013b), can be consumed and enjoyed, and can't easily be exchanged for cigarettes. Hence, by using these non-drug rewards, I hopefully (1) kept the consummatory nature of the reward types similar; (2) allowed for an investigation into liking of reward consumption; and (3) did not provide participants with a reward that could later be exchanged for cigarettes.

1.6 Summary

Most people who try drugs do not go on to become addicted; reward processing may play a fundamental role in the development of drug dependence in those who do. The iRISA theory suggests addiction is associated with a hypersensitivity to drug rewards and a hyposensitivity to non-drug rewards. However, the existing research in favour of both of these claims is remarkably mixed for nicotine and cannabis dependence. For instance, self-administration of cigarettes and cannabis in the laboratory have not always been associated with the respective addictions. Furthermore, the relationship between the severity of dependence and the pleasure taken from drug consumption is unclear. The evidence in favour of a hyposensitivity to non-drug rewards is also contentious. For example, both animal studies and human studies have shown opposite effects of chronic nicotine and cannabis use on different aspects of non-drug reward processing. In terms of motivation for non-drug rewards specifically, both null and significant differences have been reported between cigarette smokers and controls, following acute nicotine deprivation and satiation.

It is advantageous to investigate drug and non-drug reward processing within the same paradigm, so that clear comparisons on the same scale can be made and the balance between the two can be

examined. To my knowledge, only one study has compared cigarette and non-drug reward processing, within the same paradigm, in dependent and occasional smokers (Bühler et al., 2010). This study demonstrated a perturbed balance in cigarette and non-drug reward processing in dependent smokers, but there are two important points to make: (1) there was a surprising null effect of nicotine abstinence and (2) they used money as the alternative, non-drug reward.

Therefore, the extent to which nicotine dependence is associated with concurrent changes in cigarette and non-drug reward processing, and whether this is moderated by acute nicotine abstinence, is unclear. It is critical to examine various components of reward processing to determine whether these changes occur across the reward processing spectrum or only in specific components. Furthermore, examining the neural and pharmacological underpinnings of these potential differences in drug and non-drug reward processing will hopefully contribute to knowledge about *why* differences exist, if they do.

Finally, despite the burgeoning problem of cannabis dependence, there is an obvious gap in the literature concerning possible reward processing deficits that are associated with acute and chronic cannabis use. This is an especially topical and important research direction given the globally changing legal status of cannabis, the increasing use of the drug (Hasin et al., 2015) and the 'amotivational syndrome' which has been anecdotally associated with its use (McGlothlin & West, 1968). Furthermore, the endocannabinoid system putatively plays an important role in other drug addictions (Maldonado et al., 2006; Parsons & Hurd, 2015), including nicotine dependence. Therefore, acute and chronic manipulations of the endocannabinoid system, and their effects on reward processing, should aid our understanding of how this system is related to particular addictive behaviours.

1.7 Research questions and hypotheses

1) Do dependent cigarette smokers differ from occasional cigarette smokers on their processing of cigarette and non-drug rewards across a range of metrics? Is this moderated by acute nicotine abstinence?

Despite mixed evidence concerning reward processing differences between dependent and occasional/non-smokers, based on the iRISA theory (Goldstein & Volkow, 2011) I predicted that dependent smokers, relative to occasional smokers, would be hypersensitive to cigarette rewards and hyposensitive to non-drug rewards. Furthermore, I predicted that acute nicotine abstinence would further polarise these differences.

2) Can an acute dopaminergic challenge beneficially disrupt cigarette smokers' processing of cigarette and non-drug rewards?

Based on the literature concerning dopaminergic adaptations in nicotine dependence (Dagher et al., 2001; Fehr et al., 2008; Leroy et al., 2012) and the role of dopamine in drug and non-drug reward processing (Volkow et al., 2004), I predicted that a dopaminergic agonist challenge would disrupt cigarette and non-drug reward processing. Furthermore, based on previous work investigating dopamine agonists' effects on smoking and reward processing (Freeman, Das, Kamboj, & Curran, 2015; Freeman, Morgan, Brandner, Almahdi, & Curran, 2013; Jarvik et al., 2000), which is introduced fully in chapter 4, I specifically predicted that an acute dose of a dopamine D2/3 receptor agonist would reduce motivation for cigarettes and increase motivation for non-drug rewards.

3) Is cannabis use associated with non-drug reward processing alterations?

There is a lack of research in this area. However, based on two small studies showing amotivational effects of acute and chronic cannabis use (Cherek et al., 2002; Lane et al., 2005), I predicted that (1) acute cannabis administration would lead to, and (2) cannabis dependence would be associated with, non-drug reward processing deficits.

1.8 Methodological approaches to these questions: a road map of this thesis

The first question is addressed in chapters 2, 3 and 4. The second question is addressed in chapter 4. The third question is addressed in chapter 5.

The studies in this thesis employ a range of methodologies. For the study reported in chapter 2, I created a novel task named the Drug, Reward and Motivation – Choice (DReaM-Choice) Task, which allows participants to earn real rewards (cigarettes, music and chocolate, as well as a neutral commodity: paper) to consume later. This task measures (1) choices for each reward, which I term 'relative preference' and (2) motivation for each reward. After the task, participants were allowed to consume the actual rewards they had won, thus allowing for an assessment of reward liking. Dependent and occasional smokers completed this procedure twice, once when in their 'normal' state and once after 12 hours of nicotine abstinence.

This was followed up by an fMRI study which is reported in chapter 3. This study investigated the behavioural and neural processing of cigarette and music reward processing in dependent and occasional smokers, when they were in their 'normal' (non-deprived) states. In order to investigate the BOLD response during anticipation of and feedback about these rewards, I adapted a well-validated task called the monetary incentive delay task (MIDT) (Knutson et al., 2000), which I described above.

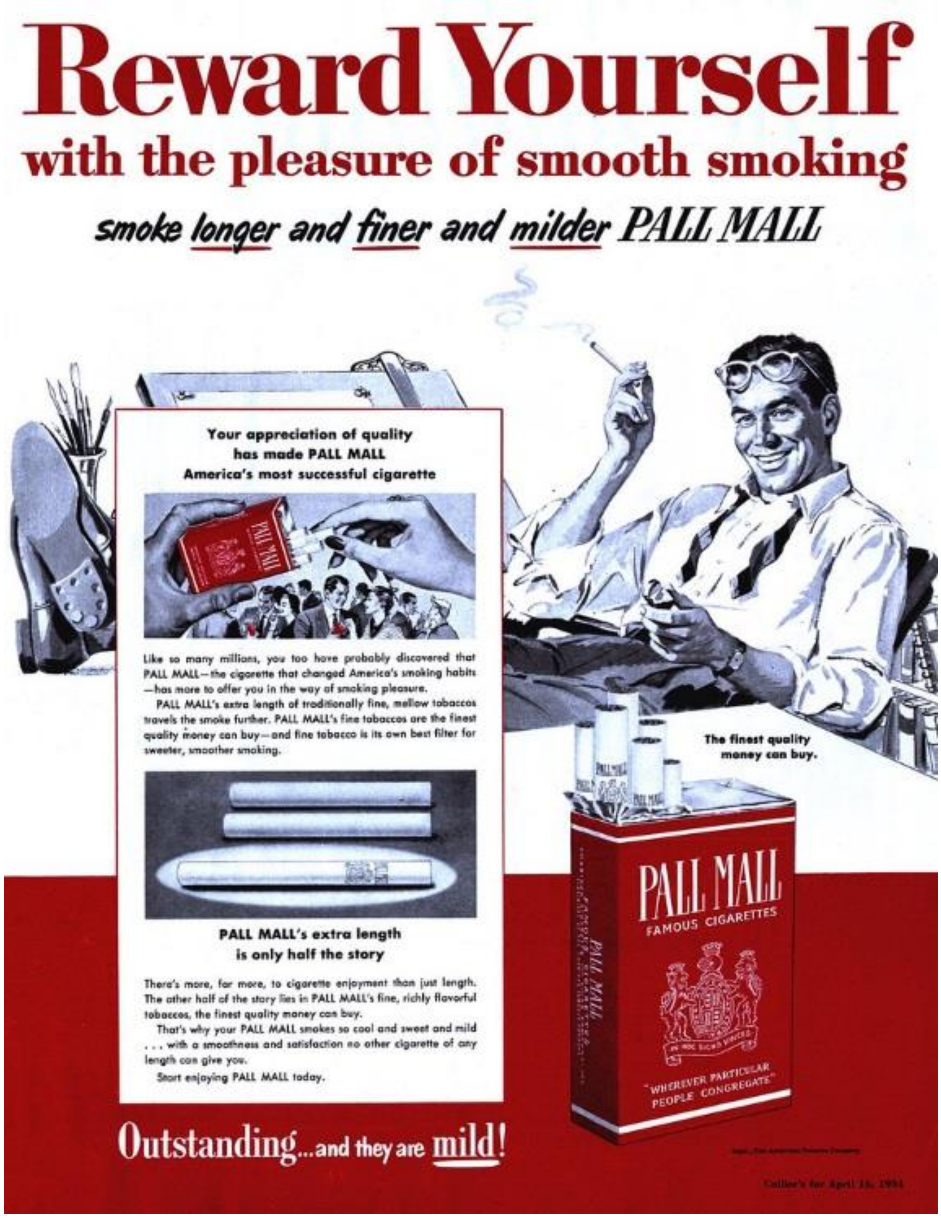
In the study reported in chapter 4, the effects of pramipexole, a dopamine D2/D3 receptor agonist, on cigarette and non-drug reward processing were tested. Concurrent cigarette and non-drug reward processing was assessed with a simplified version of the DReaM-Choice task. The behavioural economics of cigarette consumption were assessed with a cigarette purchase task (Mackillop et al., 2008). Non-drug reward processing was more thoroughly investigated using an effort-related decision-making task (Treadway et al., 2009) and a reward learning task (Pizzagalli et al., 2005). Hence, I was able to investigate the effects of dopaminergic manipulation different aspects of cigarette and non-drug reward processing, while also comparing dependent and occasional smokers on these other measures.

The relationships between cannabis use and reward processing deficits were examined in the studies reported in chapter 5. The chapter is split into two studies: the first examined the acute effects of two

types of cannabis (with and without cannabidiol) on effort-related decision-making (Treadway et al., 2009) and the second examined the associations between cannabis dependence and possible deficits in effort-related decision-making and reward learning (Pizzagalli et al., 2005).

Finally, in chapter 6, I bring these results together and discuss what they can tell us in terms of drug and non-drug reward processing in nicotine and cannabis dependence. I also discuss the limitations of my work and provide some thoughts about future research that should be conducted within this field.

Chapter 2: Cigarette and non-drug reward processing in dependent and occasional cigarette smokers during ad libitum smoking and acute nicotine abstinence



2.1 Introduction

As described in chapter 1, drug addiction is theoretically associated with a hypersensitivity to drug rewards and a hyposensitivity to non-drug rewards (Goldstein & Volkow, 2011). There have been suggestions that it is the *balance* between drug and non-drug reward processing that is critical in the maintenance of addiction and relapse (Bühler et al., 2010; Versace et al., 2014; Versace et al., 2012). Furthermore, this imbalance is thought to become more polarised during acute abstinence and at times of craving (Goldstein & Volkow, 2011). Currently, the findings concerning the relationships between nicotine dependence, nicotine abstinence and cigarette and non-drug reward processing are somewhat unclear. A better understanding of which reward processing aspects are altered could contribute to more successful treatments of nicotine dependence.

2.1.1 Processing of cigarette rewards

In humans, nicotine dependence has been shown to be associated with motivation to earn cigarettes in behavioural economic tasks (MacKillop et al., 2008; Murphy et al., 2011) and choice tasks (Hogarth, 2012; Hogarth & Chase, 2011). However, other fixed and progressive-ratio button-pressing tasks have failed to demonstrate significant relationships between nicotine dependence and motivation for cigarettes (Barrett, 2010; Bühler et al., 2010). These latter findings are surprising, and demand further investigation, as addiction is often defined in terms of powerful motivations for the drug (West & Brown, 2013).

Studies that have investigated the relationship between nicotine dependence and hedonic responses to cigarette smoking within dependent smokers have found divergent results (Pomerleau & Pomerleau, 1992; Shiffman & Kirchner, 2009). To my knowledge, occasional, non-dependent smokers have not been compared with frequent, dependent smokers on their liking of cigarettes however.

Unsurprisingly, nicotine abstinence usually (Barrett, 2010; Kollins et al., 2013), but not always (Bühler et al., 2010), leads to increased cigarette craving and self-administration; this indicates a heightened

incentive properties of cigarettes during deprivation. Thus, there is mixed evidence that nicotine dependence is associated with enhanced motivational processing of cigarette rewards in the laboratory and that acute abstinence augments this. The relationship between the pleasure taken from smoking cigarettes and nicotine dependence is even less clear. Hence, more laboratory studies are required to clarify these discrepancies.

2.1.2 Processing of non-drug rewards

Animal research suggests that nicotine acutely enhances, while short-term withdrawal lowers, reward sensitivity (Epping-Jordan et al., 1998; Kenny & Markou, 2006; LeSage et al., 2006). However, there is also evidence of long-term enhancement of reward sensitivity after extended nicotine self-administration (Kenny & Markou, 2006).

Human evidence concerning non-drug reward processing alterations in dependent smokers is mixed. Dependent smokers, compared with non-smokers, have been shown to have a reduced motivation for monetary reward using the CARROT and self-reported anhedonia only after overnight abstinence (Al-Adawi & Powell, 1997; Dawkins et al., 2006; Powell et al., 2002). However, a difference in motivation for monetary reward between high and low dependence smokers has been shown regardless of nicotine satiation or abstinence (Kalamboka, 2008), although this result was not replicated in later experiments reported in the same thesis. When investigating motivation for money and cigarettes concomitantly, Buhler et al. (2010) showed that dependent smokers had similar motivation for these rewards but occasional smokers worked harder for money compared with cigarettes; nicotine deprivation did not moderate this effect. No difference between smokers and non-smokers on a reward learning task was found after 4 hours of abstinence (Peechatka et al., 2015) and neither was there a difference between dependent and occasional smokers on motivation for music or money, regardless of abstinence (Perkins & Karelitz, 2013b). Hence, there is mixed evidence for group differences in non-drug reward processing, with and without nicotine abstinence.

Whether or not acute abstinence affects non-drug reward processing is therefore also unclear. Reward learning was sensitive to 24 hours of abstinence, but not 9 hours, in dependent smokers (Audrain-McGovern et al., 2014; Pergadia et al., 2014); motivation for music, but not money, was affected by overnight abstinence in dependent and occasional smokers (Perkins & Karelitz, 2013b); and anticipatory BOLD response for money was sensitive to 24 hours of abstinence in dependent smokers (Sweitzer et al., 2013). However, both Buhler et al. (2010) and Kalamboka et al. (2009) found no evidence of acute nicotine abstinence on motivation for monetary reward.

2.1.3 Use of consummatory rewards

As described in chapter 1, it is important to examine drug and non-drug reward processing using the same paradigm so that direct comparisons within and between groups can be made. This allows for an investigation into the balance in reward processing, which may be disrupted in nicotine dependence, as observed by Buhler et al. (2010). However, as argued previously, money may not be the ideal comparison reward. Therefore, I chose to use two consummatory rewards that have previously been used in smoking research: chocolate (Hogarth & Chase, 2011) and music (Perkins & Karelitz, 2013b). Furthermore, it may be wise to examine a variety of reward processing components, so that any specific, rather than global, deficits can be elucidated.

2.1.4 Drug, Reward and Motivation-Choice (DReaM-Choice) task

In order to attempt to address the questions and ambiguities raised above, I employed the new Drug, Reward and Motivation-Choice (DReaM-Choice) task (briefly introduced in chapter 1 and described in detail in section 2.2.2.1). I aimed to combine paradigms which offer rewards concurrently (e.g. Bisaga et al., 2006; Hogarth & Chase, 2011) and those that assess motivation for individual rewards (e.g. Buhler et al., 2010). Hence, the task involved a series of two-option choices, in which two rewards were pitted against each other, this was followed by a button-pressing stage where participants could earn points for the chosen reward. The rewards (cigarettes, music and chocolate, and the neutral

commodity - paper) were available in two magnitudes (large and small) so that I could also explore the effect of magnitude on reward processing. This task produces two complementary outcome variables: (1) number of choices for each reward, assessing relative preference and (2) average number of button-presses for each reward, assessing motivation. During different points of the experiment, participants also rated their wanting of each reward. After the task, participants consumed and rated their liking of the rewards they won. Hence, I also collected data on self-reported wanting and self-reported liking.

2.1.5 Summary and hypotheses

In summary, there is a mixed literature concerning drug and non-drug reward processing alterations in nicotine dependence, and the moderating effects of acute abstinence. Furthermore, very few studies have investigated cigarette and non-drug reward processing concurrently or used consummatory non-drug rewards, which may have advantages over monetary reward. Finally, the examination of a wide range of reward process, including motivation and self-reported wanting and liking, has been limited. Therefore, in the current study, I investigated cigarette and non-drug reward processing in dependent and occasional smokers, using the newly developed DReaM-Choice task, following acute (12h) nicotine abstinence and ad libitum smoking. Based on the iRISA theory of addiction (Goldstein & Volkow, 2011), I predicted that:

1. Dependent smokers, compared with occasional smokers, would be hypersensitive to cigarette rewards and hyposensitive to non-drug rewards, across a range of metrics.
2. 12 hours of nicotine abstinence, compared with ad libitum smoking, would enhance cigarette and reduce non-drug reward processing in the dependent smokers but not the occasional smokers.

2.2 Methods

2.2.1 Design and participants

A fully factorial, crossover design with a between-subjects factor of group (dependent or occasional) and within-subjects factors of smoking-condition (ad libitum or abstinent), reward-type (cigarettes, music, chocolate or paper) and reward-magnitude (large or small) was used.

Twenty dependent (10 females) and 20 occasional (12 females) smokers were recruited by advertisements at University College London and on Gumtree. Eligibility criteria for and sample size of the two groups were based on Buhler et al. (2009). A sample size of 20 per group is sufficient to detect a between-within subject interaction of small (f=0.1) effect size in a 4x2x2x2 design, assuming a correlation of 0.5 between measures, an alpha of 0.05 and a beta of 0.8. Note: this power analysis was in error. With a sample of 20 per group, power of 0.8, an alpha of 0.05 and a correlation among repeated measures of 0.5, I would be able to detect an effect size of f=0.27, not an effect size of f=0.1.

Inclusion criteria for dependent smokers were: age 18-50; reporting smoking ≥10 cigarettes per day; scoring ≥6 in the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al., 1991); and a current diagnosis of severe tobacco use disorder according to DSM-5. Inclusion criteria for occasional smokers were: age 18-50; reporting smoking 0.25-5 cigarettes per week; never having been a regular, daily smoker; an FTND score of 0; and no DSM-5 diagnosis of tobacco use disorder. Exclusion criteria for all participants were: use of nicotine replacement therapy or any other smoking cessation pharmacotherapy; addiction to another drug; not liking chocolate; a current mental health problem; and a learning impairment.

Participants were reimbursed £7.50/hour and were informed they could also win cigarettes, chocolates, music, and pieces of lined paper (a neutral control commodity) during the experiment.

All participants provided written, informed consent. This study was approved by the University College London (UCL) Ethics Committee and was conducted in accordance with the Declaration of Helsinki.

2.2.2 Assessments

2.2.2.1 Drug, Reward and Motivation – Choice (DReaM-Choice) Task (Figure 2.2)

The DReaM-Choice task was programmed using Presentation (v. 16.5) software (NeuroBehavioural Systems, California). The task involved a series of two-option choices. During each choice, two cues were presented side by side, which represented the type and magnitude of the reward that could be worked for. Four different reward types (cigarette, music, chocolate and paper) and two different reward-magnitudes (large and small) were used. Figure 2.1 shows the cues that were used to represent the different rewards. Reward-magnitude was represented by presenting large or small versions of these cues.

Figure 2.1 Cues that represented the different reward types. From left to right: cigarette, music, chocolate, paper. The size of the cue was either large or small to represent the two magnitudes of the reward.

Figure 2.2 depicts an example trial in which either a small chocolate or a large cigarette reward could be chosen. First a choice was made between the two rewards, then the *chosen reward* was worked for in a fixed-ratio schedule: participants could press the spacebar as quickly as desired for seven seconds with the little finger on the non-dominant hand (as in Treadway et al., 2009). The more times the spacebar was pressed, the more points were won for the chosen reward, while no points were won for the foregone reward. Reward-magnitude (large, small) and baseline button-pressing speed (b), which was determined before the task, were used to calculate the number of points earned:

The number of points won on a single trial when a small reward was chosen was:

$$Points = \frac{100 \times spacebar\ presses\ during\ 'respond\ stage'}{b}$$

The number of points won on a single trial when a large reward was chosen was:

$$Points = \frac{1000 \times spacebar\ presses\ during\ 'respond\ stage'}{b}$$

There were 144 trials in total in the task, split into 3 separate blocks. The DreaM-Choice outputted two main dependent variables: number of choices for each reward and average number of button-presses (BP) during the 7 second response stage, for each reward.[1]

Malboro Gold cigarettes (tar: 6mg, nicotine: 0.5mg), Cadbury's Dairy Milk chocolate, individually chosen music rated ≥75/100 in terms of 'liking' (Perkins and Karelitz, 2013), and pieces of lined paper were the real delivered-rewards awarded after the task. 4,000 points were required for one 'unit' of delivered-reward (1/4 of a cigarette, one chunk of chocolate, 30s of music and one piece of paper). All delivered-rewards were given to the participants after the DReaM-Choice task was completed. Previous studies have used two-option choices between two rewards without a neutral 'non-reward' option (Hogarth, 2012; Hogarth & Chase, 2011). Here I included paper as a control option, enabling me to examine whether cigarettes, chocolate and music were indeed motivating rewards for both dependent and occasional smokers relative to a 'neutral commodity'.

[1] If one of the rewards was never selected, e.g. 'paper small', the BP for that outcome was set to 0.

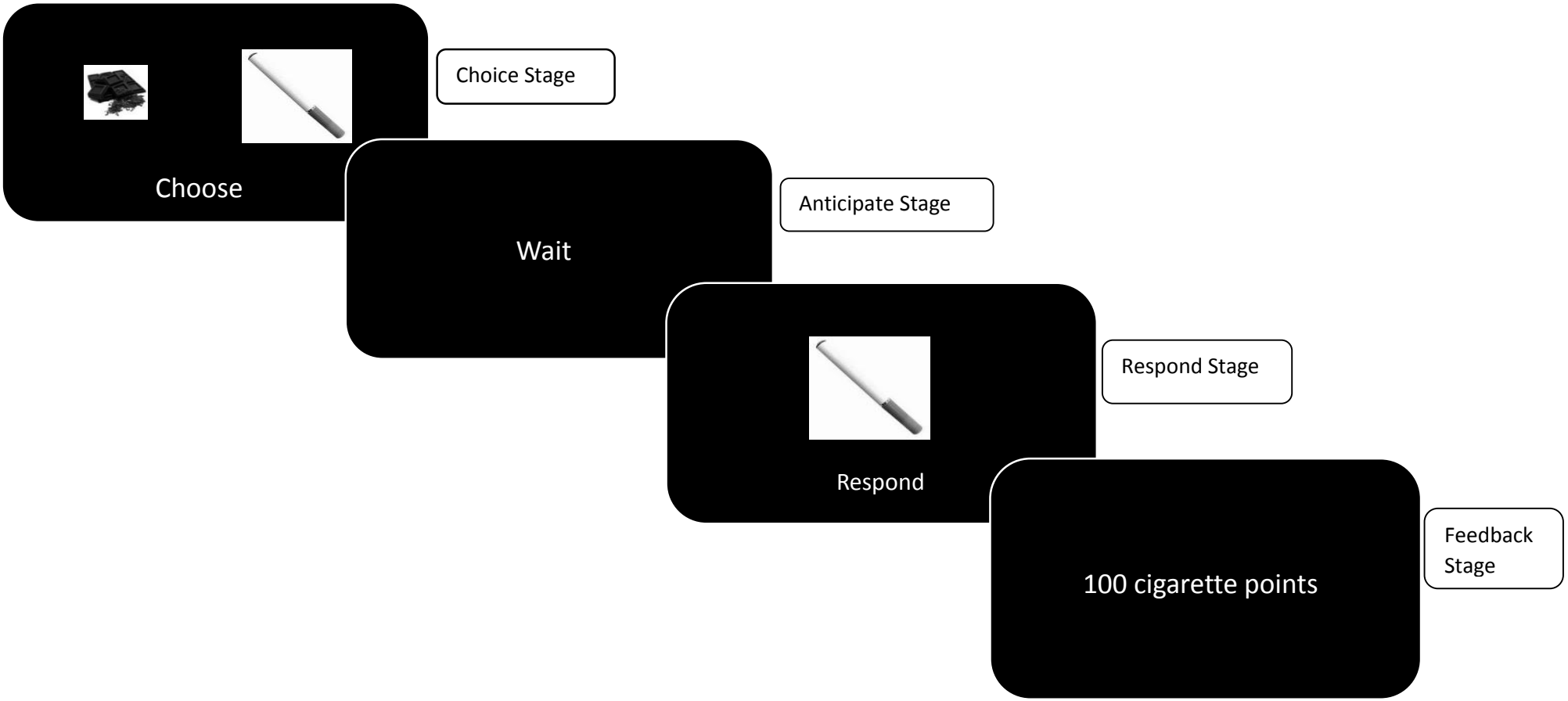


Figure 2.2 An example trial of the DReaM-Choice Task. During the 'choice stage', the cues were presented and a choice was made with button F (left option) or J (right option) (unlimited time); during the 'anticipate stage' the word 'wait' was shown and there was a pause of 1s; during the 'respond stage' the word 'respond' was shown and the spacebar was pressed as many times as desired with the non-dominant little finger in 7s (as in Treadway et al., 2009), in order to win points for the chosen reward; during the 'feedback stage' feedback concerning the amount of points won was provided for 1s. Each of the 48 possible choices were presented in 3 blocks, making a total of 144 trials, with trial order pseudo-randomized and left/right cue position counterbalanced.

2.2.2.2 Self-rated assessments

Trait measures

Beck Depression Inventory (BDI-II)

This scale of depression severity consisted of 21 items that were rated for their frequency between 0 and 3 in the last week (Beck, Steer, Ball, & Ranieri, 1996). Higher scores reflected greater depression severity.

Fagerstrom Test for Nicotine Dependence (FTND)

This scale consisted of six items that were rated between 0 and 3, with total scores ranging from 0 (low dependence) to 10 (high dependence) (Heatherton et al., 1991).

Temporal Experience of Pleasure Scale (TEPS)

This scale consisted of 18 items that were rated between 1 (very false for me) and 6 (very true for me) (Gard et al., 2006). There were two subscales: anticipatory and consummatory pleasure. Higher scores reflected greater ability to experience pleasure.

State measures

Minnesota Nicotine Withdrawal Scale (MNWS)

This scale consisted of 9 items, including one that assessed craving, that were rated between 0 (none) and 4 (severe) for 'right now' (J. Hughes & Hatsukami, 2007). Higher scores reflected greater severity of nicotine withdrawal.

Snaith-Hamilton Pleasure Scale (SHAPS)

This scale of consisted of 14 items that were rated between 0 (definitely agree) and 3 (definitely disagree) for 'right now' (Franken, Rassin, & Muris, 2007; Snaith et al., 1995). Higher scores reflected greater anhedonia. Both the TEPS and the SHAPS were used so that a trait and a state measurement of anhedonia were recorded, respectively.

Wanting and Liking Likert Scales

These consisted of a single item, which was rated between -10 (extremely don't want/like) to 10 (extremely want/like) for each reward available.

2.2.2.3 Other assessments

Carbon monoxide

Expired carbon monoxide (CO) levels were determined with a Bedfont Micro Smokerlyzer (Bedfont Scientific, Harrietsham, UK).

Spot-The-Word

This test, which correlates highly with premorbid verbal intelligence, consisted of pairs of items, one a word and one a non-word; participants selected the item they thought was a real word (Baddeley, Emslie, & Nimmo-Smith, 1993). Scores were calculated by summing the total number of correct answers.

Tobacco use disorder (DSM-5 American Psychiatric Association, 2013)

Participants were asked questions about whether various symptoms were present over the past 12 months, including: (1) taking tobacco in larger amounts than intended, (2) unsuccessful efforts to cut down tobacco use, (3) a great deal of time smoking or acquiring tobacco, (4) cravings, (5) failure to fulfil obligations because of tobacco use, (6) continued tobacco use despite interpersonal problems, (7) alternative activities are given up or reduced because of tobacco use, (8) recurrent tobacco use

when it is physically dangerous, (9) continued tobacco use despite physical problems, (10) tolerance, (11) withdrawal symptoms. Two to three symptoms is considered a mild use disorder, four to five is considered a moderate use disorder, and six or more symptoms is considered a severe use disorder.

2.2.3 Procedure

Participants attended two 90 minute experimental sessions during both 12 hour nicotine abstinence and ad libitum smoking, which were separated by approximately one week (range: 5 to 14 days). Following Freeman et al. (2012), the experiment was conducted under single-blind conditions whereby the experimenter was blinded to smoking condition. An assistant provided participants with their instructions for smoking condition in a randomised order, and checked adherence to abstinence before the experiment began (≤10ppm CO was considered acceptable) (Benowitz et al., 2002)[2]. The SHAPS, MNWS and wanting scores were completed at time 'pre-task' and the DreaM-Choice was then administered. Consequently, the wanting scores were recorded again at time 'pre-consumption' and the amount of delivered-rewards was calculated. Participants were then allowed to 'consume' the delivered-rewards whenever they wanted during a 25 minute period. Their liking (-10 = 'extremely don't like' to 10 = 'extremely like') of each delivered-reward was recorded; only the first liking rating for each reward was analysed so that satiation did not affect the results. The order in which rewards were consumed was recorded. After the 25 minute consummatory phase, participants completed the SHAPS, MNWS and wanting scores again, at time 'post-consumption'.

2.2.4 Statistical analyses

All analyses were carried out using IBM Statistical Package for Social Sciences (IBM SPSS version 21). Data were checked for normality, homogeneity of variance and sphericity using inspection of histograms, Levene's test and Mauchley's test, respectively. Where residuals were not normally

[2] Two participants did not complete the experiment due to having too high a CO reading on the abstinent session.

distributed or the group variances were not homogenous, non-parametric tests were used when available and appropriate. Where sphericity was violated, a Greenhouse-Geisser correction was applied. Adjusted values of degrees of freedom (df) and p are reported in these instances. Multiple comparisons were corrected using the Bonferroni correction via SPSS syntax.

Group differences on trait measures were investigated using t-tests or Mann-Whitney U tests, depending on distributions. CO data were investigated via a mixed-design analysis of variance (ANOVA) with a between-subjects factor of group (dependent and occasional) and a within-subjects factor of smoking-condition (ad libitum and abstinent). The time since last smoked was analysed using non-parametric comparisons as the errors were non-normally distributed. MNWS, craving (from MNWS) and SHAPS scores were investigated via mixed-design ANOVAs with a between-subjects factor of group and within-subjects factors of smoking-condition and time.

Choice and BP data were investigated using mixed-design ANOVAs with a between-subjects factor of group and within-subjects factors of reward-type (cigarette, music, chocolate and paper), reward-magnitude (large and small) and smoking-condition. Given a priori hypotheses, I investigated the effects of acute nicotine abstinence on choices and BP for music, chocolate and cigarettes within the dependent group regardless of the significance of interactions. Wanting data were investigated using a mixed-design ANOVA with a between-subjects factor of group and within-subjects factors of reward-type, smoking-condition and time (pre-task, pre-consumption and post-consumption). Liking data were investigated using a mixed-effects model approach due to missing data. Group, reward-type and smoking-condition were entered as fixed effects and the intercept was allowed to vary randomly, so that the mixed-effects model behaved like a repeated-measures ANOVA while dealing with the missing data appropriately. Between-subjects differences in order of first-reward-consumed were investigated using chi-square tests.

To assess whether order of testing (abstinent on day one or ad libitum on day one) had any main or interactive effects, the factor of order was added to the aforementioned ANOVAs. Order had no significant main effect or any interactive effect and therefore analyses continued without it.

We also conducted an exploratory analysis into the time taken to choose each reward-type. This analysis was conducted in order to determine if certain rewards were chosen more quickly than others and therefore perhaps elicited a response with greater motivation. The time taken to choose each reward was averaged across all trials and a mixed ANOVA with a between-subjects factor of group and within-subjects factors of reward-type (cigarette, music and chocolate), reward-magnitude (large and small) and smoking-condition was carried out. Paper was not included in this analysis as 19 participants never chose paper.

Correlations were carried out, within each group separately. Both the number of choices and BP for each reward, collapsed across reward-magnitude, during both smoking-conditions were correlated with: number of cigarettes smoked per day, craving, SHAPS and TEPS-total. Change in choices and button-presses across smoking-conditions for each reward-type were correlated with change in SHAPS score. The alpha level was adjusted to 0.001 to account for multiple tests.

2.3 Results

2.3.1 Trait measures (Table 2.1)

The dependent group had significantly higher FTND (U_{38}=0.000, p<0.001), DSM-5 tobacco use disorder scores (U_{38}=0.000, p<0.001) and average number of cigarettes smoked/day and /week (U_{38}=0.000, p<0.001 for both) than the occasional group. The dependent group also listened to music more frequently than the occasional group (U_{37}=114.000, p=0.033) and had lower spot-the-word scores (t_{35}=2.445, p=0.020). All other demographic and trait measures did not differ between the groups.[3]

[3] Data for BDI, BIS, TEPS and how many days per week participants listen to music and eat chocolate and liking ratings of these activities were missing for one participant in the dependent group.

Table 2.1 Group means (SD) for trait measures.

	Dependent	Occasional
Current age	23.10 (6.98)	22.85 (3.80)
FTND* **	6.35 (0.59)	0.00 (0.00)
DSM* **	6.80 (0.95)	0.40 (0.50)
Cigarettes/Day* **	16.70 (6.37)	0.47 (0.281)
Cigarettes/Week* **	116.90 (44.57)	3.26 (1.97)
Age started smoking (years)	15.29 (2.81)	17.22 (3.39)
Years smoking more than 10/day	6.13 (7.34)	NA
Quit Attempts in Lifetime	3.60 (4.16)	NA
Most Successful Quit attempt (weeks)	7.65 (10.28)	NA
Years in formal education	15.47 (2.40)	16.33 (2.33)
Days/week listen to music*	7.00 (0.00)	5.55 (2.19)
Days/week eat chocolate	2.71 (1.77)	3.05 (1.86)
Like music in general (-10 to 10)	8.52 (1.98)	7.90 (2.40)
Like chocolate in general (-10 to 10)	6.37 (2.43)	7.13 (2.08)
BDI	7.79 (7.01)	4.85 (5.49)
TEPS (anticipatory)	44.32 (8.96)	44.60 (5.63)
TEPS (consummatory)	36.21 (5.99)	37.90 (6.18)
Spot the word*	45.33 (5.91)	49.58 (4.60)

*BDI: Beck Depression Inventory; BIS: Barratt Impulsiveness Scale; TEPS: Temporal Experience of Pleasure; NA: Not Applicable. *p<0.05; ***p<0.001.*

2.3.2 State measures

Carbon monoxide (CO) and hours since last smoked (Table 2.2)

The dependent group's CO level was greater in the ad libitum condition compared with the abstinent condition (t_{18}=7.915, p<0.001). The occasional group's CO level did not differ between conditions.

Dependent smokers had smoked more recently before the experiment during the ad libitum condition compared to during abstinence (W_{19}=3.827, p<0.001) but, as expected, there was no difference for occasional smokers.

Table 2.2 Group means (SD) of CO and time since last smoked.

	Dependent		Occasional	
	Abstinent	**Ad Libitum**	**Abstinent**	**Ad Libitum**
CO*, ᵒᵒᵒ**	5.15 (2.13)	14.95 (6.75)	2.80 (1.06)	2.95 (1.50)
Last Smoked (hours)*, ᵒᵒᵒ**	14.52 (3.38)	0.50 (0.54)	89.73 (77.20)	83.28 (102.65)

*CO = carbon monoxide. *p<0.05; ***p<0.001 within-subjects significance; ᵒ p<0.05, ᵒᵒᵒ p<0.001 between-subjects significance*

Minnesota Nicotine Withdrawal Scale (MNWS), Craving (from MNWS) and SHAPS (Table 2.3)

Group, smoking-condition and time all significantly affected overall MNWS and the craving item. The dependent group's MNWS score was greater than the occasional group's score only during pre-task on the abstinence condition (t_{38}=3.905, p<0.001). The dependent group's craving decreased between pre-task and post-consumption on the abstinence condition (t_{19}=7.192, p<0.001) and, to a lesser extent, the ad libitum smoking condition (t_{19}=2.667, p=0.011), whereas there were no changes between pre-task and post-consumption for the occasional smokers on either condition.

SHAPS data were analysed with the updated scoring system (Franken et al., 2007). There were significant interactions between smoking-condition, time and group ($F_{1,38}$=20.584, p<0.001) and smoking-condition and group ($F_{1,38}$=7.216, p=0.011). Furthermore, there were main effects of time, with greater anhedonia at 'pre-task' than 'post-consumption' ($F_{1, 38}$=9.281, p=0.004) and group, with greater anhedonia in the dependent compared with the occasional smokers ($F_{1,38}$=7.958, p=0.008). The three-way interaction was driven by greater anhedonia following abstinence, compared with ad libitum smoking, at time 'pre-task' in the dependent smokers only (t_{19}=4.284, p<0.001). Similarly, the two-way interaction was driven by greater anhedonia following abstinence, compared with ad libitum smoking, in the dependent smokers only (t_{19}=3.012, p=0.005).

2.3.3 DReaM-Choice

Baseline button-presses

There were no significant group differences in average number of button-presses at baseline on either of the smoking-conditions or between either of the smoking-conditions for either of the groups. Hence, analysis continued without incorporating baseline button-pressing speed as a covariate.

Choices (Figure 2.3a)

There were interactions between group and reward-type ($F_{2.435,92.513}$=10.112, p<0.001), reward-type and smoking-condition ($F_{3,114}$=7.880, p<0.001) and reward-type and reward-magnitude ($F_{3,114}$=64.322, p<0.001). There were main effects of reward-type ($F_{2.435,92.513}$=97.966, p<0.001), with all non-paper rewards chosen more than paper, and reward-magnitude ($F_{1,38}$=157.652, p<0.001), with large rewards chosen more than small rewards.

Exploration of the group X reward-type interaction showed that, compared with the occasional group, the dependent group chose cigarettes more (t_{38}=4.117, p<0.001) and chocolate less (t_{38}=3.470, p=0.005). The dependent group chose cigarettes more than chocolate (t_{19}=2.837, p=0.043) and music (t_{19}=2.841, p=0.044), while the occasional group chose chocolate more than cigarettes (t_{19}=3.762, p=0.003). Exploration of the reward-type X smoking-condition interaction showed that, across both groups, cigarettes were chosen more (t_{39}=4.257, p<0.001) and music less (t_{39}=2.692, p=0.042) during abstinence than ad libitum smoking.

Given I had a priori hypotheses about the acute effects of abstinence on reward processing only in the dependent smokers I investigated these effects separately within each group, despite the null group by smoking-condition by reward interaction.

Within the dependent group, there was an interaction between reward and smoking-condition ($F_{3,57}$=7.854, p<0.001). There was an effect of abstinence on the number of cigarette choices with more cigarette choices during abstinence compared with ad libitum smoking (t_{19}=3.853, p<0.001). There was also an effect of abstinence on the number of music choices with more music choices during ad libitum smoking compared with abstinence (t_{19}=3.443, p=0.003).

When looking within the occasional group, there was no interaction between reward and smoking-condition ($F_{2.112, 40.119}$, p=0.267).

Table 2.3 Group means (SDs) of state measures at pre-task and post-consumption.

	Dependent				**Occasional**			
	Abstinent		**Ad Libitum**		**Abstinent**		**Ad Libitum**	
	Pre-task	**Post-consumption**	**Pre-task**	**Post-consumption**	**Pre-task**	**Post-consumption**	**Pre-task**	**Post-consumption**
MNWS	13.55 (7.75)	3.85 (3.13)	4.55 (4.38)	2.55 (3.0)	5.65 (4.67)	4.55 (3.47)	4.65 (3.28)	3.55 (3.55)
Craving (from MNWS)	2.80 (1.40)	0.70 (0.80)	1.10 (1.17)	0.50 (0.61)	0.75 (0.91)	0.30 (0.47)	0.50 (0.61)	0.40 (0.75)
SHAPS	29.10 (7.13)	24.85 (4.97)	24.25 (5.46)	24.35 (5.71)	21.25 (4.99)	21.25 (5.49)	23.35 (4.17)	20.55 (4.84)

MNWS = Minnesota Nicotine Withdrawal Scale; SHAPS = Snaith-Hamilton Pleasure Scale.

Average number of button-presses (BP) (Figure 2.3b)

There were interactions between group and reward-type ($F_{2.042,77.610}$=3.821, p=0.025) and reward-type and reward-magnitude ($F_{1.496,56.850}$=10.706, p<0.001), and main effects of reward-type ($F_{2.042,114}$=100.167, p<0.001), with all non-paper rewards pressed for more than paper, and reward-magnitude ($F_{1,38}$=49.731, p<0.001), with large rewards pressed for more than small rewards.

Exploration of the group X reward-type interaction showed that the dependent group pressed for cigarettes more than the occasional group (t_{38}=2.655, p=0.046). There were no differences in BP for cigarettes, music and chocolate within the dependent group; whereas, within the occasional group, chocolate was pressed for more than cigarettes (t_{19}=2.798, p=0.010).

Given I had a priori hypotheses about the acute effects of abstinence on reward processing only in the dependent smokers I investigated these effects separately within each group, despite the null group by smoking-condition by reward interaction.

Within the dependent group, there was no interaction between reward and smoking-condition ($F_{2.191,4.637}$,p=0.162). Despite this null interaction, I investigated the effect of abstinence on each reward. There was a null effect of abstinence on cigarette button-pressing going in the direction of increased button-pressing during abstinence compared with ad libitum smoking (t_{19}=1.625, p=0.121) and a null effect of abstinence on music button-pressing going in the direction of increased button-pressing during ad libitum smoking compared with abstinence (t_{19}=1.527, p=0.143).

Within the occasional group, there was no interaction between reward and smoking-condition ($F_{3,57}$=0.024, p=0.995). There were no discernible effects of abstinence on button-pressing for any of the rewards (ps>0.6).

Furthermore, during abstinence the dependent smokers pressed for chocolate marginally more than the occasional smokers (t_{38}=1.755, p=0.087). During ad libitum smoking there was no discernible difference between the groups (p>0.340). During both conditions the dependent smokers pressed

more for cigarettes than the occasional smokers (ps<0.027). And during both conditions there were no differences in terms of pressing for music (ps>0.6).

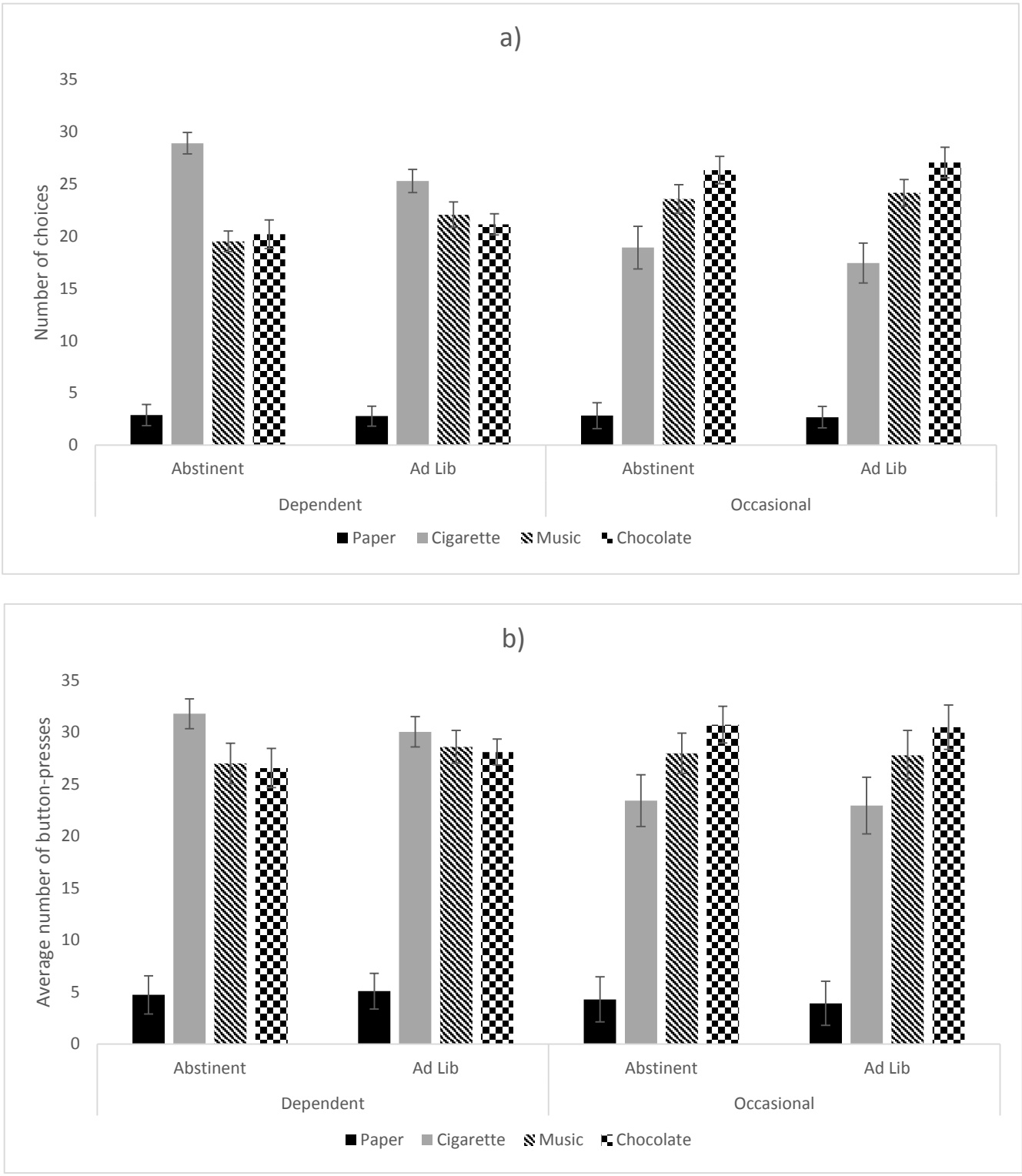


Figure 2.3 DReaM-Choice task performance showing (a) number of choices for paper, cigarettes, music and chocolate, collapsed across reward-magnitude; (b) average number of button presses in 7 seconds (BP) for paper, cigarettes, music and chocolate, collapsed across reward-magnitude. Error bars represent ± standard error.

Time to choose each reward (Figure 2.4)

There was an interaction between group, reward-type and reward-magnitude ($F_{1.664, 63.226}$, p=0.016) and a main effect of reward-magnitude, with larger rewards chosen faster than smaller rewards ($F_{1, 38}$=12.317, p=0.001). Exploration of the group X reward-type X reward-magnitude interaction showed that the dependent group were faster to choose large compared to small rewards for music (t_{19}=2.940, p=0.006) and chocolate (t_{19}=3.265, p=0.002), but not for cigarettes. On the other hand, the occasional group were faster to choose large compared to small rewards for cigarettes (t_{19}=2.591, p=0.014) and music (t_{19}=2.036, p=0.049), but not for chocolate.

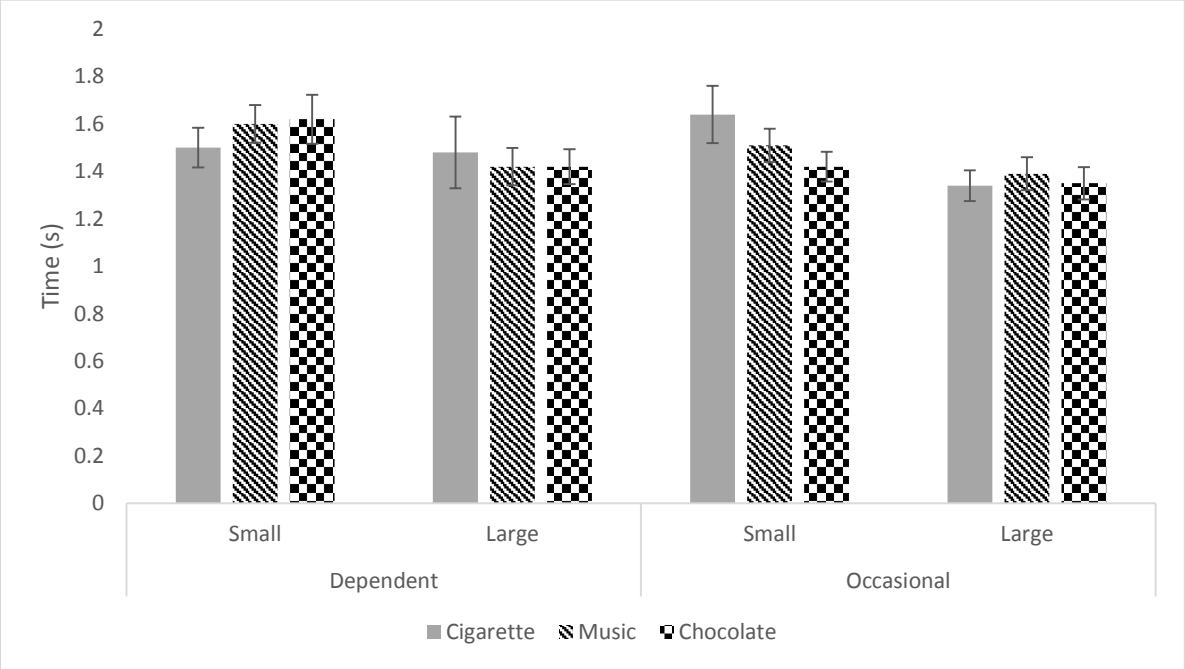


Fig 2.4 Average time taken (in seconds) to choose each reward type (cigarette small, cigarette large, music small, music large, chocolate small, chocolate large) in the DReaM-Choice task, collapsed across smoking-condition. Error bars represent ± standard error.

2.3.4 Self-reported wanting (Figure 2.5)

There were interactions between group and reward-type ($F_{2.473,93.988}$=5.004, p=0.005) and time and reward-type ($F_{2.654,100.870}$=10.096, p<0.001), and main effects of time ($F_{1.247,47.385}$=29.115, p<0.001) and reward-type ($F_{2.473,93.988}$=119.107, p<0.001), with all non-paper rewards wanted more than paper.

Exploration of the group X reward-type interaction showed that the dependent group wanted cigarettes more than occasional group (t_{38}=3.376, p=0.007). Within the dependent group, music was wanted more than chocolate (t_{19}=3.332, p=0.012), whereas, within the occasional group, music was wanted more than cigarettes (t_{19}=5.052, p<0.001) and chocolate (t_{19}=3.184, p=0.017).

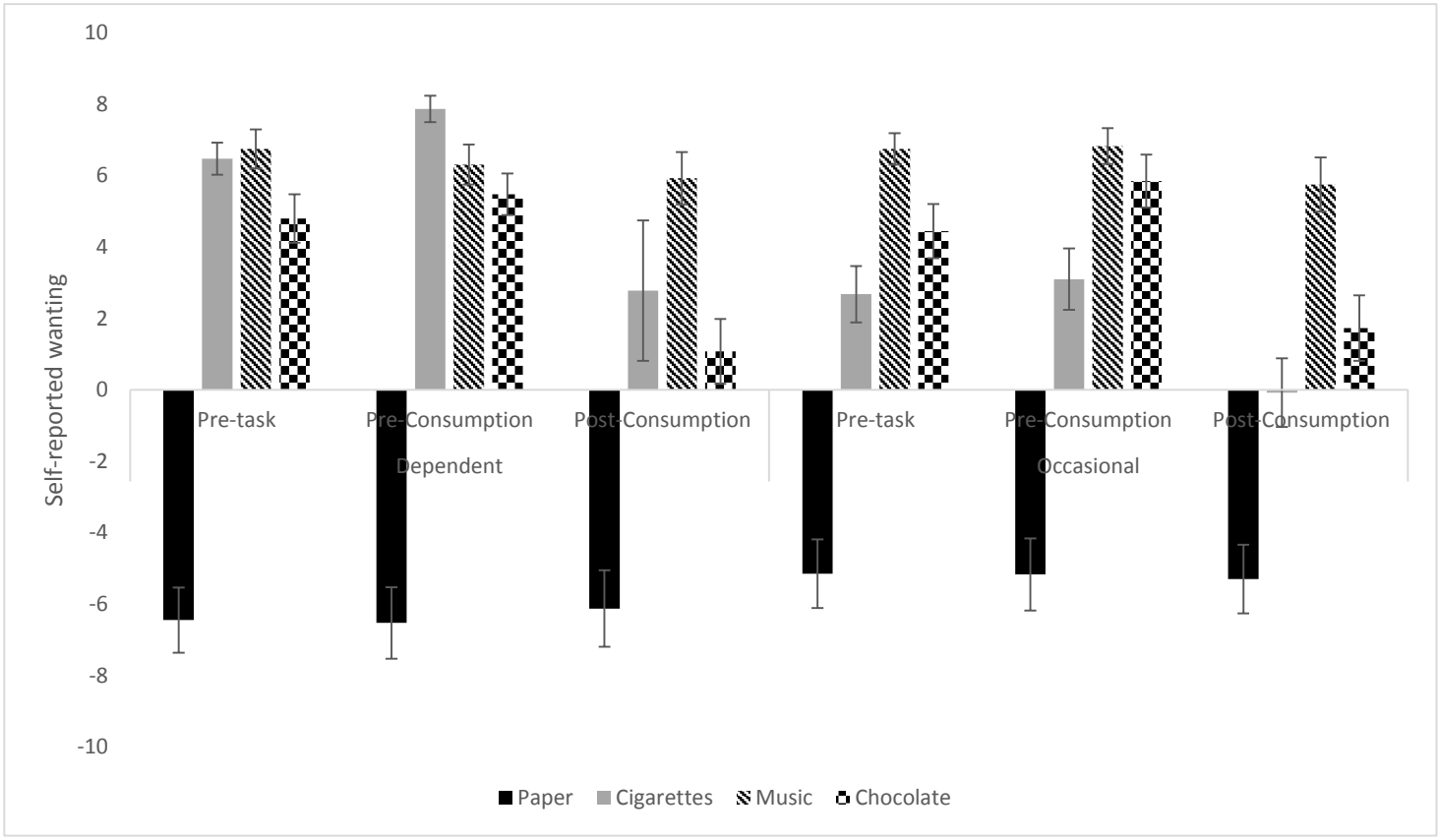


Figure 2.5 Wanting (-10 to +10) of paper, cigarettes, music and chocolate at time 'pre-task', 'pre-consumption' and 'post-consumption' collapsed across smoking-conditions. Error bars represent ± standard error.

2.3.5 *Self-reported liking (Figure 2.6)*

There was an interaction between group and reward-type ($F_{2, 173.531}$=9.178, p<0.001) and main effects of group ($F_{1,36.505}$=5.905, p=0.020) and reward-type ($F_{2, 173.531}$=6.836, p=0.001).[4]

Exploration of the group X reward-type interaction showed liking of cigarettes was greater for the dependent than the occasional smokers (t_{32}=4.073, p<0.001). Within the dependent group, there were no differences in liking ratings for cigarettes, music and chocolate. Within the occasional group, cigarettes were liked less than music (t_{13}=3.785, p=0.007). Overall, the dependent group gave higher liking ratings than the occasional group (t_{25}=2.710, p=0.012).

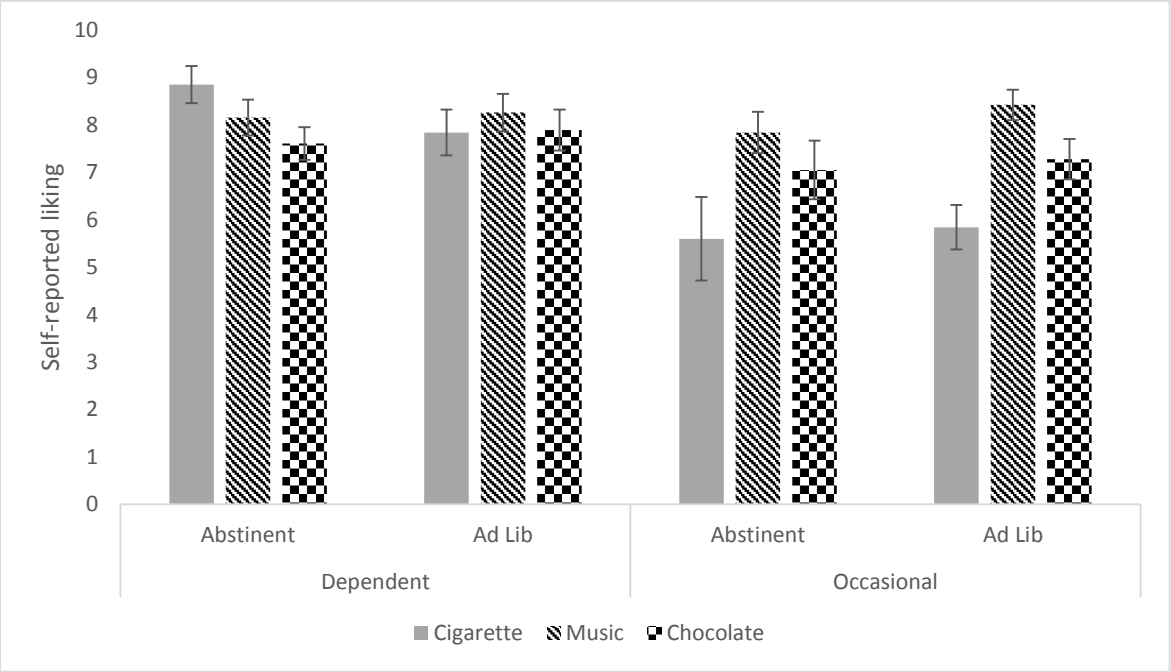


Figure 2.6 Liking (-10 to +10) of the first 'unit' of cigarettes, music and chocolate during consumption. Error bars represent ± standard error.

2.3.6 Order of consumption

During ad libitum smoking, in the dependent group 6 participants smoked first, 3 listened to music first and 11 ate chocolate first and in the occasional group 6 participants smoked first, 4 listened to

[4] 19 out of 140 data points were missing due to some participants not consuming all of their rewards.

music first and 10 ate chocolate first. This pattern of first-reward-consumed was not different from that expected by chance (χ^2=0.190, p=0.909).

During abstinence, in the dependent group 11 participants smoked first, 2 listened to music first and 7 ate chocolate first and in the occasional group 4 smoked first, 7 listened to music first and 9 ate chocolate first. This pattern of first-reward-consumed was different from that expected by chance (χ^2=6.294, p=0.043). During abstinence, the dependent group, compared to the occasional group, were more likely to smoke first (OR=4.889) and less likely to listen to music (OR=0.206) or eat chocolate (OR=0.658) first.

2.3.7 *Correlations*

No hypothesized correlations reached significance at the adjusted alpha level of <0.001.

2.4 Discussion

This study used a variety of indices to investigate the effects of nicotine dependence and abstinence on reward processing of cigarette and non-drug rewards. As hypothesised, I demonstrated that dependent smokers, compared with occasional smokers, were hypersensitive to cigarette reward across a variety of metrics. They made more choices for, pressed more for and reported more wanting and liking of a cigarette reward. However, there was not much evidence in favour of hyposensitivity to non-drug rewards in the nicotine dependence. The dependent smokers made significantly fewer choices for chocolate than occasional smokers but there were no significant group differences on button-pressing, wanting or liking for music or chocolate. Having said that, when investigating group differences despite a null interaction, occasional smokers pressed marginally harder than dependent smokers for chocolate during abstinence.

Dependent smokers and occasional smokers also exhibited different profiles in terms of their choices, average number of button-presses (BP), wanting and liking. Occasional smokers always chose, pressed

for, wanted and liked one of the non-drug rewards more than cigarettes. Contrastingly, dependent smokers never chose, pressed for, wanted or liked either of the non-drug rewards more than cigarettes. This is indicative of a difference in the balance of cigarette and non-drug reward processing between the two groups.

Twelve hour nicotine abstinence led to more cigarette choices and fewer music choices, when collapsed across groups. Contrary to my prediction, however, the effect of nicotine abstinence was not significantly moderated by group. Subsequent analyses showed that the interaction between smoking-condition and reward was only significant in the dependent group, but that should not be taken as evidence that the effect of abstinence was significantly different between the groups. Surprisingly, abstinence did not have a significant effect on dependent and occasional smokers' BP, wanting or liking of any reward. However, dependent smokers did show a different pattern of first-reward-consumed during abstinence compared with occasional smokers: dependent smokers were more likely to smoke first and less likely to listen to music first and eat chocolate first, however this was not the case in the ad libitum smoking condition.

2.4.1 Group differences between dependent and occasional smokers in the processing of cigarette and non-drug rewards

Many theories of addiction postulate that addicts are hypersensitive to drug rewards (Goldstein & Volkow, 2002, 2011; Robinson & Berridge, 1993, 2008). I found strong evidence for this in the comparison of dependent smokers with occasional, non-dependent smokers. Dependent smokers chose cigarettes significantly more than occasional smokers, despite the presence of alternative non-drug rewards, i.e. dependent smokers' relative preference for cigarettes was greater than that of the occasional smokers. This corroborates Hogarth's work which has shown a link between dependence level and choice of tobacco over chocolate (Hogarth, 2012; Hogarth & Chase, 2011, 2012). However, both Hogarth's data and my choice data could be explained by a concomitant hypersensitivity to drug

rewards and hyposensitivity to non-drug rewards, or alternatively just a hyposensitivity of non-drug rewards.

The button-pressing part of the task speaks to this concern. It was intended as a 'purer' measure of motivation for each reward separately, as in similar reward-based studies which have used button-pressing as a measure of motivation (Bühler et al., 2010; Perkins & Karelitz, 2013b). I observed a significant difference in BP for cigarettes between the groups, suggesting a group difference in the motivation to receive cigarettes. This putative difference in motivation to receive cigarettes could therefore potentially explain the group difference in the number of choices for chocolate. If the dependent smokers were more motivated for cigarettes than the occasional smokers, this would have led them to choose cigarettes more, and therefore choose the alternative options less.

Group differences in the self-reported wanting and liking data also support the notion of stronger processing of cigarettes in the dependent group. Dependent smokers, compared to occasional smokers, reported more wanting of cigarettes overall and also reported more liking when they consumed the first 'unit' of the cigarette reward. Hence, motivation for and self-reported wanting and liking of cigarettes were greater in the dependent group, which is potentially at odds with Robinson and Berridge (1993) who predicted that addiction is associated with a marked increase in motivation for drugs but not a corresponding increase in liking. Although, it may have been that the dependent group simply always liked smoking cigarettes more than the occasional group. A within-subjects investigation of 'wanting' and 'liking' cigarettes while smokers progressed to dependence would be required to properly examine this relationship.

This study provided much less evidence to suggest there were group differences in the way that dependent and occasional smokers process non-drug rewards. Occasional smokers did choose chocolate more times than dependent smokers; however this could more likely be explained by a group difference in the preference for the cigarettes, which would necessarily affect the number of choices for the other rewards. There were no significant group differences in BP or self-reported

wanting or liking for chocolate and music, which suggests that the dependent smokers were not hyposensitive to the non-drug rewards relative to occasional smokers. Furthermore, there were no differences in self-reported liking of music and chocolate between the groups in this study. This study therefore casts doubt upon the hypothesis that nicotine addiction is associated with problematic processing of non-drug rewards (Blum et al., 2000; Goldstein & Volkow, 2002, 2011; Koob & Le Moal, 1997). On the other hand, the occasional smokers pressed marginally harder for chocolate than the dependent smokers during abstinence, which could suggest that dependent smokers had impaired motivational processing for non-drug reward during abstinence. The fact that I conducted the power analysis incorrectly and therefore underpowered my study (in order to detect a small effect (f=0.1)) may have contributed to this result: a difference that tended to go in the hypothesised direction but failed to reach the traditional significance level.

Bühler et al. (2010) reported that their dependent smokers showed a different profile of reward processing for money and cigarettes compared to occasional smokers. Likewise, I found analogous differences in the smokers' profiles of reward processing. The dependent smokers chose cigarettes more than the alternatives and worked for, wanted and liked all the rewards, similarly. Contrastingly, the occasional smokers chose, worked for, wanted and liked one of the alternatives more than cigarettes. These results support the hypothesis that addiction is associated with a disrupted *balance* in the processing of drug and non-drug rewards (Bühler et al., 2010), across a range of metrics. However, this disrupted balance appears to be driven mostly by differences in the processing of cigarettes, rather than non-drug rewards.

Like Bühler et al. (2010), I investigated the effect of reward-magnitude on cigarette and non-drug reward processing. I found that large rewards were chosen and pressed for more than small rewards, thus demonstrating that the magnitude of the reward successfully affected behaviour. However, similar to Bühler et al. (2010), I did not find any interactions involving reward-magnitude for choice and BP data. Hence, nicotine dependence and abstinence did not moderate the effect of magnitude

on drug and non-drug reward processing on these metrics. However, the time taken to choose a reward did demonstrate an interactive effect of reward-magnitude with group and reward-type. While occasional smokers chose a large cigarette faster than a small cigarette this was not the case in the dependent smokers, perhaps suggesting a less value-based and more habitual process (Everitt and Robbins, 2005) when selecting a cigarette reward. However, given the null findings for choices and BP, this interpretation is highly speculative.

One important consideration is the lack of a non-smoker control group. It could be argued that the reason there were no clear differences in non-drug reward processing between the groups was because *both* groups had impaired non-drug reward processing, rather than neither. If only a small amount of nicotine consumption, or some pre-disposing factors, are required to cause deficient non-drug reward processing, then this could explain the potentially similar deficits. However, I believe this is extremely unlikely. The dependent smokers were smoking approximately 40 times as many cigarettes/day as the occasional smokers and the dependent smokers had been smoking 10 or more cigarettes/day for more than 6 years, so the disparity in nicotine consumption was huge. It is unlikely that a small amount of nicotine exposure could result in the same non-drug reward deficits as much greater nicotine exposure. Moreover, neither group really showed *deficits*, e.g. they both chose and worked for music and chocolate much more than paper. However, the only way to check these possibilities would have been to include a non-smoker control group.

2.4.2 The effects of 12 hour nicotine abstinence on the processing of cigarette and non-drug rewards

We found that at least 12 hours of nicotine abstinence led to more cigarette choices and fewer music choices, across both groups. My results suggest that abstinence increased relative preference for cigarettes and reduced relative preference for music. However, the reduction in choices for music could have been driven purely by an increase in the preference for cigarettes. Given there were no effects of abstinence on BP it is hard to conclude whether a change in motivation for cigarettes, music or both led to the change in choices observed here. Hence, the data cannot be interpreted as a

decrease in non-drug reward sensitivity during abstinence. However, what can be said is that the balance in the processing between cigarette and non-drug rewards was further perturbed by acute nicotine deprivation, across both groups.

It is surprising that there was not a three-way interaction between group, smoking-condition and reward-type. I predicted that 12 hour nicotine abstinence would affect the dependent smokers significantly more than the occasional smokers because abstinence would unveil an impaired mesocorticolimbic dopamine system only in the dependent smokers (Dawkins et al., 2006). The occasional smokers smoked so infrequently that the smoking-condition did not significantly affect their time-since-last-smoked, hence it is unlikely that acute abstinence unveiled this impaired system. Notably, visual inspection of figure 2.3a also suggests the effects of abstinence on cigarette and music choices were larger in the dependent group than the occasional group. Furthermore, when investigating the reward by smoking-condition interaction within each group separately, it was only apparent in the dependent group. However, clearly the difference between these differences was not significant, so it should not be interpreted as such and I may have needed more power in order to detect the three-way interaction.

Like Buhler et al. (2010), I did not find a significant increase in BP for cigarettes in either group during abstinence compared with ad libitum smoking. This is surprising given abstinence has been associated with increased cigarette self-administration (Barrett, 2010; Kollins et al., 2013). Visual inspection of figure 2.3b suggests that there was some increase in BP for cigarettes during abstinence in the dependent group, so it may have, again, been an issue of power and task sensitivity that I did not detect the effect.

There is substantial evidence that nicotine abstinence can affect non-drug reward processing in dependent smokers, as described in sections 1.5.2 and 2.1.2. Nicotine deprivation has been associated with reduced motivation for (Al-Adawi & Powell, 1997; Dawkins et al., 2006; Powell et al., 2002) and learning about monetary reward (Pergadia et al., 2014), and reduced motivation for music reward

(Perkins & Karelitz, 2013b). It is therefore unexpected that there were no reductions in BP for music or chocolate during abstinence in the dependent group. However, my results are consistent with Kalamboka et al. (2009), who used an adaptation of the CARROT (Al-Adawi & Powell, 1997), and did not find a reduction in motivation during abstinence. Bühler et al. (2010) also found null effects of abstinence on BP and associated BOLD response to a monetary reward. The discrepancies between these studies may be due to a number of reasons. Firstly, Pergadia et al.'s (2014) task indexed reward learning while the others (including the DReaM-Choice) indexed incentive motivation via response vigour. Secondly, many of the tasks provided money as a reward, while ours and did not. Thirdly, given the effect of nicotine deprivation on cognition (Shiffman, Paty, Gnys, Kassel, & Elash, 1995), the different cognitive requirements of the tasks may have contributed to discrepancies. Fourthly, and perhaps most importantly, the studies differed in terms of sample size and thus power to detect an effect. However, these reasons do not cleanly differentiate which studies found an effect of nicotine abstinence on non-drug reward processing and those that did not. Given findings from previous research, visual inspection of figure 2.3a and b, and the, albeit null, results described in section 2.3.3 which went in the expected direction, I suspect that with more power, I may have detected the three way interaction.

However, the groups did behave differently in their reward consumption during abstinence, but not during ad libitum smoking. Abstinence led the dependent smokers, relative to the occasional smokers, to smoke first, in lieu of alternative rewards. Whereas, following ad libitum smoking, the two groups consumed a similar number of each reward first. This suggests that acute abstinence had a differential effect on the groups; it made only the dependent smokers more likely to consume cigarettes before other rewards. The natural consummatory phase was therefore able to detect the disrupted balance of reward consumption in the dependent group, relative to the occasional group, associated with acute nicotine abstinence.

2.4.3 Self-reported anhedonia, craving and withdrawal

Previous research has found reliable increases in self-reported anhedonia during acute nicotine abstinence in dependent smokers (Dawkins et al., 2006; Powell et al., 2002) and my data sit well with these results. Dependent smokers had significantly higher anhedonia when abstinent compared to ad libitum smoking, before any rewards (including cigarettes) were consumed. Furthermore, the abstinence manipulation was successful in that it increased craving and withdrawal symptoms in the dependent smokers only.

2.4.4 Strengths and limitations

That both groups chose and worked for all the non-paper rewards significantly more than paper demonstrated both groups were motivated by cigarettes, chocolate and music. Moreover, the increased number of choices and larger BP for large rewards relative to small rewards confirmed cigarettes, chocolate and music worked well as rewards. The conjunction of choices and BP combined a more ecologically valid dependent variable tapping 'relative preference' with a variable that represented a 'purer' measure of motivation, respectively. Furthermore, the measurement of self-reported wanting and self-reported liking, alongside choices and BP, provided a complementary set of reward processing metrics. The DReaM-Choice worked well in distinguishing dependent and occasional smokers and both the choice variable and first-reward-consumed were sensitive to an acute abstinence manipulation.

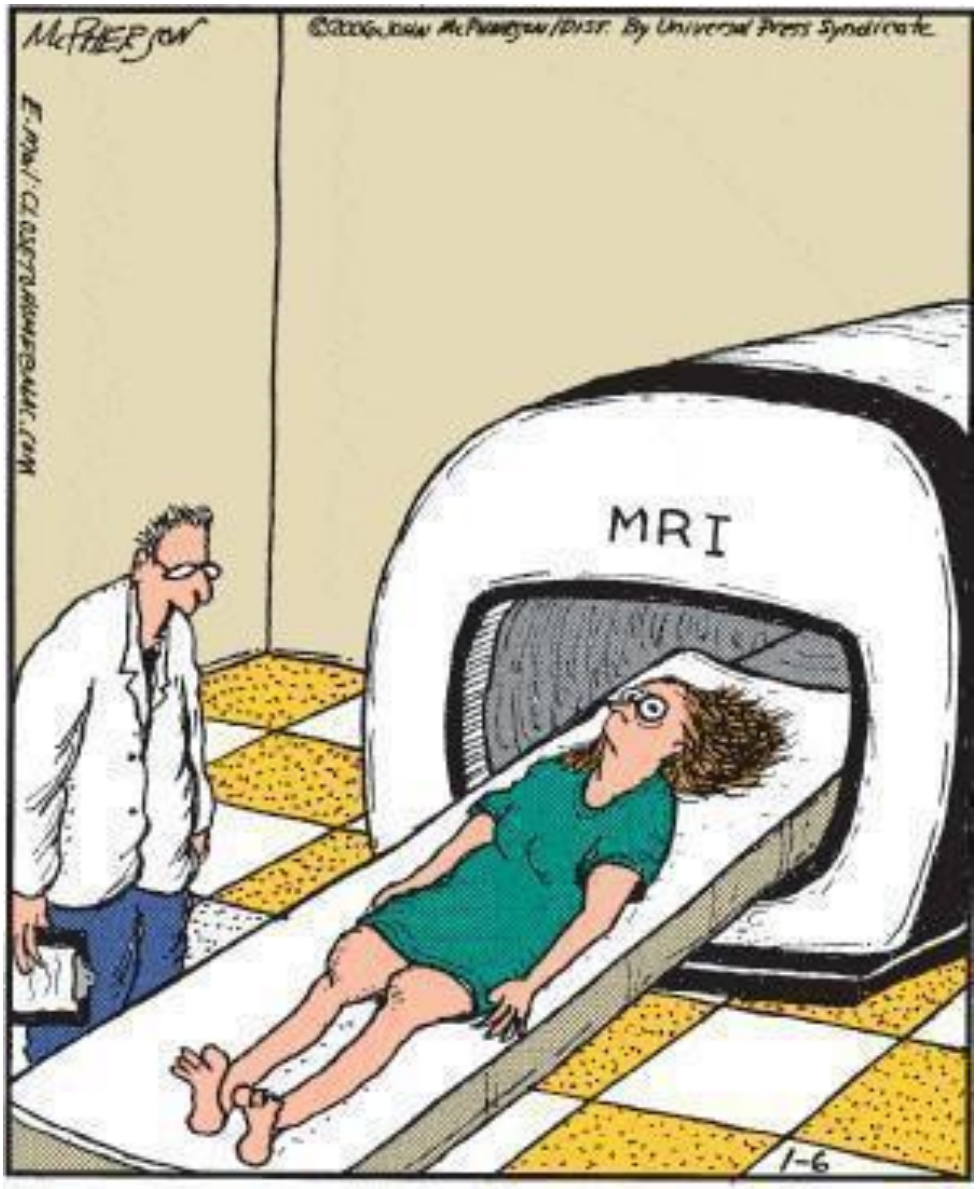
However, this study has several limitations. Firstly, the power analysis was conducted incorrectly so I did not have adequate power to detect a small effect size (f=0.1). In relation to the BP data, I cannot be sure this was as independent a measure of motivation as I would have liked. Participants chose each reward a different number of times and therefore the number of data points contributing to BP data was different for each participant, which could be a problem if familiarity of the reward affected BP. Furthermore, BP may not have been a very sensitive measure of motivation, as even cigarette BP

was not affected by abstinence. In relation to the liking data, only one liking rating for each person was analysed for each reward type due to satiation effects. Furthermore, I did not constrain the order in which participants consumed their rewards. The effect of nicotine abstinence on the liking of non-drug rewards would have been reduced in participants who consumed a cigarette before their music and chocolate; so this may have contributed to the non-significant effect of abstinence on liking. Finally, it is possible that the dependent smokers 'puff' harder on the cigarette and therefore get a larger dose of nicotine for each quarter of the cigarette smoked, which could bias the results.

2.4.5 Conclusions

This study set out to test the effects of nicotine dependence and acute abstinence on the processing of both cigarette and non-drug rewards. I developed a novel task to index various aspects of reward processing. I found evidence for a hypersensitivity to cigarettes but did not find any conclusive evidence for a hyposensitivity to non-drug rewards, across many components of reward processing. However, the dependent and occasional smokers had different cigarette and non-drug reward processing profiles consistent with a similar study (Bühler et al., 2010). Importantly, the results indicate that the DReaM-Choice task and subsequent consumption procedure worked well and successfully distinguished dependent from occasional smokers.

Chapter 3: The neural correlates of cigarette and non-drug reward anticipation and feedback in dependent and occasional smokers



"OK, Mrs. Dunn. We'll slide you in there, scan your brain, and see if we can find out why you've been having these spells of claustrophobia."

3.1 Introduction

Results from chapter 2 suggested that relative preference for, motivation for, and wanting and liking of cigarettes was greater in dependent compared with occasional smokers. There was little evidence for hyposensitivity to non-drug rewards in dependent relative to occasional smokers. Chocolate was chosen fewer times by dependent smokers compared with occasional smokers. However, this could have been driven simply by a greater motivation for cigarettes in the dependent smokers which necessarily reduced the number of choices for alternatives. On the other hand, there were consistent differences between the groups in their profiles of cigarette and non-drug reward processing. Surprisingly, the effect of abstinence that I found on choices for rewards was not moderated by group and I found a null effect of abstinence on BP. Hence, I decided to continue investigating differences between dependent and occasional smokers in their 'normal states', without any forced nicotine deprivation.

Overall, results described in chapter 2 implied that dependent and occasional smokers differ behaviourally in their profiles of drug and non-drug reward processing and that this is likely due to differences in cigarette rather than non-drug reward processing. On the other hand, as described in chapters 1 and 2, previous research has suggested differences between smokers and non-smokers on non-drug reward processing. I aimed to extend my findings in chapter 2 by using a reward anticipation task which does not involve a choice stage and therefore measures motivation in a potentially 'purer' way. Furthermore, I aimed to investigate the neural substrates underpinning the anticipation of and feedback concerning cigarette and non-drug reward and examine group differences in these neural responses.

3.1.1 Anticipation of reward

Electrophysiological studies in animals have shown that mesocorticolimbic dopamine neurons exhibit phasic firing when they receive unpredicted rewards or when cues predict anticipated reward (Schultz,

2002). These signals are critical in indicating salient, appetitive events so that animals can survive through consumption of food and pass on their genes through sexual reproduction.

As described in chapter 1, the neurobiology underlying anticipation of and feedback about reward in humans has frequently been investigated using the monetary incentive delay task (MIDT) (Knutson et al., 2000). The structure of the traditional MIDT is shown in figure 1.6. The MIDT has been used to investigate reward processing deficits in a number of clinical populations, including those diagnosed with depression (Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008), schizophrenia (Juckel et al., 2006) and attention-deficit-hyperactivity-disorder (Scheres, Milham, Knutson, & Castellanos, 2007). These results have been critical in informing theories concerning reward processing deficits in different disorders. In essence, the MIDT has become a gold standard for examining neural sensitivity to reward. The MIDT also provides behavioural measures of motivation for reward in terms of the reaction time to respond to the target.

3.1.2 MIDT in addiction research

In chapter 1 I described the studies utilising the MIDT with cigarette smokers which I am aware of. To briefly recap, there is some evidence which suggests that nicotine dependence is associated with reduced striatal anticipatory BOLD response to monetary reward (Luo et al., 2011; Peters et al., 2011; Rose et al., 2013), although one study reported no difference between smokers and non-smokers in this response (Jansma et al., 2013). One of these studies observed greater feedback BOLD response to monetary reward in the left cingulate in smokers relative to non-smokers (Rose et al., 2013), while another reported a null difference between adolescent smokers and non-smokers during feedback (Peters et al., 2011). Differences in the stage of addiction, acute abstinence/drug effects, comorbid disorders and task methodologies may account for some of these discrepancies (Balodis & Potenza, 2015).

3.1.3 Anticipating cigarette rewards

However, very few studies have investigated the neural correlates of cigarette anticipation. This is surprising given that reward processing of the actual drug involved in addiction is likely to play an important role in the maintenance of addiction. Understanding how nicotine dependence is associated with behavioural and neural processing of cigarette rewards, as well as non-drug rewards, will hopefully contribute to a better awareness of which processes to tackle therapeutically.

As described in earlier chapters, Buhler et al. (2010) investigated behavioural and neural responses in relation to cigarette and monetary reward in dependent and occasional smokers. On each trial, participants were informed whether they could win cigarettes or money, they waited for 2s (i.e. anticipation), then they repeatedly pressed a button in order to earn that reward and were subsequently given feedback about whether they had won the reward or not. Behaviourally, dependent smokers exhibited similar motivation (number of button-presses) for cigarettes and money; occasional smokers exhibited greater motivation for money compared with cigarettes. There were no significant group differences in terms of motivation for either cigarettes or money; however, the differences were in the expected direction (with an effect size of d=0.29) and with larger samples they may have detected significant group differences. Mirroring the behavioural results, opposing profiles of anticipatory BOLD response were seen. Occasional smokers had greater anticipatory BOLD response to money compared with cigarettes in frontal and striatal regions, while dependent smokers had similar anticipatory BOLD responses to money and cigarettes. The only group difference observed was greater activation during anticipation of monetary reward in the occasional smokers compared with the dependent smokers, although the brain coordinates of this effect were not reported.

Furthermore, they found that positive feedback about rewards recruited the anterior insula but there was no effect of group or reward type on this component of reward processing. Interestingly, these authors reported no effects of 36 hours of abstinence on anticipatory or feedback response to cigarette and monetary rewards. However, a more recent study did observe augmentation and

reduction of cigarette and monetary reward anticipatory BOLD responses, respectively, in the striatum following acute abstinence (Sweitzer et al., 2013). Overall, the results of Buhler et al. (2010) suggest that the processing of cigarette rewards may not significantly differ between dependent and occasional groups and that the balance between cigarette and non-drug reward processing within each population may be more important.

3.1.4 Different types of reward

These cigarette-based studies, along with others which have used social rewards in modified MIDTs (Izuma, Saito, & Sadato, 2008; Rademacher et al., 2010), have suggested that similar reward related regions are activated when anticipating money as well as other types of reward, particularly striatal regions (Knutson & Greer, 2008). The concept of striatal activation as a common currency for a reward's motivational value was supported by a recent study that investigated anticipatory BOLD response to erotic and monetary reward (Sescousse, Li, & Dreher, 2014). They demonstrated that both rewards activated the same reward related brain regions and that behavioural motivation, as assessed by reaction time, correlated with striatal BOLD response for each reward type. Similarly, a recent meta-analysis investigating reward feedback showed that money, food and erotic rewards recruit a common set of brain structures: ventromedial prefrontal cortex, ventral striatum, amygdala, anterior insula and mediodorsal thalamus (Sescousse et al., 2013). However, there were some regions which were more robustly activated by certain rewards, e.g. erotic rewards recruiting the insula more than monetary and food rewards.

These studies have demonstrated that anticipation of and feedback about various types of rewards recruit similar (although not necessarily identical) reward related brain regions. Knutson & Greer (2008) conducted a meta-analysis, using the many MIDT studies previously published, on which brain regions are usually activated by anticipation of and feedback about monetary reward (relative to no reward) (these regions are described in table 3.1). Given that money and other rewards activate similar brain regions within the MIDT framework, I used the regions from this meta-analysis as a prior

regions of interest (ROI). This allowed me to conduct more sensitive ROI analyses as well as more exploratory whole brain analyses.

A potential problem with money as a comparator non-drug reward, as described in chapter 1, is that it is not a primary or consummatory reward, while cigarettes are. Hence money may not be the ideal comparison reward for cigarettes and any differences in reward processing could, theoretically, result from this discrepancy (Sescousse et al., 2010). Moreover, money can be exchanged for cigarettes, or other rewards, making its meaning ambiguous. Therefore, I aimed to compare reward processing of cigarettes with another consummatory reward, which was successfully used in chapter 2, music.

3.1.5 Summary and hypotheses

In summary, the MIDT is a well-validated task that provides a neural measure of reward sensitivity, as assessed by anticipatory and feedback BOLD responses in specific brain regions (Knutson & Greer, 2008), and a behavioural measure of motivation, as assessed by reaction time. The results reported in chapter 2 suggested that dependent smokers, relative to occasional smokers, may have enhanced cigarette but unimpaired non-drug reward processing. Furthermore, dependent smokers appeared to have augmented cigarette reward processing relative to non-drug reward processing, and vice-versa for occasional smokers. However, my assessment of reward processing in chapter 2, using the DReaM-Choice task, was purely behavioural and may not have provided as pure a measure of motivation as I would have liked, as described in section 2.4.4. Thus the impetus for this current study was that the MIDT may provide a more sensitive assay of reward processing in that: (1) it provides neural outcomes and (2) does not involve a choice stage, so the behavioural outcome variables may provide a 'purer' measure of motivation.

Previous research has often shown reduced striatal activation during anticipation of monetary rewards in dependent smokers compared with controls, although this has not always been the case. Of the studies that reported feedback BOLD results, null differences were usually reported between smokers and controls. However, only a handful of studies have investigated the behavioural and

neural processing of cigarette and non-drug rewards concomitantly. Only one study has compared anticipatory behavioural and neural responses to cigarette and monetary reward in dependent and occasional smokers (Bühler et al., 2010). I wanted to extend this study to the MIDT framework, use only consummatory rewards and build on my results from chapter 2. Hence I used the MIDT but replaced monetary reward with cigarette and music rewards.

I based my hypotheses on the findings from chapter 2, from previous MIDT research with cigarette smokers and from the iRISA theory of addiction (Goldstein & Volkow, 2011). Specifically, it was hypothesised that dependent smokers, compared with occasional smokers, after ad libitum smoking, would:

1. Have greater behavioural motivation for cigarettes, but there would be no evidence for a group difference in behavioural motivation for music.
2. Have stronger BOLD responses when anticipating and receiving feedback about cigarettes and weaker BOLD responses when anticipating and receiving feedback about music, in reward related brain regions (Knutson & Greer, 2008).

3.2 Methods

3.2.1 Participants

A mixed factorial design was used with a between-subjects factor of group (dependent and occasional) and a within-subjects factor of reward (cigarettes, music and no reward). 22 dependent (3 women) and 20 occasional (6 women) cigarette smokers took part in the study. Power analyses are difficult to compute for fMRI studies so the number of participants was based on a similar previous study (Bühler et al., 2010).

Inclusion and exclusion criteria were very similar to those in chapter 2 with some minor changes to increase the rate of recruitment and to meet MRI requirements. Inclusion criteria were: (1) smoke, on average, ≥10 cigarettes/day (for dependent smokers) or 0.5-5 cigarettes/week (for occasional

smokers[5]); (2) have an FTND score ≥5 (for dependent smokers[6]) or 0 (for occasional smokers); (3) aged 18-50; (4) be right-handed; and (5) have normal vision or corrected-to-normal vision with contact lenses.

Exclusion criteria were: (1) have been a regular, daily cigarette smoker in the past (for occasional smokers); (2) seeking treatment for a mental health problem; (3) using psychiatric medication; (4) use of an illicit drug once per week or more; (5) using a pharmacotherapy to quit smoking; and (6) any MRI contraindications (e.g. metal implants, claustrophobia).

Participants were recruited through advertisements in the university, on Gumtree and in Exeter bus station. Participants were reimbursed £10/hour. The study was approved by the University of Exeter Ethics Committee.

3.2.2 Assessments

3.2.2.1 Adapted Incentive Delay Task (AIDT) (figure 3.1)

We based the structure of the task on the MIDT (Knutson et al., 2000) but made several adaptations: there were two types of reward trial (cigarette and classical music), there was no variation in the magnitude of the rewards and there were no loss trials. The latter two adaptations were based on a previous study and done in order to increase the power of the task in a short space of time (van Hell et al., 2010).

The task consisted of 99 trials, 33 were cigarette trials, 33 were music trials and 33 were no reward trials. Each trial lasted an average of 9s, ranging from approximately 6.5s to 11s; the length of each trial was partially determined by the participant's reaction time in response to the target. The whole task took approximately 15 minutes.

[5] Note, in chapter 2 this criterion was 0.25-5 cigarettes/week.
[6] Note, in chapter 2 this criterion was ≥6 and dependent smokers had to meet DSM-5 criteria for 'severe' tobacco use disorder

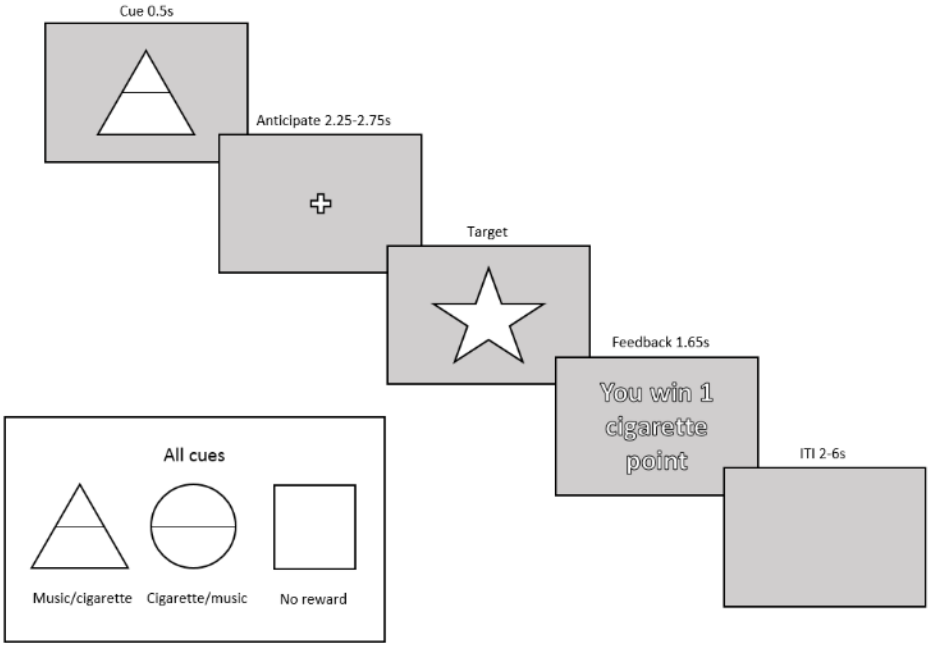


Figure 3.1 A diagrammatic representation of the adapted incentive delay task (AIDT). First, a cue was presented for 0.5s providing information about which reward is available, then there was an anticipation phase of 2.25-2.75s, then a target was presented and responded to, then feedback (dependent on the reward available and whether the previous response was quick enough) was given for 1.65s, and finally a 2-6s inter-trial-interval (ITI) = occurred.

At the start of each trial, a cue signalling the opportunity for cigarette reward, music reward or no reward was shown for 0.5s. A triangle or circle with a line through it signalled either cigarette or music; these were counterbalanced across participants. An empty square signalled no reward. Subsequently, during 'anticipation', a fixation cross was presented for 2.25-2.75s. Then the star-shaped target appeared, which participants were instructed to respond to as quickly as possible, by pressing a button near their right thumb. If participants pressed the button within the target time limit, they would win a reward point (so long as it was a reward trial). Subsequently feedback ('you win 1 music point', 'you win 1 cigarette point' or 'you win nothing') was given for 1.65s. Finally an inter-trial-interval (ITI) of 2-6s was presented before the next trial.

Prior to scanning, participants completed a practice AIDT so that they understood how the task worked and so that target time limits could be created. Two thirds of the trials had a target time limit that was their mean practice reaction time plus 400ms (van Hell et al., 2010), so that these trials were easy. The other third of the trials had a target time limit that was 150ms or their mean practice time

minus 400ms, whichever was larger, so that these trials were very difficult. This meant that on approximately one third of the trials, participants failed to respond to the target in time, which it was hoped would increase task engagement. The main behavioural outcome variable of the AIDT was reaction time (time taken to press the target), which assessed motivation for the reward.

The participants were told that the number of points they won determined how many cigarettes they could smoke and how much music they could listen to in a 20 minute period post-scanning. However, given the task was made so that all participants won approximately the same amount of points, all participants were given 1 cigarette and 8 minutes of music. In the first part of the 20 minute consumption period, participants listened to the music in the scanner and rated each 20s clip from 1 ('not at all pleasant') to 7 ('very pleasant'). Second, outside the scanner, participants had the option to smoke one cigarette and rated each quarter of a cigarette on the same scale.

I chose a set of classical music clips as rewards that are rated as 'pleasant' and have been used in previous research (Menon & Levitin, 2005). I chose this music because I wanted to further equate the two rewards; cigarettes were always Marlboro Golds (Lights) and music was always specific classical music, e.g. Mozart's Eine Kleine Nachtmusik. The presentation of the actual music always occurred approximately 20 minutes after the AIDT finished and no other music was heard in the scanner beforehand.

3.2.2.2 Self-rated assessments

Trait measures

Temporal experiences of pleasure scale (TEPS)

As described in section 2.2.2.2

Barratt impulsiveness scale (BIS) (Patton & Stanford, 1995)

This scale of impulsivity consisted of 30 items rated from 1 ('rarely/never') to 4 ('almost always/always'). There were three subscales: attentional, non-planning and motor. Higher scores reflected greater impulsivity.

Beck depression inventory (BDI-II) (Beck et al., 1996)

As described in section 2.2.2.2

Behavioural activation/inhibition systems scale (BIS/BAS) (Carver & White, 1994)

This scale activation and inhibition consisted of 24 items rated from 1 ('very true for me') to 4 ('very false for me'). There were four subscales: drive, fun-seeking, reward responsiveness and inhibition. Higher scores reflected greater behavioural activation (for the first three subscales) or inhibition (the last subscale).

Brief sensation seeking scale (BSSS) (Hoyle, Stephenson, Palmgreen, Lorch, & Donohew, 2002)

This scale of sensation-seeking consisted of 8 items rated from 1 ('strongly agree') to 5 ('strongly disagree'). Higher scores reflected greater sensation seeking.

Cigarette dependence scale (CDS-5) (Etter, Le Houezec, & Perneger, 2003)

This scale of cigarette dependence consisted of 5 items. Higher scores reflected greater cigarette dependence.

Fagerstrom test for nicotine dependence (FTND) (Heatherton et al., 1991)

As described in section 2.2.2.2

DSM-5 Tobacco use disorder.

As described in section 2.2.2.2

State measures

Snaith Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995)

As described in section 2.2.2.2

Tobacco craving questionnaire - short form (TCQ-SF) (Heishman, Singleton, & Pickworth, 2008)

This scale consisted of 12 items that were rated 'right now' from 1 (strongly disagree) to 7 (strongly agree). There were four subscales: emotionality, expectancy, compulsivity and purposefulness. Higher scores reflected greater tobacco craving.

Minnesota Nicotine Withdrawal Scale (MNWS) (J. Hughes & Hatsukami, 2007)

As described in section 2.2.2.2

3.2.2.3 *Other assessments*

Spot-the-word (Baddeley et al., 1993)

As described in section 2.2.2.3

Carbon monoxide

As described in section 2.2.2.3

3.2.3 Procedure

Participants attended one 2 hour testing session. Participants were in their 'normal' state; they were allowed to smoke beforehand if they wished[7]. First, participants provided a carbon monoxide (CO) reading, in order to indirectly assess their recent tobacco consumption, and then completed half of the trait questionnaires (BIS/BAS, BSSS, TEPS) and all of the state questionnaires. They were shown both a Marlboro Gold cigarette and heard a small clip (5s) of the classical music, so that they knew what rewards they were earning. Participants were then trained on how to complete the AIDT, which also provided the target time limit for use in the scanner, as described above. Subsequently they completed the AIDT in the scanner. They then listened to the music that they had won in the scanner,

[7] The time-since-last-smoked for each group is described in table 3.2 and section 3.3.2

left the scanner and, if they wished, smoked the cigarette they had won. Finally, they completed the other half of the trait questionnaires (spot-the-word, BDI, BIS).

3.2.4 Image acquisition

Neuroimaging data were collected on a Philips 1.5T scanner with an 8 channel sense head coil using echo-planar imaging. For functional scans, the following parameters were used: repetition time (TR) = 3s, echo time (TE) = 50ms, flip angle = 90^{o}, voxel size = 3mm isotropic, slice thickness = 3mm, number of slices in a volume = 36, slice order = ascending, slice orientation = 30^{o} tilt from the anterior commissure – posterior commissure line, field of view (FOV) = 240mm X 240 mm X 108mm. Slices were tilted in this way in an attempt to reduce drop out in the orbitofrontal cortex (Deichmann, Gottfried, Hutton, & Turner, 2003). This resulted in the whole brain not being scanned; small sections of the superior parietal and posterior frontal lobes were excluded. This was not considered problematic as I was specifically interested in reward-related brain regions (e.g. striatum and midbrain) (Knutson & Greer, 2008).

3.2.5 ***fMRI data analyses***

fMRI data were taken from the scanner computer in PAR REC format. These were transformed into analyse format using MRI Cro (http://www.mccauslandcenter.sc.edu/mricro). Subsequently, all data were analysed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm). The first five volumes of each functional scan were discarded due to T1 saturation effects; the task started 15s after the scanner started. 2nd degree B-Spline interpolation was used to realign all functional volumes to the mean volume. Each person's structural image was co-registered to their mean functional volume. Subsequently, a slice timing correction was carried out on the functional volumes using SPM12's default settings. Then, the co-registered structural image and the functional volumes were spatially normalised into Montreal Neurological Institute (MNI) space using the SPM standard template and affine regularisation. Note, tissue probability maps were not used to spatially normalise because I did

not have scans of the entire brain. Finally, the functional volumes were smoothed with an isotropic Gaussian kernel for group analysis (8mm full-width at half-maximum; voxel size = 3mm isotropic).

Functional data were analysed using the general linear model. Data analysis was performed by modelling the different events using boxcar functions convolved with the haemodynamic response function. The events were modelled as follows: 'cigarette cue + anticipate'; 'music cue + anticipate'; 'no reward cue + anticipate'; 'target'; 'cigarette win feedback'; 'cigarette do not win feedback'; 'music win feedback'; 'music do not win feedback'; and 'no reward feedback' (i.e. 'do not win feedback'). This allowed me to investigate the effect of reward type on anticipatory and feedback processing. The cue and anticipate events were combined to increase the length of this event in order to enhance the BOLD response. I did not observe the expected anticipatory activation without combining the cue and anticipate events. Movement parameters were also included in the model, as regressors of no interest.

At the first level, these contrasts were created: 'cigarette anticipate > no reward anticipate'; 'music anticipate > no reward anticipate'; 'cigarette anticipate > music anticipate'; 'music anticipate > cigarette anticipate'; 'cigarette win feedback > no reward feedback'; 'music win feedback > no reward feedback'; 'cigarette win feedback > music win feedback'; and 'music win feedback > cigarette win feedback'. All of the 'anticipate' contrasts used the 'cue + anticipate' event.

Subsequently, second-level random-effects models were used to investigate significant results in the entire sample and differences between the dependent and occasional smoker groups. A one-sample t-test was used to examine whether cigarette and music anticipation, relative to no reward anticipation, produced reward-related BOLD responses, in the entire sample. Independent t-tests were used to test whether dependent and occasional smokers' BOLD responses differed on cigarette or music anticipation, relative to no reward anticipation. One-sample t-tests were carried out, within each group, to examine whether cigarette or music anticipation produced greater activation, using

'cigarette > music' and 'music > cigarette' contrasts, in other words, these tests investigated the balance of drug and non-drug anticipatory reward processing within each group.

Similarly, a one-sample t-test was used to examine whether cigarette and music win feedback, relative to no reward feedback, produced reward related BOLD responses, in the entire sample. Independent t-tests were used to test whether dependent and occasional smokers' BOLD responses differed on cigarette or music win feedback, relative to no reward feedback. One-sample t-tests were carried out, within each group, to examine whether cigarette or music win feedback produced greater activation, using 'cigarette > music' and 'music > cigarette' contrasts, in other words these tests investigated the balance of drug and non-drug feedback reward processing within each group.

These tests were first carried out in specific regions of interest (ROI) and then across the whole brain. The ROI analyses were informed by a meta-analysis concerning brain regions significantly activated during reward anticipation and feedback in the MIDT (Knutson & Greer, 2008). The eight 'win vs. no win anticipation' and seven 'win vs. no win feedback' regions were first transformed from Talairach to MNI coordinates (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html). They are presented in table 3.1. The regions of interest were then defined using MarsBar (http://marsbar.sourceforge.net/) as spheres with these co-ordinates (table 3.1) as the centre and a radius of 4mm (Jia et al., 2011). The ROIs were combined into a single mask and included in the second level models in SPM. A family-wise-error (FWE) correction was used across the whole mask with an alpha of 0.05. If there were any group differences, I expected them to be in regions that have previously been shown to be sensitive to reward anticipation or feedback. However, I also conducted whole brain analyses to examine if there were any activations which were not in the pre-defined ROIs. I used a FWE correction with an alpha of 0.05 for whole brain analyses.

Correlations were conducted between the average BOLD response in each of the significant ROIs for cigarette or music anticipation and feedback and: (1) number of cigarettes smoked/day; (2) time-since-last-smoked; (3) CO; (4) average response time on cigarette trials; and (5) average response

time on cigarette trials minus average response time on no reward trials, within each group. The alpha value was set to 0.005 to account for multiple tests.

Table 3.1 Region of interests (ROI) taken from Knutson & Greer (2008). Each ROI was spherical with these central coordinates and a region of 4mm, as in Jia et al. (2011).

Region	x	y	z
Anticipatory ROIs			
Right ventral striatum	11	11	-1
Right thalamus	5	-9	10
Right insula	34	22	-5
Left ventral striatum	-12	10	-2
Left thalamus i	-7	-22	6
Left thalamus ii	-3	-22	8
Left medial frontal gyrus	-1	-5	53
Left culmen	-1	-61	-13
Feedback ROIs			
Right ventral striatum	13	13	-11
Right caudate	9	19	0
Right subcallosal gyrus	9	5	-13
Right parahippocampal gyrus	23	-21	-10
Left ventral striatum	-8	9	-8
Left amygdala	-16	0	-16
Left parahippocampal gyrus	-19	-25	-10

3.2.6 Behavioural statistical analyses

All behavioural data were analysed using IBM Statistical Package for Social Sciences (IBM SPSS version 21). The data were analysed using the general linear model. In order to explore significant interactions, a Bonferonni correction was applied to post hoc comparisons via the syntax in SPSS.

Self-report data were analysed using independent t-tests and Mann-Whitney U-tests when the residuals were not normally distributed.

Reward liking was analysed in the same way as in chapter 2. The liking of the first cigarette quarter and the liking of the first clip of music were analysed using a mixed effects model to account for missing data. Group and reward (and their interaction) were entered as fixed effects and the intercept

was allowed to vary randomly. This missing data was due to some occasional smokers not consuming the cigarette they won in the AIDT and a computer error that affected the presentation of music.

For the AIDT, any reaction times that were below 100ms were excluded as they were likely produced by chance; any missing trials were not included in the RT analysis. The remaining RTs were then $\log_{10}$ transformed so that their residuals were more normally distributed. The proportion of successful target hits for each reward type was calculated from the RT≥100ms trials. Both RT and proportion hit data were then analysed using mixed-design ANOVAs with a between-subjects factor of group (dependent and occasional) and a within-subjects factor of reward (cigarette, music and no reward). When sphericity was violated, the Greenhouse-Geisser correction was used and corrected degrees of freedom were reported.

3.3 Results

3.3.1 Demographics (Table 3.2)[8]

Dependent smokers, compared with occasional smokers, had fewer years of education (t_{40}=2.404, p=0.021), marginally greater BDI scores (U_{36}=115.00, p=0.056), greater motor (t_{36}=3.427, p=0.002) and non-planning (t_{36}=3.059, p=0.003) impulsivity and lower inhibition on the BISBAS (t_{34}=3.032, p=0.005). Other demographic differences were non-significant.

Furthermore, the dependent smokers, compared with the occasional smokers, smoked more cigarettes/day (U_{40}=0.00, p<0.001), had greater FTND (U_{40}=0.00, p<0.001), CDS (U_{39}=0.00, p<0.001) and DSM (U_{40}=5.50, p<0.001) scores, started smoking at a younger age (t_{40}=2.404, p=0.021) and had made more quit attempts (U_{39}=72.50, p<0.001).

[8] CDS, number of quit attempts, BISBAS, BSS and TEPS data were missing for 1 occasional smoker; BDI and BIS data were missing for 2 occasional smokers; Spot the word data were missing for 8 occasional smokers; Age started smoking 10 or more per day, spot the word, BSSS and TEPS data were missing for 1 dependent smoker; BIS data were missing for 2 dependent smokers; BISBAS data were missing for 5 dependent smokers.

3.3.2 State Measures (Table 3.3)

All of the dependent smokers, apart from one, had smoked within the last 2 hours. The exception had smoked 13.75 hours ago. All of the occasional smokers, apart from one, had smoked 10 or more hours ago. The exception had smoked 7 minutes ago. The mean times-since-last-smoked for each group are shown in table 3.3. Regardless of whether these outliers were excluded ($U=0.000$, $p<0.001$) or not ($U=16.000$, $p<0.001$), dependent smokers had smoked much more recently than occasional smokers[9]. Dependent smokers also had a greater carbon monoxide reading ($t_{39}=7.203$, $p<0.001$) than occasional smokers.

Dependent smokers, compared with occasional smokers, had greater craving on all subscales of the TCQ ($ps\leq0.001$), greater withdrawal symptoms on the MNWS ($t_{28.147}=2.930$, $p=0.007$) and marginally greater anhedonia on the SHAPS ($t_{36.129}=2.868$, $p=0.092$).

3.3.3 AIDT behavioural outcomes

Reaction time (Figure 3.2)

There was an interaction between group and reward ($F_{2,\ 80}=3.992$, $p=0.022$) and a main effect of reward ($F_{2,\ 80}=10.570$, $p<0.001$).

Dependent smokers, compared with occasional smokers, were faster to respond on cigarette trials ($t_{40}=2.27$, $p=0.027$). There were no differences on music and no reward trials.

Both the dependent smokers ($t_{19}=2.583$, $p=0.043$) and the occasional smokers ($t_{21}=3.46$, $p=0.003$) were faster to respond on music compared with no reward trials. The dependent smokers ($t_{21}=3.75$, $p=0.001$), but not occasional smokers ($t_{19}=1.25$, $p=0.664$), were faster to respond on cigarette compared with no reward trials. There was a trend for dependent smokers to be faster to respond on

[9] Data for one dependent smoker's time-since-last-smoked was lost.

cigarette compared with music trials (t_{21}=2.23, p=0.088), while occasional smokers showed no difference (t_{19}=1.92, p=0.206).

Three participants were excluded from the fMRI analysis due to a missing structural scan and pre-processing errors (see footnote 12). Therefore, the behavioural analyses were carried out again with these participants excluded (i.e. listwise). This made no difference to the pattern of results.

Proportion of hits

There were no interactions or main effects.

Table 3.2 Group means (SD) for demographic data for dependent and occasional smokers.

	Dependent	Occasional
Age	28.45 (10.29)	23.10 (4.60)
Gender (m/f)	19/3	14/6
Years in education*	12.32 (2.75)	16.45 (2.74)
Spot-the-word	46.24 (6.02)	48.58 (6.26)
Cigarettes/day***	19.32 (5.70)	0.49 (0.04)
Cigarettes/week***	135.23 (8.51)	3.40 (1.37)
Age started smoking (years)*	15.45 (2.92)	17.55 (2.70)
Age started smoking 10 or more per day	17.00 (2.10)	NA
Tried to quit smoking (y/n)***	19/3	6/14
Number of quit attempts***	3.32 (4.24)	0.58 (1.17)
Length of most successful quit attempt (days)	8.92 (11.06)	12.40 (8.29)
FTND***	6.36 (1.05)	0.00
CDS-5***	19.77 (2.46)	6.42 (1.30)
DSM-5***	6.50 (2.69)	0.75 (1.02)
BDI^{o}	10.35 (8.59)	5.33 (5.42)
BISBAS drive	11.78 (2.73)	11.42 (1.89)
BISBAS fun-seeking	13.24 (1.78)	12.42 (2.12)
BISBAS reward responsiveness	17.00 (2.03)	16.95 (2.01)
BISBAS inhibition	17.06 (4.38)	21.26 (3.73)
TEPS anticipatory	39.11 (7.73)	39.81 (8.43)
TEPS consummatory	34.71 (7.88)	36.89 (5.14)
TEPS total	74.53 (12.84)	76.00 (2.73)
BSSS	31.05 (4.52)	29.42 (4.56)
BIS attentional	18.05 (4.48)	16.39 (2.81)
BIS motor**	27.35 (3.94)	23.06 (3.77)
BIS non-planning**	29.30 (4.79)	24.78 (4.26)
BIS total**	74.70 (11.05)	64.22 (8.22)
Like smoking one cigarette, in general (-10 to 10)	4.71 (1.18)	3.40 (0.47)
Like listening to classical music, in general (-10 to 10)	2.05 (1.19)	3.58 (1.14)
Days/week listen to classical music	1.33 (0.40)	1.55 (0.51)

*FTND Fagestrom test for nicotine dependence; CDS-5 Cigarette dependence scale; DSM-5 Diagnostic and statistical manual tobacco use disorder; BISBAS Behavioural activation/inhibition systems scale; TEPS Temporal experience of pleasure scale; BSSS brief sensation seeking scale; BIS Barratt impulsiveness scale. ***p<0.001, **p<0.01, *p<0.05, ^{o}p<0.1*

Table 3.3 Group means (SD) for state-measure self-report data for dependent and occasional smokers.

	Dependent	Occasional
Time since last smoked, including outliers (minutes)* **	61.43 (176.82)	7,220 (10,151)
Time since last smoked, excluding outliers (minutes)* **	23.25 (26.27)	7,599 (10,283)
Carbon Monoxide* **	12.45 (6.72)	2.20 (1.70)
TCQ emotionality **	10.59 (4.93)	5.70 (3.73)
TCQ anticipation* **	16.55 (3.54)	10.15 (2.76)
TCQ compulsivity* **	9.86 (4.80)	4.50 (2.21)
TCQ intention* **	14.05 (4.16)	7.80 (2.65)
TCQ total* **	51.05 (14.44)	28.15 (7.7)
MNWS **	8.68 (7.20)	3.80 (2.89)
SHAPS-original*	2.05 (1.73)	0.75 (1.16)
SHAPS-new*	25.27 (1.21)	22.75 (0.81)

***p<0.001, **p<0.01, *p<0.05, °p<0.1

TCQ Tobacco Craving Questionnaire; MNWS Minnesota Nicotine Withdrawal Scale; SHAPS Snaith Hamilton Pleasure Scale.

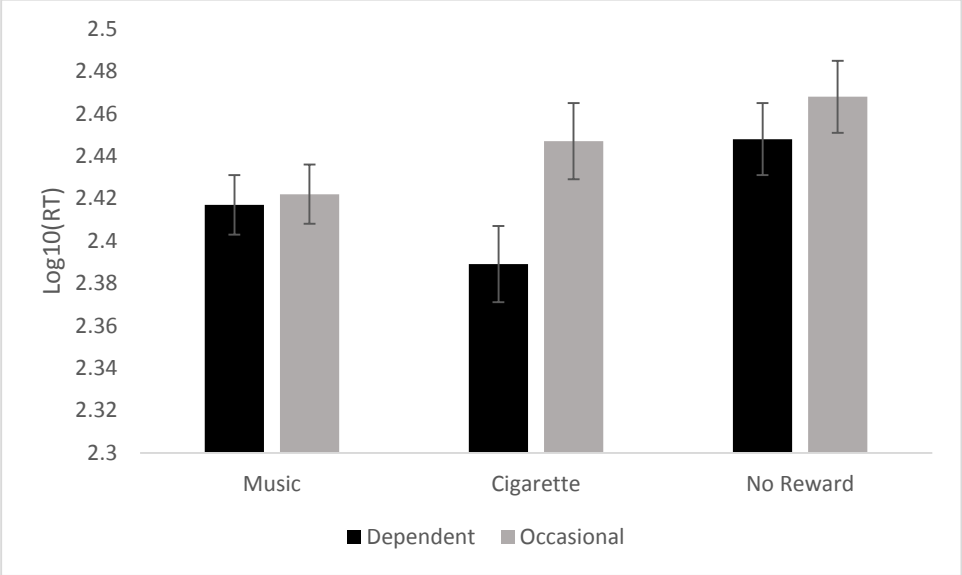


Figure 3.2 Group means of log_{10} transformed reaction times for music, cigarette and no reward trials. Error bars represent ±standard errors.

3.3.4 Self-reported liking of first reward unit consumed[10]

There was a main effect of reward ($F_{1, 60}$=17.031, p<0.001), with higher ratings for cigarettes compared with music. Despite the lack of a group by reward interaction, this main effect of reward was likely driven by the dependent smokers, who rated cigarettes more highly than music (t_{17}=4.269, p=0.001), while occasional smokers did not.

3.3.5 Functional imaging data[11]

3.3.5.1 Movement

All participants moved <5mm in all directions.

3.3.5.2 ROI analyses

Anticipation

For the 'cigarette > no reward anticipation' one-sample t-test, which included both groups, there was significant activation in the left ventral striatum ROI, bilateral thalamus ROIs and left medial frontal gyrus ROI (see table 3.4 and figure 3.3). There were no group differences in any of the ROIs for 'cigarette > no reward anticipation'.

For the 'music > no reward anticipation' one-sample t-test, which included both groups, there were no significant activations in any of the ROIs, nor were there group differences.

Within the dependent group, the 'cigarette > music anticipation' one-sample t-test produced significant activation in the left medial frontal gyrus. Within the occasional group, the same one-sample t-test produced no significant activations (see table 3.5).

[10] Ratings of music liking were missing for 3 dependent smokers and 3 occasional smokers due to computer error. Ratings of cigarette liking were missing for 1 dependent smoker and 13 occasional smokers due to these participants choosing not to smoke.

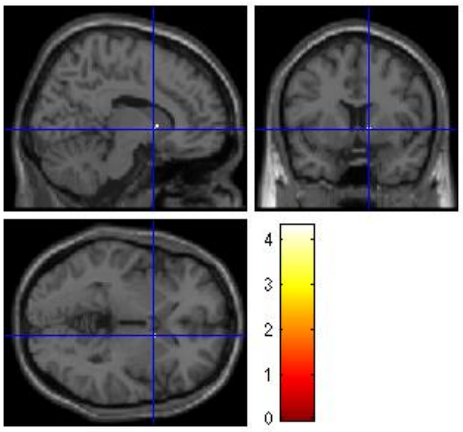
[11] One dependent smoker was excluded from fMRI analyses because his structural scan was missing. Two occasional smokers were excluded from fMRI analyses because of errors with their functional scans; their data could not be pre-processed by SPM.

For the 'music > cigarette anticipation' one-sample t-test, there were no significant activations in any of the ROIs in either group.

Table 3.4 ROI analysis: Peak and cluster-level BOLD responses for 'cigarette > no reward anticipate' contrast using a one-sample t-test with both groups included (MNI co-ordinates, t and FWE-corrected p values are shown).

Region	**x**	**y**	**z**	**Peak-level**		**Cluster-level**	
Dependent and occasional smokers together				**t**	**p (FWE corrected)**	**cluster size**	**p (FWE corrected)**
Right ventral striatum	12	8	-1	3.846	0.010	2	0.025
Right thalamus	9	-10	8	3.476	0.012	4	0.017
Left thalamus	-9	-22	5	3.871	0.003	6	0.012
Left medial frontal gyrus	0	-7	56	3.724	0.014	4	0.017

a)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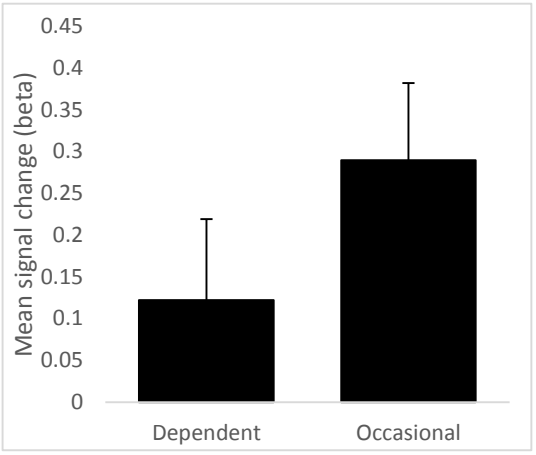
2
1
0


Mean signal change (beta)
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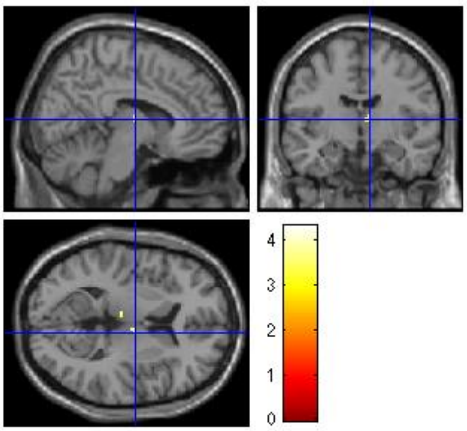
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Dependent
Occasional

b)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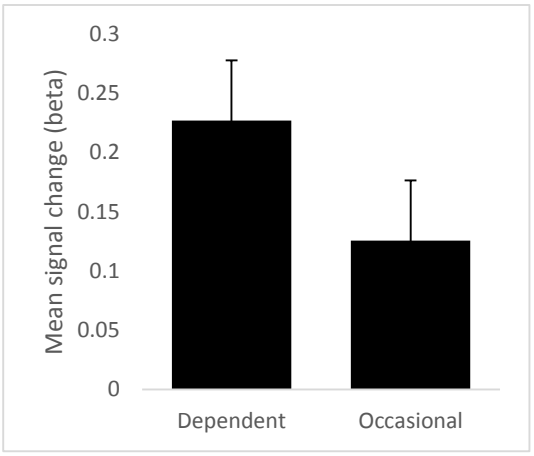
Mean signal change (beta)
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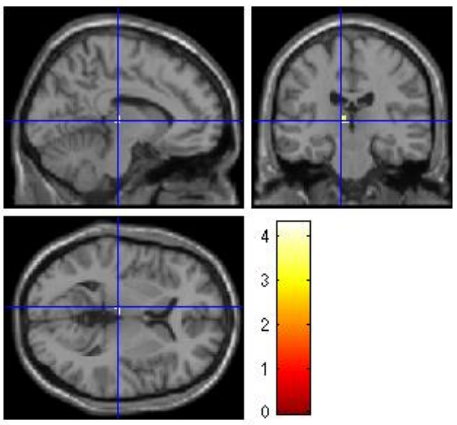
0.25
0.2
0.15
0.1
0.05
0
Dependent
Occasional

c)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3
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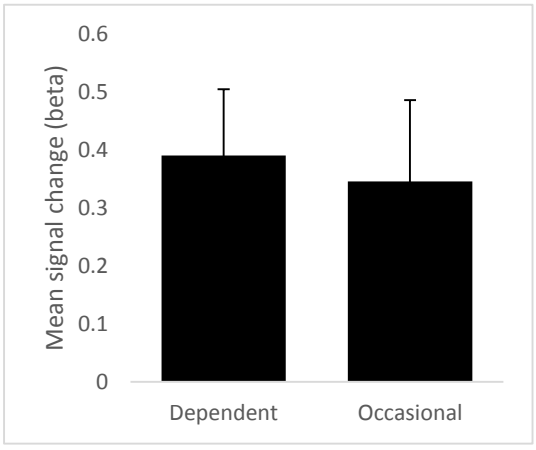
Mean signal change (beta)
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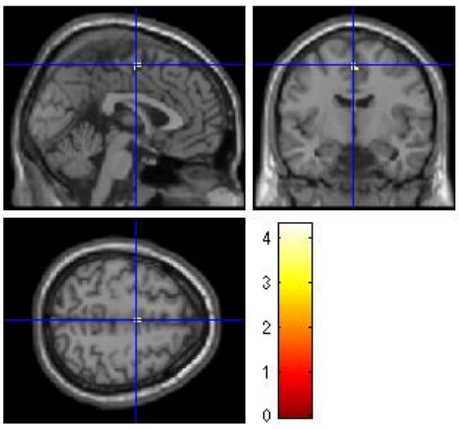
0.5
0.4
0.3
0.2
0.1
0
Dependent
Occasional

d)



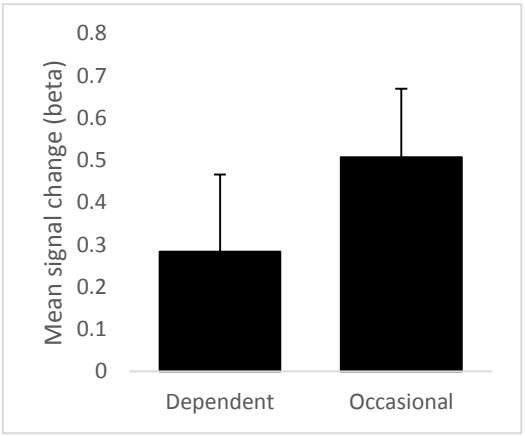


Figure 3.3 ROI analysis: Significant 'cigarette > no reward anticipation' clusters (FWE corrected for p<0.05) within a priori ROIs in both groups. Bar graphs show the lack of group differences within these ROIs. Error bars show standard error. a) Within the right ventral striatum (12, 8, -1) b) Within the left ventral striatum ROI (9, -10, 8) (c) Within the left thalamus ROI (-9, -22, 5) d) Within the left medial frontal gyrus (0, -7, 56).

Table 3.5 ROI analysis: Peak and cluster-level BOLD responses for 'cigarette > music anticipation' contrast for the dependent group using a one-sample t-test (MNI co-ordinates, t and FWE-corrected p values are shown). The occasional group showed no significant activations for this contrast.

Region	**x**	**y**	**z**	**Peak-level**		**Cluster-level**	
Dependent smokers				**t**	**p (FWE corrected)**	**cluster size**	**p (FWE corrected)**
Left medial frontal gyrus	-3	-7	53	3.762	0.0272	4	0.0145

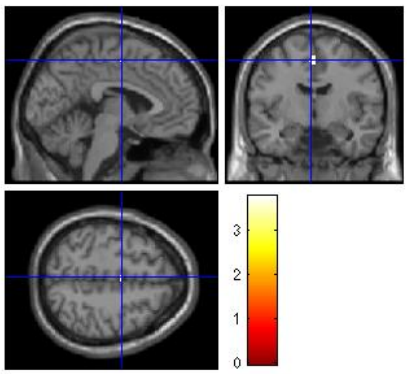


Figure 3.4 ROI analysis: Significant 'cigarette > music anticipation' cluster (FWE corrected for p<0.05) within a priori ROI: left medial frontal gyrus (-3, -7, 53), in the dependent group.

Feedback

For the 'cigarette win > no reward feedback' one-sample t-test, which included both groups, there were significant activations in the right caudate, left amygdala and left parahippocampal region (see table 3.6 and figure 3.5). On this contrast, dependent smokers showed greater activation in the right caudate than occasional smokers (see table 3.6 and figure 3.5).

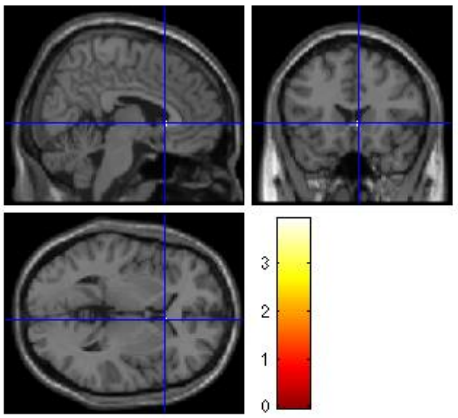
For the 'music win > no reward feedback' one-sample t-test, which included both groups, there were no significant activations. There were also no group differences on this contrast.

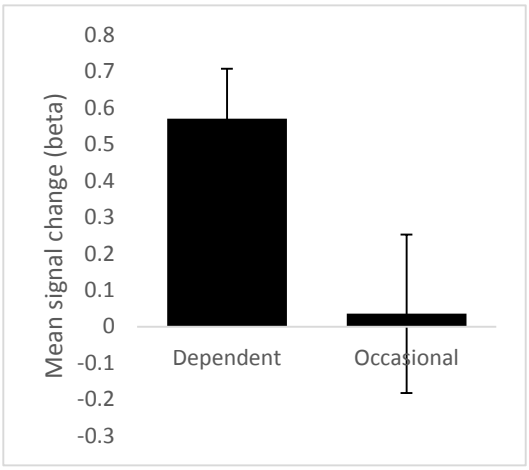
Within the dependent and occasional group, 'cigarette > music feedback' and 'music > cigarette feedback' produced no significant activations.

Table 3.6 ROI analysis: Peak and cluster-level BOLD responses for 'cigarette > no reward feedback' contrast using a one-sample t-test with both groups included. The group difference in BOLD response for 'cigarette > no reward feedback' is also shown. (MNI co-ordinates, t and FWE-corrected p values are shown).

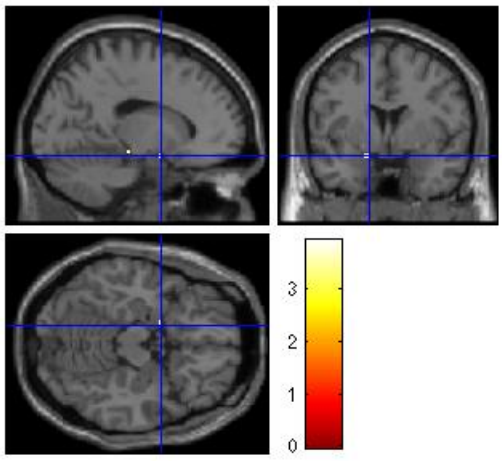
Region	**x**	**y**	**z**	**Peak-level**		**Cluster-level**	
Dependent and occasional smokers together				**t**	**p (FWE corrected)**	**cluster size**	**p (FWE corrected)**
Right caudate	6	20	2	3.847	0.009	2	0.0290
Left amygdala	-15	2	-16	3.373	0.014	2	0.0290
Left parahippocampal region	-18	-22	-13	3.575	0.007	4	0.0197
Group difference between dependent and occasional smokers							
Right caudate	6	17	-1	3.225	0.045	1	0.034

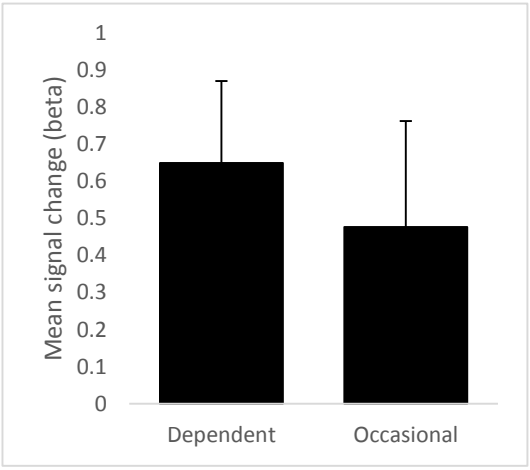
a)



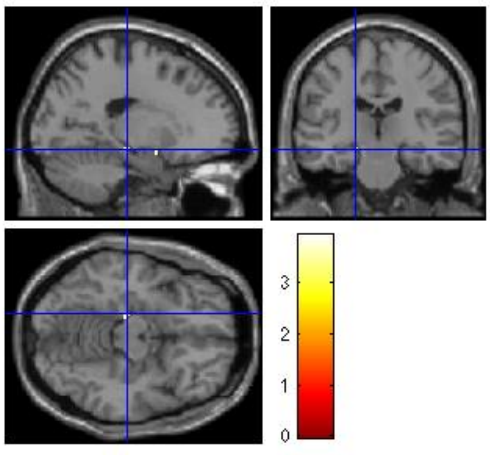


b)





c)



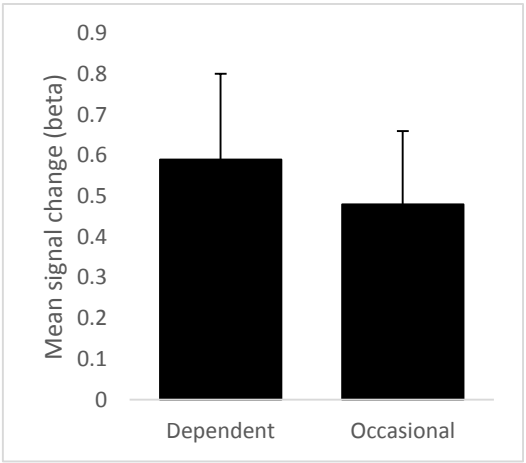


Figure 3.5 ROI analysis: Significant 'cigarette > no reward feedback' clusters (FWE corrected for p<0.05) within a priori ROIs in both groups. Bar graphs show the group difference for activity in the right caudate but the lack of group differences within the other clusters. Error bars show standard error. a) Within the right caudate (6, 20, 2), b) within the left amygdala (-15, 2, -16), c) within the left parahippocampal region (-18, -22, -13).

3.3.5.3 Whole brain analysis

Anticipation

For the 'cigarette > no reward anticipate' one-sample t-test, which included both groups, there were significant activations in right extra striate region, left thalamus, right thalamus, left insula, left inferior frontal gyrus and left putamen (see appendix table 3.1). However, there were no group differences on this contrast.

For the 'music > no reward anticipate' one-sample t-test, which included both groups, there were no significant activations. There were also no group differences on this contrast.

Within the dependent group, the 'cigarette > music anticipation' one-sample t-test produced significant activation in the right caudate (see appendix table 3.2). Within the occasional group, the same one-sample t-test produced no significant activations.

For the 'music > cigarette anticipation' one-sample t-test, there were no significant activations.

Feedback

For the 'cigarette win > no reward feedback' one-sample t-test, which included both groups, there was significant activation in the left anterior cerebellum (see appendix table 3.3). There were also no group differences on this contrast.

For the 'music win > no reward feedback' one-sample t-test, which included both groups, there were no significant activations. There were also no group differences on this contrast.

Within the dependent and occasional group, 'cigarette > music feedback' and 'music > cigarette feedback' produced no significant activations.

3.3.5.4 Correlations

There were no significant correlations between number of cigs/day, time-since-last-smoked, CO, average response time on cigarette trials and the average BOLD signal in any of the significantly activated ROIs for cigarette anticipation or feedback.

3.4 Discussion

The current study examined behavioural and neural responses to the anticipation of and feedback about cigarette and music reward in dependent and occasional smokers. Consistent with my predictions, the dependent smokers were faster at responding on cigarette trials than the occasional smokers and there were no differences on music or no reward trials. Anticipation of cigarettes recruited reward related brain regions (left ventral striatum, bilateral thalamus, left medial frontal gyrus) in both groups; as did positive feedback about cigarette reward, which activated the right caudate, left amygdala and left parahippocampal region. Dependent smokers exhibited stronger activation in the right caudate during positive cigarette feedback than occasional smokers; however there were no significant group differences on cigarette anticipatory BOLD response. Surprisingly, anticipation of and feedback about music did not produce significant activation in any brain regions.

3.4.1 Behavioural results

Results from chapter 2 suggested that dependent and occasional smokers differed behaviourally on the processing of cigarettes but not non-drug rewards. I aimed to confirm this using a task that did not have a choice stage and therefore more purely assessed motivation for each reward: the adapted incentive delay task (AIDT). Using the reaction time to respond to a target on trials in which cigarette and music points were available as a measure of motivation, I demonstrated that dependent smokers, in a non-withdrawn, or 'normal' state, compared with occasional smokers, were more motivated to earn cigarettes but no less motivated to earn music. These results support my findings in chapter 2 that nicotine-satiated dependent smokers do not suffer from motivational deficits for consummatory

non-drug rewards. This is consistent with previous findings demonstrating that dependent smokers do not differ from non-smokers in motivation to earn money on the CARROT, so long as the smokers have recently smoked a cigarette (Al-Adawi & Powell, 1997; Powell et al., 2002). Having said that, one previous study did report a difference between high and low dependence smokers on motivation for monetary reward, using a modified version of the CARROT, with no effect of abstinence (Kalamboka, 2008).

Importantly, my results in this chapter are conceptually very similar to those in chapter 2. This is despite minor changes to group inclusion criteria (in this study, dependent smokers scored ≥5 on the FTND, whereas in chapter 2 they scored ≥6 on the FTND) and minor sampling differences between the groups (in this study, the dependent smokers were non-significantly older, marginally more depressed and more impulsive than the occasional smokers). It should be noted, however, that the groups were remarkably similar to those described in chapter 2 in terms of number of cigarettes smoked per day and FTND scores.

The hypersensitivity to cigarette rewards in dependent, compared with occasional smokers, seems to drive the difference in reward processing profiles, where dependent smokers showed marginally greater motivation for cigarettes relative to music, but occasional smokers had similar motivation for cigarettes and music. Although there was no significant group by reward interaction for self-reported reward liking, a priori t-tests demonstrated a similar difference in profile for their hedonic responses. Dependent smokers liked cigarettes more than music, while this was not the case in occasional smokers. However, all of the results concerning liking of cigarettes should be interpreted very cautiously because so many (n=13) of the occasional smokers chose not to consume any of the cigarette they earned.

3.4.2 fMRI results

As expected, anticipation of and feedback about cigarette reward produced activation in various reward related brain regions that are consistently activated by anticipation of monetary reward

(Knutson & Greer, 2008). This demonstrates that the task worked as I predicted it would for cigarette rewards. Contrary to my hypotheses, the dependent smokers did not show enhanced anticipatory neural responses on cigarette trials. However, dependent smokers did have a stronger response to positive cigarette reward feedback than occasional smokers, in a small section (one 3x3x3mm voxel) of the right caudate. Hence, I demonstrated both behavioural and neural hypersensitivity to cigarette reward in nicotine dependence. However, it is surprising that the dependent smokers did not show augmented anticipatory BOLD responses to cigarettes given this anticipatory processing is thought to be particularly important for motivation (Sescousse et al., 2014).

That dependent smokers had a larger response to cigarette win feedback than occasional smokers extends my behavioural findings, from both chapter 2 and this current chapter, to show that nicotine dependence is also associated with a neural hypersensitivity to cigarette reward. Specifically, this study suggests that dependent smokers' right caudates are more sensitive than occasional smokers' right caudates to the experience of winning cigarette points. This result is novel because Buhler et al.'s (2010) study found no group difference in terms of BOLD response during cigarette feedback. Receipt of reward is thought to be a conceptually different process to the anticipation of reward, with the former being more related to consummatory responses and the latter more related to anticipatory responses (Sescousse et al., 2010). However, given neither the cigarettes nor the music were actually consumed when points were received, this interpretation may be over simplistic. Indeed, receiving cigarette points may well provoke some sort of anticipatory process given that the points will later be exchanged for real cigarettes. Therefore, comparisons between dependent and occasional smokers on their neural response to cigarette consumption should be carried out to truly investigate consummatory cigarette processing.

It is noteworthy that it was the receipt of reward, rather than anticipation, which produced a group difference in BOLD response. This result questions the superior importance of anticipatory processing relative to feedback processing in nicotine dependence. The caudate is considered to be a component

of the dorsal striatum and a crucial part of the reward processing network (Haber & Knutson, 2010). Speculatively, the caudate may be more strongly recruited by dependent smokers during cigarette reward feedback as this brain region is thought to become more critical in drug-processing as users become habitual (Everitt & Robbins, 2005). However, in order to test this claim, the caudate response would have to be associated with performance on a task measuring habitual responding for cigarettes.

One important cautionary note is that only one voxel in the right caudate ROI showed a significant group difference. Conclusions based on these findings should only be considered preliminary. A replication of this difference in feedback processing, which specifically focused on the caudate, would be useful in clarifying whether this finding is robust and meaningful. On the other hand, support for this group difference is the use of the conservative family-wise-error correction.

My cigarette anticipatory results are consistent with Buhler et al.'s (2010), who also found no significant difference between dependent and occasional smokers on anticipatory BOLD response in any brain region. Having said that, they did find a significant interaction between group and reward-type with the non-significant group differences going in the expected directions. If they had tested more participants, they may have found significant group differences. The question then becomes: why did I detect group differences on behavioural motivation for cigarettes and cigarette feedback BOLD response, but not cigarette anticipatory BOLD response? To conjecture, one possibility is simply chance. Perhaps if I had greater power, or if I repeated the experiment, the cigarette anticipatory response would have followed the same pattern as the other outcomes. Another possibility is that any kind of smoking, whether it is occasional or dependent, changes anticipatory processing similarly. Or, that neither occasional nor dependent cigarette smoking alters this aspect of reward processing. In order to test these hypotheses, I would need a control group of never smokers. Personally, I suspect the first option. Irrespective, these results may suggest that the anticipatory BOLD response to cigarette reward is not as important in nicotine dependence as one might expect. Other simpler

measures, such as behavioural motivation for cigarettes or self-reported craving, may be more sensitive in detecting differences between dependent and occasional smokers.

Acute nicotine abstinence has been shown to enhance cigarette anticipatory BOLD response in one study (Sweitzer et al., 2013) but not another (Bühler et al., 2010). Perhaps if the smokers were in a nicotine deprived state, I would have observed group differences during anticipation and a larger difference during feedback. Given my null group by abstinence interaction in chapter 2, I wanted to focus my attention on reward processing during 'normal' life when nicotine dependence is not disturbed by nicotine deprivation. Moreover, some studies have found differences between smokers and non-smokers in BOLD response during reward anticipation, even after recent smoking (Luo et al., 2011; Rose et al., 2013). However, forcing acute abstinence would have allowed an investigation into how a lack of nicotine affects the neural processing of cigarettes and non-drug reward in dependent compared with occasional smokers. On-board nicotine may simply have masked the expected effects. I did investigate the possibility that recent smoking was associated with responsiveness to cigarette reward by conducting correlations between time-since-last-smoked and CO, and average BOLD response in any significant ROIs within each group. However, neither of these correlational analyses suggested that there were relationships between brain activation and recent smoking. Given that all but one of the dependent smokers had smoked within the last two hours, there may not have been enough variance to detect these relationships, if they do exist.

There were also no significant associations between the average BOLD responses in any of the activated ROIs during cigarette trials and the average reaction time to the target on cigarette trials. One might have expected negative associations to have emerged. The faster a participant responds to the target, the more motivated they should be to earn cigarettes, and, theoretically, the more strongly reward related brain regions (especially striatal regions) should be activated. However, this was not the case. Hence, this somewhat questions the validity of the AIDT for the assessment of motivation

for cigarettes. Again, this supports my claim that other simpler measurements may be more suitable for assessing motivation to earn rewards.

I found no evidence that anticipation of or feedback about classical music elicits activation in reward related brain regions. This suggests that, in terms of neural anticipatory and feedback processing, the music trials were not more rewarding than the no reward trials. Hence, perhaps classical music was simply a poor choice of reward and it did not function as reward for these participants. As can be seen by comparing results described in chapters 2 and 3, participants did not 'like listening to classical music, in general' (chapter 3) as much as they liked 'listening to music, in general' (chapter 2). Indeed, the average score for general liking in this chapter was only just above zero and some participants reported *not liking* classical music (i.e. scores below zero). This could have contributed to the lack of effects seen in the fMRI data. However, that both groups responded more quickly on music compared with no reward trials, showing that they were behaviourally motivated by music, is strong evidence against this claim. Furthermore, the music has been rated as pleasant by previous research volunteers (Menon & Levitin, 2005). Again, it seems as though the BOLD response I measured may have been less sensitive than the behavioural measure, reaction time.

When investigating the balance of reward processing within each group separately, I found that dependent smokers displayed stronger activation in the left medial frontal gyrus (ROI analysis) and right caudate (whole brain analysis) for cigarette anticipation compared with music anticipation. Whereas, in the occasional smokers, there were no regions which showed any difference between cigarette and music anticipation. These results, on the face of it, imply the groups have different patterns of anticipatory reward processing for cigarettes and music reward. This dovetails with findings in the previous chapter, which consistently demonstrated differences in the profiles of cigarette and non-drug reward processing. Furthermore, this supports Buhler et al.'s (2010) findings concerning the difference in the profiles of cigarette and monetary processing in dependent and occasional smokers. However, there are two caveats here. First, the music reward did not seem to

produce any significant reward related brain activation during anticipation or feedback, so using it to draw conclusions about the neural processing of drug vs. non-drug reward processing is not ideal. Hence, it would be premature to conclude that I have shown a true difference in the balance between drug and non-drug reward processing between dependent and occasional smokers. Second, I have not statistically tested the difference in the differences. In other words, although the difference within the dependent group is significant in two brain regions while there are no significant differences within the occasional group, that does not necessarily mean the difference in those profiles is *significantly* different. It can only tell us that there are qualitatively different patterns within the groups.

If I had just conducted ROI analyses, one could suggest that the reason I did not observe music reward-induced activations and anticipatory group differences was because the ROIs did not cover the regions where significant activations occurred. My whole brain analyses however show that nowhere in the brain showed anticipatory or feedback music-induced activations. The regions that were significantly activated in my ROI and whole brain analyses for cigarettes were not always the same. For instance, I observed activation in the left putamen during cigarette anticipation with the whole brain analysis but not the ROI analysis. The reason for this is that the ROI analyses provide greater statistical sensitivity such that smaller effects can be detected in certain regions, while at the same time not investigating the rest of the brain. Whole brain analyses test all voxels in the brain, but because of the much greater number of tests being carried out, only larger effects can be detected.

An important note is that my 'whole brain analyses' did not always cover the whole brain. In order to get good coverage of the midbrain, striatal and prefrontal regions, the anterior parts of the parietal and frontal lobes were sometimes sacrificed. Hence, it is possible that I missed out some significant activations within these regions because I didn't examine them. However, this seems unlikely as these areas do not contain brain regions that are traditionally considered to be important in reward related processes. One potential problem is that the orbitofrontal cortex is difficult to successfully image using fMRI because of signal dropout near the eyes (Deichmann et al., 2003). As orbitofrontal cortex regions

are frequently implicated in reward processing (Chib et al., 2009), I may have failed to detect anticipatory, or more likely, feedback induced responses here.

Another potential criticism is that I combined the cue and anticipate stages to make a single event. This decision was made in order to improve the BOLD signal by extending the time of the event; when I modelled just the anticipate event, I did not observe the expected BOLD responses. In terms of what this might mean for the interpretation of the results, the BOLD response will be related to the experience of finding out which reward is on offer and anticipating the response for that reward, rather than just anticipating the response for that reward. This does not seem like a major change and clearly anticipation of cigarette reward produced the BOLD responses I expected from previous MIDTs using just the anticipation stage (Knutson & Greer, 2008). Hence, I do not think this alteration changes the interpretation substantially; it simply allowed for a stronger cue-invoked anticipatory BOLD response to be produced.

3.4.3 State questionnaires and self-reported liking

Predictably, the dependent smokers had greater craving scores than the occasional smokers. It is interesting that they also had a higher average withdrawal score, even though they were allowed to smoke approximately 15 minutes before completing this questionnaire. This may reflect generally increased negative affect in dependent smokers though (Kassel, Stroud, & Paronis, 2003). I also found higher anhedonia within the dependent smokers than the occasional smokers. In chapter 2 I did not find differences between the groups on this scale when participants were nicotine-satiated, only after acute abstinence. This current result, therefore, may simply reflect the marginally higher levels of depression in the dependent group compared with the occasional group, and the fact that anhedonia is a cardinal symptom of depression (DSM-5 American Psychiatric Association, 2013).

3.4.4 Strengths and limitations

This study had various strengths. I used a well-validated paradigm and the extension to cigarette rewards was demonstrably successful. The fact that I actually gave participants the cigarettes and music that they won, as I did in chapter 2, should have increased face validity of the experiment. I recorded neuroimaging, as well as behavioural data; measuring two related, yet distinct, types of data provide a more comprehensive look into any reward processing alterations. Furthermore, I reported a novel finding in that dependent smokers had a neural hypersensitivity to the feedback of cigarette reward, relative to occasional smokers.

In terms of limitations, the fact that anticipation on music trials, compared with no reward trials, did not elicit greater activation in reward related brain regions is obviously a problem. As described above, this could be because classical music was not rewarding enough to the participants and the BOLD response lacked sensitivity or because both groups were similarly hyposensitive to anticipation of music; the inclusion of a non-smoker control group is needed to address this issue. Finally, despite the null group by abstinence interaction in chapter 2, this experiment could have been improved by having an acute abstinence manipulation to determine if the BOLD responses change when participants are deprived of nicotine.

3.4.5 Conclusions

In summary, I extended my findings from chapter 2. I added further evidence to the claim that, on a behavioural level, nicotine-satiated dependent smokers, compared with occasional smokers, have a greater motivation for cigarette but not music reward. Furthermore, dependent smokers exhibited a stronger BOLD response than occasional smokers to positive cigarette reward feedback in the right caudate compared. Thus, I demonstrated both behavioural and neural hypersensitivity to drug reward in nicotine dependence. However, I did not find evidence for a group difference on cigarette or music anticipatory BOLD response. Future research should investigate which non-drug, consummatory rewards can be used to better probe the neurobiology of non-drug reward functioning in addicted

individuals and explore which reward-related BOLD response, if any, is most closely associated with disrupted motivational processing during addiction.

Chapter 4: The acute effects of pramipexole on cigarette and non-drug reward processing in dependent and occasional smokers: a double-blind, placebo-controlled experiment

4.1 Introduction

Results reported in chapter 2 suggested that relative preference for, motivation for and liking of cigarettes was greater in dependent compared with occasional smokers. Although the processing of non-drug rewards was similar in each group, there was a consistent difference in the balance of drug and non-drug reward processing. Results reported in chapter 3 partially supported these findings: dependent smokers, compared with occasional smokers, were more motivated to gain cigarettes but were similarly motivated to gain music, as measured by reaction time. Moreover, winning cigarettes elicited a greater BOLD response in the right caudate of dependent smokers than occasional smokers.

Various components of non-drug reward processing have been shown to predict abstinence outcomes in cigarette smokers (Leventhal, Piper, et al., 2014; Leventhal, Waters, Kahler, Ray, & Sussman, 2009; Versace et al., 2014; Versace et al., 2012; Yoon et al., 2007), although null effects have been also been found (Powell, Dawkins, West, Powell, & Pickering, 2010). Unsurprisingly, metrics related to cigarette reward processing also predict cessation (Killen & Fortmann, 1997; Powell et al., 2010; Zhou et al., 2009). Therefore, either a reduction in the processing of cigarettes or an enhancement in the processing of non-drug rewards, or both, may be therapeutically beneficial. Hence, in this study I aimed to pharmacologically challenge the imbalance in cigarette and non-drug reward processing in cigarette smokers.

4.1.1 Dopamine, reward processing and addictive drugs

As described in chapter 1, mesocorticolimbic dopaminergic functioning has been associated with a wide range of reward processes (Berridge & Robinson, 1998; Wise & Rompré, 1989). Phasic dopamine firing appears to encode temporal difference learning (Schultz et al., 1997) while nucleus accumbens dopamine levels are associated with motivation (Niv et al., 2007; Salamone et al., 2007). Furthermore, dopamine plays a key role in the acutely reinforcing properties of addictive drugs, including nicotine (Corrigall, Franklin, Coen, & Clarke, 1992; Di Chiara & Imperato, 1988), and appears critical in addictive

behaviour (Robinson & Berridge, 1993; Volkow et al., 2004). Additionally, mesolimbic dopaminergic functioning theoretically underlies the competition between drug and non-drug rewards for attention and motivation (Anselme, 2009). Hence, manipulation of the dopamine system is a promising avenue for the treatment of drug addictions (Hart, Haney, Vosburg, Rubin, & Foltin, 2008; Volkow et al., 2004). Indeed, bupropion, a dopamine and noradrenaline reuptake inhibitor (Dwoskin, Rauhut, King-Pospisil, & Bardo, 2006), is efficacious in treating nicotine dependence (Jorenby et al., 1999). Although, its anti-smoking properties may arise from its antagonism of nicotinic acetylcholine receptors rather than its action on dopamine reuptake (Dwoskin et al., 2006).

Various attempts to disrupt cigarette smoking via manipulation of the dopamine system have been undertaken. Bromocriptine, a dopamine D2 receptor preferring agonist, has been shown to acutely reduce ad libitum cigarette consumption (Caskey, Jarvik, & Wirshing, 1999; Jarvik et al., 2000), while extended use of bromocriptine is also associated with reduced cigarette smoking (Murphy et al., 2002). Acute tyrosine/phenylalanine depletion, which reduces dopamine synthesis, had differential effects: it increased demand for cigarettes and reduced an attentional bias towards cigarette images (Hitsman et al., 2008). Furthermore, selegiline, a monoamine-oxidase B inhibitor, originally showed promise as an aid to smoking cessation (George et al., 2003), however this was not replicated (Weinberger et al., 2010). The opportunity for a dopaminergic, smoking-cessation aid therefore remains.

4.1.2 Pramipexole

Pramipexole is a non-ergot derived dopamine agonist which binds to dopamine D2, D3 and D4 receptors, with the greatest affinity to the D3 receptor (Mierau et al., 1995). Pramipexole is primarily used to treat Parkinson's disease (Shannon, Bennett, Friedman, & Group, 1997) due to its activation of dopamine receptors in the degenerating basal ganglia.

Variation in extracellular, forebrain dopamine levels is thought to be determined by two processes: (i) fast-changing, phasic dopamine release caused by neuronal firing and (ii) slow-changing, tonic dopamine release regulated by prefrontal cortical afferents (Grace, 1991). A biphasic dose-response curve for pramipexole has been suggested (Samuels, Hou, Langley, Szabadi, & Bradshaw, 2006). At low doses, pramipexole is thought to preferentially act at presynaptic autoreceptors, leading to a reduction in phasic dopamine release; at high doses, pramipexole is thought to overcome these inhibitory effects and increase post-synaptic receptor activation (Maj, Rogóż, Skuza, & Kołodziejczyk, 1997). Pramipexole may, however, concomitantly decrease phasic dopamine firing via autoreceptor activation and increase tonic dopamine levels via modulation of prefrontal-striatal glutamatergic projections (Ye, Hammer, Camara, & Münte, 2011). Thus, its action is somewhat unclear.

Pramipexole has been shown to disrupt performance on standard reward processing tasks. In healthy controls, acutely administered low doses (0.25-0.5mg oral) of pramipexole resulted in riskier gambling behaviour (Riba, Krämer, Heldmann, Richter, & Münte, 2008), enhanced striatal BOLD response in anticipation of reward (Ye et al., 2011) but also reduced reward-related neural activation in response to both pleasant and aversive outcomes (McCabe, Harwood, Brouwer, Harmer, & Cowen, 2013). Moreover, in Parkinson's patients, chronic administration of pramipexole remediated reward learning deficits (Bódi et al., 2009).

Repeated administration of pramipexole also has also been found to produce antidepressant effects in people with major depressive disorder (Corrigan, Denahan, Wright, Ragual, & Evans, 2000; Szegedi et al., 1997), bipolar disorder (Zarate et al., 2004) and Parkinson's disease (Barone et al., 2010; Lemke, Brecht, Koester, & Reichmann, 2006). Furthermore, in Parkinson's patients, amotivation is partially ameliorated by pramipexole (Lemke et al., 2006).

Given the importance of D3 receptors in the self-administration of drugs (Le Foll, Goldberg, & Sokoloff, 2005) and its clear impacts on reward processing and mood, pramipexole has also been investigated for its possible anti-addictive properties. In cocaine dependent individuals, a single low dose of

pramipexole reduced attentional bias towards drug-related words (Ersche et al., 2010) and perseverative responding (Ersche et al., 2011). Similarly, in nicotine dependent individuals, the same dose reduced attentional bias to cigarette images (Freeman et al., 2015) while enhancing motivation for monetary reward in the CARROT (Freeman et al., 2013). Pramipexole's potentially beneficial effects in smokers may arise through the reduction of phasic dopamine firing and subsequently craving (Franken, 2003; Freeman et al., 2015). Hence, pramipexole holds promise as a drug that may concurrently impair cigarette reward processing while enhancing motivation for alternative, non-drug rewards.

4.1.3 Relative reinforcing efficacy of cigarettes

As an additional measure related to the motivation to smoke cigarettes, I included a cigarette purchase task (MacKillop et al., 2008). This type of behavioural economics task aims to quantify the reinforcing efficacy of cigarettes relative to money by asking participants how many cigarettes they would be willing to buy for increasing amounts of money. A demand curve is plotted and measures of reinforcing efficacy, such as breakpoint (the price at which no more cigarettes are bought), are generated. These measures are often associated with dependence (MacKillop et al., 2008) and craving (Aston et al., 2015), and have been shown to be sensitive to dopaminergic manipulation in smokers (Hitsman et al., 2008).

4.1.4 Reward learning and effort-related decision-making

Throughout this thesis, I have argued that it is important to investigate specific reward processing deficits in specific drug addicted populations. It is unlikely that sweeping statements that claim all drug addicted individuals have globally deficient non-drug reward processing will be accurate. What will be helpful is to determine what precise impairments are found in specific drug addictions, and which treatments can rectify these potential impairments. Therefore, in this chapter, I have examined different components of reward processing.

In chapter 1, I introduced the key concept of reward learning that has received recent attention with the popular Probabilistic Reward Task (Pizzagalli et al., 2005). As previously described in section 1.5.2.2, 24 hours of nicotine deprivation impaired (Pergadia et al., 2014), while acute nicotine administration improved (Barr et al., 2008), reward learning. Depressed people generally show weaker reward learning on this task (Pizzagalli, Iosifescu, et al., 2008), but tobacco smoking appears to ameliorate this (Janes et al., 2015; Liverant et al., 2014). Hence, anhedonic states such as depression and nicotine withdrawal seem to be associated with impoverished reward learning. The fact that nicotine restores this functioning may, at least in part, drive cigarette smoking (Janes et al., 2015). Furthermore, in healthy volunteers, pramipexole has been shown to impair reward learning (Pizzagalli, Evins, et al., 2008). However, this effect of pramipexole has not yet been investigated in a sample of cigarette smokers. Given that a weak response bias is associated with cigarette craving (Peechatka et al., 2015) and acute nicotine seems to enhance the response bias (Barr et al., 2008), I was concerned that, although pramipexole may have anti-smoking properties, it may also result in reduced non-drug reward learning, which could indirectly reverse the desired effect.

Another component of reward processing that has received recent attention, which is closely related to motivation, is effort-related decision-making: how one chooses between different options which require different amounts of effort. These kinds of decisions are faced by people regularly. For instance, the decision to look at inane websites rather than writing one's thesis would be a low-effort, low-reward choice. Effort-related decision-making has been operationalised in the Effort Expenditure for Rewards Task (EEfRT) (Treadway et al., 2009) and has been shown to be related to self-reported anhedonia, depression (Treadway, Bossaller, Shelton, & Zald, 2012; Treadway et al., 2009) and dopaminergic functioning, evidenced both behaviourally using amphetamine challenge (Wardle, Treadway, Mayo, Zald, & de Wit, 2011) and neurobiologically using positron emission tomography (Treadway, Buckholtz, et al., 2012). However, neither the association between nicotine dependence and task performance nor pramipexole's effects on this task have been investigated.

4.1.5 Differential effect of pramipexole in dependent and occasional smokers?

Nicotine dependence has been associated with neurobiological adaptations to the mesocorticolimbic dopamine system (Dagher et al., 2001; Fehr et al., 2008; Leroy et al., 2012) and reward processing tasks, such as the EEfRT and PRT, are both theoretically and empirically related to dopaminergic functioning. Hence, the effects of dopaminergic drugs, including pramipexole, would be expected to have different effects on these tasks in dependent and occasional smokers, as they putatively have different dopamine systems.

4.1.6 Summary and hypotheses

In summary, dopaminergic functioning is critical in various aspects of reward processing, in the acutely reinforcing effects of various drugs and also in addiction. Manipulation of the dopamine system therefore represents a viable way to disrupt addictive behaviours. Previous work with pramipexole has demonstrated its ability to reduce an attentional bias to cigarette images (Freeman et al., 2015) while improving motivation for a non-drug reward (Freeman et al., 2013). Therefore, pramipexole appears to be a promising drug with the aim of disrupting the balance between cigarette and non-drug reward processing. Results I reported in chapters 1 and 2 suggest that dependent smokers, compared with occasional smokers, have enhanced motivation for cigarette rewards but similar motivation for the non-drug rewards, music and chocolate. However, effort-related decision-making and reward learning have not yet been compared in occasional and dependent smokers. Moreover, the effects of pramipexole on performance of these tasks have not been investigated in smokers and they could be important when considering the therapeutic potential of pramipexole. Hence, this study assessed the effects of a single 0.5mg oral dose of pramipexole in dependent and occasional smokers on the motivation for cigarettes and non-drug rewards, reward learning and effort-related decision-making.

Based on results reported in chapters 1 and 2, the iRISA theory of addiction (Goldstein & Volkow, 2011), and previous research with pramipexole described above, it was hypothesised that:

1. Dependent smokers would have a stronger motivation for cigarettes than occasional smokers and pramipexole would reduce motivation for cigarettes in favour of non-drug rewards.
2. Dependent smokers would have impaired reward learning compared with occasional smokers and pramipexole would impair reward learning.
3. Dependent smokers would have impaired effort-related decision-making (i.e. weaker motivation) for monetary reward than occasional smokers and pramipexole would improve effort-related decision-making (i.e. enhance motivation) for monetary reward.

I also explored whether the effects of pramipexole were moderated by group because nicotine dependence has been associated with altered dopaminergic functioning, which could lead to a differential response to the drug. I did not make any specific hypotheses for the direction of this moderation however.

4.2 Methods

4.2.1 Design and Participants

A double-blind, placebo-controlled, crossover design with a between-subjects factor of group (dependent and occasional) and a within-subjects factor of drug (placebo and pramipexole) was used. Other factors will be discussed in relation to each specific task.

20 dependent (10 women) and 20 occasional (10 women) cigarette smokers took part in the study. Sample size was based on Buhler et al. (2010) and the study reported in chapter 2. Furthermore, a power analysis showed that a total sample size of 22 would be sufficient to detect a between-within interaction of medium effect size (f=0.25) and a correlation between repeated measures of 0.7 (based on Lawn et al., 2015), with an alpha of 0.05 and a power of 0.8. I proceeded with the larger total sample size of 40.

All participants passed eligibility criteria during telephone screening. Inclusion criteria were: (1) smoke on average ≥10 cigarettes/day (for dependent smokers) or smoke 0.5-5 cigarettes per week (for occasional smokers); (2) have an FTND score ≥5 (for dependent smokers) or 0 (for occasional smokers); (3) aged 18-50. Exclusion criteria were: (1) have been a regular, daily cigarette smoker in the past (for occasional smokers); (2) seeking treatment for a mental health problem; (3) using psychiatric medication; (4) use of an illicit drug once per week or more; (5) using a pharmacotherapy to quit smoking; (6) have a body mass index outside the range 18-30; (7) tumours of the adrenal or pituitary glands; (8) reduced functioning of the kidney or liver; (9) pregnant or breast-feeding; (10) hypersensitivity to pramipexole or domperidone; (11) current diagnosis of alcohol dependence; (12) not allergic to lactose; (13) be a vegan; (14) normal or corrected-to-normal vision.

Despite passing screening, on later inspection of drug histories, 4 dependent smokers and 1 occasional smoker would have been considered ineligible. 1 dependent smoker claimed to have a past, but not a current, diagnosis of alcohol dependence, and yet also reported drinking 18 units/day. Furthermore, 3 dependent smokers reported using cannabis regularly: 1 day/week, 2.5 days/week and 7 days/week. 1 occasional smoker reported using cannabis 1.15 days/week. The dependent smoker who reported using cannabis 2.5 days/week also previously used other illicit drugs on a regular basis, which was a further concern.

Analyses were carried out with all 40 participants to maintain power, but I also carried out each analysis without these 5 participants to test whether it altered the pattern of significant results.

4.2.2 Assessments

4.2.2.1 DReaM-Choice (figure 4.1)

This task was very similar to that described in study 1 (section 2.2.2.1, figure 2.2) but the task was modified by removing the factor of magnitude and halving the amount of trials. Furthermore, abstract stimuli were used to represent each reward and they were matched for luminance and complexity

(figure 4.2). I was concerned that the real pictures used for the DReaM-Choice cues in chapter 2 could have affected behaviour, perhaps via Pavlovian-to-instrumental transfer, and that the differences in luminance and complexity could have affected attentional processing. Finally, the anticipate stage was extended.

This version of the task was programmed with Experiment Builder (SR Research, Ontario, Canada). The basic structure of the task was the same, with some additions. On each trial participants: made a choice between two reward types (unlimited time), saw the word of the selected reward type (0.5s), anticipated working for the reward (4s), worked for the reward by pressing the spacebar with the non-dominant little finger (7s) and received feedback about how many points were won (1s). See figure 4.1 for a diagram of the task. Before completing the actual task, participants were asked to press a button as many times as they could in 7s with their dominant little finger on three occasions. The average of this was used as their baseline button-pressing speed. This was used for point calculation and to determine whether the groups differed or the drug affected general pressing speed.

The number of points won on a single trial was calculated by:

$$\frac{100 * number\ of\ spacebar\ presses}{b}$$

where b was the average number of times the spacebar was pressed during the 3 baseline button-pressing trials. As in chapter 2, this was to roughly equate the number of points each participant won.

The delivered rewards were the same as in study 1 however the unit size of chocolate was halved because many participants in study 1 ended up with leftover chocolate that they didn't want to consume. Thus 400 points were required for one unit of each reward: ¼ cigarette, 30s music, ½ chunk of chocolate, 1 piece of paper.

There were 72 trials in total in this version of the DReaM-Choice task. The task produces two main behavioural outcome variables: (1) number of choices for each reward type, which assesses 'relative

preference'; (2) average number of button-presses (BP) for each reward, which assess motivation. As in chapter 2, I also measured the average time taken to choose each reward type.

After the task, participants received their delivered rewards and had 20 minutes to consume them. Every time they consumed one unit their subjective liking (rated from -10 'extremely dislike' to +10 'extremely like') were recorded.

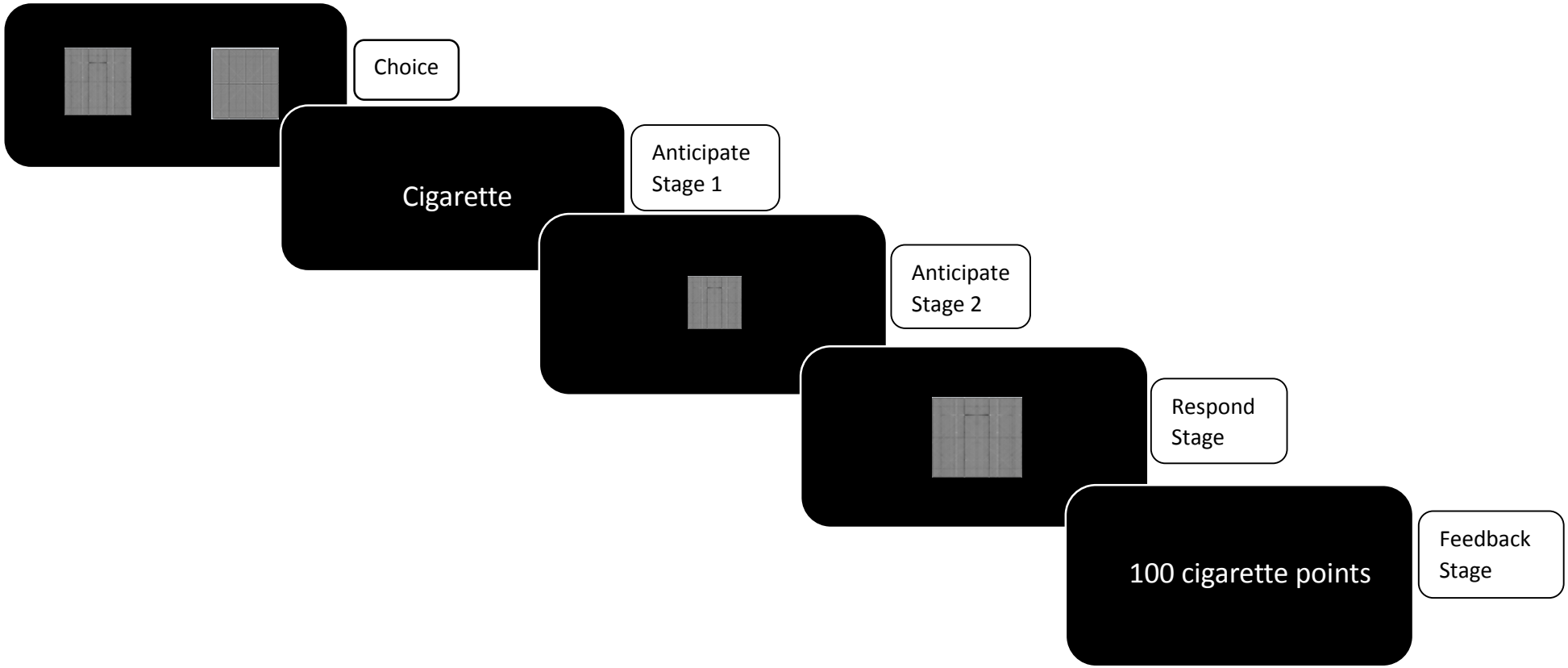


Figure 4.1 Diagrammatic representation of a single trial of the DReaM-Choice Task. During the 'choice stage' the cues were presented and a choice was made with button F (left option) or J (right option) (unlimited time); during the 'anticipate stage 1' the word of the reward, e.g. 'cigarette', was shown (0.5s); during the 'anticipate stage 2' a small version of the cue was shown (4s); during the 'respond stage' the spacebar was pressed as many times as desired with the non-dominant little finger in 7s (Treadway et al., 2009), in order to win points for the chosen reward; during the 'feedback stage' feedback concerning the amount of points won was provided for 1s. Each of the 12 possible choices were presented twice in 2 blocks, making a total of 72 trials, with trial order pseudo-randomized and left/right cue position counterbalanced.

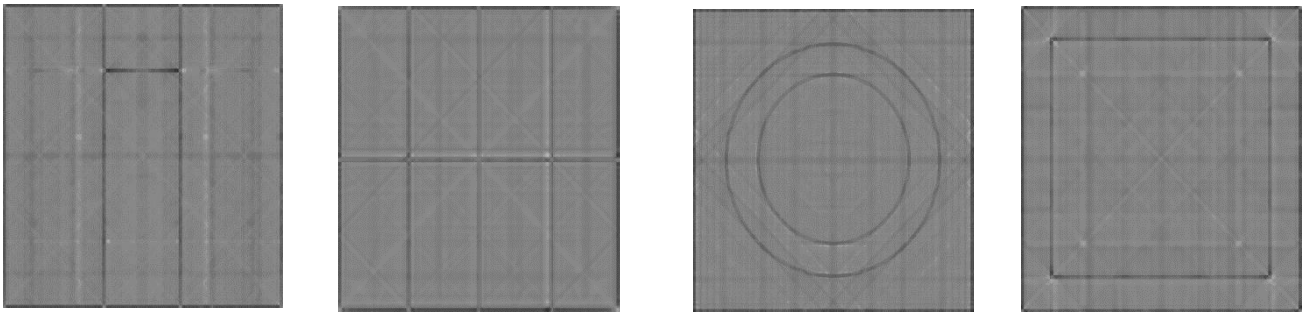


Figure 4.2 The cues used in the DReaM-Choice task to represent each reward. From left to right: cigarette, chocolate, music, paper.

4.2.2.2 Cigarette Purchase Task (CPT)

The CPT assesses the value of cigarettes relative to money and is an analogue of progressive-ratio operant tasks as consumption is investigated under progressively increasing cost. It is an established and well-validated task to examine the behavioural economic concept of 'demand' relating to cigarettes (Chase, MacKillop, & Hogarth, 2013; MacKillop et al., 2008). In this version, participants were hypothetically asked how many cigarettes they would buy for the next 3 hours at increasing prices (Hitsman et al., 2008). The instructions were as follows:

"Imagine that you could smoke RIGHT NOW AND FOR THE NEXT 3 HOURS. The following questions ask how many cigarettes you would consume if they cost various amounts of money. Assume the available cigarettes are your favourite brand. Assume that you have the same income/savings that you have now and NO ACCESS to any other cigarettes or nicotine products. In addition, assume that you cannot save or stockpile cigarettes for a later date after the 3 hours us up. Answer each question individually, i.e. the amount of cigarettes you would buy for price X should not affect the amount of cigarettes you would buy for price Y. remember it is asking you about how many cigarettes you would smoke RIGHT NOW AND FOR THE NEXT 3 HOURS."

Participants were asked “How many cigarettes would you smoke if they were _____ each”. Prices included: £0 (free), 1p, 2p, 5p, 10p, 15p, 20p, 25p, 30p, 35p, 40p, 45p, 50p, 60p, 70p, 80p, 90p, £1, £2, £3, £4, £5, and were presented in that order.

The CPT produces a demand curve and I investigated these outcome variables: (1) breakpoint, i.e. the price at which the number of cigarettes bought becomes zero; (2) intensity, i.e. the number of cigarettes bought at price £0; (3) Omax, i.e. maximum expenditure; and (4) Pmax, i.e. the price at which expenditure is maximum.

4.2.2.3 Probabilistic Reward Task (Pizzagalli et al., 2005) (figure 4.3)

As described in chapter 1, this task tapped responsiveness to reward, in terms of reward learning. The task involved two stimuli that were reinforced with an asymmetrical reinforcement schedule, such that a response bias towards the more reinforced stimulus was produced.

The task used two different lengths of mouth as the stimuli. The short mouth was 8mm and the long mouth was 9mm. The participant’s aim was to quickly determine whether the mouth was short or long and they could win money if they responded correctly.

The task comprised two blocks of 100 trials. The trials were pseudo-randomised such that a maximum of 3 long or short mouths appeared consecutively. At the start of each trial, a fixation-cross was presented for a jittered time (750ms, 800ms, 850ms, or 900ms). A mouthless face was then presented for 500ms followed by the appearance of the mouth in the face for 97ms. After the mouth disappeared, the mouthless face remained on the screen for 1500ms or until the participant responded with the ‘v’ or ‘m’ key. The participant pressed the ‘v’ key if they thought the mouth was short and pressed the ‘m’ key if they thought the mouth was long. Subsequently, feedback was provided for 1500ms, e.g. ‘Correct!!! You won 5p’ and then a blank screen was shown for 2000ms.

Not every correct response was reinforced. Critically, one of the stimuli (the 'rich' stimulus) was reinforced three times more frequently than the other stimulus (the 'lean' stimulus). Each block had 50 rich stimuli and 50 lean stimuli; 30 of the rich stimuli had the opportunity for reinforcement while 10 of the lean stimuli had the opportunity for reinforcement. If a stimulus with the opportunity for reinforcement was not correctly identified, the next stimulus of that type (rich or lean) that was not going to be reinforced became a stimulus with the opportunity for reinforcement. This was to ensure that participants had similar numbers of reinforced rich and lean stimuli (ideally 30 and 10, respectively). Before the task began, participants were told that only some of the correct responses would be reinforced but they were not told that one of the stimuli was more likely to be reinforced than the other. Half of participants had the long mouth as the rich stimulus first and half of the participants had the short mouth as the rich stimulus first. This was counterbalanced such that half of the first group had pramipexole first and half of the second group had pramipexole first.

Previously, participants' data have been excluded if they meet various criteria, e.g. more than 20 trials out of 100 in a single block had response times of <100ms (Janes et al., 2015) (see section 5.4.2.1 for exact details on exclusion criteria). However, in this study, because 23/40 of the participants did not meet these criteria, I included everyone to increase the power of the analysis. This is a clear limitation of this aspect of the experiment which is discussed in section 4.4.5.

Response bias, which indexed a person's bias towards the more frequently reinforced stimulus, was calculated using the following formula:

$$Response\ Bias = \frac{1}{2} * log \frac{Rich\_correct * Lean\_incorrect}{Lean\_correct * Rich\_incorrect}$$

Discriminability, which indexed a person's ability to differentiate the stimuli, was calculated using the following formula:

$$Discriminability = \frac{1}{2} * log \frac{Rich\_correct * Lean\_correct}{Rich\_incorrect * Lean\_incorrect}$$

Rich_correct refers to the number of rich stimuli that were correctly identified. Lean_correct refers to the number of lean stimuli that were correctly identified. Rich_incorrect refers to the number of rich stimuli that were incorrectly identified. Lean_incorrect refers to the number of lean stimui that were incorrectly identified.

The task therefore produces one main outcome: response bias, and three other important outcomes: discriminability, accuracy and reaction time.

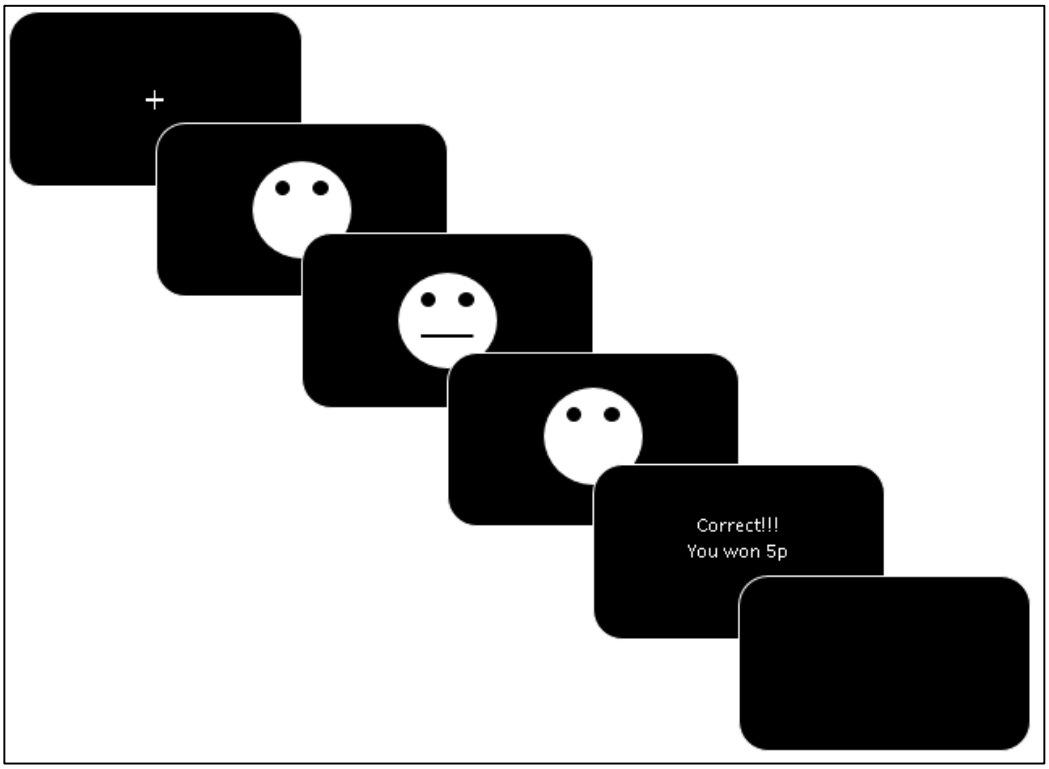


Figure 4.3 Diagrammatic representation of the Probabilistic Reward Task (Pizzagalli et al., 2005) used in this chapter. (1) A fixation cross is shown for a jittered time (750ms, 800ms, 850ms, or 900ms), (2) a mouthless face is shown for 500ms; (3) the mouth is added to the face for 97ms; (4) the mouthless face is shown for 1500ms or until the participant responds, stating they thought it is the long or short mouth; (5) feedback is given for 1500ms; (6) a blank screen is shown for 2000ms.

4.2.2.4 Effort Expenditure for Rewards Task (EEfRT) (Treadway et al., 2009)

This task tapped effort-related decision-making. Participants made a series of decisions between two different effort-options: a low-effort choice, in which a small amount of money was available to be won (50p), and a high-effort choice, in which a larger amount of money was available to be won (80p,

£1.00, £1.20, £1.40, £1.60, £1.80, £2.00). The low-effort choice required 30 spacebar presses with the little finger of the non-dominant hand in 7s. The high-effort choice required 100 spacebar presses with the little finger of the non-dominant hand in 21s. Participants were not guaranteed to win the money available if they completed the task; this was determined probabilistically. On one third of the trials there was a 12% chance (low probability), on another third there was a 50% chance (medium probability), and on another third there was an 88% (high probability) chance of winning the money if they completed the required number of spacebar presses in time. The probability level applied to both the low-effort and high-effort choice.

The probability level and the amounts of money available to be won were presented on screen to the participant (see figure 4.4). Participants had 8s to make their choice; if they did not make a choice in that time the computer randomly selected one. Following a 0.5s fixation-cross and the spacebar-pressing stage, 2s of feedback were given about whether the participant had successfully completed the spacebar-pressing in time, and if successful, 2s of feedback were given about whether money had been won or not. Participants completed 21 trials in total and the trial order was randomized. Participants kept the amounts of money won on two trials; these were randomly selected at the end of the task.

Important predictor variables in this task are probability (chance of winning on each trial if the trial is completed), magnitude (the amount of money available on the high-effort choice) and expected value (i.e. the multiplication of probability and magnitude). Furthermore, trial number has previously been associated with more low-effort choices, as participants become more tired, and being male has been associated with more high-effort choices (Treadway et al., 2009).

Trials were considered 'incomplete' if the participant did not finish the button-pressing in the allocated time. Participants were excluded from the analysis if they failed to complete 10 or more trials on any one session. This was because I wished to exclude participants who did not engage with

the task properly. The main outcome variable of the task was, on each trial, whether the participant made a low-effort or a high-effort choice.

It is possible that the speed at which a participant tapped affected choice behaviour. Hence, before the actual task, they were asked to press as fast as they could with their little finger in order to complete 30 and 100 presses; the time taken to make that number of presses (baseline button-pressing time) was recorded. This was to acquire a measurement of their baseline button-pressing speed.

It is important to note that the EEfRT used here (as described above) was slightly different to the original EEfRT (Treadway et al., 2009) in a number of ways, the original version: (1) had more trials; (2) finished after a set amount of time, not a set amount of trials; (3) used the dominant index finger for the easy option; (4) had a continuous variation in money available to be won; and (5) gave participants 5s to choose which option.

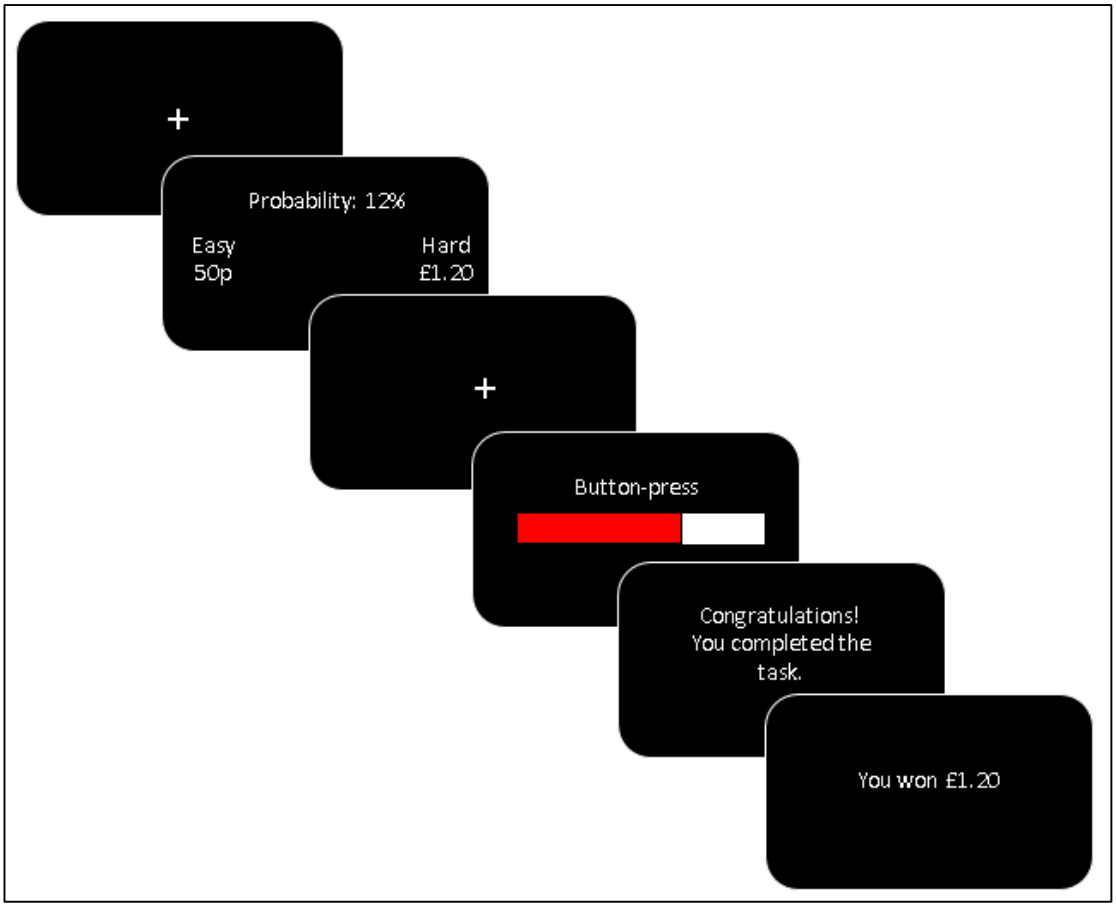


Figure 4.4 Diagrammatic representation of a single trial from the EEfRT. (1) A fixation cross is shown for 0.5s; (2) A choice is made between an easy option and a hard option. The amount of money available to be won for both the easy option and the hard option is shown. The probability of winning the money if the subsequent button-pressing is completed is shown; (3) A fixation cross is shown for 0.5s; (4) Button-pressing is completed for 7s, or until 30 presses are completed, (easy option) or 21s, or until 100 presses are completed, (hard option); (5) Feedback is given about whether the button-pressing was completed in time; (6) Feedback is given about whether money has been won and, if so, how much.

4.2.2.5 Self-rated assessments

State measures

Tobacco craving questionnaire - short form (TCQ-SF) (Heishman et al., 2008)

As described in section 3.2.2.2

Mood and physical symptoms scale (MPSS) (West & Hajek, 2004)

As described in section 3.2.2.2

Snaith Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995)

As described in section 2.2.2.2

Drug Effects Questionnaire (DEQ) (Morean et al., 2013)

This assessment comprised 5 visual-analogue-scales (VAS) rated according to how the participant feels 'right now' from 0mm ('not at all') to 100mm ('extremely'): (1) 'do you feel a drug effect'; (2) 'are you high'; (3) 'do you dislike any of the effects'; (4) 'do you like any of the effects' and (5) 'would you like more'.

Subjective Effects

'Hungry', 'nauseous', 'euphoric', 'dizzy', and 'drowsy' were rated according to how the participant felt 'right now' from 0 ('not at all') to 10 ('extremely').

Trait measures

Apathy evaluation scale (AES) (Marin, Biedrzycki, & Firinciogullari, 1991)

This scale of apathy, or 'amotivation', consisted of 18 items that were rated from 1 (not at all characteristic) to 4 (very characteristic). Higher scores reflected greater apathy.

Barratt impulsiveness scale (BIS) (Patton & Stanford, 1995)

As described in section 3.2.2.2

Beck depression inventory (BDI-II) (Beck et al., 1996)

As described in section 2.2.2.2

Behavioural activation/inhibition systems scale (BIS/BAS) (Carver & White, 1994)

As described in section 3.2.2.2

Brief sensation seeking scale (BSSS) (Hoyle et al., 2002)

As described in section 3.2.2.2

Cigarette dependence scale (CDS-5) (Etter et al., 2003)

As described in section 3.2.2.2

Drug history

Participants were asked about: (1) lifetime use; (2) number of lifetime exposures; (3) if used in lifetime, how many days used per month now.

DSM-5 Tobacco use disorder.

As described in section 2.2.2.3

Fagerstrom test for nicotine dependence (FTND) (Heatherton et al., 1991)

As described in section 2.2.2.2

Frequency and general liking of rewards

Participants were asked how many days per week, on average, they smoked a cigarette, listened to some music or ate some chocolate. They were also asked how much they liked, in general, smoking a cigarette, listening to their favourite music and eating Diary Milk chocolate (from -10 'extremely dislike' to +10 'extremely like').

Temporal experiences of pleasure scale (TEPS)

As described in section 2.2.2.2

4.2.2.6 *Other assessments*

Spot-the-word (Baddeley et al., 1993)

As described in section 2.2.2.3

Carbon monoxide

As described in section 2.2.2.3

4.2.3 Procedure

Participants attended two 3.5 hour sessions separated by a washout period lasting between 7 and 25 days (mean=9, SD=4.42). Participants were asked to fast for an hour beforehand and to avoid driving or operating heavy machinery on the day of testing. First, participants provided a carbon monoxide (CO) reading (Bedfont Micro Smokerlyzer, UK) and completed the state questionnaires (excluding the DEQ).

The drug was then orally administered, which was 0.5mg pramipexole (peak plasma levels at 1-3h) (Wright, Sisson, Ichhpurani, & Peters, 1997) or matched placebo (lactose powder). Participants were given one of two capsules, which looked identical, and they swallowed the capsule with a cup of water. Blinding was maintained by a colleague (who never tested participants) designing the code that determined which participant received which drug on which session. This same colleague also made the drugs up.

Based on previous research (Ersche et al., 2010; Freeman et al., 2013), 30mg of the peripheral dopamine D2 antagonist domperidone was orally administered on both sessions to reduce unwanted side effects such as nausea. Immediately after drug administration, participants completed trait questionnaires that were split across the two sessions. Testing began 90min post drug administration. Assessments were conducted in the following order: state questionnaires (90min), CPT (100min), EEfRT (105min), PRT (120min), DReaM-Choice (145min), consumption (175min), state questionnaires

(195min). Smoking was not permitted until the consumption stage of the experiment. Participants were reimbursed £7.50/hour and could earn extra money from the EEfRT and PRT.

In terms of ethical considerations, participants were fully informed about the potential side effects of pramipexole; were advised not to drink alcohol, drive a vehicle or operate machinery afterwards; and a doctor was always available on the telephone.

4.2.4 Statistical analyses

All data were analysed using IBM Statistical Package for Social Sciences (IBM SPSS version 22).

The majority of data were analysed using the general linear model. Where residuals were not normally distributed or the group variances were not homogenous, non-parametric tests were used when available and appropriate. In repeated-measures ANOVA, when sphericity was violated, the Greenhouse-Geisser correction was used and corrected degrees of freedom are reported. In order to explore significant interactions, a Bonferonni correction was applied to post hoc comparisons via the syntax in SPSS.

Self-report data

Subjective effects, DEQ, TCQ-SF, MPSS and SHAPS data were analysed using mixed-design ANOVAs with a between-subjects factor of group (dependent and occasional) and within-subjects factors of drug (placebo and pramipexole) and time (pre-drug, post-drug, post-consumption). Post-drug refers to approximately 90 mins after drug administration. Post-consumption refers to approximately 195 mins after drug administration, and just after the 20 mins reward consumption period.

DReaM-Choice

Choices and BP data from the DReaM-Choice were analysed using mixed-design ANOVAs with a between-subjects factor of group and within-subjects factors of drug and reward (cigarette, music,

chocolate and paper). As in chapter 2, when one reward type was never chosen, a BP score of 0 was assigned. Reaction time data were analysed in the same way but without paper included.

Liking of the first unit of each reward data were analysed using a mixed effects model with group, drug and reward (and their interactions) as fixed factors and the intercept allowed to vary randomly.

CPT

Data from the cigarette purchase task (breakpoint, intensity, Omax and Pmax) were all $\log_{10}$ transformed so that the residuals were more normally distributed. Mixed-design ANOVAs with a between-subjects factor of group and a within-subjects factor of drug were then carried out on each outcome.

PRT

Response bias (RB) and discriminability from the PRT were analysed using mixed-design ANOVAs with a between-subjects factor of group and a within-subjects factor of drug. Reaction time and accuracy were analysed in the same way with an extra within-subjects factor of stimulus (rich and lean). As many participants would have traditionally been excluded on this task for their performance, I also explored the consequences of changing the exclusion criteria on the pattern of results.

EEfRT

Generalized estimating equation (GEE) models were used to analyse the likelihood of participants making a high-effort choice. GEE models allow the outcome variable to be non-normally distributed with correlated residuals: a binary outcome in this case. GEE models allow parameters that vary on a trial-by-trial basis to be incorporated and they deal with missing data without excluding all of a participant's data. Furthermore, these characteristics mean GEE models have more power to detect effects than general linear model approaches. The outcome measure was choice (high-effort or low-

effort), modelled using a binary logistic distribution. I used an unstructured working correlation matrix.

I tested whether pramipexole and group affected the likelihood of making a high-effort choice. Using the same approach as Treadway et al. (2009), I computed 8 separate models. Each model included the standard predictors according to Treadway et al. (2009) (magnitude, probability, expected value, trial number, gender) plus drug and group. Every model included these terms plus: no others (model 1), drug X magnitude (model 2), drug X probability (model 3), drug X expected value (model 4), group X magnitude (model 5), group X probability (model 6), group X expected value (model 7), group X drug (model 8). The reference categories were: drug = placebo, group = occasional, gender = female. Magnitude, probability, expected value and trial number were modelled as continuous predictors. SPSS uses dummy coding, so the coefficients for the main effects (e.g. drug) in models which have interactions including those same variables (e.g. drug*probability) only provide information on the main effect (e.g. drug) when the other variable (e.g. probability) is set to zero, i.e. its reference category (e.g. 12%). Hence, main effects are only useful in providing information about an overall effect when there is *not* an interaction between it and another variable included in the model.

Correlations

For the DReaM-Choice task, within each group separately, correlations were computed between both the number of cigarette choices and BP, collapsed across drug condition, and the following measures: number of cigarettes smoked/day, general liking of cigarettes and total TEPS score.

Correlations were computed between total TEPS score and: PRT average response bias, PRT change in response bias, the total number of high-effort choices made in the EEfRT, average DReaM-Choice button-pressing for cigarettes and non-drug rewards, all collapsed across drug conditions. Finally, within each session and within each group, TCQ-SF total score post-drug was correlated with PRT response bias and the total number of high-effort choices made in the EEfRT.

The alpha level was adjusted to 0.005 to account for multiple tests.

Participant exclusions

Each analysis was carried out with all participants and with the 5 retrospectively ineligible participants removed to determine if these exclusions altered the pattern of significant results. Furthermore, drug order was added into the models for DReaM-Choice, PRT, CPT and EEfRT data to determine if this affected the pattern of results. If there were any differences after these changes were made, these are stated.

Successful blinding

A McNemar test was carried out to determine whether participants could guess whether they had been given placebo or pramipexole.

4.3 Results

4.3.1 Demographics (Tables 4.1 and 4.2)[12]

The groups were statistically similar on all non-smoking demographic variables. The dependent smokers had greater dependence than the occasional smokers on the FTND (U_{38}=0.00, p<0.001), CDS-5 (t_{37}=11.923, p<0.001) and DSM (U_{38}=1.00, p<0.001). The dependent smokers smoked more cigarettes per day and week (U_{38}=0.00, p<0.001), started smoking at an earlier age (t_{38}=2.504, p=0.017) and reported greater subjective liking, in general, of smoking a cigarette (t_{37}=4.687, p<0.001) compared with the occasional smokers. The difference in BDI scores approached significance on both the placebo (t_{34}=1.870, p=0.070) and pramipexole ($t_{29.297}$=1.826, p=0.066) condition. Removing the 5 participants did not change the pattern of results, except that the group differences in BDI were no longer at trend level (ps>0.1)

[12] Annual income data was missing for 2 dependent smokers; CDS-5, AES, general liking of each reward, frequency of using each reward, BAS, BIS, TEPS and BSSS data was missing for 1 dependent smoker; STW data was missing for 1 occasional smoker; BDI data on the placebo session was missing for 3 dependent smokers and 1 occasional smoker; and BDI data on the pramipexole session was missing for 1 dependent smoker. Means were calculated from the remaining participants.

Table 4.1 Group means (SD) for demographic data for dependent and occasional smokers.

	Dependent	Occasional
Age	24.35 (6.81)	22.60 (3.79)
Gender (m/f)	10/10	10/10
Body mass index	23.19 (3.24)	22.86 (2.91)
Annual income (£)	12,682 (8,210)	13,111 (7,812)
Years in education	15.83 (2.68)	16.35 (1.87)
Spot-the-word	49.00 (4.10)	50.74 (3.55)
Cigarettes/day* **	16.45 (5.80)	0.54 (0.12)
Cigarettes/week* **	115.15 (40.62)	3.78 (0.83)
Age started smoking (years)*	13.40 (2.44)	15.03 (1.58)
Age started smoking 10 or more per day	16.85 (2.30)	NA
Tried to quit smoking (y/n)	15/5	9/11
Number of quit attempts	2.00 (1.41)	11.11 (19.00)
Length of most successful quit attempt (days)	101.87 (180.95)	333.11 (60.0)
FTND* **	5.70 (1.03)	0
CDS-5* **	18.53 (3.12)	7.75 (2.51)
DSM-5* **	6.20 (1.85)	1.20 (1.00)
BDI on placebo session	9.76 (7.16)	6.05 (4.60)
BDI on pramipexole session	9.74 (7.64)	6.05 (3.46)
Apathy evaluation scale	52.16 (6.13)	51.85 (5.16)
BISBAS drive	11.11 (2.13)	12.10 (1.77)
BISBAS fun-seeking	12.95 (1.65)	12.50 (1.96)
BISBAS reward responsiveness	17.42 (1.64)	17.20 (1.74)
BISBAS inhibition	21.74 (4.55)	21.20 (3.55)
TEPS anticipatory	40.79 (6.55)	40.35 (5.95)
TEPS consummatory	38.42 (6.34)	36.10 (5.81)
TEPS total	79.53 (11.23)	76.45 (9.65)
BSSS	31.05 (4.85)	30.55 (5.37)
BIS attentional	17.79 (2.59)	16.55 (3.33)
BIS motor	24.26 (4.62)	22.30 (4.37)
BIS nonplanning	26.05 (4.62)	25.35 (5.28)
BIS total	68.11 (10.51)	64.20 (10.76)

**p<0.05, ***p<0.001. FTND Fagestrom test for nicotine dependence; CDS-5 Cigarette dependence scale; DSM-5 Diagnostic and statistical manual tobacco use disorder; BISBAS Behavioural activation/inhibition systems scale; TEPS Temporal experience of pleasure scale; BSSS brief sensation seeking scale; BIS Barratt impulsiveness scale*

Table 4.2 Group means (SD) for the frequency and general liking of rewards for dependent and occasional smokers

	Dependent	Occasional
Like smoking one cigarette, in general (-10 to 10)	8.21 (1.58)	5.15 (2.39)
Like listening to one song of favourite music, in general (-10 to 10)	8.26 (2.02)	7.20 (2.35)
Like eating Diary Milk chocolate, in general (-10 to 10)	1.84 (5.93)	4.25 (2.73)
Like receiving £1, in general (-10 to 10)	7.47 (2.27)	6.70 (2.25)
Days/week smoke at least one cigarette	7.00 (0.00)	2.73 (1.50)
Days/week listen to music	6.47 (1.17)	6.20 (1.54)
Days/week eat chocolate	2.37 (1.61)	2.70 (1.63)

4.3.2 Drug use (Table 4.3)

The groups did not differ on any measure of drug or alcohol use.

4.3.3 Subjective effects

Across both sessions, hunger increased throughout the experiment ($F_{2,76}$=24.433, p<0.001). On the pramipexole session, but not the placebo session: nausea increased from pre-drug to post-drug (t_{39}=3.420, p=0.004); dizziness increased from pre-drug to post-drug (t_{39}=3.289, p=0.006) and to post-consumption (t_{39}=3.409, p=0.005); and euphoria decreased from pre-drug to post-drug (t_{39}=3.340, p=0.006) and to post-consumption (t_{39}=3.137, p=0.010). Furthermore, at post-consumption only, drowsiness was greater on the pramipexole session than the placebo session (t_{39}=4.695, p<0.001).

4.3.4 Drug effects questionnaire

Across both sessions, ratings of 'feel drug' increased throughout the experiment ($F_{1,38}$=4.669, p=0.037). Ratings of 'feel drug' ($F_{1,38}$=6.477, p=0.015) and 'dislike drug' ($F_{1,38}$=7.684, p=0.009) were greater and ratings of 'want drug' ($F_{1,38}$=8.017, p=0.007) were smaller on the pramipexole session compared with the placebo session. On the pramipexole, but not the placebo session, 'like drug' scores decreased from post-drug to post-consumption (t_{39}=2.900, p=0.006).

Table 4.3 Group means (SD) for drug taking in dependent and occasional smokers

	Dependent	Occasional
Alcohol ever used (y/n)	20/0	20/0
Alcohol days per week	2.43 (2.33)	2.03 (1.14)
Amount in typical session (units)	8.65 (5.16)	7.73 (6.51)
Alcohol life exposures	1,294 (2,580)	617 (521)
Amphetamine ever used (y/n)	9/11	4/16
Amphetamine days per month	0.54 (1.40)	0.15 (0.13)
Amphetamine life exposures	17.07 (66.7)	0.60 (1.50)
Benzodiazepines ever used (y/n)	8/12	4/16
Benzodiazepines days per month	0.69 (1.47)	1.04 (1.97)
Benzodiazepines life exposures	17.90 (39.95)	3.33 (7.33)
Cannabis ever used (y/n)	19/1	19/1
Cannabis days per month	3.07 (7.03)	0.92 (1.38)
Cannabis life exposures	235 (318)	367 (919)
Cocaine ever used (y/n)	11/9	10/10
Cocaine days per month	0.34 (0.49)	0.18 (0.15)
Cocaine life exposures	12.45 (23.56)	17.95 (55.66)
Ketamine ever used (y/n)	7/13	6/14
Ketamine days per month	0.37 (0.65)	0.19 (0.37)
Ketamine life exposures	3.70 (9.64)	4.50 (9.84)
LSD ever used (y/n)	7/13	6/14
LSD days per month	0.19 (0.36)	0.05 (0.06)
LSD life exposures	3.30 (11.10)	0.90 (1.94)
Mushrooms ever used (y/n)	9/11	6/14
Mushrooms days per month	0.17 (0.34)	0.03 (0.04)
Mushrooms life exposures	1.50 (3.42)	0.68 (1.40)
MDMA ever used (y/n)	13/7	14/6
MDMA days per month	0.71 (0.84)	0.54 (0.55)
MDMA life exposures	46.10 (92.11)	22.20 (47.34)
Mephedrone ever used (y/n)	5/15	3/17
Mephedrone days per month	0.08 (0.17)	0.03 (0.05)
Mephedrone life exposures	4.85 (14.24)	1.75 (6.72)

4.3.5 Tobacco Craving Questionnaire (TCQ; Table 4.4)

On each subscale and the total TCQ score, there was an interaction between group and time, and main effects of both group and time. Dependent smokers, compared with occasional smokers, had greater craving on each subscale. Craving scores increased from pre-drug to post-drug and decreased from post-drug to post-consumption. These changes were greater in dependent smokers than occasional smokers. There was a main effect of drug on the compulsivity and purposefulness subscales, with greater scores on the pramipexole session than the placebo session, however there was no interaction between drug and time on these subscales.

4.3.6 Mood and Physical Symptoms Scale (Table 4.5)

'Depressed' scores decreased as the experiment progressed while 'hungry', 'poor concentration' and 'time spent with urges' increased as the experiment progressed. The dependent smokers, compared with the occasional smokers, reported greater 'time spent with urges' and 'strength of urges to smoke'. There was a main effect of drug on 'strength of urges to smoke', with greater scores on the pramipexole session than the placebo session, however there was no interaction between drug and time on these subscales.

Table 4.4 Group means (SD) for TCQ-SF pre-drug, post-drug and post-consumption for placebo and pramipexole sessions for dependent and occasional smokers

		Dependent		**Occasional**		**Group X Drug X Time**	**Group X Drug**	**Group X Time**	**Drug X Time**	**Group**	**Drug**	**Time**
		Placebo	Pramipexole	Placebo	Pramipexole	$F_{2, 76}$	$F_{1, 38}$	$F_{2, 76}$	$F_{2, 76}$	$F_{1, 38}$	$F_{1, 38}$	$F_{2, 76}$
TCQ emotionality	Pre-drug	8.40 (3.79)	9.30 (4.99)	5.90 (2.81)	5.15 (2.68)	0.904	1.116	13.683***	1.463	10.752***	1.532	20.989***
	Post-drug	9.25 (4.38)	10.80 (4.65)	5.10 (3.02)	5.90 (3.31)							
	Post-consumption	6.20 (3.19)	5.65 (2.85)	5.05 (3.41)	5.15 (2.81)							
TCQ expectancy	Pre-drug	13.25 (4.13)	14.65 (3.22)	10.10 (4.14)	9.75 (4.33)	0.286	3.035	14.170***	0.353	28.847***	0.217	49.825***
	Post-drug	16.40 (3.97)	16.85 (3.15)	9.70 (4.24)	8.75 (4.23)							
	Post-consumption	9.50 (3.91)	9.90 (3.26)	7.20 (3.69)	7.20 (2.98)							
TCQ compulsivity	Pre-drug	9.05 (4.19)	10.25 (4.32)	4.30 (1.98)	4.25 (1.83)	2.782	1.638	17.425***	0.979	31.812***	4.912*	23.998***
	Post-drug	9.90 (4.93)	12.35 (5.24)	4.55 (2.48)	4.55 (2.37)							
	Post-consumption	7.50 (4.19)	6.65 (3.79)	3.80 (1.79)	4.60 (2.60)							
TCQ purposefulness	Pre-drug	12.65 (2.89)	14.10 (3.19)	8.45 (2.84)	8.30 (3.31)	1.790	0.806	8.157 ***	0.427	48.088***	5.349*	36.362***
	Post-drug	13.30 (4.78)	15.35 (3.86)	7.35 (3.07)	7.70 (2.72)							
	Post-consumption	9.80 (4.62)	9.25 (3.81)	5.55 (2.66)	6.65 (3.00)							
TCQ total	Pre-drug	43.35 (12.88)	48.30 (13.02)	28.75 (8.97)	27.45 (9.53)	1.339	2.020	18.780***	0.263	37.186***	2.891	52.705***
	Post-drug	48.85 (15.19)	53.85 (15.79)	26.85 (10.36)	26.90 (9.66)							
	Post-consumption	33.00 (14.60)	31.45 (10.95)	21.60 (10.18)	23.60 (9.70)							

**p<0.05, ***p<0.001. TCQ Tobacco Craving Questionnaire*

Table 4.5 Group means (SD) for MPSS pre-drug, post-drug and post-consumption for placebo and pramipexole sessions for dependent and occasional smokers

		Dependent		**Occasional**		**Group X Drug X Time**	**Group X Drug**	**Group X Time**	**Drug X Time**	**Group**	**Drug**	**Time**
		Placebo	Pramipexole	Placebo	Pramipexole	$F_{2, 76}$	$F_{1, 38}$	$F_{2, 76}$	$F_{2, 76}$	$F_{1, 38}$	$F_{1, 38}$	$F_{2, 76}$
MPSS depressed	Pre-drug	1.50 (0.83)	1.45 (0.69)	1.40 (0.60)	1.50 (0.76)	0.207	0.053	1.484	0.798	0.832	0.000	8.376***
	Post-drug	1.25 (0.55)	1.30 (0.57)	1.25 (0.55)	1.35 (0.67)							
	Post-consumption	1.20 (0.70)	1.25 (0.55)	1.25 (0.55)	1.20 (0.41)							
MPSS irritable	Pre-drug	1.25 (0.55)	1.30 (0.66)	1.40 (0.68)	1.75 (0.72)	0.375	0.907	2.384	0.214	0.200	0.347	3.328*
	Post-drug	1.55 (0.76)	1.65 (0.67)	1.45 (0.69)	1.50 (0.95)							
	Post-consumption	1.35 (0.67)	1.35 (0.59)	1.55 (0.89)	1.70 (1.03)							
MPSS restless	Pre-drug	1.90 (0.79)	1.75 (0.85)	1.90 (0.79)	1.75 (0.72)	0.600	0.770	2.035	0.308	0.377	0.159	3.469*
	Post-drug	1.85 (1.09)	1.75 (0.91)	1.75 (0.85)	1.65 (1.09)							
	Post-consumption	1.80 (1.01)	1.85 (0.88)	2.25 (1.07)	2.10 (1.17)							
MPSS hungry	Pre-drug	1.95 (1.15)	1.70 (0.73)	2.15 (0.93)	1.70 (0.92)	0.054	0.139	0.389	1.079	0.006	1.468	36.516***
	Post-drug	2.85 (1.09)	2.65 (1.18)	2.90 (1.21)	2.55 (1.00)							
	Post-consumption	2.95 (1.00)	2.95 (1.15)	2.85 (1.18)	2.80 (1.44)							
MPSS poor concentration	Pre-drug	1.95 (0.94)	1.80 (1.01)	1.60 (0.82)	1.70 (0.66)	1.098	0.270	0.358	0.850	0.394	1.591	6.801**
	Post-drug	1.95 (0.89)	2.30 (1.08)	1.95 (0.94)	2.10 (0.85)							

	Post-consumption	1.95 (1.00)	2.35 (0.92)	2.10 (0.91)	2.10 (0.79)							
MPSS time spent with urges	Pre-drug	2.35 (0.82)	2.35 (0.75)	0.40 (0.50)	0.70 (0.66)	1.375	0.033	0.220	0.867	100.103***	1.619	3.415*
	Post-drug	2.40 (1.27)	2.65 (0.88)	0.50 (0.69)	0.55 (0.69)							
	Post-consumption	2.60 (0.75)	2.75 (1.02)	0.70 (0.80)	0.65 (0.67)							
MPSS strength of urges to smoke	Pre-drug	2.30 (0.73)	2.40 (0.94)	0.50 (0.69)	0.90 (0.79)	1.717	0.083	1.680	0.191	73.329***	5.756*	0.288
	Post-drug	2.30 (1.26)	2.60 (0.88)	0.45 (0.60)	0.60 (0.75)							
	Post-consumption	2.35 (0.99)	2.65 (0.99)	0.60 (0.68)	0.60 (0.60)							

**p<0.05, **p<0.01, ***p<0.001. MPSS Mood and physical symptoms scale*

4.3.7 SHAPS

There were no interactions or main effects.

4.3.8 DReaM-Choice

Choices (Figure 4.5a) [13]

There was an interaction between group and reward ($F_{2.430, 89.927}$=21.009, p<0.001) and a main effect of reward ($F_{2.430, 89.927}$=55.883, p<0.001).

Exploration of the group X reward interaction showed that the dependent smokers chose cigarettes more (t_{37}=7.259, p<0.001) and chocolate less (t_{37}=4.702, p<0.001) than the occasional smokers. The dependent smokers chose cigarettes more than music ($t_{19=}$6.463, p<0.001) and chocolate (t_{19}=5.703, p<0.001), while the occasional smokers chose chocolate more than cigarettes (t_{18}=4.616, p<0.001) and music (t_{18}=4.189, p<0.001).

Overall, all rewards were chosen more than paper (ps<0.001) and cigarettes and chocolate were chosen more than music (ps<0.006).

Average number of button-presses (Figure 4.5b) [14]

There were no differences between the groups or sessions on baseline button-pressing speed.

There was an interaction between group and reward ($F_{3, 111}$=6.999, p<0.001) and a main effect of reward ($F_{3, 111}$=35.373, p<0.001). All rewards were pressed for more than paper (ps<0.001).

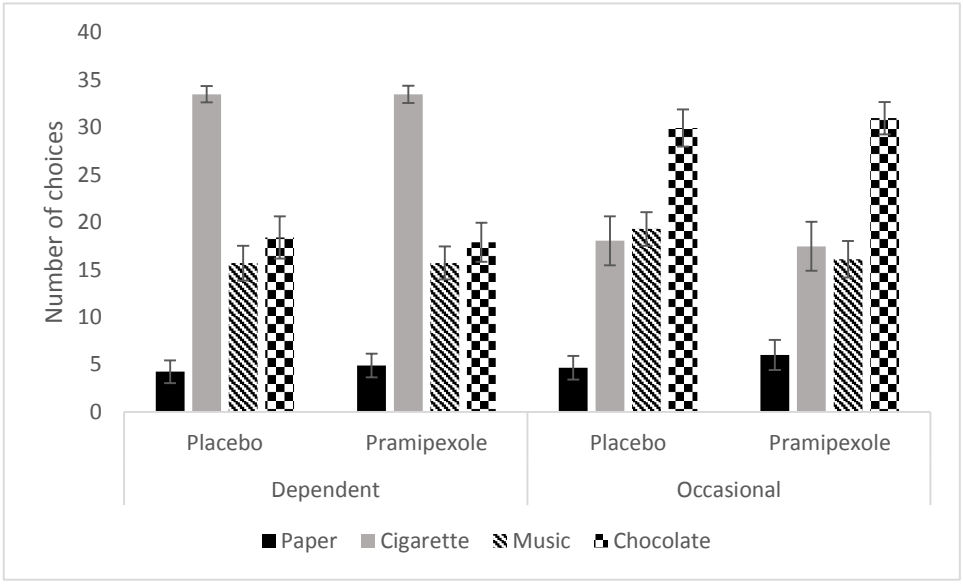
Exploration of the group X reward interaction showed that the dependent smokers pressed for cigarettes more (t_{37}=3.663, p<0.001) than the occasional smokers. The dependent smokers pressed

[13] One occasional smoker's data was missing due to a computer error.

[14] One occasional smoker's data was missing due to a computer error.

for all rewards similarly while the occasional smokers pressed for chocolate more than cigarettes (t_{18}=3.707, p=0.004).

a)



b)

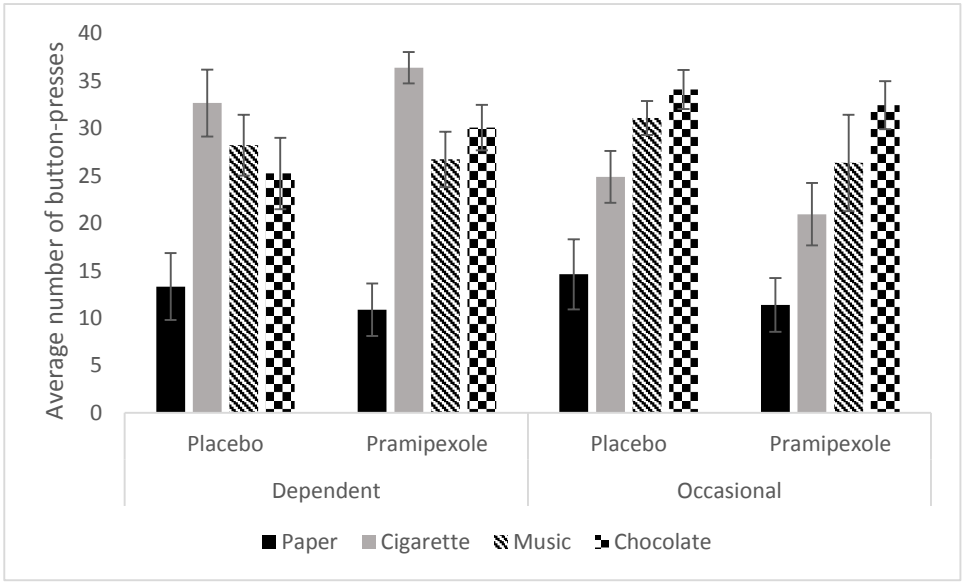


Figure 4.5 Group means for a) The number of choices for each reward type b) the average number of button-presses for each reward type, in the DReaM-Choice, for dependent and occasional smokers on the placebo and pramipexole sessions. Error bars show standard error.

Time taken to choose reward (Figure 4.6)[15]

There was an interaction between group and reward ($F_{2, 64}$=13.069, p<0.001) and a main effect of reward ($F_{2, 64}$=3.349, p=0.041). The dependent smokers chose cigarettes faster (t_{32}=3.16, p=0.003)

[15] Six participants were excluded due to never choosing one of the reward types.

than occasional smokers. Within the dependent smokers, cigarettes were chosen faster than music (t_{17}=5.707, p<0.001) and chocolate (t_{17}=3.853, p=0.002); whereas within the occasional smokers, chocolate was chosen marginally faster than cigarettes (t_{16}=2.501, p=0.053).

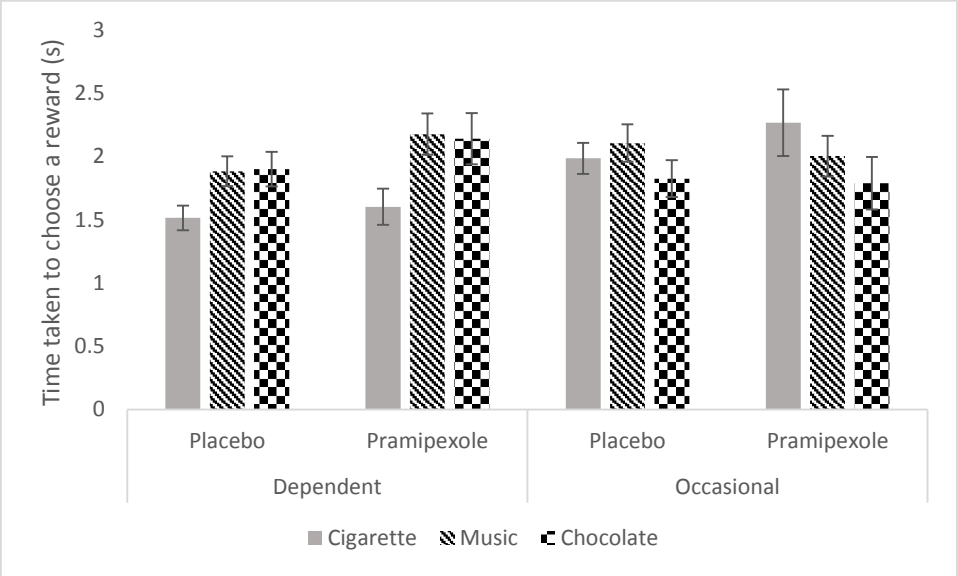


Figure 4.6 Group means for the time taken to choose a cigarette, music or chocolate reward, in the DReaM-Choice, for dependent and occasional smokers on the placebo and pramipexole sessions. Error bars show standard error.

Liking of first reward unit consumed (Figure 4.7)

There was an interaction between group and reward ($F_{2, 153}$=4.639, p=0.011) and a main effect of group ($F_{1, 153}$=18.558, p<0.001), with overall liking higher in the dependent smokers than the occasional smokers.

The group X reward interaction was explored by conducting mixed effects models within each reward separately. Dependent smokers liked cigarettes more ($F_{1, 49}$=23.500, p<0.001) and chocolate less ($F_{1, 45}$=4.296, p=0.044) than occasional smokers.

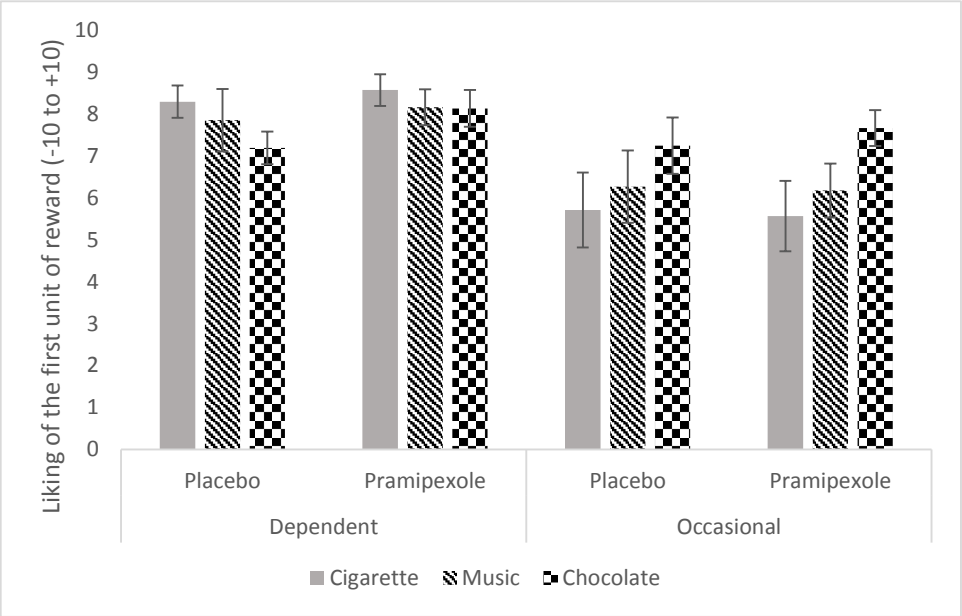


Figure 4.7 Group means for liking of (-10 'extremely dislike' to +10 'extremely like') the first consumed unit of cigarette, music and chocolate reward, in the DReaM-Choice, for dependent and occasional smokers on the placebo and pramipexole sessions. Error bars show standard error.

4.3.9 CPT (Figure 4.8)

The logarithms of breakpoint, intensity, Omax and Pmax were all significantly larger in the dependent smokers compared with the occasional smokers (ps<0.021). There was never an interaction between group and drug or an effect of drug.

4.3.10 PRT

Excluded participants

23 participants out of 40 would have been excluded if I had used the full exclusion criteria previously used for this task (Whitton, personal communication). Hence, I continued with analysis using all of the participants.

Bias (Figure 4.9)[16]

[16] 3 dependent smokers were excluded because of a computer error.

There was a main effect of drug ($F_{1, 35}$=4.566, p=0.040), with a smaller RB following pramipexole compared with placebo, and a trend effect of block ($F_{1, 35}$=3.332, p=0.076), with a marginally larger mean RB in block 2 compared with block 1.

When the original exclusion criteria were used (when 17 participants remained), the effect of drug was lost. However, there was an interaction between drug and group ($F_{1, 14}$=5.035, p=0.042) and a main effect of block ($F_{1, 14}$=6.808, p=0.021).

I also used a more liberal set of exclusion criteria[17], which used one of the traditional exclusion criteria but did not exclude people based on invalid trials, i.e. did not exclude people based on very fast reaction times, or low accuracy scores. A participant was excluded if they received reinforcement on <25 rich stimuli or received reinforcement on <6 lean stimuli on either block on either session. Using this method of exclusion, 20 participants remained (8 in the dependent group and 12 in the occasional group). The only significant effect was a drug by group interaction ($F_{1, 18}$=6.339, p=0.021).

Hence, it is clear that the nature of the exclusion criteria did affect the pattern of results.

[17] Note: reducing the reaction time which led to a trial being 'invalid' from 100ms to 75ms did not affect the exclusion of any participant, so this tactic of liberalising exclusion criteria did not affect results.

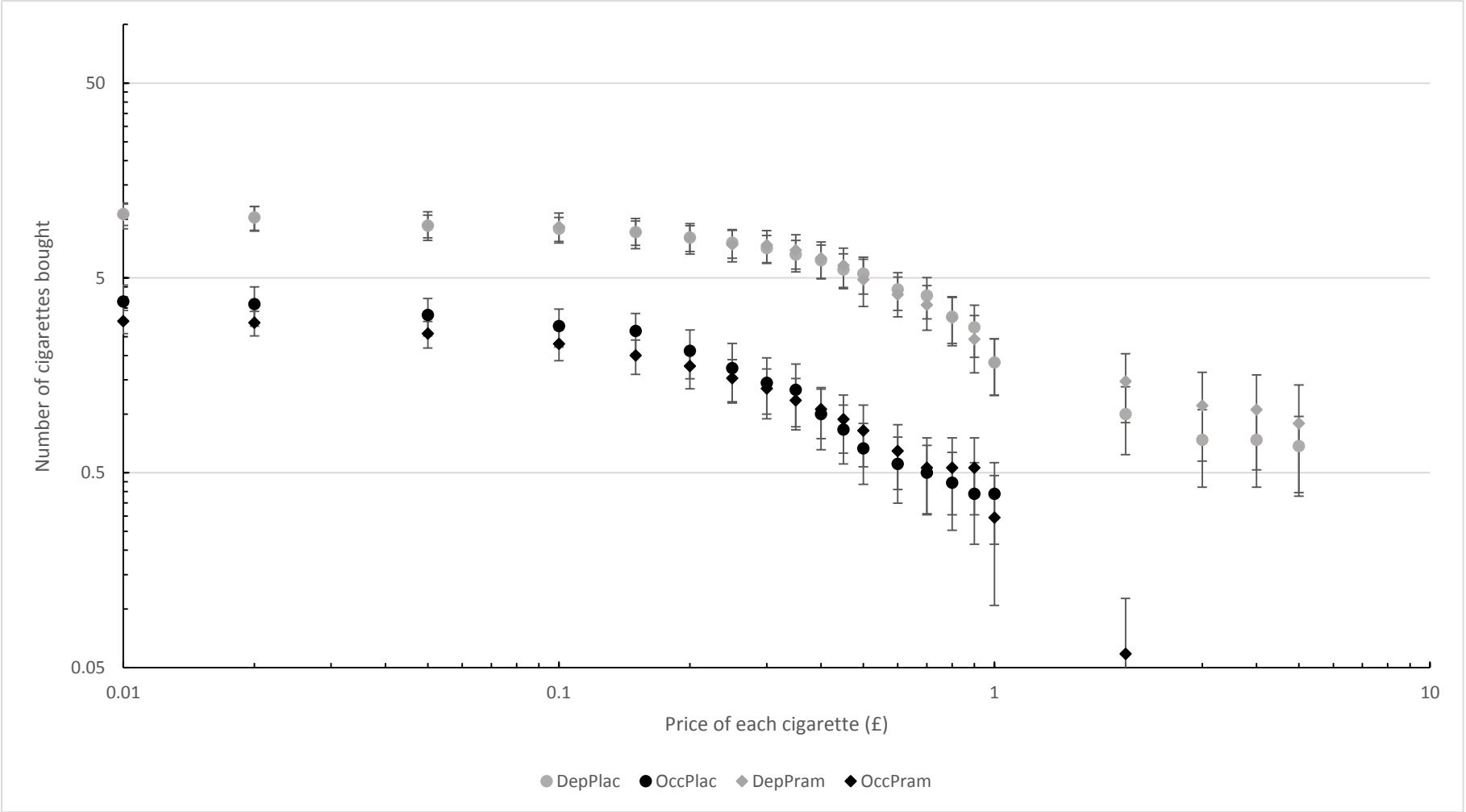


Figure 4.8 Cigarette demand curve from the CPT for dependent and occasional smokers on the placebo and pramipexole sessions. Error bars show standard error.

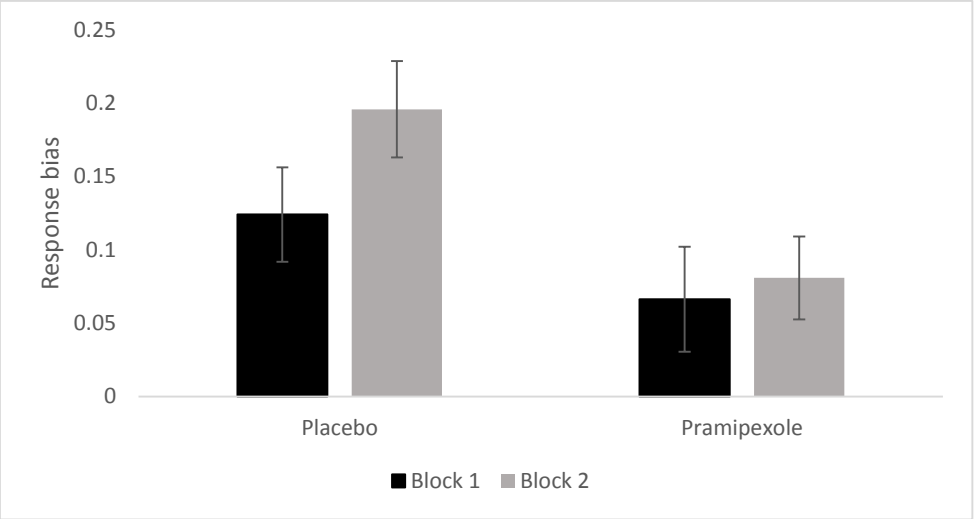


Figure 4.9 Response bias on the Probabilistic Reward Task in blocks 1 and 2 following placebo and pramipexole, collapsed across group (no extra participants were excluded in the data shown here). Error bars show standard error.

Discriminability (Figure 4.10)[18]

There was an interaction between group, drug and block ($F_{1, 35}$=5.199, p=0.029) and a main effect of drug ($F_{1, 35}$=5.907, p=0.020).

Exploration of the group X drug X bock interaction showed that discriminability on block 2 was worse on the pramipexole session compared with the placebo session in the dependent smokers (t_{16}=2.696, p=0.010) but not the occasional smokers. Overall, discriminability was worse on the pramipexole session compared with the placebo session.

Exclusion of the 5 retrospectively ineligible participants did not change the pattern of above results, apart from reducing the effect of drug to a trend (p=0.080).

[18] 3 dependent smokers were excluded because of a computer error.

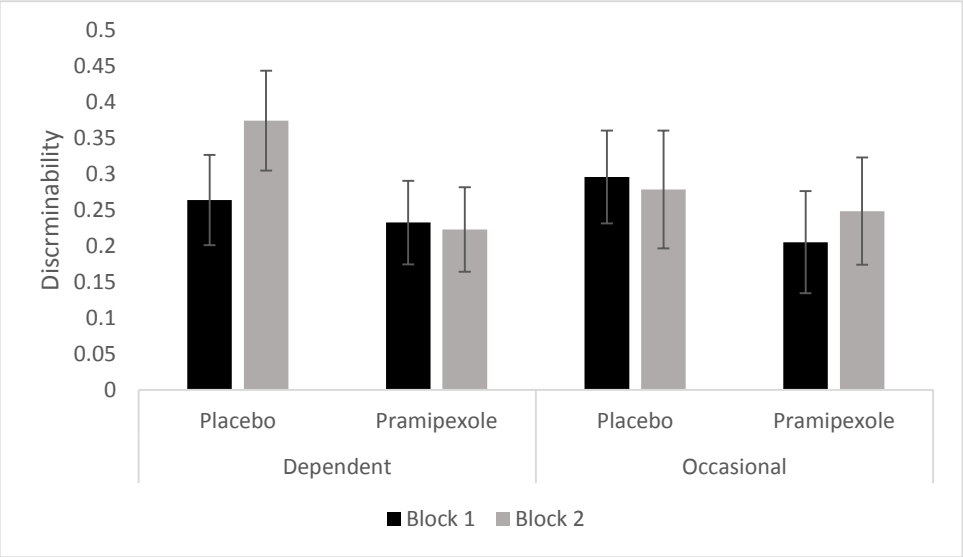


Figure 4.10 Discriminability on the Probabilistic Reward Task in blocks 1 and 2 following placebo and pramipexole. Error bars show standard error.

Accuracy[19]

There was an interaction between drug and stimulus ($F_{1, 36}$=4.448, p=0.042), and main effects of drug ($F_{1, 36}$=5.812, p=0.021) and stimulus ($F_{1, 36}$=37.601, p<0.001).

Exploration of the drug X stimulus interaction showed that accuracy was greater for the rich, compared with the lean, stimulus on the placebo session (t_{37}=5.880, p<0.001) and, to a lesser extent, on the pramipexole session (t_{37}=2.444, p=0.019). Overall, accuracy was better on the placebo session compared with the pramipexole session.

Exclusion of the 5 retrospectively ineligible participants did not change the pattern of above results, apart from reducing the effect of drug to a trend (p=0.085).

Reaction Time[20]

There was an interaction between drug and block ($F_{1, 34}$=4.472, p=0.042) and a main effect of stimulus ($F_{1, 34}$=4.472, p=0.042).

[19] 2 dependent smokers were excluded because of a computer error.

[20] 4 dependent smokers were excluded because of a computer error.

Exploration of the drug X block interaction showed that reaction time was slower on block 2 compared with block 1 (t_{35}=2.500, p=0.020). Reaction time was faster for the rich stimulus compared with the lean stimulus ($F_{1, 34}$=15.576, p<0.001).

4.3.11 EEfRT (Table 4.6 and Figure 4.11 a-c)[21]

The task parameters probability, magnitude and expected value all increased the likelihood of making a high-effort choice. In model 1, which tested the overall effects of group and drug on the likelihood of making a high-effort, neither had a significant impact. In models 2, 3 and 4, pramipexole lowered sensitivity to the augmenting effect of magnitude (p=0.017), probability (p<0.001) and expected value (p<0.001) on likelihood of making a high-effort choice, respectively. In models 5, 6 and 7, dependent smokers, compared with occasional smokers, were less sensitive to magnitude (p=0.049), probability (p<0.001) and expected value (p<0.001). Finally, in model 8, there was evidence for pramipexole having a stronger effect on the likelihood of making a high-effort choice in the dependent smokers compared with the occasional smokers (p=0.045). The main effects of drug and group in models 2-8 provide information about whether there was a main effect when the other variable in the interaction is set to its reference category, hence they should not be interpreted as main effects collapsed across all levels of all other variables.

Follow-up analyses were carried out by computing the GEE models in specific levels of each parameter. There was not a significant difference in the likelihood of making a high-effort choice on low or medium probability trials but pramipexole *reduced* the likelihood on high probability trials (b=-0.129, SE=0.0559, p=0.021, OR=0.879, 95% CI: 0.788, 0.981).

Similarly, trials were split up into equal categories of low, medium and high magnitude and low, medium and high expected value. The three categories were formed by grouping the smallest third of

[21] Two dependent smokers were excluded because they did not complete 10 or more trials on either or both sessions.

expected values/magnitudes, the middle third of expected values/magnitudes and the largest third of expected values/magnitudes. The effects of drug were non-significant at each category of magnitude and expected value and the differences between the groups were non-significant at each probability, magnitude and expected value category. However, the direction of the non-significant differences changed from low to high categories, explaining why the interactions were significant. These patterns of results are shown visually in figure 4.11 with the number of high-effort choices split between different categories.

Exclusion of the 5 retrospectively ineligible participants had these consequences: (1) removed the interaction between group and magnitude in model 5 ($p=0.251$) and (2) removed the interaction between group and drug ($p=0.145$). Inclusion of drug-order did not change the above results.

Table 4.6 GEE models for the EEfRT, showing beta coefficients for each predictor, their standard errors (S.E.), p values, odds ratios (OR) and 95% confidence intervals (CI). The reference categories were: gender – female, group – occasional, drug - placebo. The most important terms are in bold.

Model 1

	Beta	**S.E.**	**p**	**OR**	**95% CI**
Magnitude	0.133	0.0404	0.001	1.143	1.056, 1.273
Probability	0.051	0.0289	0.076	1.053	0.995, 1.114
Expected Value	0.443	0.704	<0.001	1.557	1.356, 1.787
Trial Number	-0.014	0.0019	<0.001	0.986	0.982, 0.990
Gender	0.081	0.0634	0.203	1.084	0.957, 1.227
Group	**0.008**	**0.0668**	**0.900**	**1.008**	**0.885, 1.149**
Drug	**-0.002**	**0.0319**	**0.203**	**0.954**	**1.356, 1.787**

Model 2

	Beta	**S.E.**	**p**	**OR**	**95% CI**
Magnitude	0.175	0.0395	<0.001	1.191	1.103, 1.287
Probability	0.051	0.0289	0.076	1.053	0.995, 1.114
Expected Value	0.442	0.0701	<0.001	1.556	1.357, 1.785
Trial Number	-0.014	0.0019	<0.001	0.986	0.982, 0.990
Gender	0.081	0.0632	0.200	1.084	0.958, 1.228
Group	0.008	0.0666	0.905	1.008	0.885, 1.149
Drug	0.113	0.0585	0.053	1.120	0.998, 1.256
Drug x Magnitude	**-0.083**	**0.0349**	**0.017**	**0.920**	**0.859, 0.958**

Model 3

	Beta	**S.E.**	**p**	**OR**	**95% CI**
Magnitude	0.136	0.0402	0.019	1.146	1.059, 1.240
Probability	0.103	0.0279	<0.001	1.1808	1.050, 1.171
Expected Value	0.437	0.0701	<0.001	1.547	1.349, 1.775
Trial Number	-0.014	0.0019	<0.001	0.986	0.982, 0.990
Gender	0.084	0.0402	0.019	1.099	1.015, 1.189
Group	0.008	0.0668	0.899	1.008	0.885, 1.150
Drug	0.094	0.0402	0.019	1.099	1.015, 1.189
Drug x Probability	**-0.095**	**0.0222**	**<0.001**	**0.909**	**0.871, 0.950**

Model 4

	Beta	S.E.	p	OR	95% CI
Magnitude	0.135	0.0401	0.001	1.145	1.058, 1.238
Probability	0.052	0.0293	0.075	1.054	0.995, 1.116
Expected Value	0.547	0.0793	<0.001	1.728	1.479, 2.018
Trial Number	-0.014	0.0019	<0.001	0.986	0.982, 0.990
Gender	0.085	0.0633	0.181	1.088	0.961, 1.232
Group	0.007	0.0667	0.913	1.007	0.884, 1.148
Drug	0.136	0.0417	<0.001	1.145	1.058, 1.238
Drug x Expected Value	**-0.206**	**0.0391**	**<0.001**	**0.814**	**0.754, 0.879**

Model 5

	Beta	S.E.	p	OR	95% CI
Magnitude	0.209	0.0613	0.001	1.232	1.093, 1.390
Probability	0.051	0.0292	0.081	1.052	0.994, 1.114
Expected Value	0.445	0.0707	<0.001	1.358	1.792, 1.792
Trial Number	-0.014	0.0019	<0.001	0.986	0.982, 0.990
Gender	0.081	0.0631	0.197	1.085	0.959, 1.227
Group	0.212	0.1268	0.095	1.236	0.964, 1.585
Drug	-0.002	0.0319	0.942	0.998	0.937, 1.062
Group X Magnitude	**-0.148**	**0.0750**	**0.049**	**0.0863**	**0.745, 0.999**

Model 6

	Beta	S.E.	p	OR	95% CI
Magnitude	0.130	0.0415	0.002	1.239	1.050, 1.456
Probability	0.155	0.0426	<0.001	1.168	1.074, 1.269
Expected Value	0.445	0.0726	<0.001	1.561	1.354, 1.800
Trial Number	-0.015	0.0020	<0.001	0.986	0.982, 0.989
Gender	-0.083	0.0631	0.187	0.920	0.813, 1.041
Group	0.214	0.0824	0.009	1.239	1.054, 1.456
Drug	-0.005	0.0323	0.887	0.995	0.934, 1.061
Group X Probability	**-0.203**	**0.0515**	**<0.001**	**0.817**	**0.738, 0.903**

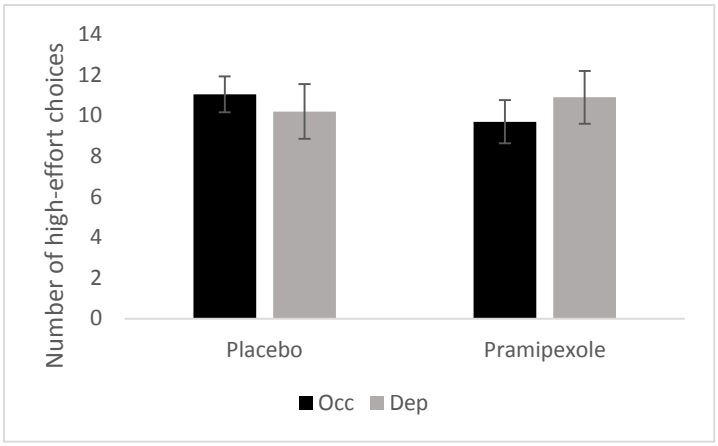
Model 7

	Beta	S.E.	p	OR	95% CI
Magnitude	0.124	0.0420	0.003	1.132	1.043, 1.229
Probability	0.041	0.0310	0.190	1.041	0.980, 1.107
Expected Value	0.704	0.0867	<0.001	2.021	1.706, 2.396
Trial Number	-0.014	0.0020	<0.001	0.986	0.982, 0.990
Gender	-0.083	0.0626	0.186	0.920	0.814, 1.041
Group	0.314	0.0928	<0.001	1.369	1.141, 1.642
Drug	-0.006	0.0325	0.862	0.994	0.993, 1.060
Group X Expected Value	**-0.456**	**0.0946**	**<0.001**	**0.634**	**0.526, 0.763**

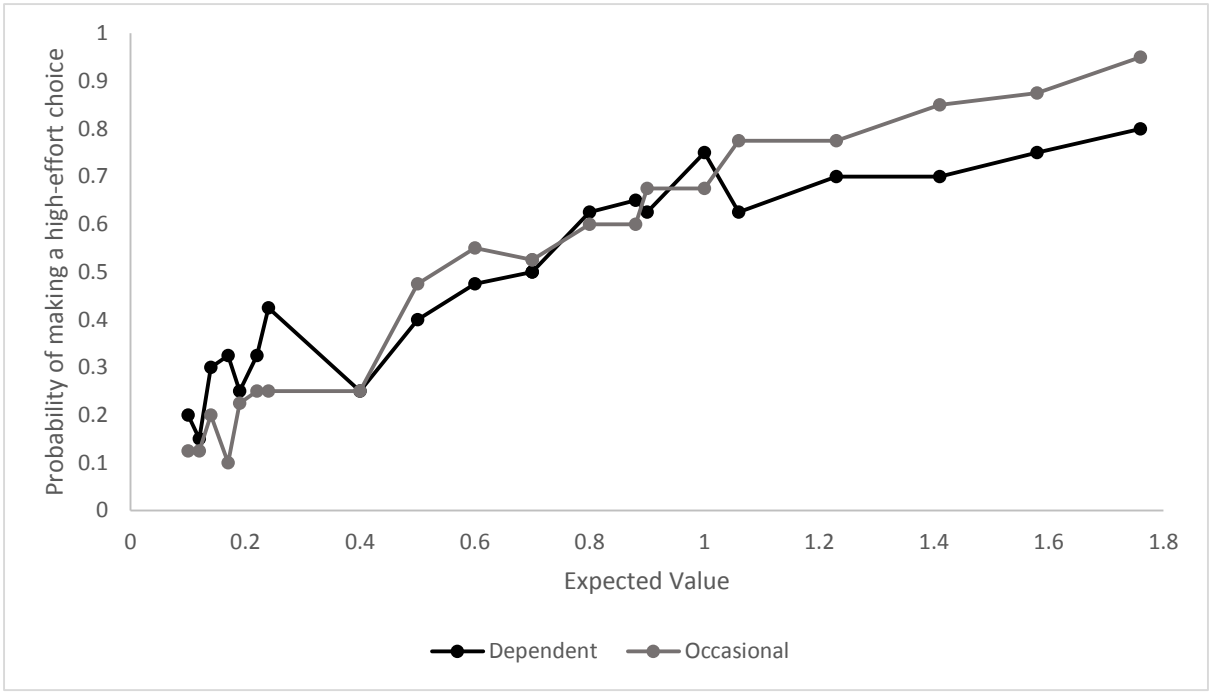
Model 8

	Beta	**S.E.**	**p**	**OR**	**95% CI**
Magnitude	0.133	0.0402	0.001	1.143	1.056, 1.236
Probability	0.052	0.0288	0.073	1.053	0.995, 1.114
Expected Value	0.441	0.0707	<0.001	1.555	1.354, 1.786
Trial Number	-0.014	0.0019	<0.001	0.986	0.982, 0.990
Gender	-0.079	0.0634	0.213	0.924	0.816, 1.046
Group	-0.057	0.0701	0.420	0.945	0.824, 1.804
Drug	-0.067	0.0347	0.054	0.935	0.874, 1.001
Group X Drug	**0.128**	**0.0641**	**0.045**	**1.137**	**1.003, 1.289**

a)


Number of high-effort choices
14
12
10
8
6
4
2
0
Placebo
Pramipexole
Occ
Dep

b)


Probability of making a high-effort choice
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
Expected Value
Dependent
Occasional

c)

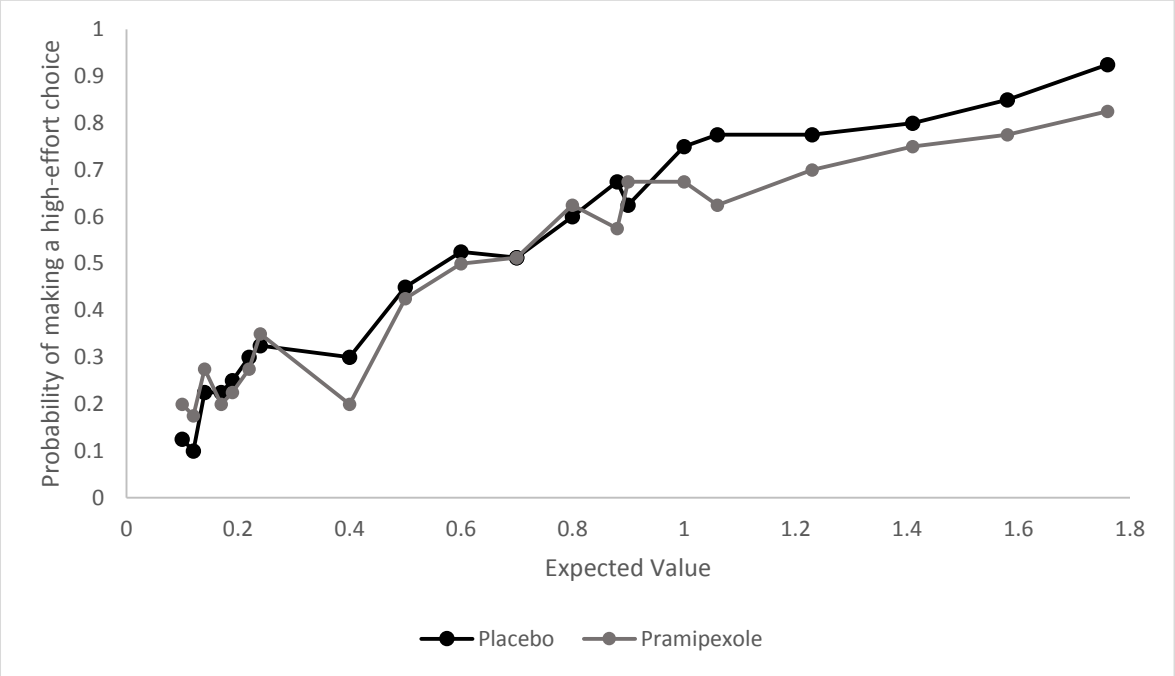


Figure 4.11 Group means for the number of high-effort choices/probability of making a high-effort choice on the EEfRT a) for dependent and occasional smokers on the placebo and pramipexole sessions, b) for dependent and occasional smokers as expected value varied, collapsed across drug conditions and c) for pramipexole and placebo sessions as expected value varied, collapsed across group.

4.3.12 Correlations

In the dependent group, none of the correlations with DReaM-Choice outcomes were significant. In the occasional group, there was a correlation between general liking of cigarettes and cigarette BP ($r=0.741$, $p<0.001$) and a marginal correlation between general liking of cigarettes and number of cigarette choices ($r=0.557$, $p=0.010$) (with the α set to 0.005). The correlations between general liking of cigarettes and cigarette BP and choices were significantly larger in the occasional group than the dependent group ($ps\leq0.02$).

Collapsed across drug condition, there were no associations between average PRT response bias, total number of high-effort choices in the EEfRT and DReaM-Choice BP for cigarettes and non-drug rewards. TEPS-total score correlated with the number of high-effort choices made in the EEfRT ($r=0.459$, $p=0.003$) but not with PRT response bias.

Within each group, the number of cigarettes smoked did not correlate with average PRT response bias or number of high-effort choices. Neither of these outcomes were associated with craving.

4.3.13 Success of the blinding

The distribution of drug guesses (whether the participant was on placebo or pramipexole) was marginally different from that of chance as determined by the McNemar test ($p=0.052$). 60% of participants correctly guessed when they had been given placebo and 67.5% of participants correctly guessed when they had been given pramipexole.

4.4 Discussion

To my knowledge, this is the first study to examine whether pramipexole influences motivation to smoke cigarettes. In dependent and occasional smokers, a single oral 0.5mg dose of pramipexole had no discernible effects on relative preference for, motivation for and liking of cigarettes or the alternative, non-drug rewards music and chocolate. Furthermore, pramipexole had null effects on

demand for cigarettes or reduce craving for cigarettes. Following results from chapter 2, dependent smokers demonstrated a greater relative preference for, motivation for and liking of cigarettes than occasional smokers.

Pramipexole significantly weakened reward learning on the PRT. However, these results are weak because many participants would have been traditionally excluded on this task – and when they were excluded the pattern of results changed. In terms of effort-related decision-making, both pramipexole administration and nicotine dependence were associated with reduced sensitivity to the pro-motivational parameters of magnitude, probability and expected value.

Our groups were well matched on demographic variables, with no significant differences on any non-smoking measure. The dependent smokers smoked an average of 16 cigarettes/day while the occasional smokers smoked an average of 0.5 cigarettes/day. Across both groups, pramipexole increased 'nausea', 'dizziness', 'feel drug' and 'dislike drug' and reduced 'euphoria' and 'want drug' ratings.

4.4.1 Pramipexole's effects on the processing of cigarette rewards in the DReaM-Choice task

Despite the strong associations between the mesocorticolimbic dopamine system, nicotine dependence (Benowitz, 2010; Dagher et al., 2001; Fehr et al., 2008) and motivation (Niv et al., 2007; Salamone et al., 2007), a single low dose of pramipexole did not affect reward processing of cigarettes in smokers. I predicted that pramipexole would reduce motivation for cigarettes because the same dose has been shown to reduce an attentional bias to cigarette images (Freeman et al., 2015) and to improve motivation for a non-drug reward (Freeman et al., 2013) in smokers who smoked a similar number of cigarettes/day as the dependent smokers in this study. Pramipexole is thought to reduce phasic dopamine firing via activation of presynaptic D3 autoreceptors (Pizzagalli, Evins, et al., 2008; Samuels et al., 2006). I predicted that a reduction in phasic dopamine firing might reduce craving (Franken, 2003; Freeman et al., 2015) and reduce the motivation to smoke. I found no evidence for

these effects, with: relative preference for, motivation for, liking of, consumption of, craving of and demand for cigarettes all unaffected by pramipexole.

Our findings question the role of D3 receptors in the maintenance of nicotine dependence and motivation to smoke. Animal research suggests D3 receptors are important in nicotine-seeking (Le Foll et al., 2005). However, I found no effects of an acutely administered D3-preferring agonist on cigarette-seeking or liking. Given bromocripine reduced ad libitum smoking (Caskey et al., 1999; Jarvik et al., 2000), D2-preferring agonists may be superior in disrupting cigarette processing. However, their results may be partially due to large increases in nausea, rather than dopamine receptor agonism. If nausea simply reduces smoking, my co-administration of domperidone may have dampened the effects of pramipexole. Future research should investigate bromocriptine's effects when domperidone is concurrently administered.

It may be that chronic, rather than acute, administration of pramipexole is needed in order to manipulate the system such that motivation to smoke is lowered. Indeed, bupropion, an approved drug for aiding smoking cessation, can increase smoking when given acutely (Cousins, Stamat, & de Wit, 2001), but reduces smoking when given chronically (Jorenby et al., 1999). Alternatively, a larger dose of pramipexole may be needed to adequately affect the motivation to smoke. If larger doses produce postsynaptic D3 receptor activation (Samuels et al., 2006) then these doses may have a qualitatively different effect on reward processing than the small dose (0.5mg) that I used in this study. Pramipexole may impair phasic *and* enhance tonic dopaminergic functioning (Ye et al., 2011); a critical balance in these changes may be required to disrupt the motivation to smoke in the way I desired.

Finally, pramipexole has been shown to reduce the strength of urges to smoke (Freeman et al., 2015). Contrastingly, in this study craving appeared to be larger (on two subscales of the TCQ-SF and the 'strength of urges' subscale of the MPSS) during the pramipexole session compared with the placebo session. Yet, there was no drug X time interaction, and the effects appeared to be driven by baseline differences (see table 4.4). So, despite these main effects, there is little evidence that pramipexole

increased craving but also no evidence that pramipexole *decreased* craving. Hence, I certainly did not replicate Freeman et al. (2015).

4.4.2 Pramipexole's effects on the processing of non-drug rewards in the DReaM-Choice

Pramipexole did not affect relative preference for, motivation for and liking of music or chocolate. I hypothesised that pramipexole would improve motivation for these non-drug rewards, given its pro-motivational acute (Freeman et al., 2013) and chronic effects (Lemke et al., 2006). I had hoped pramipexole would concomitantly enhance non-drug reward processing, while impairing cigarette reward processing (Freeman et al., 2015; Freeman et al., 2013); this potential profile of effects on drug and non-drug reward processing may have the most therapeutic benefits (Versace et al., 2014; Versace et al., 2012).

Yet, I found no effect on non-drug motivation during the DReaM-Choice button-pressing stage, nor a swing towards non-drug rewards in the choice stage. The button-pressing stage may not be very sensitive, as demonstrated by the null effect of 12h abstinence reported in chapter 2 (and similarly in Buhler et al., 2010). This could have contributed to my inability to detect an effect of pramipexole. However, the choice stage is presumably more sensitive to manipulations given my findings in chapter 2 (e.g. sensitive to abstinence) and a range of successful manipulations by Lee Hogarth (Hogarth, 2012; Hogarth & Chase, 2011). Therefore, it seems unlikely that my null results for both cigarette and non-drug reward processing are due to insensitive measures.

4.4.3 Group differences on the DReaM-Choice

Confirming results reported in chapter 2, dependent smokers, compared with occasional smokers, had greater relative preference for, motivation for and liking of cigarettes. These results corroborate my previous findings lending further support to the hypothesis that nicotine dependence is associated with a hypersensitivity to cigarettes across a wide range of reward processing metrics. My results are

remarkably similar to those reported in chapter 2, despite minor changes to the task design and group inclusion criteria.

This is perhaps unsurprising; it is common sense that people who are dependent upon cigarettes want them more than smokers who are not dependent. More interesting is the finding that the dependent smokers reported greater liking of cigarettes than occasional smokers, which replicates the finding reported in chapter 2. Furthermore, because of this increased liking of cigarettes and similar liking of music reward (despite a lower liking of chocolate), the dependent smokers had an overall greater liking of all rewards. This is potentially at odds with the hypothesis that dependent smokers have reduced overall hedonic tone compared with non-smokers. However, in order to more comprehensively investigate general hedonic tone, it would be desirable to use ecological momentary assessment and measure enjoyment and liking of various activities across many days in dependent and occasional smokers. The fact that I observed increased motivation for and liking of cigarettes in dependent compared with occasional smokers could be interpreted as evidence against the dissociation between the wanting and liking of drugs in nicotine dependence (Berridge & Robinson, 1998). Alternatively, as discussed in chapter 2, the dependent smokers may just have always liked smoking more than the occasional smokers.

Contrastingly, my correlation analyses support the dissociation between the wanting and liking of drugs during dependence. Occasional smokers' general liking of cigarette smoking was positively associated with button-pressing for cigarettes, while this was not the case for dependent smokers. Further, the correlations between task behaviour and general liking of cigarette smoking were different between the groups. This points toward a less goal-directed and potentially more model-free behaviour pattern in dependent cigarette smokers, like in alcoholism (Sebold et al., 2014). This is in partial agreement with my earlier findings (chapter 2), that only occasional smokers modulated their choice time for cigarettes as a function of reward magnitude. On the other hand, these current results could be driven by a ceiling effect in general liking and task behaviour within the dependent

smokers. These three variables were negatively skewed in the dependent group, so there might not have been enough variance to detect the association. Unfortunately I did not collect data on general liking of smoking a cigarette in the study described in chapter 2, so I cannot compare results. More research into the separation of motivation and liking, and whether their behaviour is more model-free, in dependent cigarette smokers is needed.

Again replicating results presented in chapter 2, I found few group differences in terms of music and chocolate reward processing. In terms of button-pressing and the speed in which choices were made, there were similar non-drug reward processing in the groups. This goes against the general hypothesis that nicotine dependence is associated with a hyposensitivity to non-drug rewards, across a variety of metrics. However, dependent smokers did report a lower liking of the first chocolate unit consumed. This is the first piece of evidence in the thesis which suggests dependent smokers have specifically impaired non-drug hedonic processing relative to occasional smokers, so it should be interpreted cautiously. The samples were probably not representative of the general populations of dependent and occasional smokers, as they were recruited via university and gumtree adverts, and were relatively small. Hence, I may have simply recruited a few dependent smokers who didn't like Diary Milk chocolate and this could have warped the result. The difference in general liking of Diary Milk chocolate, albeit non-significant, supports this claim.

One important factor to consider is the small length of nicotine abstinence (between 1.5 and 2.5 hours while completing the tasks for the dependent smokers) that participants experienced. They were not forced to abstain from nicotine for a long period of time. Despite the results reported in chapter 2, which showed null group X smoking-condition X reward-type interactions, previous studies have demonstrated some important effects of acute abstinence on reward processing (Al-Adawi & Powell, 1997; Dawkins, Acaster, & Powell, 2007; Dawkins et al., 2006; Pergadia et al., 2014; Perkins & Karelitz, 2013b; Powell et al., 2002). Hence, my results may have been different if I had enforced acute nicotine abstinence (e.g. 12-24 hours). It is therefore important to note that my results, from this study,

strongly suggest that dependent smokers who have undergone a very short period of abstinence do not have motivational impairments related to music and chocolate reward, but this might have been different with longer periods of abstinence. The moderating role of abstinence on non-drug reward processing is discussed more thoroughly in chapter 6.

Finally, again supporting results presented in chapter 2, there was a difference in the profile of reward processing between dependent and occasional smokers. The dependent smokers chose cigarettes more than the non-drug rewards, pressed for all rewards equally and chose cigarettes faster; in contrast, the occasional smokers chose chocolate more, pressed for it more and choose it faster than cigarettes. Hence, the balance in dependent smokers leans towards cigarettes while the balance in occasional smokers leans towards non-drug rewards, in this case chocolate. Given the putative importance of this balance in the prediction of relapse (Versace et al., 2014; Versace et al., 2012), it will be important to try and find better ways to disrupt this balance within dependent smokers.

4.4.4 Cigarette Purchase Task

Supporting the results from the DReaM-Choice task, and replicating earlier studies (MacKillop et al., 2008; Murphy et al., 2011) I found a significant association between cigarette demand, as operationalised by breakpoint, intensity, Omax and Pmax, and nicotine dependence. This provides more evidence that dependence is associated with a hypersensitivity to cigarette reward. Similar to the DReaM-Choice task, pramipexole did not affect any metric of cigarette demand, suggesting it does not affect the reinforcing efficacy of cigarettes relative to money.

4.4.5 Probabilistic Reward Task (PRT)

Corroborating findings from a previous study with healthy controls (Pizzagalli, Evins, et al., 2008), I found that pramipexole weakened response bias in cigarette smokers, suggestive of impaired reward learning (when all participants were included in the analysis). This was hypothesised given pramipexole's putative inhibitory effects on phasic dopamine firing and the importance of phasic

dopamine firing in reward learning (Schultz et al., 1997). An important factor to consider, however, is that pramipexole also reduced discriminability scores, meaning the simple discrimination between the short and long mouth, irrespective of reinforcement, became worse. This may have contributed to the reduction in response bias. Given the negative relationship between response bias and cigarette craving (Peechatka et al., 2015), any potential anti-smoking drug that reduces response bias may be problematic. However, I did not find an effect of pramipexole on either craving or motivation for cigarettes, despite pramipexole reducing response bias.

I did not find a difference between dependent and occasional smokers in terms of reward learning, which is in agreement with a recent study comparing smokers and non-smokers after 4 hours of nicotine abstinence (Peechatka et al., 2015). Thus, it may be that a longer period of abstinence is required to unmask this reward processing dysfunction, which has been seen after 24 hours (Pergadia et al., 2014).

One very important caveat is that participants were not excluded in the standard way (Alexis Whiton, personal communication). For instance, a participant who had over 20/100 trials with a reaction time of <100ms was included in my analyses. If I had excluded people as has previously been done, I would have been left with 17 out of 40 participants. This therefore means that the data quality is not as high as I would have liked and may have contained a large amount of noise. Indeed, when I re-ran the analyses with the original exclusion criteria and a set of less stringent exclusion criteria the effect of drug was lost, i.e. pramipexole did not reduce reward learning. Therefore, it is not clear whether the effect of pramipexole was simply a corollary of the inclusion of participants who did not complete the task correctly. When participants were excluded, the effect of pramipexole appeared to be moderated by group; however, with so few participants included in the analysis, interpretation is again difficult.

The reasons behind this very high number of apparently ineligible participants are unclear. In the study reported in chapter 5, only 25% of participants had to be excluded from the analysis according to these criteria. That this study was a repeated measures design, meaning there was more chance of meeting

ineligibility criteria on one session, is probably a factor, as too is the fact they had taken a somewhat unpleasant drug on one of the sessions. Furthermore, the mouths I used were 8mm and 9mm rather than 11mm and 13.5mm (which were used in the original task), and this probably made the task harder. This means that all results from the PRT reported in this chapter should be viewed with caution.

4.4.6 Effort expenditure for rewards task (EEfRT)

Both group and drug affected effort-related decision-making. Pramipexole reduced sensitivity to the pro-motivational effects of magnitude, probability and expected value. As can be seen in figure 4.11c, pramipexole led to a lower likelihood of making a high-effort choice than placebo when expected value = 0.4 and when expected value was greater than 1, but at other expected values, the conditions appear more similar. It is difficult to conceptually understand this pattern, however it demonstrates that there was a complex relationship between drug, expected value and task behaviour. Although pramipexole did not, overall, alter motivation for monetary reward, it reduced the ability of other factors to influence motivation. This is consistent with the claim that D3 receptors have differential effects at low and high cost, and low and high reward, scenarios (Le Foll et al., 2005). It seems that the perturbation of D3 receptor functioning affects motivated responding more as the outcomes become better. In the real world this may mean that changes in the environment could have less of an effect on motivation, if one was under the effects of a D3 agonist like pramipexole. As a potential treatment for nicotine dependence, this may be an undesirable feature.

Pramipexole's reduction in phasic dopamine firing may have caused the decreased sensitivity to EEfRT parameters. One may have to learn during the task which response is optimal when the outcome has a certain probability and magnitude; impaired phasic dopamine firing may disturb this learning. This is concordant with my results on the PRT in which pramipexole led participants to have impaired reward learning (when all participants were included in the analysis). Furthermore, dopaminergic functioning is associated with cognitive and behavioural flexibility (Cools & D'Esposito, 2011; Floresco,

2013) and disruption to flexibility will leave people less able to modulate behaviour as task parameters change. However, it is important to note that dopamine's role in cognitive and behavioural flexibility is thought to be an inverted 'U' shape and so the effects of pramipexole may have been different in people with different baseline dopamine levels.

My results are quite different from two similar studies. Amphetamine, which stimulates the release and blocks the reuptake of monoamine neurotransmitters (including dopamine), increased motivation for monetary reward overall, especially on low probability and expected value trials (as assessed by the EEfRT). This is different to pramipexole in that I did not find an overall increase in motivation and, although there were increases at low probability and expected value with pramipexole, these were non-significant. Amphetamine has a diverse pharmacological effect profile, affecting dopaminergic, noradrenergic and serotonergic functioning, among others. In contrast, pramipexole has quite a specific action, binding to D2, D4 and, particularly D3, receptors (Mierau et al., 1995) and at low doses is thought to act primarily on autoreceptors, which reduce phasic dopamine firing (Samuels et al., 2006). Furthermore, amphetamine is associated with increased wakefulness while pramipexole results in drowsiness. These differences may have contributed to the differential behavioural effects of pramipexole and amphetamine on effort-related decision-making.

Previously, the same dose of pramipexole in smokers had been shown to enhance motivation to monetary reward on the CARROT (Freeman et al., 2013). It is unclear why these two experiments have given quite different results. It may be that the CARROT is more sensitive than the EEfRT at detecting differences in motivation or because the magnitude of potential reward was quite low (10p) in the CARROT, which here was associated with pramipexole non-significantly increasing motivation.

The models which included group X task parameter interactions showed that dependent smokers, compared with occasional smokers, were less sensitive to magnitude, probability and expected value. Figure 4.11b shows that dependent smokers were generally more likely to make a high-effort choice when expected value was less than 0.4 but the opposite pattern was apparent when expected value

was greater than 0.4. This suggests that nicotine dependent individuals were less sensitive to changes in information concerning the reward when making effort-related decisions. This is similar to the effect seen in people with depression (Treadway, Bossaller, et al., 2012) and could suggest a common mechanism behind decreased reward sensitivity in the two groups. Importantly, this is the first piece of evidence for reduced sensitivity in the motivation for non-drug reward in this thesis. This potentially represents a specific impairment in non-drug reward processing in nicotine dependent individuals, while other non-drug reward processes remain operational. This finding should be replicated and its association with future tobacco use tested.

I found some evidence for a differential effect of pramipexole on the two groups with the EEfRT. The drug appeared to boost the likelihood of making a high-effort choice more in the dependent group than in the occasional group; this can be seen visually in figure 4.11a, where pramipexole seems to reduce high-effort choices in the occasional group. As suggested in the introduction, this may be because the dependent smokers have altered dopaminergic functioning (Dagher et al., 2001; Fehr et al., 2008; Leroy et al., 2012). However, given this result wasn't very significant ($p=0.045$) and it disappeared when the 5 retrospectively ineligible participants were removed, it should be interpreted carefully and demands replication. Furthermore, I did not find group X drug interactions in other tasks, implying this result might be a red herring, or perhaps that only effort-related decision-making is sensitive to the dopaminergic adaptations associated with nicotine dependence.

Performance on the PRT, the EEfRT and the DReaM-Choice task were not correlated, which suggests they tap different aspects of reward processing. This was expected for the PRT and EEfRT, given the PRT putatively measures reward learning while the EEfRT putatively measures effort-related decision-making, a component of motivation. However, as both the EEfRT and the DReaM-Choice tap motivational concepts it is perhaps surprising they did not correlate. These relationships are discussed more in chapter 6.

One possible reason why I detected an effect of pramipexole and a difference between the groups on the EEfRT but not on the DReaM-Choice task may be that I used a different statistical analysis approach to analyse each set of data. GEE models may provide greater sensitivity to detect effects compared with ANOVA because GEE models use every trial in the model whereas ANOVAs use only averages. This difference could have contributed to the different pattern of results in these two tasks, which both putatively assess motivation.

4.4.7 Strengths and limitations

Key strengths of this study include the placebo-controlled, double-blind, crossover design; the large overall sample size (n=40), compared with other related studies (Hamidovic, Kang, & de Wit, 2008; Riba et al., 2008; Samuels et al., 2006); the well matched groups; the wide variety of reward processing components measured; and the comparison of real cigarettes with real non-drug rewards, rather than images or hypothetical rewards.

The inclusion of 5 participants who were retrospectively found to be ineligible is a limitation, although their exclusion had no or minimal effects on the task results. The inability to exclude participants on the PRT in the standard way due to so many participants not meeting the criteria is worrying. An improvement to the experiment would have been the costly measurement of biological variables, such as pramipexole plasma levels (Wright et al., 1997), so that the ability of the drug to enter the body could have been verified. The blinding of the participants wasn't fully maintained because participants were able to guess which drug they had been given, at trend level. However, this is a problem with any experiment which administers a psychoactive drug and an inactive placebo. Ideally, the drug in question, an active placebo (e.g. a benzodiazepine) and an inactive placebo would be administered. Finally, although the total sample size was relatively large, the size of each smoker group was moderate, and so the power to detect group differences and drug by group interactions could have been improved.

4.4.8 Conclusions

We found no evidence to suggest that an acute, low dose of pramipexole reduces motivation for cigarettes or redresses the imbalance of cigarette and non-drug reward processing in dependent cigarette smokers. Confirming results from chapter 2 and 3, dependent smokers appeared to be *hypersensitive* to cigarette rewards across a variety of metrics but there wasn't evidence for *hyposensitivity* to music and chocolate rewards. However, dependent smokers were less sensitive to changes in probability, magnitude and expected value than occasional smokers in an effort-related decision-making task. Moreover, pramipexole impaired reward learning (but only when no participants were excluded from the dataset) and reduced sensitivity to these task parameters, indicative of reduced phasic dopamine release. My findings may question the role of D2 and D3 receptors in cigarette-related reward processing.

Chapter 5: Non-drug reward processing in cannabis users: (1) acute effects of different strains of cannabis and (2) associations with cannabis dependence

5.1 Introduction

Work described in the previous chapters suggests that, when assessed after ad libitum smoking, nicotine dependence is mostly not associated with non-drug reward processing deficits, although effort-related decision-making was impaired in dependent smokers compared with occasional smokers. However, I now move onto another drug: cannabis, the effects of which have been observationally linked with amotivation (McGlothlin & West, 1968). Moreover, there is currently an increasing demand for cannabis dependence treatment (Public Health England, 2013). Reward processing alterations may play a role in the development and maintenance of cannabis dependence. Furthermore, the endocannabinoid system is thought to play a role in the development of other drug addictions (Parsons & Hurd, 2015), including nicotine dependence, and in Europe cannabis is predominantly consumed with tobacco in 'spliffs' (Hindocha, Freeman, Winstock, & Lynskey, 2015). It appears there are important links between cannabis, the endocannabinoid system and nicotine dependence. In the research described in this chapter, I investigated the acute effects of different strains of cannabis on, and the associations of cannabis dependence with, effort-related decision-making and reward learning, using the same tasks that I used in chapter 4. This allowed me to broadly compare the relationships of tobacco and cannabis use with these aspects of non-drug reward processing.

5.1.1 Cannabis and the endocannabinoid system

The endocannabinoid system, which includes the cannabinoid-1 (CB1) and cannabinoid-2 (CB2) receptors and their endogenous ligands, is putatively involved in reward processing and addiction (Maldonado et al., 2006). Δ-9-tetrahydrocannabinol (THC), the main active compound in cannabis, is a CB1 receptor partial agonist (Petitet, Jeantaud, Reibaud, Imperato, & Dubroeucq, 1998) which may (Bossong et al., 2015; Bossong et al., 2009) or may not (Stokes et al., 2009) increase dopamine release in the human striatum. Individuals who met DSM-IV criteria for cannabis dependence or abuse showed reduced striatal dopamine synthesis capacity relative to non-using matched controls (Bloomfield,

Morgan, Egerton, et al., 2014), which was negatively correlated with their apathy scores (Bloomfield, Morgan, Kapur, Curran, & Howes, 2014). Moreover, cannabis dependence was associated with reduced levels of CB1 receptors (D'Souza et al., 2015). However, other studies have shown no difference between cannabis users and non-users in terms of dopamine receptor density (Albrecht et al., 2013; Sevy et al., 2008; Stokes et al., 2009; Urban et al., 2012).

Cannabis contains many cannabinoids, other than THC. Of particular interest is cannabidiol (CBD) which has a complex mode of action, including inhibition of the metabolism and reuptake of anandamide (Pertwee, 2008), inverse agonism at the CB1 receptor (Pertwee, 2008) and agonism at the GPR55 receptor (Ryberg et al., 2007). Acute THC has dose-related amnestic (Curran, Brignell, Fletcher, Middleton, & Henry, 2002), psychotic (Morrison et al., 2009) and anxiogenic (Morrison et al., 2009) effects. CBD has been shown to attenuate or block these negative effects (Bhattacharyya et al., 2010; Englund et al., 2013; Morgan, Schafer, Freeman, & Curran, 2010). Furthermore, CBD may have some anti-addictive properties in animals and humans (Morgan, Das, Joye, Curran, & Kamboj, 2013; Morgan, Freeman, Schafer, & Curran, 2010; Ren, Whittard, Higuera-Matas, Morris, & Hurd, 2009) and use of high-THC/low-CBD cannabis was especially predictive of cannabis dependence, compared with other types of cannabis (Freeman & Winstock, 2015). Given these opposing pharmacological and psychological effects of THC and CBD, I hypothesised that CBD may buffer the effects of THC on reward processing.

The endocannabinoid system is thought to contribute to other drug addictions (Maldonado et al., 2006; Parsons & Hurd, 2015). Animal research has demonstrated that CB1 agonists enhance self-administration of and conditioned place preference for alcohol, nicotine and opiates, while CB1 antagonists have the reverse effects (Parsons & Hurd, 2015). Human research has demonstrated that rimonabant, a CB1 antagonist, improves cigarette smoking cessation attempts (Foll, Forget, Aubin, & Goldberg, 2008). There is also pilot data suggesting CBD may help people reduce cigarette smoking (Morgan et al., 2013). Furthermore, cigarette smoking mediates the relationship between cannabis

use and cannabis dependence (Hindocha, Shaban, et al., 2015). Hence, there appears to be important, bidirectional relationships between cannabis and nicotine use. Investigating the acute and chronic effects of cannabis on reward processing may improve our understanding of how the endocannabinoid system is related to other drug addictions.

5.1.2 Acute effects of cannabis on motivation

Historically, cannabis use has been associated with reduced motivation (McGlothlin & West, 1968). Early, poorly controlled, studies found both amotivational (Miles et al., 1974) and null (Mendelson et al., 1976) effects of acute cannabis. More recently both promotivational (Foltin et al., 1990) and amotivational (Cherek et al., 2002) effects have been demonstrated. In the latter study, participants were asked to choose between a button-pressing option that earned more money and a do-nothing option that earned less money; this study therefore assessed effort-related decision-making. However, they had a small sample size of five participants, so there is a need to replicate with a larger sample. Hence, the acute effects of THC or cannabis on motivation remain unclear and deserve further investigation. Interestingly, it has been reported that CBD can partially shield the response-reducing effect of THC on motivated responding for a food reward in rhesus monkeys (Brady & Balster, 1980), providing some evidence that CBD may protect against the amotivational effects of THC. However, no one has examined whether CBD buffers the potentially amotivational effects of THC in humans.

5.1.3 Chronic effects of cannabis on non-drug reward processing

Early studies of chronic effects found no difference when comparing heavy with light cannabis users on fixed ratio button-pressing tasks for rewards (Mello & Mendelson, 1985; Mendelson et al., 1976). Survey data have also failed to demonstrate a link between long-term cannabis use and amotivation (Barnwell, Earleywine, & Wilcox, 2006; Musty & Kaback, 1995), although it has been shown to predict anhedonia (Bovasso, 2001). Daily, adolescent cannabis users had a lower motivation for monetary reward than non-users, although comorbid depression and other drug use were not reported and may

have confounded group differences (Lane et al., 2005). Studies that compared cannabis users with controls on the anticipatory BOLD response for monetary reward, thought to be an indicator of intact reward processing, have found opposing results (van Hell et al., 2010; Nestor et al., 2010). Again, it appears that the literature concerning amotivational and other non-drug reward processing deficits associated with chronic cannabis use is mixed.

5.1.4 Effort-related decision-making and reward learning

Two key aspects of reward processing that have been described previously (see sections 4.2.2.3 and 4.2.2.4) are effort-related decision-making (Treadway et al., 2009) and reward responsiveness, conceptualized in terms of reward learning (Pizzagalli et al., 2005). Neither the EEfRT nor the PRT have previously been examined in relation to either acute cannabinoid exposure or cannabis dependence.

5.1.5 Summary and hypotheses

Anecdotal reports suggest that cannabis use acutely and chronically results in amotivation, while reward processing deficits could theoretically play a role in cannabis dependence. However, there is a distinct lack of research in this area. Across two studies, I first tested the acute effects of cannabis without CBD (Cann-CBD) and cannabis with CBD (Cann+CBD) on effort-related decision-making. Second, I investigated associations between cannabis dependence, effort-related decision-making and reinforcement learning.

Based on a study that showed acute cannabis reduced motivation for monetary reward (Cherek et al., 2002) and studies demonstrating CBD can protect against some of THC's negative effects (Bhattacharyya et al., 2010; Englund et al., 2013; Morgan, Schafer, et al., 2010), I hypothesised that:

1. Cann-CBD would reduce motivation for monetary reward compared to placebo.
2. This amotivational effect would be weaker following Cann+CBD compared to Cann-CBD.

Based on the iRISA theory of addiction (Goldstein & Volkow, 2011) and one study showing amotivation in daily-cannabis using adolescents (Lane et al., 2005), I hypothesised that:

3. Cannabis dependence would be associated with reduced motivation and reinforcement learning.

5.2 Study 1 methods

5.2.1 Participants and design

A repeated-measures, placebo-controlled, double-blind design was used to compare Cann-CBD, Cann+CBD and placebo. Participants were randomly allocated to one of three treatment order schedules, which were based on a Latin Square design. 17 participants[22] (8 women) took part in the study; this sample size was adequately powered to detect drug X task interactions in a three-way crossover of d-amphetamine using the EEfRT (Wardle et al., 2011).

Inclusion criteria were: aged between 18 and 70; smoke cannabis 3 times/ week or less; have smoked cannabis 4 or more times in the last year. Exclusion criteria were: regular negative experiences when smoking cannabis; alcohol use >5 times/week; other illicit drug use >2 times/month, current or history of psychosis; MRI contraindications.

Participants were recruited through word-of-mouth and all provided written, informed consent. The study was approved by the University College London (UCL) Ethics Committee. They were reimbursed £7.50/hour and could win extra money via completion of various tasks.

5.2.2 Assessments

5.2.2.1 Effort Expenditure for Rewards Task (EEfRT) (Treadway et al., 2009)

As described in section 4.2.2.4

[22] As 17 is not divisible by 3, the Latin square was not completed with equal numbers of participants in each treatment order.

5.2.2.2 Self-report assessments

Trait measures

Beck depression inventory (BDI-II) (Beck et al., 1996)

As described in section 2.2.2.2

Drug history

Lifetime use was recorded as 'yes' or 'no'. Current use (≥once per month) was recorded as 'yes' or 'no' and days/month and amount/session were recorded for those who said 'yes' for current use.

Severity of dependence scale (SDS) (Gossop et al., 1995)

This standard scale of drug dependence consisted of 5 items that were rated between 0 and 4 in terms of frequency or difficulty with higher scores reflecting greater dependence severity.

Temporal experiences of pleasure scale (TEPS) (Gard et al., 2006)

As described in section 2.2.2.2

State measures

Snaith Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995)

As described in section 2.2.2.2

Subjective Effects: 'stoned' and 'like drug'

Participants gave ratings for 'stoned' and 'liked drug', 'right now' from 0 (not at all) to 10 (extremely).

5.2.2.3 Drug administration

A Volcano Medic Vaporiser (figure 5.1) (Storz and Bickel, Tuttlingen, Germany) was used to vaporize Bedrocan cannabis (Veendan, Netherlands). Across the three sessions, I aimed to administer 8mg THC

(for the Cann-CBD condition), 8mg THC + 10mg CBD (for the Cann+CBD condition) and placebo, based on previous THC/CBD vaporizer protocols (Bossong et al., 2009; Hindocha, Freeman, Schafer, et al., 2015) and Bedrocan product potencies (Brunt, van Genugten, Höner-Snoeken, van de Velde, & Niesink, 2014), see table 5.1. Drugs were stored at -20°C in foil-sealed pouches, then at ambient temperature prior to administration, and used within 6 months of purchase. Participants received two doses in each testing session. This was to maintain steady drug levels over time. Hence participants received one dose at the start of testing and then received a 50% top-up dose 90 minutes later. Each dose was vaporized in two sequentially administered balloons to minimise any cannabinoids remaining in the bag. Participants inhaled the drug at their own pace (each inhalation was held for 8 seconds) until the balloon was empty.

Figure 5.1 A picture of the Volcano Medic Vaporiser. Cannabis is put into the black filling chamber and this is placed on top of the hot air generator when it has reached the correct temperature (210°C). Hot air is then passed through the cannabis, vaporising it, and sending it into the balloon. Subsequently, the vaporised cannabis is inhaled from the balloon by the participant.

Table 5.1 THC dose and total weight were matched across sessions by adjusting the quantity of three cannabis varieties as shown below. All three cannabis types contained terpenoids, creating the distinctive smell of cannabis.

	Cann-CBD	**Cann+CBD**	**Placebo**
Target dose	8mg THC	8mg THC+10mg CBD	N/A
Total weight	133.4mg	133.4mg	133.4mg
'Bedrobinol' (12% THC, <1% CBD)	66.7mg	N/A	N/A
'Bediol' (6% THC, 7.5% CBD)	N/A	133.4mg	N/A
Placebo (derived from 'Bedrocan'; <0.3% THC, <1% CBD)	66.7mg	N/A	133.4mg

5.2.3 Procedure

Following telephone screening, participants attended a screening visit consisting of eligibility assessment, task training, drug history and trait questionnaires. Subsequently, they completed 3 testing sessions, each lasting approximately 3 hours, on which they received Cann-CBD, Cann+CBD or placebo separated by a wash-out period of $\geq$7 days. Participants were asked to abstain from alcohol and any illicit drugs for ≥24 hours before each testing session.

Testing sessions began with a urine sample to screen for pregnancy and to verify their recent self-reported drug use, assessed by 7 day Timeline Followback (Sobell & Sobell, 1992). After drug administration, participants underwent MRI scanning for 1 hour. Next, they received their top-up drug administration (approximately 90mins after the first) and began a 1.5h long battery of behavioural tasks. The EEfRT was completed approximately 1h into this battery. Participants completed ratings of 'stoned' and 'like drug' at five time points: (1) immediately before 1st drug administration (≈0 mins); (2) immediately after 1st drug administration (≈5 mins); (3) immediately before 2nd drug administration (≈90 mins); (4) immediately after 2nd drug administration (≈95 mins); and (5) end of the session (≈180 mins). Participants completed ratings of 'like drug' at time points 2-5.

In terms of ethical considerations, all participants had at least moderate experience with cannabis and all reported not regularly experiencing negative effects when they smoked cannabis. They were all

informed of the potential effects cannabis could have on them before they consented. Therefore, every participant had their own personal experience and were appropriately informed about the experiment. Participants were able to withdraw from the study at any point and a doctor was available via the telephone at all times.

5.2.4 Statistical analyses

All analyses were carried out using IBM Statistical Package for Social Sciences (IBM SPSS version 22).

'Stoned' and 'like drug' ratings were analysed using repeated-measures ANOVA with two within-subjects factors: drug (placebo, Cann-CBD, Cann+CBD) and time (1,2,3,4,5 for 'stoned' and 2,3,4,5 for 'like drug'). Interactions were explored with Bonferroni corrected t-tests. Furthermore, an ANCOVA, with the same factors as above, and cannabis days/month as the covariate was used to determine if the extent of recreational use affected hedonic responses to the drug.

A repeated-measures ANOVA with a within-subjects factor of drug was used to analyse SHAPS scores.

As in chapter 4, I used Generalized Estimating Equation (GEE) models to analyse the likelihood of participants making a high-effort choice in the EEfRT. I tested the effects of drug condition on effort-related decision-making across 4 models. Each model had standard predictors (see section 4.2.4) plus drug, with these additional predictors: no others (model 1), drug X magnitude (model 2), drug X probability (model 3), drug X expected value (EV; reflecting probability X magnitude) (model 4). Cann-CBD was used as the reference category to evaluate my hypotheses comparing Cann-CBD with (1) placebo and (2) Cann+CBD.

5.3 Study 1 Results

5.3.1 Demographics (Table 5.2)[23]

Participants were aged 26.18 (SD=7.13) years. On average, they smoked cannabis 8.06 (5.48) days per month, took 25.88 (33.73) days to smoke an 8th ounce (3.5g) of cannabis and scored 1.13 (1.26) on the cannabis SDS.

5.3.2 Drugs in urine

During the placebo session, THC was detected in 8 and MDMA in one participants' urine. During the Cann+CBD session, THC was detected in 9 and PCP in one participants' urine. During the Cann-CBD session, THC was detected in 8 participants' urine. No participants reported using any drugs within the last 24 hours.

[23] Data was missing for one participant for BDI, TEPS and drugs history

Table 5.2 Means (S.D.) and frequencies for demographic data and drug use for participants in study 1. Data were missing for one participant for BDI, TEPS and drugs history.

	Participants
Age	26.18 (7.13)
Gender (m/f)	9/8
BDI	3.38 (3.12)
TEPS consummatory	43.50 (5.61)
TEPS anticipatory	42.06 (4.85)
TEPS total	86.56 (9.30)
Cannabis SDS	1.13 (1.26)
Alcohol ever used (y/n)	16/0
Alcohol use now (y/n)	16/0
Alcohol days per month	10.81 (4.86)
Alcohol units/session	5.93 (2.08)
Amphetamine ever used (y/n)	8/8
Amphetamine use now (y/n)	0/16
Amphetamine days per month	NA
Amphetamine grams/session	NA
Cannabis ever used (y/n)	16/0
Cannabis use now (y/n)	16/0
Cannabis days per month	8.06 (5.48)
Cannabis days to smoke an 8th	25.88 (33.73)
Cocaine ever used (y/n)	11/5
Cocaine use now (y/n)	3/13
Cocaine days per month	1.0 (0.0)
Cocaine grams/session	0.5 (0.0)
Heroin ever used (y/n)	0/16
Heroin use now (y/n)	0/16
Heroin days per month	NA
Heroin grams/session	NA
Ketamine ever used (y/n)	10/6
Ketamine use now (y/n)	2/14
Ketamine days per month	1.50 (0.71)
Ketamine grams/session	0.75 (0.35)
Mephedrone ever used (y/n)	7/9
Mephedrone use now (y/n)	0/16
Mephedrone days per month	NA
Mephedrone grams/session	NA
MDMA ever used (y/n)	14/2
MDMA use now (y/n)	6/10
MDMA days per month	1.50 (0.84)
MDMA grams/session	0.31 (0.19)
Tobacco ever used (y/n)	15/1
Tobacco use now (y/n)	15/1
Tobacco days per month	11.30 (10.27)
Tobacco cigs/day (when smoking)	3.63 (3.62)
Tobacco average cigs/day	2.16 (3.48)

5.3.3 'Stoned' and 'like drug' ratings[24]

Stoned (Figure 5.2a)

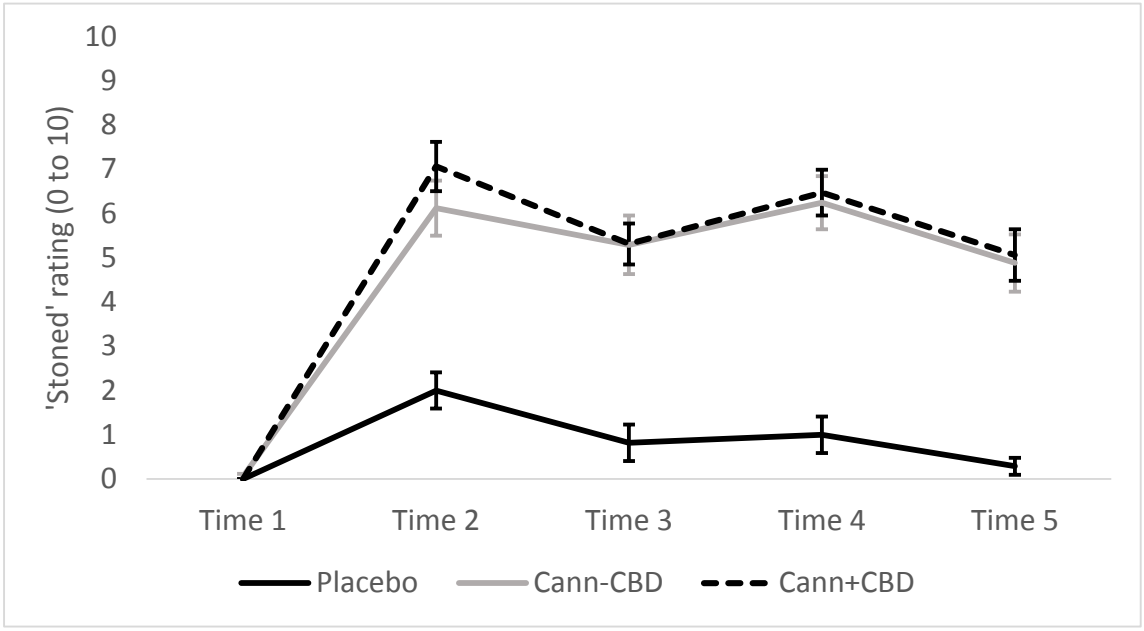
There was an interaction between time and drug ($F_{8,128}$=20.296, p<0.001), main effects of time ($F_{4,64}$=82.443, p<0.001) and drug ($F_{2,32}$=56.154, p<0.001). Ratings of 'stoned' were the same immediately before drug administration for all drug conditions. For every other time, both Cann-CBD and Cann+CBD conditions had greater ratings of 'stoned' compared with placebo (all ps<0.001) but did not differ from other. Stoned ratings did not differ after the 1st and 2nd doses for Cann-CBD or Cann+CBD (both ps=1.000), demonstrating equivalent intoxication from the original dose and the 50% top-up dose.

Like drug (Figure 5.2b)

There were main effects of drug ($F_{2, 32}$=64.564, p<0.001) and time ($F_{3, 48}$=14.170, p<0.001). Ratings were greatest at time 2 and time 4, after drug administrations. Ratings were greater for Cann-CBD and Cann+CBD than placebo (ps<0.001). There were never any differences between Cann-CBD and Cann+CBD. Cannabis days/month was not associated with liking ratings.

[24] One participant missed a rating at time 3 on the Cann+CBD session; this was imputed with the group mean.

a)



b)

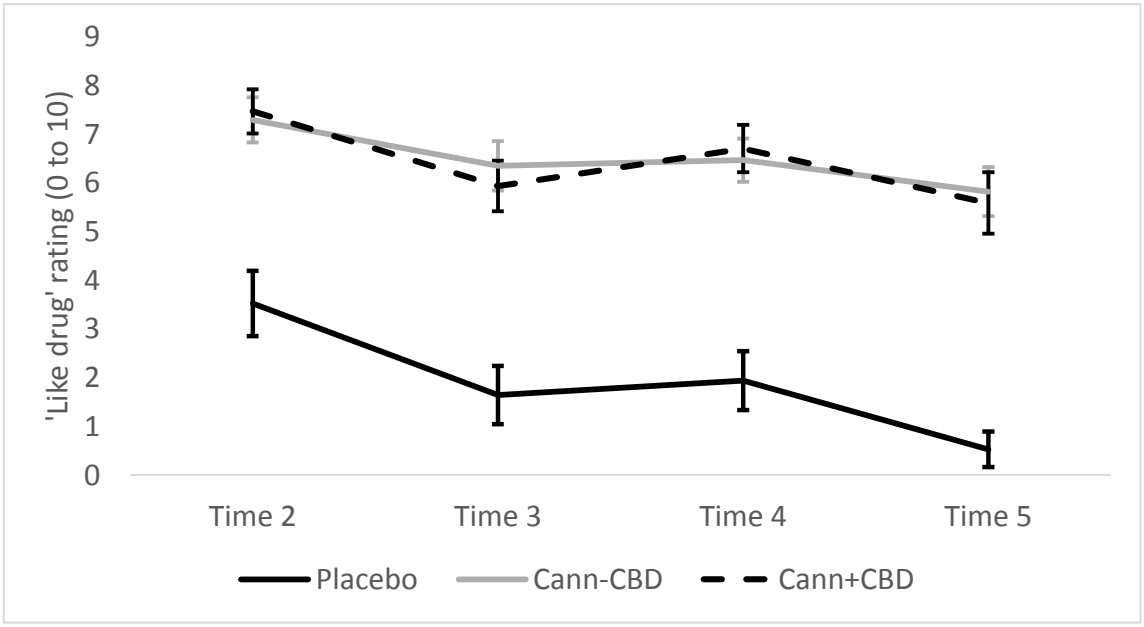


Figure 5.2 Mean (S.E.) scores for subjective ratings of a) 'stoned' and b) 'like drug' at five/four time points in study 1. Only 4 time points were used for 'like drug' because no drug had been consumed at time 1. Time 1 = immediately before 1st drug administration, time 2 = immediately after 1st drug administration, time 3 = immediately before 2nd drug administration, time 4 = immediately after 2nd drug administration, time 5 = end of the session.

5.3.4 EEfRT

Baseline button-pressing time

There were no differences in baseline button-pressing time between any of the sessions.

GEE models (Table 5.3)[25]

Reward magnitude and probability both positively and significantly predicted making a high-effort choice in all models (ps<0.01). The effect of EV approached significance in all models (ps<0.1). As shown in model 1, Cann-CBD led to a lower likelihood of making a high-effort choice than placebo (p=0.042) but there was no difference between Cann-CBD and Cann+CBD (figure 5.3). Model 3 found an interaction between drug and probability, such that Cann-CBD augmented the effect of probability on the likelihood of making a high-effort choice relative to placebo (p=0.029). Model 4 found an interaction between drug and EV, such that Cann-CBD augmented the effect of EV on the likelihood of making a high-effort choice relative to both placebo (p=0.014) and Cann+CBD (p=0.006).

The drug by probability interaction in model 3 was explored by carrying out GEE models within each level of probability. At low probability, Cann-CBD led to a *lower* likelihood of making high-effort choice than placebo (b=0.188, SE=0.0718, OR=1.207, 95% CI: 1.049, 1.390). At medium and high probabilities, there were no significant differences on the likelihood of making a high-effort choice between Cann-CBD and placebo conditions.

The drug by expected value interaction in model 4 was explored by carrying out GEE models within three levels of expected value (figure 5.4). The three levels were formed by grouping the smallest third of expected values, the middle third of expected values and the largest third of expected values.

[25] I excluded one participant for failing to complete 13 and 14 trials on two of his sessions, thus he clearly did not complete the task as instructed.

At low expected value, Cann-CBD led to a *lower* likelihood of making a high-effort choice than placebo (b=0.188, SE=0.0718, OR=1.207, 95% CI: 1.049, 1.390)[26]. However, at low expected value, there was not a significant difference on the likelihood of making a high-effort choice between the Cann-CBD and Cann+CBD conditions. Furthermore, at medium and high probabilities, there were no significant differences on the likelihood of making a high-effort choice between the Cann-CBD and placebo conditions, or the the Cann-CBD and Cann+CBD conditions.

Visual inspection of figure 5.4 shows that, overall, the differences between the drug conditions did not change a great deal between expected value levels. However, it does show that both cannabis types had lower likelihoods than placebo at each expected value level and that Cann+CBD had a greater likelihood than Cann-CBD at low and medium expected value levels, but not at the high expected value level. However, as the post-hoc GEE models showed, these differences between Cann-CBD and Cann+CBD were not significant at any expected value level, despite the significant interaction in model 4.

[26] This is the same as for probability because the low probability trials are exactly the same as the low expected value trials. The medium and high probability and expected value trials do differ, however.

Table 5.3 GEE Models for EEfRT from study 1. Beta coefficients for each predictor term, standard errors, p-values, odds ratios (OR) and 95% confidence intervals (CI) for these ORs are shown. The reference category for gender was female. The most important terms are in bold.

Model 1

	Beta	**S.E.**	**p**	**Odds Ratio**	**95% CI OR**
Magnitude	0.114	0.0315	<0.001	1.188	1.054, 1.193
Probability	0.172	0.0352	<0.001	1.121	1.109, 1.272
Expected value	0.134	0.0786	0.089	1.143	0.980, 1.333
Trial number	-0.008	0.0015	<0.001	0.992	0.989, 0.995
Gender	0.220	0.0720	0.002	1.246	1.082, 1.435
Placebo vs. Cann-CBD	**0.050**	**0.0247**	**0.042**	**1.051**	**1.002, 1.103**
Cann+CBD vs. Cann-CBD	**-0.001**	**0.0280**	**0.976**	**0.999**	**0.946, 1.056**

Model 2

	Beta	**S.E.**	**p**	**Odds Ratio**	**95% CI OR**
Magnitude	0.140	0.0405	0.001	1.151	1.063, 1.246
Probability	0.173	0.0353	<0.001	1.189	1.110, 1.274
Expected value	0.131	0.0786	0.095	1.140	0.978, 1.330
Trial number	-0.008	0.0015	<0.001	0.992	0.989, 0.995
Gender	0.220	0.0721	0.002	1.246	1.082, 1.435
Placebo vs. Cann-CBD	0.097	0.054	0.073	1.102	0.991, 1.224
Cann+CBD vs. Cann-CBD	0.055	0.0590	0.347	1.057	0.942, 1.187
(Placebo vs. Cann-CBD) X magnitude	**-0.033**	**0.0375**	**0.385**	**0.968**	**0.899, 1.042**
(Cann+CBD vs. Cann-CBD) X magnitude	**-0.039**	**0.0395**	**0.320**	**0.961**	**0.890, 1.039**

Model 3

	Beta	**S.E.**	**p**	**Odds Ratio**	**95% CI OR**
Magnitude	0.115	0.0313	<0.001	1.122	1.055, 1.193
Probability	0.206	0.0405	<0.001	1.229	1.135, 1.331
Expected value	0.131	0.0783	0.094	1.140	0.978, 1.329
Trial number	-0.008	0.0015	<0.001	0.992	0.989, 0.995
Gender	0.219	0.0716	0.002	1.245	1.082, 1.433
Placebo vs. Cann-CBD	0.123	0.0342	<0.001	1.131	1.057, 1.209
Cann+CBD vs. Cann-CBD	0.044	0.0356	0.212	1.045	0.975, 1.121
(Placebo vs. Cann-CBD) X probability	**-0.060**	**0.0276**	**0.029**	**0.942**	**0.892, 0.994**
(Cann+CBD vs. Cann-CBD) X probability	**-0.036**	**0.0199**	**0.073**	**0.965**	**0.928, 1.003**

Model 4

	Beta	S.E.	p	Odds Ratio	95% CI OR
Magnitude	0.117	0.0313	<0.001	1.124	1.057, 1.195
Probability	0.175	0.0352	<0.001	1.192	1.112, 1.277
Expected value	0.201	0.0793	0.011	1.223	1.047, 1.428
Trial number	-0.008	0.0015	<0.001	0.993	0.990, 0.995
Gender	0.219	0.0717	0.002	1.245	1.082, 1.433
Placebo vs. Cann-CBD	0.149	0.0387	<0.001	1.161	1.076, 1.253
Cann+CBD vs. Cann-CBD	0.078	0.0388	0.045	1.081	1.002, 1.166
(Placebo vs. Cann-CBD) X EV	**-0.121**	**0.0494**	**0.014**	**0.886**	**0.804, 0.976**
(Cann+CBD vs. Cann-CBD) X EV	**-0.093**	**0.0337**	**0.006**	**0.911**	**0.853, 0.973**

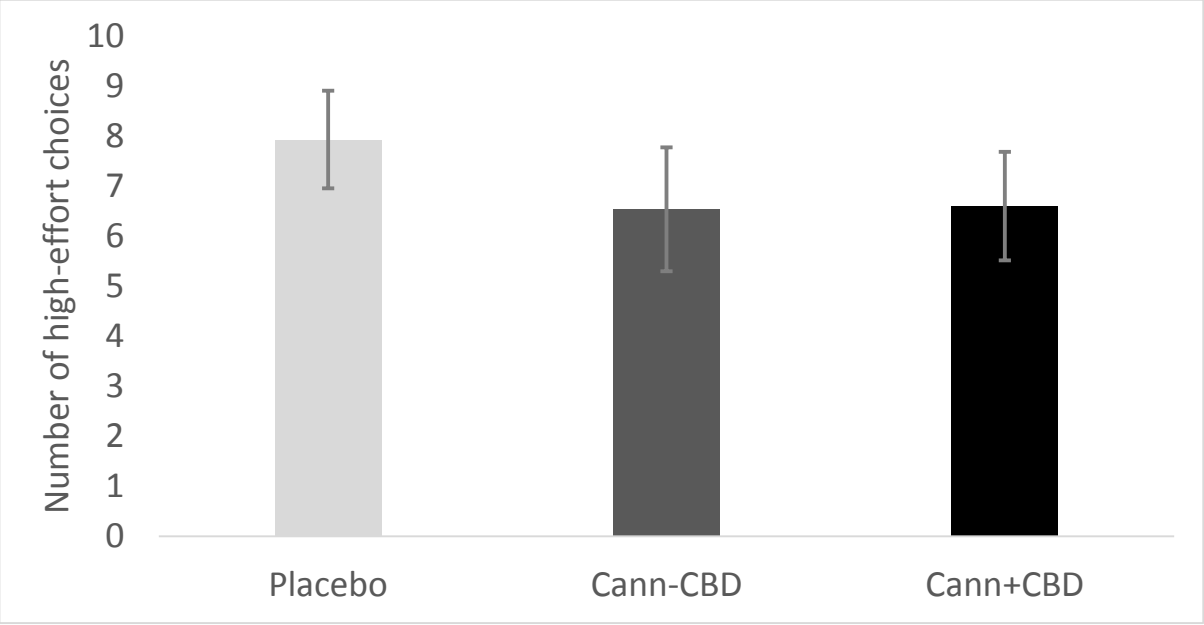


Figure 5.3 Results from study 1. Mean (S.E.) numbers of high-effort choices made during each drug condition, collapsed across probability and magnitude, in study 1. Error bars show standard error.

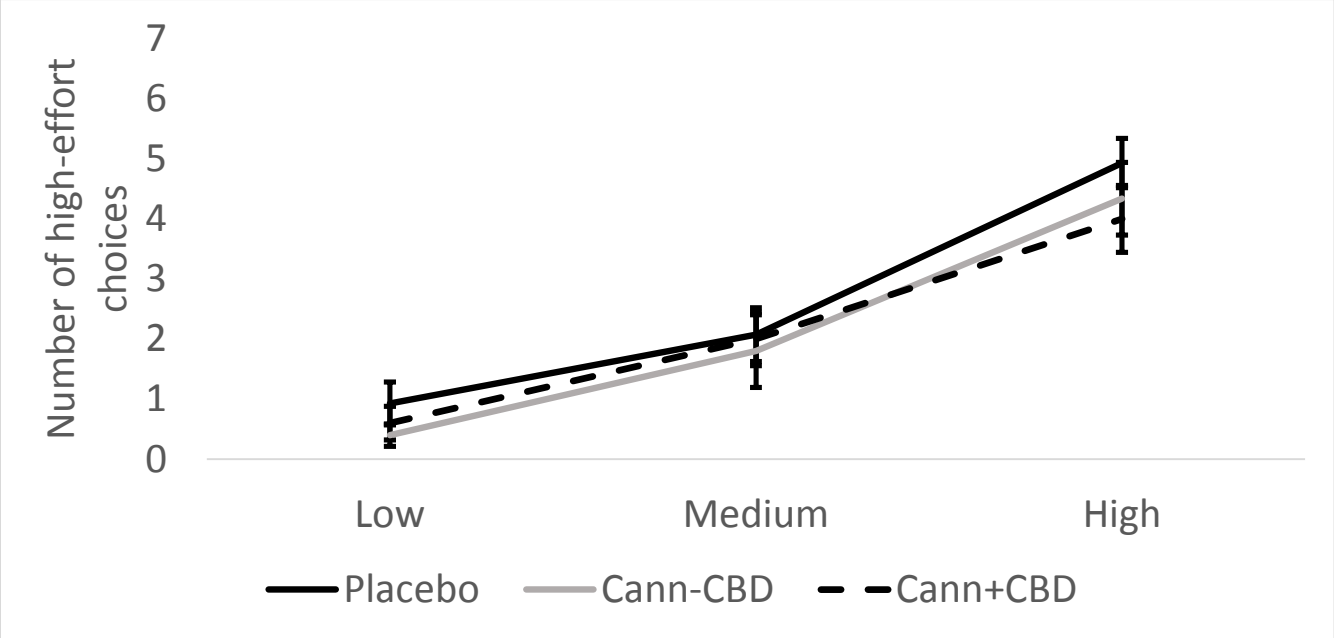


Figure 5.4 Mean (S.E.) numbers of high-effort choices made during each drug condition at each of three expected value levels: low, medium and high. These levels were formed by grouping the third lowest expected values, the middle expected values and the largest expected values. There were 7 trials for within each of these expected value levels, so there were a maximum of 7 high-effort choices to be made. Error bars show standard error.

5.3.5 SHAPS

There was no effect of drug ($F_{2, 32}$=0.248, p=0.782).

5.4 Study 2 Methods

5.4.1 Participants and design

20 cannabis-dependent individuals were compared with 20 controls, with eligibility criteria based on Morgan et al. (2012). Inclusion criteria for the cannabis-dependent participants were: score ≥3 on the severity of dependence scale (SDS) for cannabis (indicative of dependence: Swift, Copeland, and Hall (1998)); smoke high-potency cannabis ('skunk') on 50% or more of the occasions that they smoke cannabis; score ≤2 on the SDS for all other drugs, except tobacco and alcohol. Participants in the control group were selected to match the cannabis-dependent group in terms of other (non-cannabis) drug use and had to score <3 on the SDS for all drugs, except tobacco and alcohol. Exclusion criteria

for either group were: currently seeking treatment for a mental health problem; current use of psychiatric medication or diagnosis of alcohol dependence.

Participants were reimbursed £10/hour. The study was approved by the UCL Ethics Committee and all participants provided written informed consent.

5.4.2 Assessments

The following measures were used as described in study 1: EEfRT, BDI, TEPS, drug history, cannabis SDS.

5.4.2.1 Probabilistic-Reward-Task (PRT) (Pizzagalli et al., 2005)

As described in section 4.2.2.3

Unlike in the experiment reported in chapter 4, I excluded participants based on task performance as only 11 out of 40 participants had to be excluded. Trials were excluded if the participant responded with an RT<100ms or an RT>1500ms. Participants were excluded if, on either block, they: had >20% excluded trials; received reinforcement on <25 rich stimuli; received reinforcement on <6 lean stimuli; had <55% accuracy for the rich stimulus; had <55% accuracy overall (Alexis Whitton, personal communication).

5.4.2.2 **Other assessments**

Spot-the-word (Baddeley et al., 1993)

As described in 2.2.2.3

5.4.3 Procedure

Following telephone screening, participants completed one 2h testing session. Participants were instructed to abstain from all drugs (apart from nicotine and caffeine) for at least 12 hours before the

session. This meant that cannabis-dependent participants, if they followed the instructions, had not smoked cannabis for at least 12 hours. First, participants answered demographic and drug use questions, stated which drugs they had taken over the last 48 hours and completed the spot-the-word test. Subsequently, they completed the EEfRT, the BDI, the TEPS, the PRT and provided a urine sample. Participants also completed three other cognitive tasks and questionnaires concerning psychosis-like symptoms, which are not reported in this thesis.

5.4.4 Statistical Analyses

All analyses were carried out using IBM Statistical Package for Social Sciences (IBM SPSS version 22). Where appropriate, errors were checked for normality, unbiasedness and homoscedasticity using inspection of histograms and Levene's test. Non-parametric tests were used when data did not meet the above assumptions and a suitable test was available.

Analysis of the EEfRT was conducted in the same way as in study 1, using the standard predictors plus group, with the additional predictors: no others (model 1), group X magnitude (model 2), group X probability (model 3), group X expected value (model 4). Each model also included BDI, average number of cigarettes/day and baseline button-pressing time because of group differences. The models were also run without these three extra predictors to see if it affected results.

For the PRT, response bias (RB) and discriminability were analysed with mixed ANOVAs with a between-subjects factor of group (controls, cannabis) and within-subjects factors of block (1, 2). Accuracy and RTs were analysed in the same way but with an extra within-subjects factor of stimulus (rich, lean). ANCOVAs were used to investigate whether inclusion of BDI and average number of cigarettes/day affected results.

Correlations were computed for composite-RB (averaged across block 1 and 2) and ΔRB (change between block 1 and 2) with: BDI, average number of cigarettes/day (which includes those who don't smoke and those who don't smoke every day) and cannabis-SDS in each group separately.

5.5 Study 2 Results

5.5.1 Demographics (Table 5.4)

The groups did not differ in gender, age, highest level of education achieved or any measure of illicit drug use. However, compared with the controls, the cannabis group, on average, had a higher BDI score[27] (t_{38}=2.932, p=0.006), a lower spot-the-word score (t_{38}=2.585, p=0.014) and smoked more cigarettes (t_{38}=4.411, p<0.001).

All but two of the cannabis group smoked cannabis every day; one participant smoked approximately 22 days per month and another smoked approximately 12 days per month. The cannabis group smoked an average of 1.49 (1.41)g per session and had an average cannabis SDS score of 7.30 (3.39). Eight controls smoked cannabis at least once per month, with an average of 3.94 (1.78) days per month and an average of 0.31 (0.28)g per session. None of the controls scored >0 on the cannabis SDS.

5.5.2 Recent drug use

No participants reported using cannabis, alcohol or any other illicit drug within 12 hours of testing.

In the control group, there were positive urine tests for: THC (n=4), benzodiazepines (n=2), buprenorphine (n=2), cocaine (n=1), PCP (n=1) and opioids (n=1)[28]. In the cannabis group, there were positive urine tests for: THC (n=19), cocaine (n=2) and opioids (n=2).

[27] One control's BDI score was missing so it was imputed from the group mean
[28] One control's urine test results were missing

*Table 5.4 Demographic details and drug history for non-dependent, drug-using controls and cannabis-dependent participants in study 2. *p<0.05, **p<0.01, ***p<0.001*

	Control	**Cannabis**
Age	27.25 (6.80)	27.75 (7.31)
Gender (f/m)	6/14	7/13
Highest education level (GCSE/NVQ-BTEC-Diploma/A-Levels/Undergraduate Degree/Postgraduate Degree)	2/2/5/9/2	5/3/1/10/1
BDI**	5.32 (5.41)	12.20 (9.00)
TEPS consummatory	39.25 (6.21)	35.80 (6.70)
TEPS anticipatory	46.45 (6.69)	46.10 (7.45)
TEPS total	86.10 (11.76)	81.90 (12.63)
Spot-the-word*	48.30 (3.36)	45.35 (3.84)
Cannabis SDS***	0	7.30 (3.39)
Alcohol ever used (y/n)	20/0	20/0
Alcohol use now (y/n)	20/0	17/3
Alcohol days per month	14.11 (7.49)	10.97 (8.64)
Alcohol units/session	7.75 (4.61)	7.72 (4.26)
Amphetamine ever used (y/n)	9/11	9/11
Amphetamine use now (y/n)	0/20	1/19
Amphetamine days per month	NA	1
Amphetamine grams/session	NA	0.1
Benzodiazepines ever used (y/n)	9/11	10/10
Benzodiazepines use now (y/n)	1/19	3/17
Benzodiazepines days per month	2	2.83 (1.04)
Benzodiazepines tablets per session	1	1.25 (1.06)
Cannabis ever used (y/n)	20/0	20/0
Cannabis use now (y/n)***	8/12	20/0
Cannabis days per month***	3.94 (1.78)	28.19 (4.74)
Cannabis grams/session***	0.31 (0.28)	1.49 (1.41)
Cocaine ever used (y/n)	16/4	14/6
Cocaine use now (y/n)	8/12	4/16
Cocaine days per month	1.88 (0.84)	3.00 (1.41)
Cocaine grams/session	0.59 (0.33)	0.75 (0.29)
Hallucinogens use now (y/n)	1/19	1/19
Hallucinogens days per month	1	1
Heroin ever used (y/n)	2/18	3/17
Heroin use now	0/20	0/20
Heroin days per month	NA	NA
MDMA ever used (y/n)	18/2	16/4
MDMA use now (y/n)	7/13	5/15
MDMA days per month	1.43 (0.787)	1.40 (0.548)
MDMA grams/session	0.34 (0.33)	0.44 (0.13)
Mephedrone ever used (y/n)	7/13	6/14
Mephedrone use now (y/n)	0/20	0/20
Mephedrone days per month	NA	NA
Mephedrone grams/session	NA	NA
Tobacco ever used (y/n)	18/2	20/0
Tobacco use now (y/n)**	9/11	19/1
Tobacco days per month*	18.39 (12.95)	29.26 (3.21)
Tobacco cigs/day (when smoking)*	2.92 (3.14)	7.55 (5.19)
Tobacco average cigs/day*	1.14 (2.54)	7.01 (5.38)

5.5.3 EEfRT

Baseline button-pressing time

The controls were faster than the cannabis-dependent participants to complete 30 and 100 button-presses (t_{37}=3.113, p=0.004). As a result, baseline button-pressing time was included in the GEE models.

GEE models (Table 5.5)[29]

Reward magnitude and probability positively predicted making a high-effort choice in all models (ps<0.05) and EV did so in all but one of the models (ps<0.05). Participants were less likely to make a high-effort choice as the task went on, as demonstrated by the negative effect of trial-number (ps<0.001). However, there was no overall difference in motivation between the groups and there were no interactions between group and magnitude, probability or EV. The pattern of these results did not change when I removed baseline button-pressing, BDI and average number of cigarettes/day.

[29] One cannabis-dependent participant was excluded because they failed to complete 16 trials.

Table 5.5 GEE Models for EEfRT from study 2. Beta coefficients for each predictor term, their standard errors, associated p-values, odds ratios (OR) and 95% confidence intervals (CI) for these ORs are shown. Av-Cigs/Day = average number of cigarettes smoked per day. The most important terms are in bold.

Model 1

	Beta	**S.E.**	**p**	**Odds Ratio**	**95% CI OR**
Magnitude	0.236	0.0845	0.005	1.266	1.073, 1.494
Probability	0.278	0.0814	0.001	1.320	1.126, 1.549
Expected Value	0.278	0.1132	0.014	1.321	1.058, 1.649
Trial Number	-0.015	0.0028	<0.001	0.985	0.980, 0.990
Gender	0.125	0.0909	0.169	1.133	0.948, 1.354
BDI	-0.006	0.0048	0.232	0.994	0.985, 1.004
Av-Cigs/Day	-0.007	0.0069	0.297	0.993	0.979, 1.006
Baseline button-pressing time	0.011	0.0215	0.617	1.011	0.969, 1.054
Cannabis vs. Controls	**0.047**	**0.1369**	**0.731**	**1.048**	**0.802, 1.371**

Model 2

	Beta	**S.E.**	**p**	**Odds Ratio**	**95% CI OR**
Magnitude	0.218	0.0829	0.008	1.255	1.057, 1.463
Probability	0.279	0.0816	0.001	1.322	1.127, 1.551
Expected Value	0.276	0.1134	0.015	1.318	1.055, 1.646
Trial Number	-0.015	0.0027	<0.001	0.985	0.980, 0.990
Gender	0.126	0.0910	0.167	1.134	0.949, 1.356
BDI	-0.006	0.0048	0.232	0.994	0.985, 1.004
Av-Cigs/Day	-0.007	0.0069	0.294	0.993	0.979, 1.006
Baseline button-pressing time	0.011	0.0215	0.615	1.011	0.969, 1.054
Cannabis vs. Controls	-0.005	0.1819	0.980	0.995	0.697, 1.422
Cannabis vs Controls*Magnitude	**0.038**	**0.1053**	**0.715**	**1.039**	**0.845, 1.277**

Model 3

	Beta	**S.E.**	**p**	**Odds Ratio**	**95% CI OR**
Magnitude	0.237	0.0853	0.006	1.267	1.072, 1.497
Probability	0.251	0.0904	0.005	1.285	1.077, 1.535
Expected Value	0.280	0.1136	0.014	1.323	1.059, 1.653
Trial Number	-0.015	0.0028	<0.001	0.980	0.980, 0.990
Gender	0.126	0.0910	0.1267	1.134	0.949, 1.356
BDI	-0.006	0.0048	0.237	0.994	0.985, 1.004
Av-Cigs/Day	-0.007	0.0069	0.294	0.993	0.979, 1.006
Baseline button-pressing time	0.010	0.0215	0.635	1.010	0.969, 1.054
Cannabis vs. Controls	0.004	0.1652	0.979	1.004	0.727, 1.389
Cannabis vs. Controls*Probability	**0.054**	**0.1059**	**0.607**	**1.056**	**0.858, 1.300**

Model 4

	Beta	S.E.	p	Odds Ratio	95% CI OR
Magnitude	0.237	0.0852	0.005	1.268	1.073, 1.498
Probability	0.278	0.0817	0.001	1.321	1.125, 1.550
Expected Value	0.215	0.1629	0.188	1.239	0.901, 1.705
Trial Number	-0.015	0.0028	<0.001	0.985	0.979, 1.006
Gender	0.128	0.0910	0.161	1.136	0.951, 1.358
BDI	-0.006	0.0048	0.235	0.994	0.985, 1.004
Av-Cigs/Day	-0.007	0.0070	0.289	0.993	0.979, 1.006
Baseline button-pressing time	0.010	0.0215	0.635	1.010	0.969, 1.054
Cannabis vs. Controls	-0.025	0.1727	0.885	0.975	0.695, 1.368
Cannabis vs. Controls*EV	**0.133**	**0.1769**	**0.451**	**1.142**	**0.808, 1.616**

5.5.4 PRT

Response Bias (Figure 5.5)[30]

Repeated measures ANOVA revealed a trend interaction between group and block ($F_{1,27}$=3.579, p=0.069), a main effect of group, indicating lower RB in the cannabis group ($F_{1,27}$=8.531, p=0.007) and a trend effect of block, reflecting increased RB from block 1 to 2 ($F_{1,27}$=2.978, p=0.096).

Exploration of the trend group by block interaction showed that RB increased from block 1 to 2 in controls (t_{19}=2.604, p=0.015) but not cannabis users (t_{19}=0.109, p=0.909). Furthermore, RB was significantly greater in controls than cannabis users during block 2 (t_{38}=3.00, p=0.005) but only marginally so in block 1 (t_{38}=1.831, p=0.082).

All of these effects were lost when BDI and average number of cigs/day were included as covariates. There was a trend main effect of BDI ($F_{1, 25}$=3.464, p=0.075) and no effect of cigs/day.

The pattern of results did not change if all of the participants were included in the analysis.

[30] 11 out of 40 participants were excluded due to not meeting task criteria.

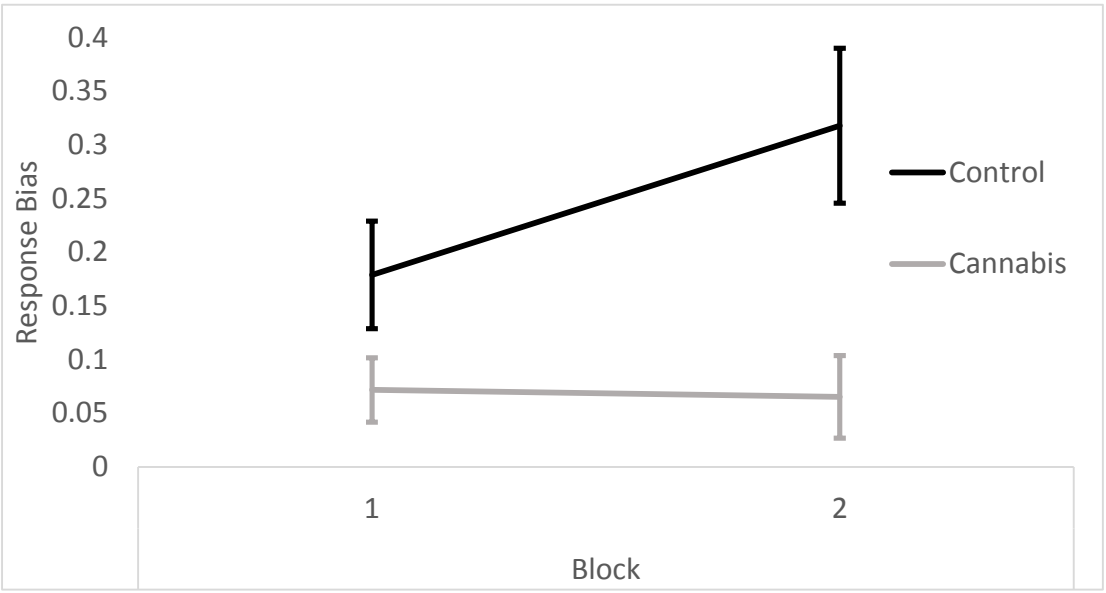


Figure 5.5 Means (S.E.) for response bias on the PRT for the control participants (control) and the cannabis-dependent (cannabis) participants, on blocks 1 and 2, in study 2. Error bars show standard error.

Discriminability

There was a trend towards an effect of block, with greater discriminability in block 2 compared with block 1 ($F_{1,27}$=3.605, p=0.068), no effect of group nor an interaction between the two. The effect of block was lost when BDI and average number of cigs/day were included as covariates.

Accuracy

There was an interaction between group and stimulus ($F_{1,27}$=8.723, p=0.006) and a main effect of stimulus, with greater accuracy for the rich stimulus ($F_{1,27}$=28.109, p<0.001). No other effects or interactions were significant. The main effect of stimulus remained after including the covariates, but the interaction between group and stimulus was lost.

Exploration of the interaction showed that the controls had greater accuracy for the rich stimulus compared with the lean stimulus (t_{14}=5.941, p<0.001) while the cannabis group did not.

RT

There was a main effect of stimulus, with a faster response to the rich stimulus compared with the lean stimulus ($F_{1,27}$=7.684 p=0.010). No other effects or interactions were significant. This effect was unchanged when including the covariates.

Correlations

Within each group separately, none of the correlations examined reached significance.

5.6 Discussion

Historically, cannabis use has been linked to amotivation (McGlothlin & West, 1968) and dependence is theoretically associated with non-drug reward processing deficits (Goldstein & Volkow, 2011), although empirical evidence for this is lacking. To my knowledge, this report is the first to delineate the acute effects of different cannabinoids on effort-related decision-making and cannabis dependence's associations with effort-related decision-making and reward learning.

In study 1, acute administration of cannabis without CBD (Cann-CBD) reduced the overall likelihood of making high-effort choices for monetary reward compared with placebo. Contrary to my hypothesis, this effect was not, overall, attenuated by cannabis containing CBD (Cann+CBD). However, Cann-CBD increased sensitivity to expected value of the monetary outcomes, relative to both placebo and Cann+CBD, although these effects were not large enough to be detected in post-hoc GEE models within each level of expected value. These data therefore suggest that acute cannabis administration can lead to transient amotivation and they provide some evidence that CBD partially moderates the effects of THC on motivation, via altering the way THC interacts with expected value. In study 2, no relationship between cannabis dependence and effort-related decision-making emerged. However, cannabis-dependent participants, who were instructed to abstain from cannabis (and other drugs) for at least 12 hours, had overall weaker reward learning than the controls, and the cannabis-dependent participants also failed to improve their response bias between blocks. Due to confounding group differences and the nature of the study, it is hard to conclude whether these effects were driven by cannabis dependence or confounding variables.

5.6.1 Acute cannabis and effort-related decision-making

Despite enduring beliefs that cannabis acutely reduces motivation, I could find only one controlled study which used a work-for-reward design (Cherek et al., 2002), and they had a sample of 5 participants. Some older work had suggested null (Mello & Mendelson, 1985; Mendelson et al., 1976) or pro-motivational (Foltin et al., 1990) effects of acute cannabis, however these studies were not well controlled or did not provide a clear reward, respectively. Here, the results provide strong evidence to support this hypothesis using a task that has previously demonstrated sensitivity to anhedonia, major depressive disorder, and dopaminergic function (Treadway, Bossaller, et al., 2012; Treadway, Buckholtz, et al., 2012; Treadway et al., 2009; Wardle et al., 2011). In the first model, placebo, relative to Cann-CBD, was a significant, positive predictor of the likelihood of making a high-effort choice. Hence, the administration of Cann-CBD reduced motivation for monetary reward and this supports a transient amotivational effect. It is difficult to speculate on the pharmacology underlying this effect. THC may boost dopamine release (Bossong et al., 2009), which would be expected to enhance motivation, but I found the opposite. The endocannabinoid system's role in motivation must be more clearly elucidated before attempting to explain in detail THC's amotivational effects, but this result at least suggests that functioning of CB1 receptors is important in effort-related decision-making.

Although CBD has been shown to shield individuals against some of the negative effects of THC (Englund et al., 2013; Hindocha, Freeman, Schafer, et al., 2015; Morgan, Freeman, et al., 2010), the overall difference between Cann-CBD and Cann+CBD was null in the first model. There is thus no evidence that cannabidiol reduced the overall amotivational effects of THC. It may be the case that a higher dose of cannabidiol or a different time of administration relative to THC is needed to produce a stronger pro-motivational effect.

However, Cann-CBD influenced the effects of expected value on effort-related decision-making differently to Cann+CBD. Expected value refers to the multiplication of the outcome value with the probability of receiving the outcome, so it represents how good an option is and how much it is worth.

According to model 4, expected value increased the likelihood of making a high-effort choice more following administration of Cann-CBD than placebo and Cann+CBD. This implies that CBD affected the way people made decisions about different effortful outcomes. Furthermore, these results could suggest that the presence of CBD attenuated THC's effects on the processing of expected value, such that Cann+CBD was more similar to placebo than Cann-CBD, in this regard. Alternatively, one could conclude that the presence of CBD made it less like placebo: Cann-CBD augmented the effect of expected value more than Cann+CBD and placebo, so this means that as expected value increased, participants who were given Cann-CBD somewhat recovered from the original amotivational effects, while participants who were given Cann+CBD did not. Moreover, when the interaction was explored using GEE models at three separate levels of expected value, no significant differences between Cann-CBD and Cann+CBD emerged, which suggests that, although there clearly was a significant interaction in model 4, the differences between the cannabis types within each expected value level were not large. Therefore, CBD's role in effort-related decision-making is slightly ambiguous. Replications of this study are needed before any conclusive remarks about CBD's motivational qualities are made.

Importantly, becoming stoned and liking the drug effects are major motivators for cannabis use and it is noteworthy that CBD did not compromise this desired effect of THC, consistent with previous findings (Hindocha, Freeman, Schafer, et al., 2015). The lack of CBD's effect on stoned ratings may be important in harm reduction messages, if users wish to maintain the degree to which they feel subjective effects while potentially reducing some of the harmful consequences of THC (Englund et al., 2013; Morgan, Schafer, et al., 2010). It is also of note that the degree of recreational cannabis use, as measured by average number of days smoking cannabis/month, did not affect the hedonic response to the drug, as might have been expected from tolerance. However, none of the participants were particularly heavy users (all smoked <4 times per week, and most smoked much less), so tolerance may not have occurred.

As described above, the endocannabinoid system is thought to play a role in other drug addictions. The administration of cannabinoid drugs can alter drug-taking behaviour in animals and humans, and chronic alcohol and nicotine exposure is associated with changes to CB1 receptor density and functioning (Parsons & Hurd, 2015). My findings thus indicate that the endocannabinoid system is involved in effort-related decision-making. Much more human research is needed to elucidate the ways in which the endocannabinoid system contributes to other drug addictions, including basic studies which describe the physiological changes to the endocannabinoid system in different addicted populations. Given my results, one possible research direction would be to examine whether changes to effort-related decision-making link the endocannabinoid system and dependence severity. Furthermore, as most people in Europe smoke cannabis with tobacco (Hindocha, Freeman, Winstock, et al., 2015), and results in chapter 4 showed that dependent smokers had impaired effort-related decision-making, it would be interesting to test the effects of simultaneous administration of nicotine and cannabis on effort-related decision-making.

5.6.2 Cannabis dependence and effort-related decision-making

No association emerged between cannabis dependence and effort-related decision-making. The results are concordant with previous survey-based research which have failed to find a relationship between long-term cannabis use and self-reported motivation (Barnwell et al., 2006; Musty & Kaback, 1995). Given the participants were instructed not to consume drugs (apart from nicotine and caffeine) for 12 hours before the session in study 2, the results from these two studies imply that cannabis acutely but not chronically alters effort-related decision-making. People who were dependent on cannabis but who were not currently intoxicated on cannabis had similar motivation to drug-using controls; whereas healthy controls given cannabis demonstrated transient amotivation. However, given the cross-sectional nature of study 2, the results should be interpreted cautiously. A large, longitudinal study that records frequency of cannabis use, type of cannabis used and different aspects of motivation is needed to more thoroughly address the question of how chronic use might relate to

amotivation. Furthermore, an investigation into the effects of cannabis withdrawal/recent cannabis consumption on motivational processing in cannabis dependent people is warranted. In general, the different effects of acute cannabis abstinence and acute nicotine abstinence in the respective dependent populations should be further examined.

5.6.3 Cannabis dependence and reward learning

Similar to the associations with depression (Pizzagalli, Iosifescu, et al., 2008) and nicotine withdrawal (Pergadia et al., 2014), I demonstrated that cannabis dependence (with >12 hours of abstinence) was associated with reduced reward learning compared with non-dependent, drug-using controls. Not only did the cannabis-dependent individuals have an overall reduced response bias, indicative of a generally lower reward responsiveness, but they did not improve their response bias between blocks, as is usually seen in healthy controls (Pizzagalli et al., 2005).

Drug addiction has been associated with deficits in non-drug reward processing (Goldstein & Volkow, 2002; Lubman et al., 2009) and anhedonia (Hatzigiakoumis et al., 2011; Leventhal et al., 2008). Given cannabis's putative effects on reward circuitry (Bloomfield, Morgan, Egerton, et al., 2014; Maldonado et al., 2006), and the depressive effects of cannabis withdrawal (Budney & Hughes, 2006), this finding was expected. Whether this reward deficiency was a consequence of: chronic cannabis; a predisposing factor for cannabis use; caused by other factors; or a combination of these remains to be seen and will require longitudinal studies. Whatever the causal relationships, a reduced capacity to direct behaviour towards more reinforced stimuli is an important finding as it may contribute to reduced subjective wellbeing and could negatively impact treatment success, as seen in depression (Vrieze et al., 2013).

Although the groups were very similar in terms of other illicit drug use, age, gender and educational achievement, they did differ significantly in depression levels and tobacco use. This is not surprising, given that depression and tobacco use are positively associated with cannabis dependence (Hindocha,

Shaban, et al., 2015). I found that when I included these factors as covariates the effects of group and block were lost. Given this result, and the strong relationship between depression and reward responsiveness on the PRT (Pizzagalli, Iosifescu, et al., 2008; Pizzagalli et al., 2005), as well as emerging evidence that tobacco use and nicotine withdrawal affect task behaviour (Janes et al., 2015; Liverant et al., 2014; Pergadia et al., 2014), drawing any conclusions about specific relationships between cannabis use, tobacco use, depression and reward learning is difficult. However, just because the effect of group was lost when depression and cigarette smoking were included as covariates does not mean cannabis dependence is not associated with reduced reward learning. As a relatively large amount of variance was shared between group and tobacco use (approximately 30%) and depression (approximately 20%), covarying for these variables could be considered statistically inappropriate (Miller & Chapman, 2001). Future case-control studies should therefore aim to match groups on depression and cigarette smoking.

5.6.4 Strengths and Limitations

Study 1 was a placebo-controlled, double-blind experiment, and so provides strong evidence for cannabis *causing* transient amotivation. To my knowledge, this is only the second time this has been shown (Cherek et al., 2002), and the first study had a sample size of five. Furthermore, the investigation of CBD was highly novel and builds on previous work showing it may moderate the effects of THC. The top-up dose of cannabis clearly worked well as 'stoned' ratings were similar immediately after the first and second doses. Although cannabis-dependent participants were more depressed and smoked more cigarettes than drug-using controls in study 2, they were well matched on all other demographic variables, including other drug use, which is a strength.

While the two studies have addressed the acute effects of cannabis on and association of cannabis dependence with reward processing, I only employed one type of reward. As discussed in previous chapters, money may be considered a way of buying drugs, rather than being seen as a reward in itself, and cannot be consumed. Future studies should investigate reward processing of a variety of

rewards, including cannabis itself, so that comparisons between drug and non-drug reward processing can be made, as they have been in chapters 2-4 with cigarette smokers. Furthermore, although urinalysis was conducted in both experiments, I was not able to relate task performance to quantitative indices of cannabinoid metabolites, which could have improved my ability to infer acute and chronic effects of THC and CBD (C. Morgan et al., 2012). Finally, study 2 could obviously have been improved if depression and cigarette smoking were not different between the groups.

5.6.5 Conclusions

In conclusion, cannabis without CBD led to an overall reduction in motivation as evidenced by a lower likelihood of making a high-effort choice to earn monetary reward. Cannabis with CBD did not appear to reduce this effect, but did moderate THC's effects on expected value. Cannabis dependence was associated with preserved motivation and impaired reward learning; however, given the observational nature of the data, the causal roles of cannabis dependence, depression and tobacco smoking cannot be determined.

Chapter 6: General discussion

In this thesis, I set out to address the following questions:

1. Do dependent cigarette smokers differ from occasional cigarette smokers on their processing of cigarette and non-drug rewards across a range of metrics? Is this moderated by acute nicotine abstinence?
2. Can an acute dopaminergic challenge beneficially disrupt cigarette smokers' processing of cigarette and non-drug rewards?
3. Is cannabis use associated with non-drug reward processing alterations?

I will discuss how my results help to answer these questions along with their theoretical and clinical implications. I will then suggest future directions for this field of research, discuss the limitations of my work and consider, with hindsight, what could have been improved.

6.1 Summary of findings

Many theoretical accounts of drug addiction centre on altered reward processing (Goldstein & Volkow, 2011; Koob & Le Moal, 1997; Robinson & Berridge, 1993). The work in this thesis was based on the general hypothesis that drug addiction is associated with a hypersensitivity to drug rewards and a hyposensitivity to non-drug rewards (Bühler et al., 2010; Goldstein & Volkow, 2011; Sweitzer et al., 2013). Despite strong theoretical predictions, the empirical literature concerning reward processing changes in tobacco and cannabis addictions is mixed. I therefore aimed to investigate associations between nicotine dependence and the processing of cigarette and non-drug rewards, across a range of metrics. Furthermore, I also aimed to examine non-drug reward processing alterations associated with acute cannabis use and cannabis dependence.

In order to do this I designed a novel task named the Drug, Reward and Motivation – Choice (DReaM-Choice) Task which provided participants with the opportunity to win both cigarettes and other

consummatory, non-drug rewards through choice and button-pressing. Subsequently, participants could consume and rate their subjective liking of these rewards. For my first three empirical chapters, I employed between-subjects designs to compare dependent cigarette smokers with non-dependent cigarette smokers (who were well-matched on the majority of demographic variables) on reward processing tasks. This allowed me to make comparisons between the groups on different drug and non-drug reward processing measures *and* comparisons within groups in terms of the balance of reward processing. Furthermore, I used two commonly used non-drug reward processing tasks to investigate effort-related decision-making (Treadway et al., 2009) and reward learning (Pizzagalli et al., 2005).

In chapter 2, I found that dependent smokers, in comparison to occasional smokers, were hypersensitive to cigarette reward in terms of relative preference, motivation, and subjective wanting and liking, regardless of recent nicotine consumption (abstinent or ad libitum smoking). Furthermore, there was very little evidence of dependent smokers being hyposensitive to non-drug rewards compared with occasional smokers: dependent smokers made fewer choices for chocolate but that was probably driven by their greater number of choices for cigarettes. There was a consistent pattern of drug vs. non-drug reward processing within each group. Occasional smokers always chose, worked for and liked one or both of the non-drug rewards more than cigarettes, while dependent smokers usually chose, worked for and liked cigarettes more than the non-drug rewards. Surprisingly, I did not find an interaction between group, reward and smoking-condition; acute nicotine abstinence increased cigarette and decreased music choices across both groups (although this result may well have been a consequence of inappropriately low power). These results suggested that irrespective of 12-hour nicotine abstinence, nicotine dependence was associated with a hypersensitivity to cigarette rewards but not a hyposensitivity to non-drug rewards. Therefore, my following studies investigated group differences after ad libitum smoking.

In chapter 3, using an adapted version of the Monetary Incentive Delay task (Knutson et al., 2000), I reported that dependent smokers, compared with occasional smokers, had greater behavioural motivation for cigarettes but not for music. Anticipation of and positive feedback about cigarettes triggered activation in reward-related brain regions in both groups. Furthermore, dependent smokers displayed greater right caudate activation when they received feedback about winning cigarette points than occasional smokers. However, there were no group differences during anticipation of cigarette reward. Moreover, anticipation of and feedback about music did not produce the expected pattern of activations. These results corroborated and extended findings from chapter 2, suggesting that nicotine dependence, at least following ad libitum smoking, is associated with a behavioural and neural hypersensitivity to cigarettes but not a hyposensitivity to a consummatory non-drug reward, music.

In chapter 4, I examined the role of dopamine D2 and D3 receptors in cigarette and non-drug reward processing. Pramipexole (0.5mg oral) did not affect any component of reward processing in the DReaM-Choice. These results questioned the importance of D2 and D3 receptors in motivation for cigarettes and consummatory, non-drug rewards.

However, pramipexole compromised both effort-related decision-making and reward learning across both groups. These results indicated that D2 and D3 receptor functioning may be specifically related to certain aspects of non-drug reward processing. In accordance with chapter 2, I found that dependent smokers, compared with occasional smokers (both of whom had been nicotine abstinent for at least 1.5 hours following ad libitum smoking), were hypersensitive to cigarette rewards, in terms of relative preference, motivation, choice time and subjective liking. As before, there was little evidence for a hyposensitivity to consummatory, non-drug rewards in the dependent group. However, nicotine dependence was associated with impaired effort-related decision-making for monetary reward.

Taking a different tack, in chapter 5 I found that acute cannabis administration led to a reduction in motivation to earn monetary reward and that cannabidiol (CBD) subtly altered the effects of THC on motivation. Moreover, I observed that cannabis dependence was associated with impaired reward learning but preserved effort-related decision-making. Hence, these results implied that cannabis use can disrupt non-drug reward processing in specific ways.

Throughout this thesis I also recorded many secondary outcomes, including self-reported craving, anhedonia, withdrawal and drug effects. The results of these secondary outcomes have nearly always confirmed expectations. For instance, in chapter 2, there were three way interactions between group, smoking-condition and time for self-reported withdrawal and anhedonia scores. Similarly, in chapter 4, I observed the expected effects of pramipexole on 'feel drug' and 'nausea', amongst others, while dependent smokers craved cigarettes more than occasional smokers. And, in chapter 5, I observed the expected effects of cannabis on 'stoned' and 'like drug'. Thus, I was able to replicate many basic effects. This demonstrates that the important manipulations in my studies worked successfully.

In summary, the research in this thesis has provided evidence for hypersensitivity to cigarette rewards across a range of reward processing metrics in nicotine dependence. However, I found much less evidence in favour of impaired non-drug reward processing in nicotine dependence, when assessed mostly after ad libitum smoking. This research also questioned the role of D2/3 receptors in nicotine dependence. Furthermore, contrasting with nicotine dependence, specific non-drug reward processing deficits associated with cannabis use were revealed.

6.2 The iRISA theory of addiction

Goldstein & Volkow (2011, page 652) state that addiction is: 'a syndrome that is characterized by attributing excessive salience to the drug and drug-related cues, decreased sensitivity to non-drug reinforcers and decreased ability to inhibit maladaptive or disadvantageous behaviours'; this is their 'impaired response inhibition and salience attribution' (iRISA) theory of addiction. Furthermore, they

claim that (page 654): during addiction 'drug-related neuropsychological processes, including drug-related anticipation (and other conditioned responses), suppress or eclipse non-drug related processes, such as anticipation of — or the motivation to — pursue non-drug related goals'. Their theory stems from neurobiological work investigating the role of the prefrontal cortex in addiction. However, their theory and predictions can and should be applied to behaviour, otherwise it should not be considered a theory of addiction, but rather a theory of brain changes associated with addiction.

For my purposes, these statements can be condensed into three chief, theoretical claims: (1) addiction is associated with a hypersensitivity to drugs, (2) addiction is associated with a hyposensitivity to non-drug rewards and (3) non-drug reward-related goals are suppressed or eclipsed by drug-related goals. Goldstein & Volkow (2011) are not specific about which aspects of reward processing should be particularly affected by addiction, although they consider motivation and salience as key processes. Therefore, I can assess each statement, relating to nicotine dependence, across a variety of reward processing metrics using the results reported in this thesis.

6.2.1 Claim 1 - Addiction is associated with a hypersensitivity to drugs: hypersensitivity to cigarette reward in nicotine dependence

In both chapters 2 and 4, dependent smokers chose, pressed for and liked cigarettes more than occasional smokers. Moreover, dependent smokers, compared with occasional smokers, reported greater wanting of cigarettes in chapter 2, reacted more quickly to the cigarette target in chapter 3 and also chose cigarettes faster than occasional smokers in chapter 4. Therefore, on nearly every measure of cigarette reward processing that I recorded, ranging from the preference of one reward over another to the subjective liking associated with consuming cigarettes, nicotine dependence was associated with a hypersensitivity to cigarette reward. This provides strong support for the first theoretical claim (Goldstein & Volkow, 2011) and clearly answers one part of my first research question.

These results are unsurprising and some, to be cynical, are a little unexciting. It would be odd if addiction was not associated with perturbations in the motivation for the drug of choice. That is, by definition, part of what drug dependence is (DSM-5 American Psychiatric Association, 2013). Had the dependent smokers not worked harder for cigarettes than occasional smokers, I would have been very concerned that the tasks were invalid. Having said that, previous research, with both cigarette and cannabis users, has sometimes failed to demonstrate a significant association between dependence level and the motivation to earn cigarettes/cannabis (Barrett, 2010; Bühler et al., 2010; Mendelson & Mello, 1984). Hence, although it was an expected result, it is an encouraging validation of the DReaM-Choice task that it was able to show a group difference in terms of motivation for cigarettes, when some other laboratory studies have failed to show this.

Other results are perhaps more interesting. Firstly, dependent smokers chose cigarettes more than music and chocolate in both chapters 2 and 4, in situations where these rewards were directly pitted against each other. This demonstrates that when push comes to shove, dependent smokers are willing to sacrifice alternative rewards for cigarettes. Importantly, in chapter 2, one unit of chocolate (one chunk) was worth approximately the same amount of money as one unit of a cigarette (one quarter); they were both worth approximately 10p. Thus, it cannot be argued that the smokers were just choosing the most valuable option. This supports a lot of previous research showing a strong relationship between the level of nicotine dependence and the extent to which cigarettes are chosen over chocolate (Chase et al., 2013; Hogarth, 2012; Hogarth & Chase, 2011). These results are important because it shows that when faced with exclusive choices, cigarettes powerfully direct behaviour away from non-drug rewards, which supports the DSM's criterion of reduction or termination of alternative activities (DSM-5 American Psychiatric Association, 2013). However, I believe that this reduction in non-drug reward choices is driven by a hypersensitivity to cigarette rewards rather than a change in the value of non-drug rewards.

My finding in chapter 3 that dependent smokers displayed greater activation in a small region of the right caudate while they earned points for cigarette reward compared with occasional smokers is also noteworthy. Firstly, this extends my findings in other chapters from behavioural hypersensitivity to cigarette reward in nicotine dependence to one aspect of neural cigarette reward processing. Thus, the pattern of hypersensitivity appears consistent across different metrics. Furthermore, this is a novel finding. Only one other study has investigated BOLD responses while cigarette smokers of varying levels of nicotine dependence earn points for real cigarettes (Bühler et al., 2010). They found no group differences on anticipatory or feedback BOLD responses. Hence, this enhanced activity in the right caudate, a structure putatively involved in habitual drug-seeking (Everitt & Robbins, 2005), during positive cigarette feedback demonstrates an unreported form of hypersensitivity to cigarette reward in nicotine dependence. This result provides neural support for the first theoretical claim (Goldstein & Volkow, 2011).

Another interesting aspect of the hypersensitivity to cigarettes was the greater self-reported liking of smoking a cigarette in the dependent compared with the occasional smokers. One previous study found that, in a group of dependent smokers, euphoria was associated with the number of years smoking but not level of dependence (Pomerleau & Pomerleau, 1992). While another found no relationship between dependence and the reported pleasantness of smoking (Shiffman & Kirchner, 2009). My studies compared very occasional, non-dependent smokers with dependent smokers, which, to my knowledge, has not previously been done. My results suggest that nicotine dependence, despite tolerance, is associated with greater hedonic responses to cigarettes and this therefore supports the first theoretical claim described above (Goldstein & Volkow, 2011) and helps answer my first research question. Interestingly, and supporting these findings, survey data suggests that the greater the frequency of drug use, the greater the positive outcomes that the drug user reports (Lawn & Winstock, unpublished observations).

For most activities and commodities in the world, increased use or consumption is associated with greater pleasure. For example, people who enjoy playing football are likely to play football again, and people who eat a lot of chocolate are likely to enjoy eating it. These proposed associations say nothing about whether pleasure drives motivation or motivation drives pleasure, but they do highlight the reasonable claim that they frequently occur together. It is unsurprising to me that drugs, tobacco in this case, are no different. However, I feel it is fair to say that a lay assumption about an addict is that they no longer take as much pleasure from drug consumption as they used to, or even that they do not take any pleasure from it at all any more. This is also theoretically suggested in the incentive-sensitization theory, which claims that, as addiction takes hold, 'wanting' increases while 'liking' falls, or at least remains stable (Robinson & Berridge, 1993). Furthermore, 'wanting' and 'liking' are thought to be distinct concepts and not necessarily related.

My results imply that dependence is certainly not associated with a termination of cigarette-induced pleasure, and that nicotine-dependent people take more pleasure than non-dependent people. However, without longitudinal studies, it is impossible to determine whether the pleasure changes as the addictive state grows. It may have been that the dependent smokers in my studies always really liked smoking, even when they were only occasional smokers. However, given large numbers of highly dependent smokers still report great pleasure from smoking (Shiffman & Kirchner, 2009), I predict that pleasure increases, in the transition from occasional to frequent cigarette use. The pleasure associated with, and other short-term positive consequences of, drug use have rarely been investigated by the psychopharmacology community and may be considered to be the 'elephant in the room'. A greater focus on the enjoyable aspects of drugs may provide greater insight into the experience of the many non-dependent drug users (Anthony et al., 1994), while at the same time improving our understanding of the transition to problematic use. Important caveats for my liking data in this thesis are: (1) that many occasional smokers chose not to smoke any cigarettes at all and (2) that I only reported data on the first quarter of the first cigarette consumed.

As discussed in chapter 4, I found some evidence for the dissociation of 'liking' and 'wanting'. In the occasional smokers, the degree to which they generally 'liked smoking a cigarette' was associated with their button-pressing for cigarettes, but this was not the case in the dependent smokers. This might suggest that nicotine dependence is associated with a reduction of a liking-wanting relationship, which would support Robinson and Berridge's (1993) theory. However, as this study used a cross-sectional design, it may have been that this relationship never existed in the dependent smokers. Alternatively, a ceiling effect in the dependent smokers' general liking ratings and button-pressing for cigarettes may have negated any relationship between the two.

6.2.2 Claim 2 - Addiction is associated with a hyposensitivity to non-drug rewards: hyposensitivity to non-drug rewards in nicotine dependence

The second theoretical claim, that addiction is associated with a hyposensitivity to non-drug rewards (Goldstein & Volkow, 2011), received little support from my research. In the studies reported in chapters 2 and 4 there were no group differences between dependent and occasional smokers on the average number of button-presses for music or chocolate, the primary measure of motivation. Furthermore, there were no differences in the self-reported wanting of music or chocolate in chapter 2, no differences in the time taken to choose music or chocolate in chapters 2 or 4, and no difference in the reaction time to respond to the music target in chapter 3. There was essentially no evidence to indicate any motivational differences for consummatory, non-drug rewards between the nicotine dependent and occasional smokers in the DReaM-Choice (chapters 2 and 4) and Adapted Incentive Delay (chapter 3) task.

This is in direct opposition to the second statement described above (Goldstein & Volkow, 2011). Furthermore, it conflicts with a number of other theories that rely on non-drug reward processing deficits in addiction (Blum et al., 2000; Koob & Le Moal, 1997; Solomon & Corbit, 1974). The results described in this thesis indicate that non-drug reward processing deficits do not exist in dependent smokers compared with occasional during ad libitum smoking. Therefore, my results suggest that it is

inappropriate to claim that 'addiction is associated with reduced motivation for alternative non-drug rewards'. This may be true for some addictions, it may also be true for nicotine dependence in certain circumstances, however it is demonstrably untrue for nicotine dependence during ad libitum smoking (which is the most common state to be in for a smoker). Therefore, sweeping statements in this area should be avoided so that readers and other researches do not assume that all addictions (including nicotine dependence), in all circumstances, are associated with non-drug reward processing deficits.

My null findings concerning non-drug reward processing could be for two reasons: (1) nicotine dependence does not cause and is not associated with non-drug reward motivational deficits whatsoever; or (2) these non-drug reward processing deficits are only apparent during short-term nicotine deprivation. In other words, my results may have been substantially different if I had investigated acutely abstaining cigarette smokers in chapter 3 and 4.

There is evidence that motivational deficits for monetary reward are only apparent when dependent smokers are deprived of nicotine (Al-Adawi & Powell, 1997; Powell et al., 2002). It is argued that dysregulation of the reward system is only revealed when the chronic administration of nicotine is stopped (Powell et al., 2002). These data are supported by other studies which have shown significant, impairing effects of acute nicotine abstinence on non-drug reward processing (Pergadia et al., 2014; Perkins & Karelitz, 2013b; Sweitzer et al., 2013), although a variety of other studies have not found these effects (Audrain-McGovern et al., 2014; Bühler et al., 2010; Kalamboka et al., 2009). It may be that neuroadaptations to the dopamine system, such as lower dopamine D2 receptor (Fehr et al., 2008), D1 receptor (Dagher et al., 2001) and dopamine transporter (Leroy et al., 2012) densities, show their psychological effects only after chronic nicotine administration is stopped for a certain period of time. This idea is further supported by nicotine's acutely enhancing capacities in reward learning (Barr et al., 2008) and motivation for non-drug reward (Perkins & Karelitz, 2013b), which could mask the underlying problems.

Therefore, although no group differences in motivation for consummatory, non-drug rewards were reported in chapters 2, 3 and 4, these results may have been different after 12-48 hours of abstinence. However, I had good reason not to include an acute nicotine abstinence condition in the studies described in chapter 3 and 4: I didn't find the expected differential effect of acute nicotine abstinence on dependent and occasional smokers in chapter 2. Consequently, it made sense to continue investigating group differences in just one state – ad libitum smoking. My results, in the most part, therefore speak to the question concerning non-drug reward processing in cigarette smokers when they are smoking as usual. My study described in chapter 2 helps to answer the question of 'how does acute nicotine abstinence affect reward processing', however the rest of the work described in this thesis does not. My conclusions are therefore much more focused on reward processing alterations in dependent cigarette smokers during ad libitum smoking. However, I will now briefly discuss my thoughts on why I did not find the hypothesised effect of acute nicotine abstinence in chapter 2.

Despite conducting a power analysis (with n=20 for both groups), I now suspect my null interaction in chapter 2 was driven by (1) random sampling effects, (2) the subtlety of the effect (especially after only 12 hours of nicotine abstinence, compared with 24-48 hours) and (3) my sample size. My reasons for suspecting this are: (1) a large amount of previous research has demonstrated an important effect of abstinence and (2) my results went in the predicted direction (see figure 2.3). In support of my second point, although I did not report this in section 2.3.3 (as the interaction was non-significant), button-pressing for chocolate reward was marginally greater in the occasional than the dependent smokers during abstinence ($p=0.087$) but not during ad libitum smoking ($p=0.340$). Furthermore, in the dependent smokers, the number of choices for music decreased during abstinence relative to ad libitum smoking ($p=0.003$), but this was not the case in the occasional smokers ($p=0.515$). However, the differences between these differences were not great enough to produce significant interactions. These results tentatively imply that some motivational impairments were developing in the dependent smokers during abstinence. Hence, it is difficult to know exactly what to make of my results concerning the effects of nicotine abstinence on reward processing in dependent and occasional

smokers. Future research should clarify and explore these effects with larger samples and variable lengths of nicotine deprivation. However, I will now concentrate on my findings concerning non-drug reward processing during ad libitum smoking, rather than speculating about why I failed to find the expected three-way interaction in chapter 2.

My studies have demonstrated that, when dependent smokers have recently smoked, they do not have deficient motivation for the consummatory, non-drug rewards music and chocolate. Theoretically, this means that hyposensitivity to non-drug reward is not apparent in nicotine dependence, following ad libitum smoking, and so it does not support the second statement described above (Goldstein & Volkow, 2011). These results are important because they highlight the fact that impairments in non-drug reward processing in addicted individuals should not be taken for granted. They are likely to be moderated by factors such as short-term abstinence, individual differences and the component of reward processing under examination. Importantly, theories of addiction that rely on non-drug reward processing to explain addictive behaviours (Blum et al., 2000; Goldstein & Volkow, 2011; Koob & Le Moal, 1997) may not be able to account for these findings, at least within the scope of nicotine dependence.

An important point to consider is that there were fewer choices for the non-drug rewards in dependent compared with occasional smokers, but that is more likely explained by the increased number of cigarette choices. Enhanced motivation for cigarettes in the dependent compared with the occasional smokers was demonstrated by greater button-pressing for cigarettes. Hence, it seems very unlikely that the fewer chocolate choices actually reflected weaker motivation for chocolate reward in the dependent smokers, but rather a stronger desire for cigarettes, which necessarily affected the number of choices of alternatives.

Given that dependent smokers were more motivated for cigarettes but similarly motivated for consummatory non-drug rewards compared with occasional smokers, it follows that, in absolute terms (drug + non-drug reward motivation), the dependent smokers expressed greater motivation for

reward overall. If a certain level of nicotine dependence, combined with ad libitum smoking, does not impair one's motivation for non-drug rewards, then dependent smokers may be experiencing more overall reward than occasional or non-smokers. For some addicts, motivation for the drug may reduce the amount of non-drug reward consumed (through life choices and limited availability of non-drug reward or impaired motivation processing) and therefore it may reduce the absolute amount of reward. However, the ability to maintain motivation for and pleasure taken from non-drug rewards while simultaneously experiencing drug reward could be a driving force for drug (in this case tobacco) use. One way to examine whether dependent smokers have an overall greater motivation for reward (drug + non-drug) than occasional smokers would be to alter the DReaM-Choice slightly so that drug and non-drug rewards could be worked for simultaneously.

Despite the lack of group differences in non-drug reward processing on the DReaM-Choice, there were group differences on the EEfRT. Namely, the dependent smokers were less sensitive to the pro-motivational effects of magnitude, probability and expected value. This implies that nicotine dependence, even after recent smoking, is associated with a worse ability to use these factors in successful effort-related decision-making. It is interesting that I found no group differences on button-pressing for non-drug rewards in the DReaM-Choice, which putatively measures motivation, but I did find group differences on the EEfRT. Importantly, I did not find an overall group difference in the likelihood of making a high-effort choice on the EEfRT, which should index overall motivation for money. The group difference concerned the sensitivity to task parameters. This may go some way to explain this potential discrepancy between the findings on these two tasks. Nicotine dependence may be associated with a specific impairment in using important variables in effort-related decision-making, but not a global deficit in motivation. Moreover, the EEfRT provides monetary reward while the DReaM-Choice provides consummatory drug and non-drug rewards. This could feasibly contribute to the results if money is more sensitively affected by nicotine dependence.

I did not find a difference between the dependent and occasional smokers in terms of reward learning, as measured by the probabilistic reward task (Pizzagalli et al., 2005). This supports previous work which did not find a difference on this task between smokers (after 4 hours of abstinence) and non-smokers (Peechatka et al., 2015). Hence, 24 hours of nicotine abstinence may be required to demonstrate differences on this task (Pergadia et al., 2014).

There was a small amount of evidence that the dependent smokers liked chocolate less than the dependent smokers in the study reported in chapter 4. This was probably due to recruiting a few dependent smokers who, by chance, didn't particularly like Dairy Milk chocolate. Hence, I cannot conclude that nicotine dependence is associated with reduced liking of chocolate, especially given that this result was not seen in chapter 2. More research investigating the pleasurable response to rewards, with much larger, representative samples, must be conducted with dependent smokers to determine if they suffer deficient hedonic processing of non-drug rewards.

On a related note, my studies were not designed to carefully assess the effect of nicotine dependence and abstinence on hedonic processing with complete experimental control. I provided a naturalistic situation in which participants could consume their rewards at their leisure. Furthermore, each participant had a different amount of each reward. This was because I wanted to create a situation which (1) was ecologically valid, in the sense that consumption of rewards was not forced and participants could behave in a way that suited them and (2) was determined by the behaviour in the preceding DReaM-Choice task – hence the amount of each reward that participants received could not have been kept constant. These features, which I chose for good reason, meant that the manipulation of nicotine abstinence was disrupted for some participants in the study described in chapter 2. For instance, an 'abstaining' dependent smoker might smoke a cigarette before listening to music, and so they would no longer be deprived from nicotine. Moreover, it is possible that a participant who consumed a large amount of chocolate may then feel ill and subsequently rate the music they consumed afterwards poorly. Therefore, future research, which aims specifically at

investigating hedonic processing in nicotine dependence, should manipulate acute abstinence and control the order of consumption and amount of non-drug rewards.

The research described in this thesis, as well as previously published research, suggests that the effects of nicotine dependence on non-drug reward processing are often quite subtle, may require nicotine abstinence, or are simply non-existent. Two reasons why the effects on non-drug reward processing might be quite subtle or only found during acute abstinence are that, unlike many other addictive drugs of abuse, nicotine putatively acts as a cognitive enhancer (Levin, McClernon, & Rezvani, 2006), and does not appear to negatively interfere with everyday tasks. Someone who smokes 20 cigarettes/day can function perfectly well at work and at home, for most of their life, while someone who drinks 20 drinks/day usually cannot. Poor functioning in day-to-day life could then negatively feedback on the processing of everyday non-drug rewards. This speculative lack of disturbance to other activities in life, possibly due to cognitive enhancement, may contribute to my null findings concerning non-drug reward processing.

Moreover, individual differences in the effects of nicotine dependence and acute abstinence likely play an important role. Despite not finding any associations between questionnaire measures or demographic variables and abstinence-induced changes in chapter 2, baseline anhedonia appears to moderate the effect of acute abstinence on various reward processing measures. Higher levels of anhedonia, following nicotine deprivation, have been associated with greater urges to smoke (Cook et al., 2004; Leventhal et al., 2009), greater willingness to pay for cigarettes (Leventhal, Trujillo, et al., 2014) and weaker interference from happy faces (Leventhal et al., 2012). Similarly, depression-prone smokers have greater positive affect while smoking compared to during abstinence, whereas non-prone smokers do not show this profile (Audrain-McGovern et al., 2014). This implies that people are likely to experience the effects of nicotine abstinence differently. Therefore, it may be simplifying the question to ask: do dependent smokers have non-drug reward processing deficits during nicotine satiation/deprivation? The answer to this question may depend on the kind of smokers who have

taken part in the experiment. Future research should aim to stratify smokers into those who do and do not experience reward processing deficits following nicotine deprivation and investigate why these smokers are more sensitive or vulnerable.

6.2.3 Claim 3 – Non-drug reward-related goals are suppressed or eclipsed by drug-related goals: the balance of cigarette and non-drug reward processing in nicotine dependence

One consistent finding throughout chapters 2-4 was that the dependent smokers generally processed (e.g. choices, button-pressing, liking etc…) cigarettes more positively than or similarly to non-drug rewards; on the other hand, occasional smokers generally processed non-drug rewards more positively than cigarettes. This was the case for choices, button-pressing and liking (in chapters 2 and 4), for choice time (in chapter 4) and marginally so for reaction time (in chapter 3). This may be considered evidence to support the third theoretical claim described above (Goldstein & Volkow, 2011) and perhaps adds weight to the hypothesis that the balance between cigarette and non-drug reward processing is particularly important in nicotine dependence (Bühler et al., 2010).

In dependent smokers, there was often a stronger motivation to earn cigarettes than alternative, non-drug rewards. This could be described as the drug-related goal 'eclipsing' non-drug related goals. In my opinion though, that is too strong a word to use. 'Eclipsing' of non-drug related goals implies that there is a substantial disruption of these non-drug related goals. However, compared with occasional smokers, dependent smokers did not have impoverished non-drug reward processing. Hence, there is a simpler way to interpret these consistent findings concerning the balance between cigarette and non-drug reward processing. Across most metrics, non-drug reward processing was similar between the groups and cigarette reward processing was greater in the dependent smokers; this leads to the difference in the balance described here, and essentially is nothing more than a difference in cigarette processing. There is thus little evidence that the pursuit of non-drug rewards was 'eclipsed' or 'suppressed' as a consequence of enhanced cigarette reward processing, except from when cigarettes

and non-drug rewards were directly pitted off against each other in the choice stage of the DReaM-Choice task.

The question of whether or not this 'balance' is particularly important in nicotine dependence, more so than either cigarette or non-drug reward processing separately, is an interesting one. This can be partially assessed by some of the data I presented in this thesis. For instance, is nicotine dependence significantly more associated with the *difference* between the motivation for cigarettes and music/chocolate than the motivation for cigarettes, per se? Although I did not present these results in the previous chapters, the answer to this question (using the button-pressing metric in chapters 2 and 4, and the reaction time metric in chapter 3) is no. There was not a significantly larger difference between dependent and occasional smokers when using the *difference* in the motivation for cigarette and non-drug rewards as the outcome variable, compared with using the motivation for cigarettes, per se, as the outcome variable. Hence, results in this thesis suggest that the balance in cigarette and non-drug motivation is no more associated with nicotine dependence than just motivation for cigarettes. However, this question could be more thoroughly answered using a longitudinal design in which maintenance of addiction in continuing smokers or cessation success in quitting smokers is predicted by: (1) cigarette processing; (2) non-drug reward processing; and (3) the balance between cigarette and non-drug reward processing.

To summarise, in answer to my first research question, the data reported in this thesis suggests nicotine dependence, when assessed mostly during ad libitum smoking, is associated with a hypersensitivity to cigarette rewards but generally not a hyposensitivity to non-drug rewards. There is a consistent difference in the pattern of cigarette and non-drug reward processing between the groups, but that is driven simply by a difference in cigarette processing. There is very little evidence to suggest that there are substantial non-drug reward processing impairments in dependent smokers compared to occasional smokers, during ad libitum smoking. Finally, the results in this thesis do not provide enough data on the abstinence-induced moderation of reward processing to make strong

conclusions about its effects. Future research will have to be carried out to further elucidate the effects of acute nicotine abstinence on consummatory non-drug reward processing. With regards to Goldstein & Volkow's (2011) theoretical claims within the remit of nicotine dependence, my research supports their first claim, does not support their second claim and may or may not support their third claim, depending on how 'eclipsed' and 'suppressed' are interpreted.

6.3 Transition from occasional to dependent tobacco use

I began my thesis by describing the statistics which show that most people who try a drug do not go on to become addicted to it. I proposed that changes to reward processing that occur following drug use, or perhaps existed beforehand, could play a role in the transition to and maintenance of dependence. Although cross-sectional, and therefore a weak form of evidence, I believe that my studies suggest that deficient non-drug reward processing is unlikely to substantially contribute to the development and maintenance of nicotine dependence. If these deficits do substantially contribute, and they are not masked by recent cigarette smoking, then they should have appeared in my experiments (chapters 2-4), but they did not. Even if they are masked by recent cigarette smoking, given a smoker who smokes 15 cigarettes/day is smoking approximately one cigarette/hour, if non-drug reward processing deficits were playing a major role in the maintenance of addiction, they would likely reveal themselves following 1.5 hours of abstinence (as in chapter 4), as well as after 12 hours of abstinence (as in chapter 2).

I have argued above that non-drug reward processing deficits in nicotine dependence are subtle, if they exist at all. I believe that if non-drug reward processing deficits were playing an important role in the maintenance of nicotine dependence, they would have been evident in my results. As described above, I always found the expected effects and group differences on craving and withdrawal symptoms, which demonstrates that my experiments were conducted successfully. It also demonstrates that variables which are known to be somewhat important in the maintenance of nicotine dependence (craving and withdrawal symptoms) (Killen & Fortmann, 1997; Zhou et al., 2009),

were robustly affected in the way that I expected in my studies. If non-drug reward processing deficits were similarly important in the development and maintenance of nicotine dependence as craving and withdrawal symptoms are, then I should have seen non-drug reward processing deficits appear similarly robustly. That is not to say that other aspects of non-drug rewards, like their availability and cost, do not play a role in nicotine dependence, as they demonstrably do (Audrain-McGovern, Rodriguez, Rodgers, & Cuevas, 2011). However, I think *deficient processing* of non-drug rewards, when they are available, is probably not hugely important in the development of nicotine dependence. Certainly, the current evidence suggests that if it plays a role at all, it will likely be a poor target for treatment compared to management of craving, for instance.

Of course, longitudinal studies would be desirable to assess the importance of non-drug reward processing in the maintenance or development of addiction. It would be fascinating to determine whether aspects such as effort-related decision-making and reward learning predict future cigarette use, especially the transition to dependence. However, research has mostly focused on relapse in smokers attempting to quit. Recent evidence suggests motivation for monetary reward as assessed by the EEfRT is not associated with later relapse in smokers attempting to quit (Das, 2015). However, one consistent finding is that self-reported anhedonia predicts likelihood of relapse in real-life quit attempts (Cook et al., 2010; Leventhal, Piper, et al., 2014; Leventhal et al., 2009). Other studies have shown the importance in the balance of cigarette and non-drug reward image processing in future smoking (Versace et al., 2014; Versace et al., 2012), however, it is unclear whether the association would have remained if only the response to non-drug reward images were analysed. Furthermore, performance in the CARROT, which assesses motivation for monetary reward, did not predict relapse (Powell et al., 2010). Hence, the evidence in favour of various non-drug reward processes playing key roles in future tobacco use is mixed, with self-reported anhedonia seeming to be the most reliable predictor.

However, overall my studies do imply that sensitivity to cigarette rewards might be important in the development and maintenance of addiction. Dependent smokers were more motivated for and reported greater liking of cigarettes than occasional smokers; these results were very reliable. It makes logical sense that the more sensitive one is to the reinforcing actions of cigarettes, the more they will go back for more, and the higher the likelihood of developing dependence (DiFranza et al., 2004). In terms of cigarette reward processing, longitudinal studies should therefore focus on why it is that some people become more sensitive to cigarette rewards, in terms of motivation and pleasure, and how to weaken these processes in already dependent smokers. Of course, many other factors play extremely important roles in the development and maintenance of nicotine (and other drug) dependence, including socio-economic status (Anthony et al., 1994), comorbid mental health problems (Lopez-Quintero et al., 2011), concurrent drug dependencies (Lopez-Quintero et al., 2011), and partners who dislike smoking (West, McEwen, Bolling, & Owen, 2001), to name just a few. Hence, sensitivity to cigarette reward is likely to contribute to nicotine dependence alongside many other critical factors.

I will now move onto a discussion of dopamine's role in reward processing, which relates specifically to the study described in chapter 4. Following this section, I will discuss my findings concerning the acute and chronic effects of cannabis on non-drug reward processing, which were reported in chapter 5.

6.4 Dopaminergic disruption of reward processing

Despite strong theoretical (Volkow et al., 2004) and empirical (Freeman et al., 2015; Freeman et al., 2013) foundations, 0.5mg of oral pramipexole, a dopamine D2/3 receptor agonist, did not affect relative preference for, motivation for or liking of cigarettes, music or chocolate. Furthermore, it did not affect willingness to pay for cigarettes in the hypothetical cigarette purchase task. This could essentially mean one or more of three things: (1) D2/3 receptors are not important in these aspects of reward processing; (2) D2/3 receptors are important but the dose of pramipexole was not sufficient

to cause changes; and/or (3) D2/3 receptors are important but the task was not sensitive enough to detect changes. Given the evidence concerning dopamine in response vigour for rewards (Niv et al., 2007), bromocriptine's effects on ad libitum smoking (Jarvik et al., 2000), and a previous significant finding with the same dose of pramipexole boosting motivation to earn monetary reward (Freeman et al., 2013), I suggest that my results were due to a combination of (2) and (3).

In order to test this hypothesis, one would have to examine various doses of pramipexole on different tasks with potentially greater sensitivities. Possibilities for such tasks would be a button-pressing progressive ratio task, which would provide breakpoints as measurements of motivation for individual rewards, or an ad libitum smoking/consumption task. As discussed in chapter 4, pramipexole putatively has a complex effect on dopaminergic functioning: at low doses, like the 0.5mg oral dose I used, it is thought to reduce phasic dopamine release due to pre-synaptic, auto-receptor activation and at high doses it is thought to overcome this effect and enhance post-synaptic receptor activation (Maj et al., 1997). Therefore, different doses of the drug may have markedly different effects on motivation for cigarette and non-drug rewards. All that can be concluded is that motivation for cigarettes, music and chocolate were not sensitive to an acute dose of 0.5mg pramipexole, and therefore this acute dose is probably not a useful treatment for nicotine dependence. However, other doses of pramipexole, chronic treatment or administration within treatment-seeking cigarette smokers may have substantially different effects on cigarette reward processing. One should not conclude that pramipexole will never be effective at reducing smoking from my results. Nor should one conclude that medicinal drugs which do not act directly on the receptors which the abused drug acts on will be poor treatments. Bupropion (for nicotine dependence) and naltrexone (for alcohol dependence) are good examples of why this is not necessarily the case.

Interestingly, it has recently been argued that too much emphasis has been placed on dopamine as the final, common pathway to non-psychostimulant drug addiction (Nutt et al., 2015). They argue that dopamine functioning is critical in addiction to cocaine or amphetamine, but not addiction to cannabis,

opiates or nicotine. Evidence in favour of this hypothesis is that these latter drugs do not have such profound effects on dopamine levels in the striatum and D2 receptor density is often found to be unchanged in addicts of these drugs. Other neurotransmitters, including endocannabinoids and GABA, are suggested to be more heavily involved. My pramipexole data could, speculatively, support this claim, given that the dopaminergic manipulation had null effects on motivation to earn cigarettes, music and chocolate. Alternatively, dopaminergic manipulations may only disrupt very specific components of motivation (which were not tapped by the DReaM-Choice task); it may be unwise to lump many components of reward processing together and propose they are all underpinned by dopamine (Salamone & Correa, 2002).

However, the roles of D2/3 receptors in effort-related decision-making and reward learning were supported. Pramipexole reduced sensitivity to the task parameters of probability, magnitude and expected value, such that as these values increased, the likelihood of high-effort choices did not increase as fast as in the placebo condition. Thus, D2/3 receptors appear to be important in effort-related decision-making, in which reward value is pitted against effort cost. These results are consistent with the theory that nucleus accumbens dopamine is critical in this process (Salamone et al., 2007) and that phasic dopamine release is important in cognitive and behavioural flexibility (Floresco, 2013). The effects of pramipexole on reward learning were as expected, with a reduction in response bias, as shown previously in healthy controls (Pizzagalli, Evins, et al., 2008). This effect has also been attributed to impaired phasic dopamine release. However, as discussed in chapter 4, my results should be interpreted very cautiously because the effect of pramipexole reducing response bias was only apparent when all participants were included in the analysis (and not when participants who would traditionally be excluded were actually excluded).

6.5 Non-drug reward processing deficits associated with cannabis use

My findings concerning cannabis can be summarised as follows:

(1) Cannabis without cannabidiol (Cann-CBD; 8mg THC) acutely reduced motivation for monetary reward.
(2) Cann-CBD acutely enhanced sensitivity to expected value and probability relative to placebo and enhanced sensitivity to expected value relative to cannabis with cannabidiol (Cann+CBD; 8mg THC + 10mg CBD).
(3) Cannabis dependent individuals did not have altered effort-related decision-making compared with non-dependent, drug-using controls.
(4) Cannabis dependent individuals demonstrated worse reward learning than non-dependent, drug-using controls, although greater depression levels and tobacco smoking could have played a role in this difference.

I demonstrated, in a carefully controlled cross-over design, that cannabis acutely reduced motivation for monetary reward. Importantly, this illuminates a role for the endocannabinoid system in effort-related decision-making. Only one previous study had investigated the effects of acutely administered cannabis on the motivation for monetary reward in a double-blind, placebo-controlled way (Cherek et al., 2002). However, they had a sample of only five participants and so this demanded replication. Hence, this finding, from a much larger study, represents a major step forward in our understanding of whether cannabis can transiently produce amotivation. It is an important result because people have claimed for many years that cannabis reduces motivation (McGlothlin & West, 1968), but very little well-controlled experimental work has been conducted. I have demonstrated that being stoned on cannabis leads to a small, but significant, reduction in the amount of work people are willing to put in to earn monetary reward on a well validated task (Green, Horan, Barch, & Gold, 2015; Treadway, Bossaller, et al., 2012; Treadway et al., 2009; Wardle et al., 2011). This research finding should be

communicated to the public so that cannabis users are aware that there is now stronger evidence that acute intoxication on cannabis can result in lowered motivation.

Moreover, Cann-CBD influenced the effects of expected value on effort-related decision-making differently from Cann+CBD. Expected value refers to the multiplication of the outcome value with the probability of receiving the outcome, so it represents how good an option is and how much it is worth. Expected value increased the likelihood of making a high-effort (with a larger reward) choice more following administration of Cann-CBD than placebo and Cann+CBD. This suggests that CBD affects the way people make decisions about different effortful outcomes. However, the interpretation of this result is unclear. One could argue that CBD made the cannabis more like placebo, and therefore it buffered a negative effect of the THC. Alternatively, one could argue that the absence of CBD had a positive effect on task performance. Cann-CBD *enhanced* the *pro-motivational* effects of expected value compared to both placebo and Cann+CBD. Future research must clarify this effect with replication in a larger sample and a longer version of the EEfRT, as the version I used in the studies described in this thesis was about half the length of the original task.

CBD has a range of proposed pharmacological actions, including inhibition of the metabolism and reuptake of anandamide (Pertwee, 2008), inverse agonism of the CB1 receptor (Pertwee, 2008) and agonism of the GPR55 receptor (Ryberg et al., 2007), and the pharmacology of effort-related decision-making is relatively unknown. Hence, it is difficult currently to pinpoint pharmacologically how CBD may diminish the effect of expected value on effort-related decision-making. Future experiments which test the effects of a wide range of dopaminergic and cannabinoid drugs on effort-related decision-making tasks will hopefully clarify the underlying pharmacology of this motivational process.

Interestingly, and in accordance with previous research (Haney et al., 2015; Hindocha, Freeman, Schafer, et al., 2015), CBD did not affect participant's 'stoned' or 'like drug' ratings. Thus, CBD may be a harm-reducing cannabinoid, in terms of memory (Morgan, Schafer, et al., 2010), psychotic effects (Morgan & Curran, 2008; Morgan, Schafer, et al., 2010), and addiction (Freeman & Winstock, 2015;

Morgan et al., 2013; Morgan, Freeman, et al., 2010), but its presence does not alter the desired subjective effects following acute administration. If CBD is indisputably proved to reduce the harms of THC acutely and chronically, this knowledge will be important in a harm reduction message for cannabis users: one can smoke cannabis without sacrificing the desired effects while also limiting the harms.

Perhaps surprisingly, there was not a significant association between the frequency of recreational cannabis use and the self-reported 'liking' of the drug. This implies that previous cannabis exposure may not moderate the desirable effects of the drug. Previous research has reported greater (Kirk & De Wit, 1999) and similar (D'Souza et al., 2008; Hindocha, Freeman, Schafer, et al., 2015) effects of cannabis on the desirable effects of the drug in heavy compared with light cannabis users. These discrepancies may have been due to differences in how much cannabis the heavy and light user groups were smoking. For instance, in my study, no participant smoked more than 3 times per week, whereas in other studies, daily users have been recruited (Hindocha, Freeman, Schafer, et al., 2015). More research is needed to carefully examine the associations between chronic cannabis use and the rewarding experience of cannabis intoxication across a wide range of recreational cannabis use frequencies and quantities.

As described in chapter 5, the endocannabinoid system is thought to be involved in the neurobiological underpinnings of various drug addictions, including nicotine dependence (Maldonado et al., 2006; Parsons & Hurd, 2015). That both THC and CBD appear to affect motivational processing of a non-drug reward (money) supports the endocannabinoid system's role in reward processing and addiction. The cornucopia of cannabinoid drugs available has only recently been exploited by addiction researchers (Morgan et al., 2013) and this area represents a major opportunity for future research into psychopharmacological agents that may aid quit attempts. Experimental work should investigate whether different cannabinoid drugs can alter the motivation for addictive drugs in samples of addicted individuals, using tasks such as the DReaM-Choice task or more basic progressive ratio

(Comer, Collins, & Fischman, 2001) or purchase (Hart et al., 2008) tasks. Subsequently, clinical trials could be taken forward with cannabinoid drugs that showed promise in these experimental models of drug-seeking.

I will now move onto the ramifications of my second cannabis study which compared dependent cannabis users with non-dependent, drug-using controls. People dependent on cannabis demonstrated an impaired ability to develop a response bias on the probabilistic reward task compared with drug-users who were not dependent on any drug (apart from nicotine). This therefore provides some tentative evidence for Goldstein & Volkow's (2011) second claim that addiction is associated with a hyposensitivity to non-drug rewards, specifically that reward learning may be compromised in cannabis dependence. In contrast, reward learning did not appear to be impaired in the dependent cigarette smokers compared with the occasional cigarette smokers. This is a good demonstration of why it is important to be specific about which type of drug addiction and which aspect of reward processing when considering whether addiction is associated with hyposensitivity to non-drug rewards. In this case, cannabis dependence was, but nicotine dependence was not, associated with weakened reward learning. Hence, any general statement about 'drug addiction' and 'non-drug reward processing deficits' will inevitably miss out important details.

These results could indicate that chronic cannabis use is more damaging to reward learning than nicotine use. Potential reasons for this might be: the more generally life-disrupting effects associated with heavy cannabis use, compared with heavy tobacco use; the additive and interactive effects of tobacco and cannabis (given the vast majority of cannabis users smoke cannabis with tobacco and also normal cigarettes); and the different roles of the endocannabinoid and nicotinic acetylcholine systems in reward learning. Another important difference to note is that the cigarette smokers described in chapter 4 had only abstained from nicotine for about 2 hours before they completed the PRT; whereas, the cannabis users described in chapter 5 were instructed to not consume cannabis for at least 12 hours beforehand. Hence, when comparing the pattern of results, it must be remembered that the

smokers were perhaps in a more 'natural' state than the cannabis group, which could have contributed to the difference in results. However, a potentially simpler explanation is that the cannabis dependent individuals were more depressed than the controls in that study, and the dependent smokers in chapter 4. Given depression is strongly linked with performance on this task (Pizzagalli, Iosifescu, et al., 2008), this probably contributed to my results. Unfortunately, it is very difficult to separate out the effects of cannabis dependence and depression (and other potentially important variables such as cigarette smoking) in cross-sectional studies such as this. Given cannabis dependence and depression were highly collinear, analysis of covariance (with depression as the covariate) could be considered inappropriate (Miller & Chapman, 2001). Future research could use samples that are better matched on depression and cigarette smoking. However, as most cannabis dependent individuals (in Europe) smoke tobacco (Hindocha, Freeman, Winstock, et al., 2015) and have greater depression than healthy controls (Degenhardt, Hall, & Lynskey, 2003), one might not be able to generalise the findings to the population of dependent cannabis users as a whole.

Surprisingly, given anecdotal reports and a previous study with significant findings (Lane et al., 2005), cannabis dependence, in my participants, was not associated with altered effort-related decision-making. This could be because cannabis's amotivational effects are transient and as the participants had been asked to abstain for at least 12 hours, they were no different to controls. Alternatively, the task may not have had adequate data to detect effects. In chapter 4, where dependent cigarette smokers were found to be less sensitive to task parameters than occasional cigarette smokers, I had data from two sessions. Given I used generalised estimating equations to analyse the data, which incorporates every trial into the model, this repeated measures design may have afforded greater power to detect a group difference, which I did not have in chapter 5 with the dependent cannabis users. Clearly, much more objective research needs to be carried out in order to elucidate the relationship between chronic cannabis use and amotivation.

6.6 Different tasks assessing reward processing

I have argued in this thesis that it is important to consider different components of reward processing rather than 'reward processing' in general because different clinical conditions are likely to have different profiles of reward processing deficits, with some components unaffected and others impaired. A good example of this is that dependent smokers, relative to occasional smokers, were somewhat impaired in effort-related decision-making, but they had preserved reward learning. Here I will discuss the different reward processing tasks that I used, their strengths and weaknesses, and their potential relationships.

6.6.1 The DReaM-Choice Task

I specifically designed the DReaM-Choice task and subsequent procedure so that it had certain characteristics:

(1) It assessed cigarette and non-drug reward processing within the same paradigm.

(2) It included a choice stage and a button-pressing stage.

(3) It used consummatory rewards.

(4) It included a subsequent consumption stage with real rewards.

No previous task had these four characteristics and so its design and utilisation was necessary for my research, which aimed to investigate cigarette and non-drug reward processing using consummatory rewards. The successful use of the task (as demonstrated by the large group differences and the effect of abstinence on cigarette and music choices) represents a step forward in reward processing research within nicotine dependence.

These four characteristics have both strengths and weaknesses. The first characteristic allowed direct comparisons between the processing of cigarette and non-drug rewards, such that the 'balance' in drug and non-drug reward processing could be assessed. This style of task has been recommended by

previous authors (Bühler et al., 2010; Versace et al., 2011) and the consistent difference in the balance of reward processing was an interesting aspect of this thesis.

The second characteristic brought two styles of task design together: choice (Hogarth & Chase, 2011) and button-pressing (Bühler et al., 2010). This choice stage was useful because it is ecologically valid, in the sense that drug users regularly have to face decisions between their drug and alternative rewards, and because results from choice tasks show strong associations between task behaviour and dependence level (Hogarth & Chase, 2011, 2012). The button-pressing stage was useful because the choice stage cannot provide a direct, or 'pure', measure of motivation, as every decision is affected by the motivational value of both rewards available. Hence, together, they represent an efficient way of assessing both relative preference of and motivation for each reward.

However, there is a downside to this design. As button-pressing only occurred after making a choice for a reward, the number of trials for each reward where motivation was measured inevitably differed. For example, the number of trials in which button-pressing for chocolate occurred was lower in dependent smokers than in occasional smokers, and the number of trials in which button-pressing occurred for paper was minimal for both groups. If the number of choices for each reward affected button-pressing, separate from the fact that they are highly related because they both tap motivation for that reward, then this would be problematic; my 'purer' measure of motivation would no longer be so 'pure'. In other words, if I had simply provided participants with the opportunity to button-press for each reward on the same number of trials, my button-pressing results may have changed. Hence, it may have been better to use a progressive-ratio task for each reward separately, as has been used to examine the acute reinforcer enhancing effects of nicotine (Perkins et al., 2009; Perkins & Karelitz, 2013b). However, I believe that this discrepancy is unlikely to be large and I doubt my results would have changed drastically. Moreover, I would have had to forgo my choice stage, which was one of the only measures to detect the effect of abstinence in chapter 2 (albeit not a group X smoking-status X reward-type interaction).

The third characteristic was used because I wanted to equate the comparison rewards with cigarettes as much as possible. Money is: (1) not consummatory and (2) can be exchanged for cigarettes at a later date. Hence, I chose to use music and chocolate instead because they had been used previously with smokers (Hogarth & Chase, 2011; Perkins & Karelitz, 2013b), albeit in different ways, and because they are both consummatory. However, these rewards have their problems too. Chocolate was not ideal because acute nicotine and nicotine abstinence (J. Hughes & Hatsukami, 2007; Spring, Pagoto, McChargue, Hedeker, & Werth, 2003) have effects on hunger, which may have confounded the primary effects of nicotine dependence and acute abstinence on motivation for chocolate. Furthermore, I used participants' chosen music because previous studies did it this way (Perkins & Karelitz, 2013b) and I was concerned unchosen music might not be particularly motivating. Therefore, the cigarettes (Marlboro Gold) and chocolate (Dairy Milk) were not chosen but the music was chosen by the participants, which therefore makes the rewards less similar and potentially confounds results. Finally, the effects of nicotine abstinence have been shown in tasks using money as a reward (Al-Adawi & Powell, 1997; Pergadia et al., 2014; Powell et al., 2002). Reward processing may be more sensitive to the effects of nicotine dependence and abstinence when money is the reward compared to consummatory, non-drug rewards. Future research should therefore investigate motivation for cigarettes, consummatory non-drug rewards and money concomitantly to test this hypothesis.

The fourth characteristic facilitated an examination of the 'liking' of rewards, the order of reward consumption (in chapter 2) and made the DReaM-Choice task ecologically meaningful, in that performance led to actual delivered rewards. This was useful because I believe it is important to investigate a range of reward processes. Furthermore, I feel that the actual hedonic experiences, associated with drug and non-drug reward consumption, have been somewhat neglected in the field of reward processing in addiction. To my knowledge, the DReaM-Choice consummatory phase, in which consumption of cigarettes and consummatory non-drug rewards took place following completion of the task, is unique. Previous experimental procedures have allowed participants to smoke cigarettes that they won after the task finished (Bühler et al., 2010; Sweitzer et al., 2013), but

they did not record the subjective pleasure, liking or enjoyment of these. Morevoer, they gave people money as the non-drug reward, which cannot be consumed. Lee Hogarth's work has involved hypothetical rewards or deceiving participants that chocolate and cigarettes will be given following the task, but then simply paying participants with money (Hogarth, 2012; Hogarth & Chase, 2011, 2012). Hence, my use of consummatory rewards, with the opportunity for participants to consume them, allowed for the combined investigation of motivation (wanting) and pleasure (liking). This is a strength of the procedure because various aspects of reward processing should be investigated before we draw conclusions about how reward processing is affected by nicotine dependence (and other drug addictions). Furthermore, we maintained ecological validity by allowing participants to consume the rewards they received at their leisure, which hopefully created a more realistic and rewarding scenario.

However, because of this more ecologically valid setting, the 'liking' data were not collected in the most controlled fashion. Because the amount of each reward won had to be dependent upon the behaviour in the actual task, each participant had different quantities of each reward; this is one reason why only the liking of the first 'unit' of each reward was analysed. Furthermore, participants were not required to consume each reward, as it may have been unethical to require people to smoke a cigarette at a time when they didn't want to. Finally, participants could consume their rewards in any order, at their own pace. This may have affected the relationships between experimental manipulations and hedonic responses because previous smoking would reduce abstinence effects and affect liking of subsequently consumed rewards. Hence, although the consumption stage was useful, it did not provide the best setting for examining hedonic responses to cigarette and non-drug rewards. That would have involved: (1) the same amount of reward consumed by each participant and (2) a consistent, or counterbalanced, order of reward consumption.

Overall, the novel DReaM-Choice task functioned well. The cigarette choices and button-pressing were sensitive to dependence; cigarette and music choices were sensitive to abstinence (although not

differentially so between groups); all rewards were chosen and pressed for more than paper (the neutral commodity); large rewards were worked for harder than small rewards (in chapter 2); and different components of reward processing were assessed. Another strength of the task is that the findings in chapters 2 and 4 were highly consistent. This was the case even though various adaptations were made to the task and some of the inclusion criteria for the dependent smoker group were slightly changed. The characteristics described above, and the fact it worked successfully, make it an important addition to the experimenter's toolkit for assessing reward processing in addiction. However, it could be further refined as I retain some concerns: (1) the sensitivity of the button-pressing measure, given it was not significantly affected by acute abstinence; (2) the fact that the number of trials button-pressing occurred for on each reward was not the same; (3) the various problems associated with the way I collected the liking data.

One final, conceptual point about the DReaM-Choice task is that it may have assessed much more of the goal-directed ('model-based') rather than the habitual ('model-free') nature of reward seeking behaviour. Goal-directed behaviour refers to the situation in which an organism uses an explicit value of the prospective outcome to guide behaviour (Balleine & Dickinson, 1998). Habitual behaviour refers to the situation in which an organism does not use an explicit value of the prospective outcome, but instead simply carries out behaviours that in the past have been associated with future reward. Given the DReaM-Choice never involved responses that were followed by temporally contiguous reinforcement (of the real reward), I believe it is unlikely that strong habitual associations would have formed. I would have thought that people's behaviour was driven mostly by the explicit expectation of each reward's value. If this is the case, then I examined goal-directed reward-seeking. Given addiction is putatively associated with enhanced habitual behaviour (Everitt & Robbins, 2005), my task may have missed out on some potential differences between dependent and occasional cigarette smokers.

6.6.2 The monetary incentive delay task

The other reward processing tasks I used (monetary incentive delay task (MIDT), probabilistic reward task (PRT), effort expenditure for rewards task (EEfRT), cigarette purchase task (CPT)) are all well validated and used by researchers in many laboratories. I will now discuss the strengths and weaknesses of these tasks, as well as the success of my adaptations to these tasks.

My adapted MIDT clearly worked, in terms of anticipatory and feedback BOLD responses for cigarette reward, but did not work for classical music reward. As discussed in chapter 3, this is strange given that music trials did produce faster reaction times than no reward trials, which indicates enhanced motivation. If a reward is a motivating outcome, then it should be associated with reward related activity during anticipation and feedback. Hence, explanations for this lack of BOLD response may be: (1) classical music was not a particularly motivating reward, combined with poor sensitivity of the BOLD response relative to reaction time, and/or (2) something went wrong with the fMRI aspect of the experiment. Given I observed the expected activations in reward-related regions for cigarette anticipation and detected a group difference during feedback of cigarettes, option 2 seems unlikely, and so I argue that the behavioural outcome of reaction time was more sensitive than the anticipatory and feedback BOLD response. Interestingly, I found no significant correlations between motivation to earn cigarettes (as indexed by reaction time to the target) and the BOLD response in any of the anticipatory or feedback ROIs. Future work will have to carefully examine whether, and under which conditions, behavioural or neuroimaging data are more closely associated with problematic drug use.

In general, I think that the research field of reward processing in addiction would benefit from more attention being paid to specific, behavioural aspects of reward processing, with fewer studies simply repeating the MIDT in different addicted populations (I obviously recognise my hypocrisy here). I believe that any noticeable, behavioural drug or reward processing impairment will be more helpful in understanding how treatments can be improved than fMRI studies investigating somewhat abstracted components of reward processing. This is, of course, an empirical question, and only time

will tell whether behavioural or neuroimaging research provide greater improvements to treatment for drug addicts.

6.6.3 The probabilistic reward task

The PRT appeared to work well in chapter 5 and not so well in chapter 4. Both of the tasks I used differed from the original (Pizzagalli et al., 2005) in that I used shorter mouths (approximately 8 and 9mm rather than 11.5 and 13mm) and fewer trials (200 rather than 300). The shorter mouths made the task harder, as evidenced by lower discriminability scores compared with previous research (Pizzagalli et al., 2005), and I believe this may have reduced engagement and led to the greater numbers of task-related exclusions in chapters 4 and 5, relative to other academics' research (Alexis Whitton, personal communication). This problem was particularly apparent in chapter 4. I put this down to the repeated-measures element of the design, which approximately doubles the chance of exclusion, and the sometimes unpleasant feelings provoked by pramipexole administration.

A recent computational analysis of the PRT suggests behaviour on the task is related to two distinct processes: reward sensitivity and learning rate (Huys et al., 2013). Reward sensitivity (ρ) refers to the extent to which the presentation of a reward (*r*) affects the associated prediction error (δ), computed by the difference between the expected reward value (*q*) and the experienced reward value:

$$\delta = \rho . r - q$$

The learning rate (ε) refers to the extent to which the prediction error is used to update the subsequent expected reward value (*Q*) from the previous reward value (*q*):

$$Q = q + \varepsilon . \delta$$

Therefore, the PRT may evaluate too many aspects of reward processing simultaneously. As well as these two processes, participants' behaviour will be related to: (1) their propensity to go with previous learning (i.e. the more reinforced mouth) vs. their propensity to go with the mouth they think was

actually presented on that trial and (2) the interaction between this and their ability to discriminate the mouths. It may therefore be advisable to remove one of these aspects by either presenting only one length of mouth or explicitly telling the participants before the task begins that one of the mouths is more frequently reinforced than the other (Liu et al., 2015). Clearly the PRT is good at elucidating reward learning impairments. However, it may have a problem in that it cannot easily reveal which of the above components are affected and therefore why reward learning, as it is operationalised in the PRT, is impaired.

Interestingly, Huys et al. (2013) re-analysed the experimental data from Pizzagalli et al. (2008), where the effects of pramipexole on PRT task performance was investigated in healthy controls. Huys et al. (2013) conclude that pramipexole disrupted the learning rate rather than the reward sensitivity. Without carrying out Huys et al.'s (2013) analysis it is difficult to ascertain which factor was affected in my experiment. However, visual inspection of figure 4.9 suggests that response bias was low in block 1 and block 2, which implies that participants may have had lower sensitivity to the reward outcome from the beginning of the task.

6.6.4 The effort expenditure for rewards task

The EEfRT, although adapted in various ways (see section 4.2.2.4), worked well. In all three of its uses in this thesis, increases in the task parameters (probability, magnitude and expected value) increased the likelihood of making a high-effort choice, thus demonstrating it worked as it should have. The generalised estimating equations (GEE) models were sensitive in detecting the effects of pramipexole, cannabis and nicotine dependence. I am slightly concerned that the reason I didn't detect an association between cannabis dependence and amotivation is because, compared with the other studies, I didn't have as much data, as there was only one testing session. GEE models use all the trials available so having twice as much data should theoretically improve the power to detect an effect. Another concern, although not reported in the results sections, is that my results reported in the GEE models often do not replicate in the analogous ANOVAs. This is perhaps unsurprising given that the

data do not conform to parametric analysis assumptions and GEE models have greater sensitivity. However, previous studies using the EEfRT have found results using ANOVAs (Treadway, Peterman, Zald, & Park, 2015; Wardle et al., 2011), which makes me think that my effects cannot be particularly large. One final consideration is that the EEfRT high-effort choices take a longer time to complete than the low-effort choices. Hence, there is an element of temporal-discounting, as well as effort-discounting, in the task (Green et al., 2015), which could confound results pertaining to effort-related decision-making.

6.6.5 The cigarette purchase task

The CPT worked as I expected it would. Participants were less willing to buy more cigarettes as the price of each cigarette increased. Furthermore, dependent smokers had much greater demand for cigarettes than occasional smokers across all metrics. Pramipexole did not affect behaviour on this task, and similarly did not affect cigarette reward processing in the DReaM-Choice task. This corroboration supports the null finding. Moreover, this task has been shown to be sensitive to manipulations of catecholamine levels (Hitsman et al., 2008) and drug cues (Acker & MacKillop, 2013; MacKillop et al., 2010), so it clearly has the sensitivity to be acutely manipulated.

6.7 Clinical Implications

My most consistent findings were enhanced motivation for and liking of cigarettes in dependent compared to occasional smokers, alongside mostly null differences in motivation for and liking of non-drug reward. Hence, despite much recent work emphasising the potential importance of non-drug reward processing in cigarette smoking (Pergadia et al., 2014; Sweitzer et al., 2015; Versace et al., 2014; Versace et al., 2012), my results suggest that nicotine dependence is much more strongly associated with perturbations in cigarette reward processing, and so this is probably the area where most gains can be made. Hence, a clear implication of my findings is that a drug that reduces motivation for cigarettes is probably much more likely to be successful in aiding a quit attempt than a drug that enhances motivation for alternative, non-drug rewards. Furthermore, a focus on weakening

the motivational value of drug rewards is likely to be critical in helping people reduce drug use. One promising avenue of research is via manipulating the reconsolidation of maladaptive memories (Das, Lawn, & Kamboj, 2015). That way, the very strong associations between drug-seeking/consumption and reward are weakened or even eliminated, such that motivational responses are likely to be reduced.

Having said that, as my studies weren't longitudinal, it is nigh on impossible to make conclusions about what factors lead to changes in cigarette use. There is good evidence that behavioural activation treatment reduces cigarette smoking more than treatment as usual (MacPherson et al., 2010), which implies that engagement with non-drug rewards does improve cessation. However, this study gave everyone nicotine replacement therapy as well, so it would be interesting to see how behavioural activation therapy faired on its own. I did find that dependent smokers were less sensitive to parameters such as expected value in the effort-related decision-making task, so perhaps behavioural activation remediates this aspect of non-reward processing. Along these lines, other treatments such as motivational interviewing may be improved by exploring the ways that dependent smokers use future outcomes and their expected values to make effort-related decisions.

Other treatments for drug addictions, such as contingency management, require non-drug rewards to retain their value, or else they would not work. Contingency management involves the reinforcement of abstinence with money or vouchers and has been successful in helping smokers quit (Roll, Higgins, & Badger, 1996). That contingency management helps dependent cigarette smokers quit suggests, like my results, that nicotine dependence does not eradicate the motivation for alternative rewards. Having said that, non-drug reward processing may be substantially impaired in some cigarette smokers after a few days of nicotine deprivation, and these may be the people who are most likely to relapse despite the incentives provided via contingency management (Sweitzer et al., 2015).

A clear ramification of my fourth chapter is that an acute dose of pramipexole (0.5mg) does not reduce motivation for cigarettes. This is an important piece of evidence given that previous research has

suggested that dopaminergic agonists can reduce ad libitum smoking (Jarvik et al., 2000) and that pramipexole can weaken an attentional bias to cigarette images (Freeman et al., 2015). As mentioned above, other doses and chronic treatment of pramipexole could still have therapeutic benefits, but this research does slightly dampen the hopes of pramipexole becoming an anti-smoking drug.

Reward learning impairments are associated with depression (Pizzagalli, Iosifescu, et al., 2008), anhedonia (Pizzagalli et al., 2005) and stress (Bogdan & Pizzagalli, 2006), and they have predicted persistence of depression symptoms (Vrieze et al., 2013). Furthermore, in adolescents, worse reward-related decision-making predicted anxiety and depression symptoms (Forbes, Shaw, & Dahl, 2007; Rawal, Collishaw, Thapar, & Rice, 2013). Hence, it is clear that impairments in some reward processes are predictive of future psychological problems. Given these relationships, it is potentially worrying that cannabis and nicotine dependent individuals showed compromised reward learning and effort-related decision-making, respectively, as these could be mediating factors in later depression. However, this is highly speculative as there may well be a whole host of other causal relationships driving those associations, such as existing depressive symptoms leading to both cannabis use and reduced reward learning. However, if drug use has caused these non-drug reward processing deficits, then it may well be helpful to attempt to improve these psychological processes in order to stave off later psychological problems. Of course, tactics to improve reward learning and effort-related decision-making would have to be designed first.

My acute cannabis study has important clinical implications, which were briefly described in section 6.5. Notably, acutely administered cannabis reduced motivation for monetary reward. This indicates that when people are intoxicated on cannabis they are less willing to work hard for larger rewards. Despite many decades in which people claimed cannabis reduces motivation for rewards (McGlothlin & West, 1968), this is only the second empirical, placebo-controlled study which has examined this topic, and the first study had a sample of only five participants (Cherek et al., 2002). Hence, this is an important step forward in demonstrating that cannabis transiently produces amotivational effects.

Cannabis users should be informed of this important result. It will be of critical importance in the future to more conclusively determine whether chronic cannabis use leads to long-term and irreversible amotivational effects. My study with cannabis dependent individuals, and previous research survey data (Barnwell et al., 2006; Musty & Kaback, 1995), suggest that these effects may not exist. Therefore, amotivational effects observed in cannabis users may be a product of recent cannabis intoxication, rather than a long-term effect of chronic cannabis use. However, future research that uses large, longitudinal samples with objective, validated ways of assessing motivation should be conducted.

6.8 Limitations and regrets

The various limitations and regrets of my work have been mentioned frequently throughout my discussion. I will consolidate them here. Many of the problems could only have been avoided if I had had substantially more time and money to complete my research. However, it is still important to note what changes could have improved the work.

Firstly, having a non-smoker control group in chapters 2-4 would have improved my ability to draw conclusions about the effect of tobacco exposure on both cigarette and non-drug reward processing. From my data I cannot conclude: (1) whether a relatively small amount of nicotine exposure (occasional smoking) is associated with cigarette or non-drug reward processing changes relative to no nicotine exposure (non-smoking) and, therefore (2) if the null group differences in non-drug reward processing are due to neither group being different from non-smokers or both groups being different from non-smokers. The obstacles to this improvement were ethical, in that it might be considered unethical to provide non-smokers with the opportunity to smoke cigarettes. Furthermore, this addition would have increased the cost of the study by one third.

As described at length in section 6.2.2, my results in the studies reported in chapters 3 and 4 may have been quite different if I had included an abstinent as well as an ad libitium smoking condition. Various

studies have indicated that acute nicotine deprivation produces non-drug reward processing deficits (Al-Adawi & Powell, 1997; Dawkins et al., 2006; Pergadia et al., 2014; Perkins & Karelitz, 2013b; Powell et al., 2002). I may have uncovered more differences between dependent and occasional smokers if I had continued studying these groups during nicotine satiation and abstinence, as well as increasing the sample size. Having said that, there is also other research which has not found significant effects of acute nicotine abstinence on non-drug reward processing (Audrain-McGovern et al., 2014; Bühler et al., 2010; Kalamboka et al., 2009), including my own research described in chapter 2 (in terms of button-pressing for music and chocolate). Furthermore, if I had included an abstinence condition in each of those studies it would have increased the cost and workload by 100% and so I would have had to sacrifice other aspects of my thesis. When interpreting my findings it is important to remember that they mostly speak to the issue of reward processing alterations during nicotine satiation. Future research is certainly need to clarify under which conditions acute nicotine deprivation affects consummatory, non-drug reward processing and how this is associated with real-life cigarette smoking.

The occasional smokers I recruited smoked 0.25-5 cigarettes/week (chapter 2) or 0.5-5 cigarettes/week (chapters 3 and 4). The ≤5 cigarettes/week was based on a previous study (Bühler et al., 2010), however they provided no minimum cut-off. I increased the minimum from 0.25 to 0.5/week because I thought smoking one cigarette/month was too little. Despite basing the criteria on this previous study, on retrospect, I think recruiting slightly heavier 'occasional' smokers might have been preferable. The main reason for this is that some of the occasional smokers chose not to smoke the cigarettes they won, thus limiting the conclusions about the pleasure associated with smoking in that group. Various definitions of light or intermittent smokes exist (Coggins, Murrelle, Carchman, & Heidbreder, 2009). One that might have been more useful may have been: a non-daily smoker who smokes at least 5 cigarettes per week. That may have increased the number of occasional smokers who smoked the cigarettes they won during the experiment while still ruling out dependent smokers.

Finally, as proposed in chapter 1, I believe it is important to consider drug and non-drug reward processing together, in order to investigate whether dependent individuals differ from controls on both measures, but also to examine the balance between them within the groups. Hence, although chapter 5 provided important new data on the acute effects of cannabis and the associations of cannabis dependence with non-drug reward processing deficits, it would have been desirable to provide a task in which participants could earn cannabis alongside other rewards, as is done in the DReaM-Choice task.

The dependent and occasional cigarette smokers in chapters 2, 3 and 4 were well matched in terms of their smoking behaviour, which is a strength of my successive studies. For instance, in the dependent group, the average numbers of cigarettes smoked per day were: 16.7 (chapter 2), 19.3 (chapter 3) and 16.5 (chapter 4); in the occasional group, the average numbers of cigarettes smoked per week were: 3.3 (chapter 2), 3.4 (chapter 3) and 3.8 (chapter 4). The FTND scores for the dependent smokers across the chapters were also similar, and each occasional smoker always scored zero on this questionnaire. There were no significant differences between studies for the dependent or occasional smokers on these measures. However, the dependent smokers reported in chapter 3 were older (and sometimes significantly so) than the dependent and occasional smokers reported in chapters 2 and 4. These dependent smokers reported in chapter 3 also had greater BDI scores than the other groups (and these differences sometimes reached significance). Furthermore, the studies reported in chapters 2 and 4 had similar and equivalent numbers of males and females, respectively; while the study in chapter 3 had many fewer females. Hence, it would have been desirable (although quite difficult) to have: (1) had no group differences between dependent and occasional smokers on any important, non-smoking demographic variable and (2) maintained similar scores on all demographic variables across the studies.

The participants in the acute cannabis study and the drug-using controls in the cannabis dependence study, described in chapter 5, both had similar demographics to the occasional cigarette smokers.

Whereas the cannabis dependent participants had more similar demographics to the dependent cigarette smokers. This represents a more general problem that by separating people into groups determined by one behaviour (e.g. being nicotine or cannabis dependent), other variables, like depression, are often dissimilar between the groups.

Cross-sectional studies that compare one group of people to another group of people frequently suffer the problems described above. This makes drawing conclusions about causation very difficult. Within the monetary and temporal limitations of PhD research, cross-sectional studies are useful in determining crude associations between two variables, which cannot be manipulated experimentally (e.g. nicotine dependence). However, in terms of refining progress in the field of reward processing in addiction research, I think it would be beneficial if large, longitudinal studies were conducted in place of small, cross-sectional studies.

6.9 Future research

I believe that this thesis provides a good example of how the use of various reward processing tasks can elucidate different profiles of impairments in different populations. For instance, cannabis dependence was associated with impaired reward learning but not alterations in effort-related decision-making, while nicotine dependence was associated with reduced sensitivity to various parameters during effort-related decision-making but was not associated with impaired reward learning. Irrespective of the reasons for these associations (e.g. covariate depression), these results demonstrate that different drug addictions manifest different reward deficits and that different reward processing tasks tap dissociable constructs. Support for this latter claim comes from the dissociations described above and the absence of any correlation between outcomes in either chapter 4 or 5.

It is interesting to note that the researchers who designed the PRT and the EEfRT both defined their tasks as objective measures of 'anhedonia' (Pizzagalli et al., 2005; Treadway et al., 2009). As discussed

in section 1.5.2.2, I feel the word 'anhedonia' should be saved for impaired hedonic processing, which these tasks may be associated with, but are certainly not measuring. Hence, I argue that it is helpful for the future of this field not to use the terms 'anhedonia' and 'reward sensitivity' in such a general way, but be specific about which reward processing component is being assessed and make the clear statement that any impairments in one component do not necessitate impairments in others, as has been demonstrated in this thesis.

As mentioned already, I believe that another major step forward will be made by carrying out large, longitudinal studies. This thesis has given indications of important relationships, but they cannot be fully explored in cross-sectional designs. Many important questions rely on examining the temporal relationships between variables. Measuring outcome *y* and predictor *x* at various time points (ideally with *x*=0 at the first time point), allows the researcher to make stronger inferences about the causal relationships between *x* and *y*. For example, cross-sectional research has frequently demonstrated associations between cannabis use and cognitive deficits (Solowij & Battisti, 2008). However, that relationship could be driven by one or more of: (1) cannabis use causing cognitive deficits, (2) cognitive deficits causing cannabis use, (3) external variables (e.g. alcohol use) causing both. A longitudinal cohort study means the researcher can measure cognitive deficits both before any cannabis use has begun and then, in a subset of the cohort, after the onset of cannabis use. Therefore, the baseline cognitive deficits can be taken into account when investigating cannabis's relationship with future cognitive deficits. Furthermore, external variables that can contribute to both the predicted cause and effect (e.g. alcohol use) can be more carefully recorded and modelled. Recent longitudinal research has now shown conflicting results about cannabis's effects on cognitive ability (Meier et al., 2012; Mokrysz et al., 2014). Although these longitudinal designs do not provide extremely powerful causal knowledge, like randomised controlled trials do, they allow for a better possible understanding of causes than cross-sectional studies. Moreover, they are critical in the investigation of topics which cannot be ethically studied using randomised controlled trials, such as the effects of long-term nicotine and cannabis use.

In terms of how longitudinal designs should be employed more frequently in the field of reward processing in addiction, it would be fascinating to investigate how reward processing abnormalities predict the initiation of drug use, the transition to dependence and the ability to quit (and vice versa), as has been done in some cases already (Lubman et al., 2009; Powell et al., 2010; Sweitzer et al., 2015). Without longitudinal designs, it is impossible to investigate, for example, whether nicotine dependence causes an impairment in effort-related decision-making or vice versa.

I believe an important step in this field will be to determine what components really make up reward processing and how they relate to one-another. In the same way that intelligence is a broad concept made up of various components, such as visuospatial processing and working memory, reward processing can and should be considered to consist of separable components. A study which investigated performance on many known aspects of reward processing, using reliable and valid tasks and questionnaires, in a very large sample could be carried out. One could examine how performance on all of the tasks are associated with each other and then carry out a factor analysis so that distinct components of reward processing were revealed. The tasks that best load onto each factor could then be used as exemplars for assessing that particular component, such that a battery of tasks could be created which fully captured all aspects of reward processing. This could be used to systematically investigate transdiagnostic reward processing deficiencies across a variety of clinical populations so that profiles of impairments were clearer. Furthermore, a more detailed understanding of the structure of reward processing would then allow much more precise, psychological mechanisms underpinning psychopathology to be illuminated. Ideally, longitudinal studies that predict disorder severity from pre-determined reward processing components would mean specific endophenotypes, e.g. impaired hedonic processing (but not other impairments), could be linked to disease aetiology and treatments improved with highly specific targets.

My thesis produces nowhere near as clear a picture of the nature of reward processing in nicotine and cannabis dependence as could feasibly be produced with a battery of reward processing tasks that tap

components that are known to be distinct. However, it is a start in terms of attempting to be more specific and precise in profiling reward processing impairments in these addictions. Furthermore, I have provided evidence that the PRT, the EEfRT and my own DReaM-Choice task are not associated with one another, and that self-reported measures of anhedonia are not as clearly associated with PRT and EEfRT performance as previously reported. This provides support for my claim that researchers should not talk about 'anhedonia' or 'reward sensitivity' so generally.

Therefore, questions following on from my findings, which I think are particularly pertinent, are:

1. What are the distinct components of reward processing?
2. Does cigarette use predict changes in cigarette and non-drug reward processing? And if so, in which components of reward processing?
3. Do the processing of cigarette and non-drug rewards predict changes in cigarette use? And if so, from which components of reward processing?
4. Is the balance between cigarette and non-drug reward processing a better predictor of changes in cigarette use than either of them on their own?
5. Do changes in cannabis use predict changes in non-drug reward processing (particularly motivational processing)?

For questions 2, 3, 4 and 5, I would be particularly interested in various stages of drug use, including: (1) the initiation of drug use; (2) the transition from occasional use to dependence; (3) the maintenance and hardening of dependence; and (4) the successful cessation of use following dependence. Although these would be all long, expensive and difficult studies to complete, they would provide a highly detailed picture of how changes in tobacco and cannabis use are associated with reward processing changes, to the point where one would be able to provide strong evidence in favour or against statements like: 'cannabis use leads to amotivation' or 'nicotine dependence leads to an increase in motivation for but a decrease in liking of cigarettes'. Without these large, longitudinal studies, this field of research will forever be in a state of speculation.

6.10 My PhD journey: a truly rewarding process

6.10.1 Changing ideas

As described in the acknowledgments section, I feel so privileged to have been given the opportunity to study psychopharmacology and addiction. I have been genuinely fascinated by psychoactive drugs, their role in society, their underlying pharmacology, and their positive and negative effects, for many years – long before I first studied psychology at university. To be actively involved in researching these topics, and so developing my own (and hopefully other people's) understanding, is extremely rewarding.

Over the last three years, my ideas of what might drive addiction have changed a lot. Naively, I originally began my PhD thinking that neuroscience held all of the answers and that neuroimaging techniques were be the best way of getting these answers. It has been thoroughly enjoyable shattering these expectations, mostly by reading other people's research, but also from my own research described in this thesis. For instance, I administered a drug (pramipexole) that is known to robustly alter dopaminergic functioning, and yet I found no effects on the motivation to seek drugs (cigarettes in this case). Given the critical importance many neurobiological theories of addiction place on dopamine (Volkow et al., 2004), this was an unexpected result. Furthermore, I conducted an fMRI experiment and my reaction time measurements appeared to be more sensitive than the BOLD responses. Furthermore, I have loved learning things which contradict well-held beliefs and theories, for instance: that most people who try drugs never become addicted (Anthony et al., 1994); that many people who are addicted recover without help (Heyman, 2009); that medicinal drugs, which show promise in treating addiction in experimental models, often do not translate successfully in human clinical trials (Kahn et al., 2009; M Shoaib, Swanner, Beyer, Goldberg, & Schindler, 1998).

These findings have undoubtedly contributed to my general suspiciousness of theories which claim that the entirety of addictive behaviour is best explained exclusively through neurophysiological

changes in the brain. Obviously all behaviour is determined by neural signals and so addiction might one day be comprehensively explained by neuroscience alone. However, given our current rudimentary understanding of how biology is related to concepts like choice, compulsion and will-power, I believe it is unwise to not explain parts of addictive behaviour through sociology and psychology. To make an analogy, trying to understand addiction entirely through neuroscience is like trying to understand tuberculosis entirely through basic chemistry and atomic physics; both of these phenomena can be logically reduced to more basic scientific levels, but our explanations of these phenomena are worse if we do reduce them to such an extent. I started my PhD thinking that neuroscience would answer all of the many questions I had about addiction. I still think neuroscience has a big and important role to play in understanding addiction. But I am pleased that I now understand a bit more about the wealth of other reasons why people might have drug problems, and therefore I think I am a little closer to answering some of my questions about addiction.

6.10.2 Opportunities along the way

I have had many fantastic opportunities during my PhD research which I am very thankful for. These opportunities contributed to the experiments I conducted and the thoughts I have about addiction research now. While working at the Clinical Psychopharmacology Unit (CPU), we conducted a study, as a group, into the effects of different strains of cannabis on a variety of psychological and neural outcomes. This was funded by Channel 4 and the results were broadcast on television. It was a thoroughly exciting project to be involved in and it was in this study that I conducted my experiment into the acute effects of cannabis on effort-related decision-making. I have learned so much by being part of a group that has such extensive experience of acute psychopharmacological experiments. I was very fortunate in being able to spend a few months at Exeter University with Professor Celia Morgan (my second supervisor), where I conducted the fMRI experiment, which I reported in chapter 3. I would never have been able to carry out this experiment here at University College London (UCL), and I was so pleased to learn about a contemporary, cognitive neuroscience methodology under the

guidance of Professor Celia Morgan and Dr Chris Dodds (despite my current thinking that addiction research should focus more on behaviour than neuroimaging!).

Finally, I was also very lucky to receive a Bogue Scholarship, where I worked with Dr Gill Bedi at the New York Psychiatric Institute, on the neural correlates of drug purchase, in crack cocaine and cannabis users. Working directly with people who are often stigmatised (crack cocaine users) was a very informative experience: they were all kind and thoughtful people – not what one might expect from some descriptions of what addiction turns people into. It was there in New York where I was also able to meet Dr Carl Hart, whose book 'High Price: A Neuroscientist's Journey of Self-Discovery That Challenges Everything You Know About Drugs and Society' inspired me to think about many aspects of addiction I had not before.

Overall, the thing I am most appreciative of is the incredible company and support my friends, colleagues and supervisors at UCL. They been invaluable in so many ways.

6.11 Final comments

The research described in this thesis was informed by theories claiming that drug and non-drug reward processing alterations are critical in the aetiology of addition (Goldstein & Volkow, 2011; Koob & Le Moal, 1997; Robinson & Berridge, 1993). The previous empirical work concerning the relationships between nicotine and cannabis dependence and these alterations was mixed, however (Bühler et al., 2010; Kalamboka et al., 2009; Lane et al., 2005; Powell et al., 2002). The major findings of this thesis include:

- Across a wide range of metrics, nicotine dependence (assessed mostly after ad libitum smoking) was associated with a hypersensitivity to cigarette rewards and was not associated with a hyposensitivity to non-drug rewards, apart from disrupted effort-related decision-making.

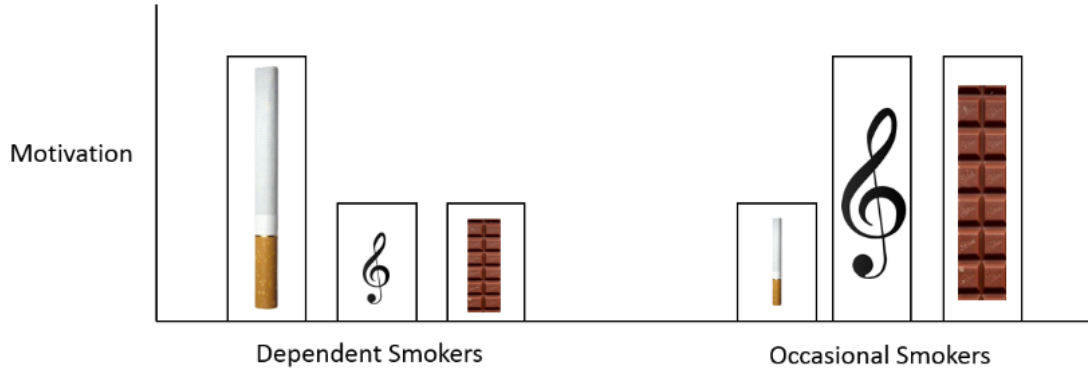
- In dependent and occasional smokers, an acute dose of pramipexole (0.5mg, oral) did not disrupt motivation for cigarettes but did impair reward learning and effort-related decision-making.
- Acute cannabis administration transiently reduced motivation for monetary reward and CBD influenced the way that cannabis affected effort-related decision-making.
- Cannabis dependence was associated with perturbed reward learning but not amotivation for monetary reward, although confounding factors cannot be disregarded.

Although my research has inevitably produced more questions than answers, I would like to think that it has made important theoretical contributions to the field. Firstly, after ad libitum smoking, nicotine dependent individuals appear to have very few non-drug reward processing deficits, questioning several theories of addiction. Further, researchers should beware of making claims such as 'smokers have blunted responses to non-drug rewards' (Wilson et al., 2014) as they are unhelpful, unless they are clarified by statements about the potentially moderating influences of nicotine deprivation. Secondly, I hope this work develops the appreciation that reward processing should be considered as a very broad construct and that potential impairments in clinical populations should be examined with different tasks that tap distinct components. In essence, I hope that researchers are careful in their choice of tasks and the subsequent description of their findings, so that precise reward processing alterations can be identified and the mechanisms underlying various psychopathologies better understood.

Finally, many of my research hypothesises were based on Goldstein & Volkow's (2011) iRISA theory of addiction. The findings described in this thesis can help determine whether this is a suitable theory for nicotine dependence during ad libitum smoking. My results can specifically address whether the motivational aspect of the theory is supported, but my results cannot address the response inhibition aspect of the theory. Figure 6.1a shows what the iRISA theory might predict in terms of motivation for cigarette, music and chocolate rewards for dependent and occasional cigarette smokers. However,

what I actually found is represented by figure 6.1b. After ad libitum smoking, dependent smokers had stronger motivation for cigarettes than occasional smokers, as the iRISA theory predicts, but dependent smokers did not have weaker motivation for non-drug rewards than occasional smokers, which the iRISA theory does not predict. This suggests that the iRISA theory of addiction does not explain cigarette smoking behaviour in nicotine dependent individuals when they are in their 'smoking-as-normal' state. Thus, when considering nicotine dependence, during ad libitum smoking, the most accurate conclusion about cigarette and non-drug reward processing may be the simplest one: motivation for cigarettes is enhanced, but motivation for non-drug rewards remains intact.

a)



b)

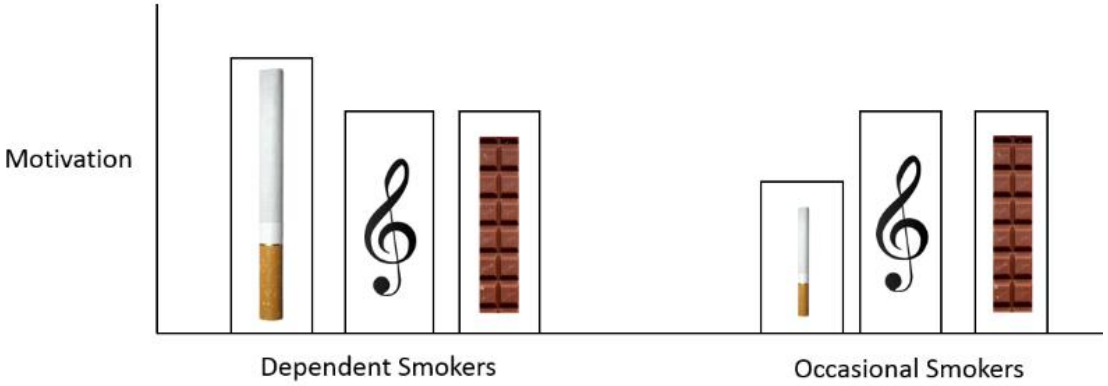


Figure 6.1 a) What the iRISA theory of addiction would predict about dependent and occasional smokers' motivation for cigarette, music and chocolate rewards. The dependent smokers would have stronger motivation for cigarettes than the occasional smokers. The occasional smokers would have stronger motivation for the non-drug rewards than the dependent smokers. The dependent smokers would have stronger motivation for cigarettes than the non-drug rewards. The occasional smokers would have stronger motivation for the non-drug rewards than cigarettes. b) What the data reported in this thesis actually suggests. The dependent smokers had stronger motivation for cigarettes than the occasional smokers. The occasional smokers did not have stronger motivation for the non-drug rewards than the dependent smokers. The dependent smokers had stronger (or similar) motivation for cigarettes than the non-drug rewards. The occasional smokers had stronger motivation for the non-drug rewards than cigarettes. These results suggest that the profiles of cigarette and non-drug reward processing in dependent and occasional smokers, when they are smoking normally, can be described simply by the fact that dependent smokers have a stronger motivation for cigarettes than occasional smokers. Hence, theories of addiction based on reward processing need not focus on the processing of non-drug rewards when considering nicotine dependence during ad libitum smoking.

References

Acker, J., & MacKillop, J. (2013). Behavioral economic analysis of cue-elicited craving for tobacco: a virtual reality study. *Nicotine & Tobacco Research*, nts341.

Action on Smoking and Health. (2014). Smoking Statistics: Illness and Health.

Ahmed, S. H., Kenny, P. J., Koob, G. F., & Markou, A. (2002). Neurobiological evidence for hedonic allostasis associated with escalating cocaine use. *Nature neuroscience, 5*(7), 625-626.

Al-Adawi, S., & Powell, J. (1997). The influence of smoking on reward responsiveness and cognitive functions: a natural experiment. *Addiction, 92*(12), 1773-1782.

Albrecht, D. S., Skosnik, P. D., Vollmer, J. M., Brumbaugh, M. S., Perry, K. M., Mock, B. H., . . . Herring, C. M. (2013). Striatal D 2/D 3 receptor availability is inversely correlated with cannabis consumption in chronic marijuana users. *Drug and alcohol dependence, 128*(1), 52-57.

Amlung, M. T., Acker, J., Stojek, M. K., Murphy, J. G., & MacKillop, J. (2012). Is talk "cheap"? An initial investigation of the equivalence of alcohol purchase task performance for hypothetical and actual rewards. *Alcoholism: Clinical and Experimental Research, 36*(4), 716-724.

Anselme, P. (2009). The effect of exposure to drugs on the processing of natural rewards. *Neuroscience & Biobehavioral Reviews, 33*(3), 314-335.

Anthony, J. C., Warner, L. A., & Kessler, R. C. (1994). Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. *Experimental and clinical psychopharmacology, 2*(3), 244.

Aston, E. R., Metrik, J., & MacKillop, J. (2015). Further validation of a marijuana purchase task. *Drug and alcohol dependence*.

Audrain-McGovern, J., Wileyto, E. P., Ashare, R., Cuevas, J., & Strasser, A. A. (2014). Reward and affective regulation in depression-prone smokers. *Biological psychiatry, 76*(9), 689-697.

Audrain-McGovern, J., Rodriguez, D., Rodgers, K., & Cuevas, J. (2011). Declining alternative reinforcers link depression to young adult smoking. *Addiction, 106*(1), 178-187.

Baddeley, A., Emslie, H., & Nimmo-Smith, I. (1993). The Spot-the-Word test: A robust estimate of verbal intelligence based on lexical decision. *British Journal of Clinical Psychology, 32*(1), 55-65.

Balleine, B. W., & Dickinson, A. (1998). Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. *Neuropharmacology, 37*(4), 407-419.

Balodis, I. M., & Potenza, M. N. (2015). Anticipatory reward processing in addicted populations: a focus on the monetary incentive delay task. *Biological psychiatry, 77*(5), 434-444.

Barnwell, S. S., Earleywine, M., & Wilcox, R. (2006). Cannabis, motivation, and life satisfaction in an internet sample. *Substance Abuse Treatment, Prevention, and Policy, 1*(1), 2.

Barone, P., Poewe, W., Albrecht, S., Debieuvre, C., Massey, D., Rascol, O., . . . Weintraub, D. (2010). Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *The Lancet Neurology, 9*(6), 573-580.

Barr, R. S., Pizzagalli, D. A., Culhane, M. A., Goff, D. C., & Evins, A. E. (2008). A single dose of nicotine enhances reward responsiveness in nonsmokers: implications for development of dependence. *Biological psychiatry, 63*(11), 1061-1065.

Barrett, S. P. (2010). The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers. *Behavioural pharmacology, 21*(2), 144-152.

Barrett, S. P., Boileau, I., Okker, J., Pihl, R. O., & Dagher, A. (2004). The hedonic response to cigarette smoking is proportional to dopamine release in the human striatum as measured by positron emission tomography and [11C] raclopride. *Synapse, 54*(2), 65-71.

Batalla, A., Bhattacharyya, S., Yücel, M., Fusar-Poli, P., Crippa, J. A., Nogué, S., . . . Martin-Santos, R. (2013). Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings. *PloS one, 8*(2), e55821.

Bechara, A., Dolan, S., & Hindes, A. (2002). Decision-making and addiction (part II): myopia for the future or hypersensitivity to reward? *Neuropsychologia, 40*(10), 1690-1705.

Beck, A. T., Steer, R. A., Ball, R., & Ranieri, W. F. (1996). Comparison of Beck Depression Inventories-IA and-II in psychiatric outpatients. *Journal of personality assessment, 67*(3), 588-597.
Bedi, G., Lindquist, M. A., & Haney, M. (2015). An fMRI-Based Neural Signature of Decisions to Smoke Cannabis. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*.
Benowitz, N. L. (2010). Nicotine addiction. *The New England journal of medicine, 362*(24), 2295.
Benowitz, N. L., Jacob, P., Hall, S., Tsoh, J., Ahijevych, K., Jarvis, M., . . . Henningfield, J. (2002). Biochemical verification of tobacco use and cessation. *Nicotine and Tobacco Research, 4*(2), 149-159.
Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain research reviews, 28*(3), 309-369.
Berridge, K. C., & Robinson, T. E. (2003). Parsing reward. *Trends in neurosciences, 26*(9), 507-513.
Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., . . . Allen, P. (2010). Opposite effects of Δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 35*(3), 764-774.
Bisaga, A., Padilla, M., Garawi, F., Sullivan, M. A., & Haney, M. (2007). Effects of alternative reinforcer and craving on the choice to smoke cigarettes in the laboratory. *Human Psychopharmacology: Clinical and Experimental, 22*(1), 41-47.
Bjork, J. M., Smith, A. R., & Hommer, D. W. (2008). Striatal sensitivity to reward deliveries and omissions in substance dependent patients. *Neuroimage, 42*(4), 1609-1621.
Bloomfield, M. A., Morgan, C. J., Egerton, A., Kapur, S., Curran, H. V., & Howes, O. D. (2014). Dopaminergic function in cannabis users and its relationship to cannabis-induced psychotic symptoms. *Biological psychiatry, 75*(6), 470-478.
Bloomfield, M. A., Morgan, C. J., Kapur, S., Curran, H. V., & Howes, O. D. (2014). The link between dopamine function and apathy in cannabis users: an [18F]-DOPA PET imaging study. *Psychopharmacology, 231*(11), 2251-2259.
Bloomfield, M. A., Pepper, F., Egerton, A., Demjaha, A., Tomasi, G., Mouchlianitis, E., . . . Selvaraj, S. (2014). Dopamine Function in Cigarette Smokers: An [18F]-DOPA PET Study. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 39*(10), 2397-2404.
Blum, K., Braverman, E. R., Holder, J. M., Lubar, J. F., Monastra, V. J., Miller, D., . . . Comings, D. E. (2000). The Reward Deficiency Syndrome: A Biogenetic Model for the Diagnosis and Treatment of Impulsive, Addictive and Compulsive Behaviors. *Journal of Psychoactive Drugs, 32*(sup1), 1-112.
Bódi, N., Kéri, S., Nagy, H., Moustafa, A., Myers, C. E., Daw, N., . . . Gluck, M. A. (2009). Reward-learning and the novelty-seeking personality: a between-and within-subjects study of the effects of dopamine agonists on young Parkinson's patients. *Brain*, awp094.
Bogdan, R., & Pizzagalli, D. A. (2006). Acute stress reduces reward responsiveness: implications for depression. *Biological psychiatry, 60*(10), 1147-1154.
Boileau, I., Assaad, J. M., Pihl, R. O., Benkelfat, C., Leyton, M., Diksic, M., . . . Dagher, A. (2003). Alcohol promotes dopamine release in the human nucleus accumbens. *Synapse, 49*(4), 226-231.
Bossong, M. G., Mehta, M. A., van Berckel, B. N., Howes, O. D., Kahn, R. S., & Stokes, P. R. (2015). Further human evidence for striatal dopamine release induced by administration ofΔ 9-tetrahydrocannabinol (THC): selectivity to limbic striatum. *Psychopharmacology*, 1-7.
Bossong, M. G., van Berckel, B. N., Boellaard, R., Zuurman, L., Schuit, R. C., Windhorst, A. D., . . . Kahn, R. S. (2009). Δ9-tetrahydrocannabinol induces dopamine release in the human striatum. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 34*(3), 759-766.

Bovasso, G. B. (2001). Cannabis abuse as a risk factor for depressive symptoms. *American Journal of Psychiatry*.

Brody, A. L., Mandelkern, M. A., Olmstead, R. E., Allen-Martinez, Z., Scheibal, D., Abrams, A. L., . . . Monterosso, J. (2009). Ventral striatal dopamine release in response to smoking a regular vs a denicotinized cigarette. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 34*(2), 282-289.

Brody, A. L., Olmstead, R. E., London, E. D., Farahi, J., Meyer, J. H., Grossman, P., . . . Mandelkern, M. A. (2004). Smoking-induced ventral striatum dopamine release. *American Journal of Psychiatry, 161*(7), 1211-1218.

Brunt, T. M., van Genugten, M., Höner-Snoeken, K., van de Velde, M. J., & Niesink, R. J. (2014). Therapeutic satisfaction and subjective effects of different strains of pharmaceutical-grade cannabis. *Journal of clinical psychopharmacology, 34*(3), 344-349.

Budney, A. J., & Hughes, J. R. (2006). The cannabis withdrawal syndrome. *Current Opinion in Psychiatry, 19*(3), 233-238.

Bühler, M., Vollstädt-Klein, S., Kobiella, A., Budde, H., Reed, L. J., Braus, D. F., . . . Smolka, M. N. (2010). Nicotine dependence is characterized by disordered reward processing in a network driving motivation. *Biological psychiatry, 67*(8), 745-752.

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.

Caskey, N. H., Jarvik, M. E., & Wirshing, W. C. (1999). The effects of dopaminergic D_2 stimulation and blockade on smoking behavior. *Experimental and clinical psychopharmacology, 7*(1), 72.

Changeux, J.-P. (2010). Nicotine addiction and nicotinic receptors: lessons from genetically modified mice. *Nature Reviews Neuroscience, 11*(6), 389-401.

Chapman, L. J., Chapman, J. P., & Raulin, M. L. (1976). Scales for physical and social anhedonia. *Journal of abnormal psychology, 85*(4), 374.

Chase, H. W., MacKillop, J., & Hogarth, L. (2013). Isolating behavioural economic indices of demand in relation to nicotine dependence. *Psychopharmacology, 226*(2), 371-380.

Chen, J., Paredes, W., Li, J., Smith, D., Lowinson, J., & Gardner, E. L. (1990). Δ9-Tetrahydrocannabinol produces naloxone-blockable enhancement of presynaptic basal dopamine efflux in nucleus accumbens of conscious, freely-moving rats as measured by intracerebral microdialysis. *Psychopharmacology, 102*(2), 156-162.

Cherek, D. R., Lane, S. D., & Dougherty, D. M. (2002). Possible amotivational effects following marijuana smoking under laboratory conditions. *Experimental and clinical psychopharmacology, 10*(1), 26.

Chib, V. S., Rangel, A., Shimojo, S., & O'Doherty, J. P. (2009). Evidence for a common representation of decision values for dissimilar goods in human ventromedial prefrontal cortex. *The Journal of neuroscience, 29*(39), 12315-12320.

Coggins, C. R., Murrelle, E. L., Carchman, R. A., & Heidbreder, C. (2009). Light and intermittent cigarette smokers: a review (1989–2009). *Psychopharmacology, 207*(3), 343-363.

Cohen, A., Koob, G. F., & George, O. (2012). Robust escalation of nicotine intake with extended access to nicotine self-administration and intermittent periods of abstinence. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 37*(9), 2153-2160.

Comer, S. D., Collins, E. D., & Fischman, M. W. (2001). Buprenorphine sublingual tablets: effects on IV heroin self-administration by humans. *Psychopharmacology, 154*(1), 28-37.

Compton, D. R., Dewey, W. L., & Martin, B. R. (1990). Canabis dependence and tolerance production. *Advances in alcohol & substance abuse, 9*(1-2), 129-147.

Cook, Piper, M. E., Leventhal, A. M., Schlam, T. R., Fiore, M. C., & Baker, T. B. (2015). Anhedonia as a component of the tobacco withdrawal syndrome. *Journal of abnormal psychology, 124*(1), 215.

Cook, Spring, B., McChargue, D., & Doran, N. (2010). Effects of anhedonia on days to relapse among smokers with a history of depression: A brief report. *Nicotine & Tobacco Research, 12*(9), 978-982.

Cook, Spring, B., McChargue, D., & Hedeker, D. (2004). Hedonic capacity, cigarette craving, and diminished positive mood. *Nicotine & Tobacco Research, 6*(1), 39-47.

Cools, R., & D'Esposito, M. (2011). Inverted-U–shaped dopamine actions on human working memory and cognitive control. *Biological psychiatry, 69*(12), e113-e125.

Cools, R., Lewis, S. J., Clark, L., Barker, R. A., & Robbins, T. W. (2007). L-DOPA disrupts activity in the nucleus accumbens during reversal learning in Parkinson's disease. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 32*(1), 180-189.

Cooper, K., Chatters, R., Kaltenthaler, E., & Wong, R. (2015). Psychological and psychosocial interventions for cannabis cessation in adults: a systematic review short report.

Corrigall, W. A., Coen, K. M., & Adamson, K. L. (1994). Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. *Brain research, 653*(1), 278-284.

Corrigall, W. A., Franklin, K. B., Coen, K. M., & Clarke, P. B. (1992). The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. *Psychopharmacology, 107*(2-3), 285-289.

Corrigan, M. H., Denahan, A. Q., Wright, C. E., Ragual, R. J., & Evans, D. L. (2000). Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. *Depression and anxiety, 11*(2), 58-65.

Cousijn, J., Goudriaan, A. E., Ridderinkhof, K. R., van den Brink, W., Veltman, D. J., & Wiers, R. W. (2013). Neural responses associated with cue-reactivity in frequent cannabis users. *Addiction biology, 18*(3), 570-580.

Cousins, M. S., Stamat, H. M., & de Wit, H. (2001). Acute doses of d-amphetamine and bupropion increase cigarette smoking. *Psychopharmacology, 157*(3), 243-253.

Curran, V. H., Brignell, C., Fletcher, S., Middleton, P., & Henry, J. (2002). Cognitive and subjective dose-response effects of acute oral Δ9-tetrahydrocannabinol (THC) in infrequent cannabis users. *Psychopharmacology, 164*(1), 61-70.

D'Souza, D. C., Ranganathan, M., Braley, G., Gueorguieva, R., Zimolo, Z., Cooper, T., . . . Krystal, J. (2008). Blunted psychotomimetic and amnestic effects of Δ-9-tetrahydrocannabinol in frequent users of cannabis. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 33*(10), 2505-2516.

D'Souza, D. C., Cortes-Briones, J. A., Ranganathan, M., Thurnauer, H., Creatura, G., Surti, T., . . . Normandin, M. (2015). Rapid changes in CB1 receptor availability in cannabis dependent males after abstinence from cannabis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*.

Dagher, A., Bleicher, C., Aston, J. A., Gunn, R. N., Clarke, P., & Cumming, P. (2001). Reduced dopamine D1 receptor binding in the ventral striatum of cigarette smokers. *Synapse, 42*(1), 48-53.

Daglish, M. R., Williams, T. M., Wilson, S. J., Taylor, L. G., Eap, C. B., Augsburger, M., . . . Grasby, P. (2008). Brain dopamine response in human opioid addiction. *The British Journal of Psychiatry, 193*(1), 65-72.

Dalley, J. W., Fryer, T. D., Brichard, L., Robinson, E. S., Theobald, D. E., Lääne, K., . . . Probst, K. (2007). Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science, 315*(5816), 1267-1270.

Das, R. (2015). *Manipulating Maladaptive Motivational Memories via Reconsolidation.* UCL (University College London).

Das, R., Lawn, W., & Kamboj, S. (2015). Rewriting the valuation and salience of alcohol-related stimuli via memory reconsolidation. *Translational psychiatry, 5*(9), e645.

David, S. P., Munafò, M. R., Johansen-Berg, H., Smith, S. M., Rogers, R. D., Matthews, P. M., & Walton, R. T. (2005). Ventral striatum/nucleus accumbens activation to smoking-related pictorial cues in smokers and nonsmokers: a functional magnetic resonance imaging study. *Biological psychiatry, 58*(6), 488-494.

Dawes, G. M., Sitharthan, T., Conigrave, K. M., Phung, N., & Weltman, M. (2011). Patients admitted for inpatient cannabis detoxification: withdrawal symptoms and impacts of common comorbidities. *Journal of Substance Use, 16*(5), 392-405.

Dawkins, L., Acaster, S., & Powell, J. H. (2007). The effects of smoking and abstinence on experience of happiness and sadness in response to positively valenced, negatively valenced, and neutral film clips. *Addictive behaviors, 32*(2), 425-431.

Dawkins, L., Powell, J. H., Pickering, A., Powell, J., & West, R. (2009). Patterns of change in withdrawal symptoms, desire to smoke, reward motivation and response inhibition across 3 months of smoking abstinence. *Addiction, 104*(5), 850-858.

Dawkins, L., Powell, J. H., West, R., Powell, J., & Pickering, A. (2006). A double-blind placebo controlled experimental study of nicotine: I—effects on incentive motivation. *Psychopharmacology, 189*(3), 355-367.

Dayan, P., & Balleine, B. W. (2002). Reward, motivation, and reinforcement learning. *Neuron, 36*(2), 285-298.

De Wit, H., Uhlenhuth, E., & Johanson, C. (1986). Individual differences in the reinforcing and subjective effects of amphetamine and diazepam. *Drug and alcohol dependence, 16*(4), 341-360.

Deci, E. L., & Ryan, R. M. (2008). Hedonia, eudaimonia, and well-being: An introduction. *Journal of Happiness Studies, 9*(1), 1-11.

Degenhardt, L., Ferrari, A. J., Calabria, B., Hall, W. D., Norman, R. E., McGrath, J., . . . Whiteford, H. A. (2013). The global epidemiology and contribution of cannabis use and dependence to the global burden of disease: results from the GBD 2010 study.

Degenhardt, L., Hall, W., & Lynskey, M. (2003). Exploring the association between cannabis use and depression. *Addiction, 98*(11), 1493-1504.

Deichmann, R., Gottfried, J. A., Hutton, C., & Turner, R. (2003). Optimized EPI for fMRI studies of the orbitofrontal cortex. *Neuroimage, 19*(2), 430-441.

Der-Avakian, A., & Markou, A. (2010). Withdrawal from chronic exposure to amphetamine, but not nicotine, leads to an immediate and enduring deficit in motivated behavior without affecting social interaction in rats. *Behavioural pharmacology, 21*(4), 359.

Destrebecqz, A., & Cleeremans, A. (2001). Can sequence learning be implicit? New evidence with the process dissociation procedure. *Psychonomic bulletin & review, 8*(2), 343-350.

Di Chiara, G., & Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Sciences, 85*(14), 5274-5278.

DiFranza, J. R., Savageau, J. A., Fletcher, K., Ockene, J. K., Rigotti, N. A., McNeill, A. D., . . . Wood, C. (2004). Recollections and repercussions of the first inhaled cigarette. *Addictive behaviors, 29*(2), 261-272.

Domino, E. F., Tsukada, H., & Harada, N. (2009). Positron emission tomographic measure of brain dopamine dependence to nicotine as a model of drugs of abuse. *Psychopharmacology, 204*(1), 149-153.

Dorard, G., Berthoz, S., Phan, O., Corcos, M., & Bungener, C. (2008). Affect dysregulation in cannabis abusers. *European child & adolescent psychiatry, 17*(5), 274-282.

DSM-5 American Psychiatric Association. (2013). *The Diagnostic and Statistical Manual of Mental Disorders: DSM 5*: bookpointUS.

DSM-IV American Psychiatric Association. (2000). *Diagnostic and statistical manual-text revision (DSM-IV-TRim, 2000)*: American Psychiatric Association.

Dwoskin, L. P., Rauhut, A. S., King-Pospisil, K. A., & Bardo, M. T. (2006). Review of the pharmacology and clinical profile of bupropion, an antidepressant and tobacco use cessation agent. *CNS drug reviews, 12*(3-4), 178-207.

Ehrman, R. N., Robbins, S. J., Bromwell, M. A., Lankford, M. E., Monterosso, J. R., & O'Brien, C. P. (2002). Comparing attentional bias to smoking cues in current smokers, former smokers, and non-smokers using a dot-probe task. *Drug and alcohol dependence, 67*(2), 185-191.

Eissenberg, T., & Balster, R. L. (2000). Initial tobacco use episodes in children and adolescents: current knowledge, future directions. *Drug and alcohol dependence, 59*, 41-60.

Engelmann, J. M., Versace, F., Robinson, J. D., Minnix, J. A., Lam, C. Y., Cui, Y., . . . Cinciripini, P. M. (2012). Neural substrates of smoking cue reactivity: a meta-analysis of fMRI studies. *Neuroimage, 60*(1), 252-262.

Englund, A., Morrison, P. D., Nottage, J., Hague, D., Kane, F., Bonaccorso, S., . . . Holt, D. (2013). Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *Journal of psychopharmacology, 27*(1), 19-27.

Epping-Jordan, M. P., Watkins, S. S., Koob, G. F., & Markou, A. (1998). Dramatic decreases in brain reward function during nicotine withdrawal. *Nature, 393*(6680), 76-79.

Epstein, L. H., Bulik, C. M., Perkins, K. A., Caggiula, A. R., & Rodefer, J. (1991). Behavioral economic analysis of smoking: money and food as alternatives. *Pharmacology Biochemistry and Behavior, 38*(4), 715-721.

Ersche, K. D., Bullmore, E. T., Craig, K. J., Shabbir, S. S., Abbott, S., Müller, U., . . . Sahakian, B. J. (2010). Influence of compulsivity of drug abuse on dopaminergic modulation of attentional bias in stimulant dependence. *Archives of general psychiatry, 67*(6), 632-644.

Ersche, K. D., Roiser, J. P., Abbott, S., Craig, K. J., Müller, U., Suckling, J., . . . Sahakian, B. J. (2011). Response perseveration in stimulant dependence is associated with striatal dysfunction and can be ameliorated by a D 2/3 receptor agonist. *Biological psychiatry, 70*(8), 754-762.

Etter, J.-F., Le Houezec, J., & Perneger, T. V. (2003). A self-administered questionnaire to measure dependence on cigarettes: the cigarette dependence scale. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 28*(2), 359-370.

European Monitoring Centre for Drugs and Drug Addiction. (2015). European Drug Report.

Everitt, B. J., & Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nature neuroscience, 8*(11), 1481-1489.

Fattore, L., Melis, M., Fadda, P., Pistis, M., & Fratta, W. (2010). The endocannabinoid system and nondrug rewarding behaviours. *Experimental neurology, 224*(1), 23-36.

Fawcett, J., Clark, D. C., Scheftner, W. A., & Gibbons, R. D. (1983). Assessing anhedonia in psychiatric patients: the pleasure scale. *Archives of general psychiatry, 40*(1), 79-84.

Fehr, C., Yakushev, I., Hohmann, N., Buchholz, H.-G., Landvogt, C., Deckers, H., . . . Scheurich, A. (2008). Association of low striatal dopamine D 2 receptor availability with nicotine dependence similar to that seen with other drugs of abuse. *American Journal of Psychiatry, 165*(4), 507-514.

Fergusson, D. M., Horwood, L. J., Lynskey, M. T., & Madden, P. A. (2003). Early reactions to cannabis predict later dependence. *Archives of general psychiatry, 60*(10), 1033-1039.

Fibiger, H., Zis, A., & McGeer, E. (1973). Feeding and drinking deficits after 6-hydroxydopamine administration in the rat: similarities to the lateral hypothalamic syndrome. *Brain research, 55*(1), 135-148.

Fidler, J. A., & West, R. (2011). Enjoyment of smoking and urges to smoke as predictors of attempts and success of attempts to stop smoking: a longitudinal study. *Drug and alcohol dependence, 115*(1), 30-34.

Field, & Cox, W. M. (2008). Attentional bias in addictive behaviors: a review of its development, causes, and consequences. *Drug and alcohol dependence, 97*(1), 1-20.

Field, Mogg, K., & Bradley, B. P. (2004). Eye movements to smoking-related cues: effects of nicotine deprivation. *Psychopharmacology, 173*(1-2), 116-123.

Field, M. (2005). Cannabis 'dependence'and attentional bias for cannabis-related words. *Behavioural pharmacology, 16*(5-6), 473-476.
Flagel, S. B., Clark, J. J., Robinson, T. E., Mayo, L., Czuj, A., Willuhn, I., . . . Akil, H. (2011). A selective role for dopamine in stimulus-reward learning. *Nature, 469*(7328), 53-57.
Floresco, S. B. (2013). Prefrontal dopamine and behavioral flexibility: shifting from an "inverted-U" toward a family of functions. *Frontiers in neuroscience, 7*.
Foll, B. L., Forget, B., Aubin, H. J., & Goldberg, S. R. (2008). Blocking cannabinoid CB1 receptors for the treatment of nicotine dependence: insights from pre-clinical and clinical studies. *Addiction biology, 13*(2), 239-252.
Foltin, R. W., Fischman, M. W., Brady, J. V., Bernstein, D. J., Capriotti, R. M., Nellis, M. J., & Kelly, T. H. (1990). Motivational effects of smoked marijuana: behavioral contingencies and low-probability activities. *Journal of the Experimental Analysis of Behavior, 53*(1), 5.
Forbes, E. E., Shaw, D. S., & Dahl, R. E. (2007). Alterations in reward-related decision making in boys with recent and future depression. *Biological psychiatry, 61*(5), 633-639.
Franken, I. H. (2003). Drug craving and addiction: integrating psychological and neuropsychopharmacological approaches. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 27*(4), 563-579.
Franken, I. H., Rassin, E., & Muris, P. (2007). The assessment of anhedonia in clinical and non-clinical populations: further validation of the Snaith–Hamilton Pleasure Scale (SHAPS). *Journal of affective disorders, 99*(1), 83-89.
Freeman, Das, R. K., Kamboj, S. K., & Curran, H. V. (2015). Dopamine, urges to smoke, and the relative salience of drug versus non-drug reward. *Social cognitive and affective neuroscience, 10*(1), 85-92.
Freeman, Morgan, C., Beesley, T., & Curran, H. (2012). Drug cue induced overshadowing: selective disruption of natural reward processing by cigarette cues amongst abstinent but not satiated smokers. *Psychological medicine, 42*(1), 161.
Freeman, Morgan, C. J., Brandner, B., Almahdi, B., & Curran, H. V. (2013). Dopaminergic involvement in effort-based but not impulsive reward processing in smokers. *Drug and alcohol dependence, 130*(1), 109-114.
Freeman, & Winstock, A. (2015). Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. *Psychological medicine*, 1-9.
Gard, D. E., Gard, M. G., Kring, A. M., & John, O. P. (2006). Anticipatory and consummatory components of the experience of pleasure: a scale development study. *Journal of Research in Personality, 40*(6), 1086-1102.
Garfield, J. B., Lubman, D. I., & Yücel, M. (2014). Anhedonia in substance use disorders: A systematic review of its nature, course and clinical correlates. *Australian and New Zealand Journal of Psychiatry, 48*(1), 36-51.
George, T. P., Vessicchio, J. C., Termine, A., Jatlow, P. I., Kosten, T. R., & O'Malley, S. S. (2003). A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation. *Biological psychiatry, 53*(2), 136-143.
Geracioti Jr, T. D., West, S. A., Baker, D. G., Hill, K. K., Ekhator, N. N., Wortman, M. D., . . . Norman, A. B. (1999). Low CSF concentration of a dopamine metabolite in tobacco smokers. *American Journal of Psychiatry, 156*(1), 130-132.
Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry, 159*(10), 1642-1652.
Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Reviews Neuroscience, 12*(11), 652-669.

Gossop, M., Darke, S., Griffiths, P., Hando, J., Powis, B., Hall, W., & Strang, J. (1995). The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. *Addiction, 90*(5), 607-614.

Grace, A. (1991). Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience, 41*(1), 1-24.

Green, M. F., Horan, W. P., Barch, D. M., & Gold, J. M. (2015). Effort-based decision making: a novel approach for assessing motivation in schizophrenia. *Schizophrenia bulletin*, sbv071.

Haber, S. N., & Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 35*(1), 4-26.

Hamidovic, A., Kang, U. J., & de Wit, H. (2008). Effects of low to moderate acute doses of pramipexole on impulsivity and cognition in healthy volunteers. *Journal of clinical psychopharmacology, 28*(1), 45-51.

Haney, M., Comer, S., Ward, A. S., Foltin, R., & Fischman, M. (1997). Factors influencing marijuana self-administration by humans. *Behavioural pharmacology*.

Haney, M., Malcolm, R., Babalonis, S., Nuzzo, P., Cooper, Z., Bedi, G., . . . Sparenborg, S. (2015). Oral Cannabidiol does not Alter the Subjective, Reinforcing or Cardiovascular Effects of Smoked Cannabis. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*.

Hart, C. L., Haney, M., Vosburg, S. K., Rubin, E., & Foltin, R. W. (2008). Smoked cocaine self-administration is decreased by modafinil. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 33*(4), 761-768.

Harvey, D. M., Yasar, S., Heishman, S. J., Panlilio, L. V., Henningfield, J. E., & Goldberg, S. R. (2004). Nicotine serves as an effective reinforcer of intravenous drug-taking behavior in human cigarette smokers. *Psychopharmacology, 175*(2), 134-142.

Hasin, D. S., Saha, T. D., Kerridge, B. T., Goldstein, R. B., Chou, S. P., Zhang, H., . . . Smith, S. M. (2015). Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013. *JAMA psychiatry*, 1-9.

Hatzigiakoumis, D. S., Martinotti, G., Di Giannantonio, M., & Janiri, L. (2011). Anhedonia and substance dependence: clinical correlates and treatment options. *Frontiers in psychiatry, 2*.

Health and Social Care Information Centre. (2014). Statistics on Smoking. *Health and Social Care Information Centre*.

Heath, R. G. (1963). Electrical self-stimulation of the brain in man. *American Journal of Psychiatry, 120*(6), 571-577.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K. (1991). The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. *British journal of addiction, 86*(9), 1119-1127.

Heishman, S. J., Singleton, E. G., & Pickworth, W. B. (2008). Reliability and validity of a Short Form of the Tobacco Craving Questionnaire. *Nicotine & Tobacco Research, 10*(4), 643-651.

Hendricks, P. S., Ditre, J. W., Drobes, D. J., & Brandon, T. H. (2006). The early time course of smoking withdrawal effects. *Psychopharmacology, 187*(3), 385-396.

Hernandez, L., & Hoebel, B. G. (1988). Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. *Life sciences, 42*(18), 1705-1712.

Heyman, G. M. (2009). *Addiction: A disorder of choice*: Harvard University Press.

Hikosaka, O., Bromberg-Martin, E., Hong, S., & Matsumoto, M. (2008). New insights on the subcortical representation of reward. *Current opinion in neurobiology, 18*(2), 203-208.

Hindocha, C., Freeman, T. P., Schafer, G., Gardener, C., Das, R. K., Morgan, C. J., & Curran, H. V. (2015). Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: A randomised, double-blind, placebo-controlled study in cannabis users. *European neuropsychopharmacology, 25*(3), 325-334.

Hindocha, C., Freeman, T. P., Winstock, A. R., & Lynskey, M. T. (2015). Vaping cannabis (marijuana) has the potential to reduce tobacco smoking in cannabis users. *Addiction*.

Hindocha, C., Shaban, N. D., Freeman, T. P., Das, R. K., Gale, G., Schafer, G., . . . Curran, H. V. (2015). Associations between cigarette smoking and cannabis dependence: A longitudinal study of young cannabis users in the United Kingdom. *Drug and alcohol dependence, 148*, 165-171.

Hitsman, B., MacKillop, J., Lingford-Hughes, A., Williams, T. M., Ahmad, F., Adams, S., . . . Munafò, M. R. (2008). Effects of acute tyrosine/phenylalanine depletion on the selective processing of smoking-related cues and the relative value of cigarettes in smokers. *Psychopharmacology, 196*(4), 611-621.

Hogarth, L. (2012). Goal-directed and transfer-cue-elicited drug-seeking are dissociated by pharmacotherapy: evidence for independent additive controllers. *Journal of Experimental Psychology: Animal Behavior Processes, 38*(3), 266.

Hogarth, L., & Chase, H. W. (2011). Parallel goal-directed and habitual control of human drug-seeking: implications for dependence vulnerability. *Journal of Experimental Psychology: Animal Behavior Processes, 37*(3), 261.

Hogarth, L., & Chase, H. W. (2012). Evaluating psychological markers for human nicotine dependence: Tobacco choice, extinction, and Pavlovian-to-instrumental transfer. *Experimental and clinical psychopharmacology, 20*(3), 213.

Hommer, D. W., Bjork, J. M., & Gilman, J. M. (2011). Imaging brain response to reward in addictive disorders. *Annals of the New York Academy of Sciences, 1216*(1), 50-61.

Hoyle, R. H., Stephenson, M. T., Palmgreen, P., Lorch, E. P., & Donohew, R. L. (2002). Reliability and validity of a brief measure of sensation seeking. *Personality and individual differences, 32*(3), 401-414.

Hughes, Keely, J., & Naud, S. (2004). Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction, 99*(1), 29-38.

Hughes, J., & Hatsukami, D. (2007). Instructions for use of the Minnesota Withdrawal Scale-Revised. *Retrieved from www/uvm. edu/~ hbpl*.

Huys, Q., Pizzagalli, D. A., Bogdan, R., & Dayan, P. (2013). Mapping anhedonia onto reinforcement learning: a behavioural meta-analysis. *Biol Mood Anxiety Disord, 3*(1), 12.

Izuma, K., Saito, D. N., & Sadato, N. (2008). Processing of social and monetary rewards in the human striatum. *Neuron, 58*(2), 284-294.

Janes, A. C., Pedrelli, P., Whitton, A. E., Pechtel, P., Douglas, S., Martinson, M. A., . . . Evins, A. E. (2015). Reward Responsiveness Varies by Smoking Status in Women with a History of Major Depressive Disorder. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*.

Janes, A. C., Pizzagalli, D. A., Richardt, S., Chuzi, S., Pachas, G., Culhane, M. A., . . . Kaufman, M. J. (2010). Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. *Biological psychiatry, 67*(8), 722-729.

Janiri, L., Martinotti, G., Dario, T., Reina, D., Paparello, F., Pozzi, G., . . . De Risio, S. (2005). Anhedonia and substance-related symptoms in detoxified substance-dependent subjects: a correlation study. *Neuropsychobiology, 52*(1), 37-44.

Jansma, J., van Hell, H., Vanderschuren, L., Bossong, M., Jager, G., Kahn, R., & Ramsey, N. (2013). THC reduces the anticipatory nucleus accumbens response to reward in subjects with a nicotine addiction. *Translational psychiatry, 3*(2), e234.

Jarvik, M. E., Caskey, N. H., Wirshing, W. C., Madsen, D. C., Iwamoto-Schaap, P. N., & Elins, J. L. (2000). Bromocriptine reduces cigarette smoking. *Addiction, 95*(8), 1173-1183.

Jia, Z., Worhunsky, P. D., Carroll, K. M., Rounsaville, B. J., Stevens, M. C., Pearlson, G. D., & Potenza, M. N. (2011). An initial study of neural responses to monetary incentives as related to treatment outcome in cocaine dependence. *Biological psychiatry, 70*(6), 553-560.

Johnson, K. A., Bonn-Miller, M. O., Leyro, T. M., & Zvolensky, M. J. (2009). Anxious arousal and anhedonic depression symptoms and the frequency of current marijuana use: Testing the

mediating role of marijuana-use coping motives among active users. *Journal of studies on alcohol and drugs, 70*(4), 543.
Jorenby, D. E., Leischow, S. J., Nides, M. A., Rennard, S. I., Johnston, J. A., Hughes, A. R., . . . Doan, K. (1999). A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *New England Journal of Medicine, 340*(9), 685-691.
Juckel, G., Schlagenhauf, F., Koslowski, M., Wüstenberg, T., Villringer, A., Knutson, B., . . . Heinz, A. (2006). Dysfunction of ventral striatal reward prediction in schizophrenia. *Neuroimage, 29*(2), 409-416.
Kable, J. W., & Glimcher, P. W. (2009). The neurobiology of decision: consensus and controversy. *Neuron, 63*(6), 733-745.
Kahn, R., Biswas, K., Childress, A.-R., Shoptaw, S., Fudala, P. J., Gorgon, L., . . . Li, S.-H. (2009). Multi-center trial of baclofen for abstinence initiation in severe cocaine-dependent individuals. *Drug and alcohol dependence, 103*(1), 59-64.
Kalamboka, N. (2008). *Reward responsivity and the development of nicotine dependence.* University of Southampton.
Kalamboka, N., Remington, B., & Glautier, S. (2009). Nicotine withdrawal and reward responsivity in a card-sorting task. *Psychopharmacology, 204*(1), 155-163.
Kassel, J. D., Stroud, L. R., & Paronis, C. A. (2003). Smoking, stress, and negative affect: correlation, causation, and context across stages of smoking. *Psychological bulletin, 129*(2), 270.
Kelley, A. E., & Berridge, K. C. (2002). The neuroscience of natural rewards: relevance to addictive drugs. *The Journal of neuroscience, 22*(9), 3306-3311.
Kenny, P. J., & Markou, A. (2006). Nicotine self-administration acutely activates brain reward systems and induces a long-lasting increase in reward sensitivity. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 31*(6), 1203-1211.
Killen, J. D., & Fortmann, S. P. (1997). Craving is associated with smoking relapse: findings from three prospective studies. *Experimental and clinical psychopharmacology, 5*(2), 137.
Kirk, J., & De Wit, H. (1999). Responses to oral Δ 9-tetrahydrocannabinol in frequent and infrequent marijuana users. *Pharmacology Biochemistry and Behavior, 63*(1), 137-142.
Klein, C., Hill, M. N., Chang, S. C., Hillard, C. J., & Gorzalka, B. B. (2012). Circulating endocannabinoid concentrations and sexual arousal in women. *The journal of sexual medicine, 9*(6), 1588-1601.
Knutson, B., Adams, C. M., Fong, G. W., & Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci, 21*(16), RC159.
Knutson, B., Bhanji, J. P., Cooney, R. E., Atlas, L. Y., & Gotlib, I. H. (2008). Neural responses to monetary incentives in major depression. *Biological psychiatry, 63*(7), 686-692.
Knutson, B., & Greer, S. M. (2008). Anticipatory affect: neural correlates and consequences for choice. *Philosophical Transactions of the Royal Society of London B: Biological Sciences, 363*(1511), 3771-3786.
Knutson, B., Westdorp, A., Kaiser, E., & Hommer, D. (2000). FMRI visualization of brain activity during a monetary incentive delay task. *Neuroimage, 12*(1), 20-27.
Kollins, S. H., English, J. S., Roley, M. E., O'Brien, B., Blair, J., Lane, S. D., & McClernon, F. J. (2013). Effects of smoking abstinence on smoking-reinforced responding, withdrawal, and cognition in adults with and without attention deficit hyperactivity disorder. *Psychopharmacology, 227*(1), 19-30.
Koob, G. F. (2013). Addiction is a reward deficit and stress surfeit disorder. *Frontiers in psychiatry, 4*.
Koob, G. F., & Le Moal, M. (1997). Drug abuse: hedonic homeostatic dysregulation. *Science, 278*(5335), 52-58.
Koob, G. F., & Le Moal, M. (2008). Neurobiological mechanisms for opponent motivational processes in addiction. *Philosophical Transactions of the Royal Society B: Biological Sciences, 363*(1507), 3113-3123.

Kringelbach, M. L., & Berridge, K. C. (2010). *Pleasures of the brain*: Oxford University Press.
Kringelbach, M. L., O'Doherty, J., Rolls, E. T., & Andrews, C. (2003). Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. *Cerebral cortex, 13*(10), 1064-1071.
Lader, D., & Goddard, E. (2004). Smoking-related behaviour and attitudes. *Office for National Statistics*.
Lane, S. D., Cherek, D. R., Pietras, C. J., & Steinberg, J. L. (2005). Performance of heavy marijuana-smoking adolescents on a laboratory measure of motivation. *Addictive behaviors, 30*(4), 815-828.
Le Foll, B., Goldberg, S. R., & Sokoloff, P. (2005). The dopamine D 3 receptor and drug dependence: effects on reward or beyond? *Neuropharmacology, 49*(4), 525-541.
Lemke, M. R., Brecht, H. M., Koester, J., & Reichmann, H. (2006). Effects of the dopamine agonist pramipexole on depression, anhedonia and motor functioning in Parkinson's disease. *Journal of the neurological sciences, 248*(1), 266-270.
Lepore, M., Vorel, S. R., Lowinson, J., & Gardner, E. L. (1995). Conditioned place preference induced by Δ 9-tetrahydrocannabinol: comparison with cocaine, morphine, and food reward. *Life sciences, 56*(23), 2073-2080.
Leroy, C., Karila, L., Martinot, J. L., Lukasiewicz, M., Duchesnay, E., Comtat, C., . . . Ribeiro, M. J. (2012). Striatal and extrastriatal dopamine transporter in cannabis and tobacco addiction: a high-resolution PET study. *Addiction biology, 17*(6), 981-990.
LeSage, M. G., Burroughs, D., & Pentel, P. R. (2006). Effects of nicotine withdrawal on performance under a progressive-ratio schedule of sucrose pellet delivery in rats. *Pharmacology Biochemistry and Behavior, 83*(4), 585-591.
Leshner, A. I. (1997). Addiction is a brain disease, and it matters. *Science, 278*(5335), 45-47.
Leventhal, A. M., Kahler, C. W., Ray, L. A., Stone, K., Young, D., Chelminski, I., & Zimmerman, M. (2008). Anhedonia and amotivation in psychiatric outpatients with fully remitted stimulant use disorder. *American Journal on Addictions, 17*(3), 218-223.
Leventhal, A. M., Munafò, M., Tidey, J. W., Sussman, S., Monterosso, J. R., Sun, P., & Kahler, C. W. (2012). Anhedonia predicts altered processing of happy faces in abstinent cigarette smokers. *Psychopharmacology, 222*(2), 343-351.
Leventhal, A. M., Piper, M. E., Japuntich, S. J., Baker, T. B., & Cook, J. W. (2014). Anhedonia, depressed mood, and smoking cessation outcome. *Journal of consulting and clinical psychology, 82*(1), 122.
Leventhal, A. M., Trujillo, M., Ameringer, K. J., Tidey, J. W., Sussman, S., & Kahler, C. W. (2014). Anhedonia and the relative reward value of drug and nondrug reinforcers in cigarette smokers. *Journal of abnormal psychology, 123*(2), 375.
Leventhal, A. M., Waters, A. J., Kahler, C. W., Ray, L. A., & Sussman, S. (2009). Relations between anhedonia and smoking motivation. *Nicotine & Tobacco Research*, ntp098.
Levin, E. D., McClernon, F. J., & Rezvani, A. H. (2006). Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. *Psychopharmacology, 184*(3-4), 523-539.
Leyton, M., Boileau, I., Benkelfat, C., Diksic, M., Baker, G., & Dagher, A. (2002). Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[11C] raclopride study in healthy men. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 27*(6), 1027-1035.
Liu, W.-h., Roiser, J. P., Wang, L.-z., Zhu, Y.-h., Huang, J., Neumann, D. L., . . . Chan, R. C. (2015). Anhedonia is associated with blunted reward sensitivity in first-degree relatives of patients with major depression. *Journal of affective disorders*.
Liverant, G. I., Sloan, D. M., Pizzagalli, D. A., Harte, C. B., Kamholz, B. W., Rosebrock, L. E., . . . Kaplan, G. B. (2014). Associations among smoking, anhedonia, and reward learning in depression. *Behavior therapy, 45*(5), 651-663.

Lopez-Quintero, C., de los Cobos, J. P., Hasin, D. S., Okuda, M., Wang, S., Grant, B. F., & Blanco, C. (2011). Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug and alcohol dependence, 115*(1), 120-130.

Lubman, D. I., Yücel, M., Kettle, J. W., 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.

Luo, S., Ainslie, G., Giragosian, L., & Monterosso, J. R. (2011). Striatal hyposensitivity to delayed rewards among cigarette smokers. *Drug and alcohol dependence, 116*(1), 18-23.

MacKillop, J., Murphy, J. G., Ray, L. A., Eisenberg, D. T., Lisman, S. A., Lum, J. K., & Wilson, D. S. (2008). Further validation of a cigarette purchase task for assessing the relative reinforcing efficacy of nicotine in college smokers. *Experimental and clinical psychopharmacology, 16*(1), 57.

MacKillop, J., O'Hagen, S., Lisman, S. A., Murphy, J. G., Ray, L. A., Tidey, J. W., . . . Monti, P. M. (2010). Behavioral economic analysis of cue-elicited craving for alcohol. *Addiction, 105*(9), 1599-1607.

MacPherson, L., Tull, M. T., Matusiewicz, A. K., Rodman, S., Strong, D. R., Kahler, C. W., . . . Lejuez, C. (2010). Randomized controlled trial of behavioral activation smoking cessation treatment for smokers with elevated depressive symptoms. *Journal of consulting and clinical psychology, 78*(1), 55.

Mahler, S. V., Smith, K. S., & Berridge, K. C. (2007). Endocannabinoid hedonic hotspot for sensory pleasure: anandamide in nucleus accumbens shell enhances 'liking'of a sweet reward. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 32*(11), 2267-2278.

Maj, J., Rogóż, Z., Skuza, G., & Kołodziejczyk, K. (1997). The behavioural effects of pramipexole, a novel dopamine receptor agonist. *European journal of pharmacology, 324*(1), 31-37.

Maldonado, R., Valverde, O., & Berrendero, F. (2006). Involvement of the endocannabinoid system in drug addiction. *Trends in neurosciences, 29*(4), 225-232.

Marin, R. S., Biedrzycki, R. C., & Firinciogullari, S. (1991). Reliability and validity of the Apathy Evaluation Scale. *Psychiatry research, 38*(2), 143-162.

Martin-Sölch, C., Magyar, S., Künig, G., Missimer, J., Schultz, W., & Leenders, K. (2001). Changes in brain activation associated with reward processing in smokers and nonsmokers. *Experimental Brain Research, 139*(3), 278-286.

Martin-Soelch, C., Missimer, J., Leenders, K., & Schultz, W. (2003). Neural activity related to the processing of increasing monetary reward in smokers and nonsmokers. *European journal of neuroscience, 18*(3), 680-688.

Martinez, D., Broft, A., Foltin, R. W., Slifstein, M., Hwang, D.-R., Huang, Y., . . . Kleber, H. D. (2004). Cocaine dependence and d2 receptor availability in the functional subdivisions of the striatum: relationship with cocaine-seeking behavior. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 29*(6), 1190-1202.

McCabe, C., Harwood, J., Brouwer, S., Harmer, C. J., & Cowen, P. J. (2013). Effects of pramipexole on the processing of rewarding and aversive taste stimuli. *Psychopharmacology, 228*(2), 283-290.

McCallum, S. E., Collins, A. C., Paylor, R., & Marks, M. J. (2006). Deletion of the beta 2 nicotinic acetylcholine receptor subunit alters development of tolerance to nicotine and eliminates receptor upregulation. *Psychopharmacology, 184*(3-4), 314-327.

McClernon, Kozink, R. V., Lutz, A. M., & Rose, J. E. (2009). 24-h smoking abstinence potentiates fMRI-BOLD activation to smoking cues in cerebral cortex and dorsal striatum. *Psychopharmacology, 204*(1), 25-35.

McClernon, Kozink, R. V., & Rose, J. E. (2008). Individual differences in nicotine dependence, withdrawal symptoms, and sex predict transient fMRI-BOLD responses to smoking cues.

Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 33(9), 2148-2157.
McGlothlin, W. H., & West, L. J. (1968). The marihuana problem: An overview. *American Journal of Psychiatry, 125*(3), 370-378.
Meier, M. H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R. S., . . . Moffitt, T. E. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences, 109*(40), E2657-E2664.
Mello, N. K., & Mendelson, J. H. (1985). Operant acquisition of marihuana by women. *Journal of Pharmacology and Experimental Therapeutics, 235*(1), 162-171.
Mendelson, J. H., Kuehnle, J. C., Greenberg, I., & Mello, N. K. (1976). Operant acquisition of marihuana in man. *Journal of Pharmacology and Experimental Therapeutics, 198*(1), 42-53.
Mendelson, J. H., & Mello, N. K. (1984). Reinforcing properties of oral Δ 9-tetrahydrocannabinol, smoked marijuana, and nabilone: Influence of previous marijuana use. *Psychopharmacology, 83*(4), 351-356.
Menon, V., & Levitin, D. J. (2005). The rewards of music listening: response and physiological connectivity of the mesolimbic system. *Neuroimage, 28*(1), 175-184.
Mierau, J., Schneider, F. J., Ensinger, H. A., Chio, C. L., Lajiness, M. E., & Huff, R. M. (1995). Pramipexole binding and activation of cloned and expressed dopamine D 2, D 3 and D 4 receptors. *European Journal of Pharmacology: Molecular Pharmacology, 290*(1), 29-36.
Miles, C. G., CONGREW, G., Gibbins, R., Marshman, J., Devenyi, P., & Hicks, R. (1974). An experimental study of the effects of daily cannabis smoking on behaviour patterns. *Acta pharmacologica et toxicologica, 34*(s1), 1-44.
Miller, G. A., & Chapman, J. P. (2001). Misunderstanding analysis of covariance. *Journal of abnormal psychology, 110*(1), 40.
Mogg, Field, M., & Bradley, B. P. (2005). Attentional and approach biases for smoking cues in smokers: an investigation of competing theoretical views of addiction. *Psychopharmacology, 180*(2), 333-341.
Mokrysz, C., Gage, S., Landy, R., Munafò, M., Roiser, J., & Curran, H. (2014). Neuropsychological and educational outcomes related to adolescent cannabis use, a prospective cohort study. *Eur Neuropsychopharmacol, 24*(2), S695.
Montgomery, A. J., Lingford-Hughes, A. R., Egerton, A., Nutt, D. J., & Grasby, P. M. (2007). The effect of nicotine on striatal dopamine release in man: a [11C] raclopride PET study. *SYNAPSE-NEW YORK-, 61*(8), 637.
Morean, M. E., de Wit, H., King, A. C., Sofuoglu, M., Rueger, S. Y., & O'Malley, S. S. (2013). The drug effects questionnaire: psychometric support across three drug types. *Psychopharmacology, 227*(1), 177-192.
Morgan, & Curran, H. V. (2008). Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *The British journal of psychiatry : the journal of mental science, 192*(4), 306-307. doi: 10.1192/bjp.bp.107.046649
Morgan, Das, R. K., Joye, A., Curran, H. V., & Kamboj, S. K. (2013). Cannabidiol reduces cigarette consumption in tobacco smokers: Preliminary findings. *Addictive behaviors, 38*(9), 2433-2436.
Morgan, Freeman, T. P., Schafer, G. L., & Curran, H. V. (2010). Cannabidiol attenuates the appetitive effects of Δ9-tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 35*(9), 1879-1885.
Morgan, Schafer, G., Freeman, T. P., & Curran, H. V. (2010). Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study. *The British Journal of Psychiatry, 197*(4), 285-290.

Morgan, C., Gardener, C., Schafer, G., Swan, S., Demarchi, C., Freeman, T., . . . Tan, N. (2012). Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being. *Psychological medicine, 42*(02), 391-400.

Morrison, P., Zois, V., McKeown, D., Lee, T., Holt, D., Powell, J., . . . Murray, R. (2009). The acute effects of synthetic intravenous Δ 9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. *Psychological medicine, 39*(10), 1607-1616.

Murphy, Hey, K., Johnstone, E., Munafo, M., Walton, R., Willis, B., & Harrison, P. (2002). Bromocriptine use is associated with decreased smoking rates. *Addiction biology, 7*(3), 325-328.

Murphy, MacKillop, J., Tidey, J. W., Brazil, L. A., & Colby, S. M. (2011). Validity of a demand curve measure of nicotine reinforcement with adolescent smokers. *Drug and alcohol dependence, 113*(2), 207-214.

Musty, R. E., & Kaback, L. (1995). Relationships between motivation and depression in chronic marijuana users. *Life sciences, 56*(23), 2151-2158.

Nestor, L., Hester, R., & Garavan, H. (2010). Increased ventral striatal BOLD activity during non-drug reward anticipation in cannabis users. *Neuroimage, 49*(1), 1133-1143.

Niv, Y., Daw, N. D., Joel, D., & Dayan, P. (2007). Tonic dopamine: opportunity costs and the control of response vigor. *Psychopharmacology, 191*(3), 507-520.

Nutt, D. J., Lingford-Hughes, A., Erritzoe, D., & Stokes, P. R. (2015). The dopamine theory of addiction: 40 years of highs and lows. *Nature Reviews Neuroscience, 16*(5), 305-312.

Ohno-Shosaku, T., Maejima, T., & Kano, M. (2001). Endogenous cannabinoids mediate retrograde signals from depolarized postsynaptic neurons to presynaptic terminals. *Neuron, 29*(3), 729-738.

Olds, J. (1962). Hypothalamic Substrates of Reward1.

Olds, J., & Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *Journal of comparative and physiological psychology, 47*(6), 419.

ONS. (2013). Adult Drinking Habits in Great Britain.

Palmatier, M. I., Liu, X., Matteson, G. L., Donny, E. C., Caggiula, A. R., & Sved, A. F. (2007). Conditioned reinforcement in rats established with self-administered nicotine and enhanced by noncontingent nicotine. *Psychopharmacology, 195*(2), 235-243.

Parkinson, J. A., Robbins, T. W., & Everitt, B. J. (2000). Dissociable roles of the central and basolateral amygdala in appetitive emotional learning. *European journal of neuroscience, 12*(1), 405-413.

Parsons, L. H., & Hurd, Y. L. (2015). Endocannabinoid signalling in reward and addiction. *Nature Reviews Neuroscience*.

Paterson, N. E., & Markou, A. (2004). Prolonged nicotine dependence associated with extended access to nicotine self-administration in rats. *Psychopharmacology, 173*(1-2), 64-72.

Patton, J. H., & Stanford, M. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of clinical psychology, 51*(6), 768-774.

Paule, M. G., Allen, R. R., Bailey, J. R., Scallet, A. C., Ali, S. F., Brown, R. M., & Slikker, W. (1992). Chronic marijuana smoke exposure in the rhesus monkey. II: Effects on progressive ratio and conditioned position responding. *Journal of Pharmacology and Experimental Therapeutics, 260*(1), 210-222.

Peciña, S., Smith, K. S., & Berridge, K. C. (2006). Hedonic hot spots in the brain. *The Neuroscientist, 12*(6), 500-511.

Peechatka, A. L., Whitton, A. E., Farmer, S. L., Pizzagalli, D. A., & Janes, A. C. (2015). Cigarette craving is associated with blunted reward processing in nicotine-dependent smokers. *Drug and alcohol dependence*.

Pergadia, M. L., Der-Avakian, A., D'Souza, M. S., Madden, P. A., Heath, A. C., Shiffman, S., . . . Pizzagalli, D. A. (2014). Association between nicotine withdrawal and reward responsiveness in humans and rats. *JAMA psychiatry, 71*(11), 1238-1245.

Perkins, K. A., Epstein, L. H., Grobe, J., & Fonte, C. (1994). Tobacco abstinence, smoking cues, and the reinforcing value of smoking. *Pharmacology Biochemistry and Behavior, 47*(1), 107-112.

Perkins, K. A., Grobe, J. E., Fonte, C., Goettler, J., Caggiula, A. R., Reynolds, W. A., . . . Jacob, R. G. (1994). Chronic and acute tolerance to subjective, behavioral and cardiovascular effects of nicotine in humans. *Journal of Pharmacology and Experimental Therapeutics, 270*(2), 628-638.

Perkins, K. A., Grottenthaler, A., & Wilson, A. S. (2009). Lack of reinforcement enhancing effects of nicotine in non-dependent smokers. *Psychopharmacology, 205*(4), 635-645.

Perkins, K. A., & Karelitz, J. L. (2013a). Influence of reinforcer magnitude and nicotine amount on smoking's acute reinforcement enhancing effects. *Drug and alcohol dependence, 133*(1), 167-171.

Perkins, K. A., & Karelitz, J. L. (2013b). Reinforcement enhancing effects of nicotine via smoking. *Psychopharmacology, 228*(3), 479-486.

Perkins, K. A., Karelitz, J. L., Jao, N. C., & Stratton, E. (2012). Possible reinforcement enhancing effects of bupropion during initial smoking abstinence. *Nicotine & Tobacco Research*, nts224.

Pertwee, R. (2008). The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. *British journal of pharmacology, 153*(2), 199-215.

Pessiglione, M., Seymour, B., Flandin, G., Dolan, R. J., & Frith, C. D. (2006). Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature, 442*(7106), 1042-1045.

Peters, J., Bromberg, U., Schneider, S., Brassen, S., Menz, M., Banaschewski, T., . . . Garavan, H. (2011). Lower ventral striatal activation during reward anticipation in adolescent smokers. *American Journal of Psychiatry, 168*(5), 540-549.

Petitet, F., Jeantaud, B., Reibaud, M., Imperato, A., & Dubroeucq, M.-C. (1998). Complex pharmacology of natural cannabivoids: Evidence for partial agonist activity of Δ 9-tetrahydrocannabinol and antagonist activity of cannabidiol on rat brain cannabinoid receptors. *Life sciences, 63*(1), PL1-PL6.

Pizzagalli, D. A., Evins, A. E., Schetter, E. C., Frank, M. J., Pajtas, P. E., Santesso, D. L., & Culhane, M. (2008). Single dose of a dopamine agonist impairs reinforcement learning in humans: behavioral evidence from a laboratory-based measure of reward responsiveness. *Psychopharmacology, 196*(2), 221-232.

Pizzagalli, D. A., Iosifescu, D., Hallett, L. A., Ratner, K. G., & Fava, M. (2008). Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *Journal of psychiatric research, 43*(1), 76-87.

Pizzagalli, D. A., Jahn, A. L., & O'Shea, J. P. (2005). Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. *Biological psychiatry, 57*(4), 319-327.

Pomerleau, C. S., & Pomerleau, O. F. (1992). Euphoriant effects of nicotine in smokers. *Psychopharmacology, 108*(4), 460-465.

Powell, J., Dawkins, L., & Davis, R. E. (2002). Smoking, reward responsiveness, and response inhibition: tests of an incentive motivational model. *Biological psychiatry, 51*(2), 151-163.

Powell, J., Dawkins, L., West, R., Powell, J., & Pickering, A. (2010). Relapse to smoking during unaided cessation: clinical, cognitive and motivational predictors. *Psychopharmacology, 212*(4), 537-549.

Public Health England. (2013). Substance misuse among young people in England 2012-13.

Rademacher, L., Krach, S., Kohls, G., Irmak, A., Gründer, G., & Spreckelmeyer, K. N. (2010). Dissociation of neural networks for anticipation and consumption of monetary and social rewards. *Neuroimage, 49*(4), 3276-3285.

Rawal, A., Collishaw, S., Thapar, A., & Rice, F. (2013). 'The risks of playing it safe': a prospective longitudinal study of response to reward in the adolescent offspring of depressed parents. *Psychological medicine, 43*(01), 27-38.

Redish, A. D. (2004). Addiction as a computational process gone awry. *Science, 306*(5703), 1944-1947.

Ren, Y., Whittard, J., Higuera-Matas, A., Morris, C. V., & Hurd, Y. L. (2009). Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. *The Journal of neuroscience, 29*(47), 14764-14769.

Riba, J., Krämer, U. M., Heldmann, M., Richter, S., & Münte, T. F. (2008). Dopamine agonist increases risk taking but blunts reward-related brain activity. *PloS one, 3*(6), e2479-e2479.

Risinger, F. O., & Oakes, R. A. (1995). Nicotine-induced conditioned place preference and conditioned place aversion in mice. *Pharmacology Biochemistry and Behavior, 51*(2), 457-461.

Robbins, T., & Everitt, B. (2007). A role for mesencephalic dopamine in activation: commentary on Berridge (2006). *Psychopharmacology, 191*(3), 433-437.

Roberts, D. C., & Koob, G. F. (1982). Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area in rats. *Pharmacology Biochemistry and Behavior, 17*(5), 901-904.

Robins, L. N. (1993). Vietnam veterans' rapid recovery from heroin addiction: a fluke or normal expectation? *Addiction, 88*(8), 1041-1054.

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain research reviews, 18*(3), 247-291.

Robinson, T. E., & Berridge, K. C. (2008). The incentive sensitization theory of addiction: some current issues. *Philosophical Transactions of the Royal Society B: Biological Sciences, 363*(1507), 3137-3146.

Roll, J. M., Higgins, S. T., & Badger, G. J. (1996). An experimental comparison of three different schedules of reinforcement of drug abstinence using cigarette smoking as an exemplar. *Journal of applied behavior analysis, 29*(4), 495.

Rose, E. J., Ross, T. J., Salmeron, B. J., Lee, M., Shakleya, D. M., Huestis, M. A., & Stein, E. A. (2013). Acute nicotine differentially impacts anticipatory valence-and magnitude-related striatal activity. *Biological psychiatry, 73*(3), 280-288.

Ryberg, E., Larsson, N., Sjögren, S., Hjorth, S., Hermansson, N. O., Leonova, J., . . . Greasley, P. (2007). The orphan receptor GPR55 is a novel cannabinoid receptor. *British journal of pharmacology, 152*(7), 1092-1101.

Salamone, J. D., & Correa, M. (2002). Motivational views of reinforcement: implications for understanding the behavioral functions of nucleus accumbens dopamine. *Behavioural brain research, 137*(1), 3-25.

Salamone, J. D., Correa, M., Farrar, A., & Mingote, S. M. (2007). Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. *Psychopharmacology, 191*(3), 461-482.

Salokangas, R. K., Vilkman, H., Ilonen, T., Taiminen, T., Haaparanta, M., Solin, O., . . . Hietala, J. (2000). High levels of dopamine activity in the basal ganglia of cigarette smokers. *American Journal of Psychiatry*.

Samuels, Hou, R., Langley, R., Szabadi, E., & Bradshaw, C. (2006). Comparison of pramipexole and amisulpride on alertness, autonomic and endocrine functions in healthy volunteers. *Psychopharmacology, 187*(4), 498-510.

Scheres, A., Milham, M. P., Knutson, B., & Castellanos, F. X. (2007). Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. *Biological psychiatry, 61*(5), 720-724.

Schott, B. H., Minuzzi, L., Krebs, R. M., Elmenhorst, D., Lang, M., Winz, O. H., . . . Zilles, K. (2008). Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. *The Journal of neuroscience, 28*(52), 14311-14319.

Schultz, W. (2002). Getting formal with dopamine and reward. *Neuron, 36*(2), 241-263.

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science, 275*(5306), 1593-1599.

Sebold, M., Deserno, L., Nebe, S., Schad, D. J., Garbusow, M., Hägele, C., . . . Smolka, M. (2014). Model-based and model-free decisions in alcohol dependence. *Neuropsychobiology, 70*(2), 122-131.

Sescousse, G., Caldú, X., Segura, B., & Dreher, J.-C. (2013). Processing of primary and secondary rewards: a quantitative meta-analysis and review of human functional neuroimaging studies. *Neuroscience & Biobehavioral Reviews, 37*(4), 681-696.

Sescousse, G., Li, Y., & Dreher, J.-C. (2014). A common currency for the computation of motivational values in the human striatum. *Social cognitive and affective neuroscience*, nsu074.

Sescousse, G., Redouté, J., & Dreher, J.-C. (2010). The architecture of reward value coding in the human orbitofrontal cortex. *The Journal of neuroscience, 30*(39), 13095-13104.

Sevy, S., Smith, G. S., Ma, Y., Dhawan, V., Chaly, T., Kingsley, P. B., . . . Eidelberg, D. (2008). Cerebral glucose metabolism and D2/D3 receptor availability in young adults with cannabis dependence measured with positron emission tomography. *Psychopharmacology, 197*(4), 549-556.

Shannon, K., Bennett, J., Friedman, J., & Group, P. S. (1997). Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. *Neurology, 49*(3), 724-728.

Sherdell, L., Waugh, C. E., & Gotlib, I. H. (2012). Anticipatory pleasure predicts motivation for reward in major depression. *Journal of abnormal psychology, 121*(1), 51.

Shiffman, S., & Kirchner, T. R. (2009). Cigarette-by-cigarette satisfaction during ad libitum smoking. *Journal of abnormal psychology, 118*(2), 348.

Shiffman, S., Paty, J. A., Gnys, M., Kassel, J. D., & Elash, C. (1995). Nicotine withdrawal in chippers and regular smokers: subjective and cognitive effects. *Health Psychology, 14*(4), 301.

Shoaib, M., Stolerman, I. P., & Kumar, R. C. (1994). Nicotine-induced place preferences following prior nicotine exposure in rats. *Psychopharmacology, 113*(3-4), 445-452.

Shoaib, M., Swanner, L., Beyer, C., Goldberg, S., & Schindler, C. (1998). The GABAB agonist baclofen modifies cocaine self-administration in rats. *Behavioural pharmacology*.

Skinner, B. F. (1938). The behavior of organisms: An experimental analysis.

Small, D. M., Jones-Gotman, M., & Dagher, A. (2003). Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. *Neuroimage, 19*(4), 1709-1715.

Snaith, R., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., & Trigwell, P. (1995). A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *The British Journal of Psychiatry, 167*(1), 99-103.

Snuggs, S., & Hajek, P. (2013). Responsiveness to reward following cessation of smoking. *Psychopharmacology, 225*(4), 869-873.

Sobell, L. C., & Sobell, M. B. (1992). Timeline follow-back *Measuring alcohol consumption* (pp. 41-72): Springer.

Solinas, M., Justinova, Z., Goldberg, S. R., & Tanda, G. (2006). Anandamide administration alone and after inhibition of fatty acid amide hydrolase (FAAH) increases dopamine levels in the nucleus accumbens shell in rats. *Journal of neurochemistry, 98*(2), 408-419.

Solomon, R. L., & Corbit, J. D. (1974). An opponent-process theory of motivation: I. Temporal dynamics of affect. *Psychological review, 81*(2), 119.

Solowij, N., & Battisti, R. (2008). The chronic effects of cannabis on memory in humans: a review. *Current drug abuse reviews, 1*(1), 81-98.
Spring, B., Pagoto, S., McChargue, D., Hedeker, D., & Werth, J. (2003). Altered reward value of carbohydrate snacks for female smokers withdrawn from nicotine. *Pharmacology Biochemistry and Behavior, 76*(2), 351-360.
Stewart, J., De Wit, H., & Eikelboom, R. (1984). Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychological review, 91*(2), 251.
Stokes, P. R., Egerton, A., Watson, B., Reid, A., Lappin, J., Howes, O. D., . . . Lingford-Hughes, A. R. (2012). History of cannabis use is not associated with alterations in striatal dopamine D2/D3 receptor availability. *Journal of psychopharmacology, 26*(1), 144-149.
Stokes, P. R., Mehta, M. A., Curran, H. V., Breen, G., & Grasby, P. M. (2009). Can recreational doses of THC produce significant dopamine release in the human striatum? *Neuroimage, 48*(1), 186-190.
Stolerman, & Jarvis, M. (1995). The scientific case that nicotine is addictive. *Psychopharmacology, 117*(1), 2-10.
Stolerman, I., Fink, R., & Jarvik, M. (1973). Acute and chronic tolerance to nicotine measured by activity in rats. *Psychopharmacologia, 30*(4), 329-342.
Sweitzer, M. M. (2013). *PROCESSING OF SMOKING AND MONETARY REWARDS AMONG CHRONIC SMOKERS: CHARACTERIZATION OF NEURAL RESPONSE, MODERATION BY ABSTINENCE, AND ASSOCIATION WITH SMOKING OUTCOMES.* University of Pittsburgh.
Sweitzer, M. M., Geier, C. F., Denlinger, R., Forbes, E. E., Raiff, B. R., Dallery, J., . . . Donny, E. C. (2015). Blunted striatal response to monetary reward anticipation during smoking abstinence predicts lapse during a contingency-managed quit attempt. *Psychopharmacology*, 1-10.
Sweitzer, M. M., Geier, C. F., Joel, D. L., McGurrin, P., Denlinger, R. L., Forbes, E. E., & Donny, E. C. (2013). Dissociated Effects of Anticipating Smoking versus Monetary Reward in the Caudate as a Function of Smoking Abstinence. *Biological psychiatry*.
Swift, W., Copeland, J., & Hall, W. (1998). Choosing a diagnostic cut-off for cannabis dependence. *Addiction, 93*(11), 1681-1692.
Szegedi, A., Hillert, A., Wetzel, H., Klieser, E., Gaebel, W., & Benkert, O. (1997). Pramipexole, a Dopamine Agonist, in Major Depression: Antidepressant Effects and Tolerability in an Open-Label Study with Multiple Doses. *Clinical neuropharmacology, 20*, S36-S45.
Takahashi, H., Fujimura, Y., Hayashi, M., Takano, H., Kato, M., Okubo, Y., . . . Suhara, T. (2008). Enhanced dopamine release by nicotine in cigarette smokers: a double-blind, randomized, placebo-controlled pilot study. *International Journal of Neuropsychopharmacology, 11*(3), 413-417.
Tanda, G., & Goldberg, S. R. (2003). Cannabinoids: reward, dependence, and underlying neurochemical mechanisms—a review of recent preclinical data. *Psychopharmacology, 169*(2), 115-134.
Treadway, M. T., Bossaller, N. A., Shelton, R. C., & Zald, D. H. (2012). Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. *Journal of abnormal psychology, 121*(3), 553.
Treadway, M. T., Buckholtz, J. W., Cowan, R. L., Woodward, N. D., Li, R., Ansari, M. S., . . . Zald, D. H. (2012). Dopaminergic mechanisms of individual differences in human effort-based decision-making. *The Journal of neuroscience, 32*(18), 6170-6176.
Treadway, M. T., Buckholtz, J. W., Schwartzman, A. N., Lambert, W. E., & Zald, D. H. (2009). Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. *PloS one, 4*(8), e6598.
Treadway, M. T., Peterman, J. S., Zald, D. H., & Park, S. (2015). Impaired effort allocation in patients with schizophrenia. *Schizophrenia research, 161*(2), 382-385.

Urban, N. B., Slifstein, M., Thompson, J. L., Xu, X., Girgis, R. R., Raheja, S., . . . Abi-Dargham, A. (2012). Dopamine release in chronic cannabis users: a [11 c] raclopride positron emission tomography study. *Biological psychiatry, 71*(8), 677-683.

van Hell, H. H., Vink, M., Ossewaarde, L., Jager, G., Kahn, R. S., & Ramsey, N. F. (2010). Chronic effects of cannabis use on the human reward system: an fMRI study. *European neuropsychopharmacology, 20*(3), 153-163.

Versace, F., Engelmann, J. M., Jackson, E. F., Costa, V. D., Robinson, J. D., Lam, C. Y., . . . Cinciripini, P. M. (2011). Do brain responses to emotional images and cigarette cues differ? An fMRI study in smokers. *European journal of neuroscience, 34*(12), 2054-2063.

Versace, F., Engelmann, J. M., Robinson, J. D., Jackson, E. F., Green, C. E., Lam, C. Y., . . . Wetter, D. W. (2014). Prequit FMRI responses to pleasant cues and cigarette-related cues predict smoking cessation outcome. *Nicotine & Tobacco Research, 16*(6), 697-708.

Versace, F., Lam, C. Y., Engelmann, J. M., Robinson, J. D., Minnix, J. A., Brown, V. L., & Cinciripini, P. M. (2012). Beyond cue reactivity: blunted brain responses to pleasant stimuli predict long-term smoking abstinence. *Addiction biology, 17*(6), 991-1000.

Vezina. (2004). Sensitization of midbrain dopamine neuron reactivity and the self-administration of psychomotor stimulant drugs. *Neuroscience & Biobehavioral Reviews, 27*(8), 827-839.

Vezina, McGehee, D., & Green, W. (2007). Exposure to nicotine and sensitization of nicotine-induced behaviors. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 31*(8), 1625-1638.

Volkow, N. D., Chang, L., Wang, G.-J., Fowler, J. S., Ding, Y.-S., Sedler, M., . . . Hitzemann, R. (2014). Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *American Journal of Psychiatry*.

Volkow, N. D., Fowler, J. S., Wang, G.-J., & Swanson, J. M. (2004). Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Molecular psychiatry, 9*(6), 557-569.

Volkow, N. D., Wang, G.-J., Fischman, M., Foltin, R., Fowler, J., Abumrad, N., . . . Pappas, N. (1997). Relationship between subjective effects of cocaine and dopamine transporter occupancy.

Volkow, N. D., Wang, G. J., Fowler, J. S., Logan, J., Hitzemann, R., Ding, Y. S., . . . Piscani, K. (1996). Decreases in dopamine receptors but not in dopamine transporters in alcoholics. *Alcoholism: Clinical and Experimental Research, 20*(9), 1594-1598.

Vrieze, E., Pizzagalli, D. A., Demyttenaere, K., Hompes, T., Sienaert, P., de Boer, P., . . . Claes, S. (2013). Reduced reward learning predicts outcome in major depressive disorder. *Biological psychiatry, 73*(7), 639-645.

Wang, G.-J., Volkow, N. D., Fowler, J. S., Logan, J., Abumrad, N. N., Hitzemann, R. J., . . . Pascani, K. (1997). Dopamine D 2 receptor availability in opiate-dependent subjects before and after naloxone-precipitated withdrawal. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 16*(2), 174-182.

Wardle, M. C., Treadway, M. T., Mayo, L. M., Zald, D. H., & de Wit, H. (2011). Amping up effort: effects of d-amphetamine on human effort-based decision-making. *The Journal of neuroscience, 31*(46), 16597-16602.

Waters, A. J., Shiffman, S., Sayette, M. A., Paty, J. A., Gwaltney, C. J., & Balabanis, M. H. (2003). Attentional bias predicts outcome in smoking cessation. *Health Psychology, 22*(4), 378.

Weinberger, A. H., Reutenauer, E. L., Jatlow, P. I., O'Malley, S. S., Potenza, M. N., & George, T. P. (2010). A double-blind, placebo-controlled, randomized clinical trial of oral selegiline hydrochloride for smoking cessation in nicotine-dependent cigarette smokers. *Drug and alcohol dependence, 107*(2), 188-195.

West, & Brown, J. (2013). *Theory of addiction*: John Wiley & Sons.

West, & Hajek, P. (2004). Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. *Psychopharmacology, 177*(1-2), 195-199.

West, McEwen, A., Bolling, K., & Owen, L. (2001). Smoking cessation and smoking patterns in the general population: a 1-year follow-up. *Addiction, 96*(6), 891-902.
West, & Owen, L. (2012). Estimates of 52-week continuous abstinence rates following selected smoking cessation interventions in England.
Wikler, A. (1973). Dynamics of drug dependence: Implications of a conditioning theory for research and treatment. *Archives of general psychiatry, 28*(5), 611-616.
Wilson, S. J., Delgado, M. R., McKee, S. A., Grigson, P. S., MacLean, R. R., Nichols, T. T., & Henry, S. L. (2014). Weak ventral striatal responses to monetary outcomes predict an unwillingness to resist cigarette smoking. *Cognitive, Affective, & Behavioral Neuroscience, 14*, 1196-1207.
Wise, R. A. (1980). The dopamine synapse and the notion of 'pleasure centers' in the brain. *Trends in neurosciences, 3*(4), 91-95.
Wise, R. A., & Rompré, P.-P. (1989). Brain dopamine and reward. *Annual review of psychology, 40*(1), 191-225.
Woolverton, W. L., & Virus, R. M. (1989). The effects of a D 1 and a D 2 dopamine antagonist on behavior maintained by cocaine or food. *Pharmacology Biochemistry and Behavior, 32*(3), 691-697.
Wrase, J., Schlagenhauf, F., Kienast, T., Wüstenberg, T., Bermpohl, F., Kahnt, T., . . . Knutson, B. (2007). Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. *Neuroimage, 35*(2), 787-794.
Wright, C. E., Sisson, T. L., Ichhpurani, A. K., & Peters, G. R. (1997). Steady-State Pharmacokinetic Properties of Pramipexole in Healthy Volunteers. *The Journal of Clinical Pharmacology, 37*(6), 520-525.
Yang, Y. K., Yao, W. J., McEvoy, J. P., Chu, C. L., Lee, I. H., Chen, P. S., . . . Chiu, N. T. (2006). Striatal dopamine D 2/D 3 receptor availability in male smokers. *Psychiatry Research: Neuroimaging, 146*(1), 87-90.
Yang, Y. K., Yao, W. J., Yeh, T. L., Lee, I. H., Chen, P. S., Lu, R. B., & Chiu, N. T. (2008). Decreased dopamine transporter availability in male smokers—a dual isotope SPECT study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 32*(1), 274-279.
Ye, Z., Hammer, A., Camara, E., & Münte, T. F. (2011). Pramipexole modulates the neural network of reward anticipation. *Human brain mapping, 32*(5), 800-811.
Yoon, J. H., Higgins, S. T., Heil, S. H., Sugarbaker, R. J., Thomas, C. S., & Badger, G. J. (2007). Delay discounting predicts postpartum relapse to cigarette smoking among pregnant women. *Experimental and clinical psychopharmacology, 15*(2), 176.
Zarate, C. A., Payne, J. L., Singh, J., Quiroz, J. A., Luckenbaugh, D. A., Denicoff, K. D., . . . Manji, H. K. (2004). Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biological psychiatry, 56*(1), 54-60.
Zhou, X., Nonnemaker, J., Sherrill, B., Gilsenan, A. W., Coste, F., & West, R. (2009). Attempts to quit smoking and relapse: factors associated with success or failure from the ATTEMPT cohort study. *Addictive behaviors, 34*(4), 365-373.

Appendices

Appendix 1: Appendix table 3.1

Whole brain analysis: Peak and cluster-level BOLD responses for 'cigarette > neutral anticipate' contrast using a one-sample t-test with both groups included (MNI co-ordinates, t and FWE-corrected p values are shown).

Region	x	y	z	Peak-level		Cluster-level	
Dependent and occasional smokers together				**t**	**p (FWE corrected)**	**cluster size**	**p (FWE corrected)**
Right thalamus	12	-10	5	5.943738	0.015651	3	0.004824
Right thalamus ii	9	-19	5	5.628245	0.039903	3	0.004824
Right extrastriate cortex	30	-85	-10	7.078569	0.000443	3	0.004824
Left putamen	-27	11	5	5.545213	0.049439	1	0.016347
Left thalamus i	-12	-16	2	6.166336	0.007749	1	0.016347
Left thalamus ii	-12	-16	8	5.628245	0.039903	3	0.004824
Left insula	-30	26	-4	5.611048	0.04172	1	0.016347
Left inferior frontal gyrus	-30	17	14	5.591904	0.043837	1	0.016347

Appendix 2: Appendix table 3.2

Whole brain analysis: Peak and cluster-level BOLD responses for 'cigarette > music anticipate' contrast for the dependent group using a one-sample t-test (MNI co-ordinates, t and FWE-corrected p values are shown). The occasional group showed no significant activations for this contrast.

Region	x	y	z	Peak-level		Cluster-level	
Dependent smokers				**t**	**p (FWE corrected)**	**cluster size**	**p (FWE corrected)**
Right caudate	27	20	5	7.248217	0.012281	3	0.002951

Appendix 3: Appendix table 3.3

Whole brain analysis: Peak and cluster-level BOLD responses for 'cigarette > neutral feedback' contrast using a one-sample t-test with both groups included (MNI co-ordinates, t and FWE-corrected p values are shown).

Region	x	y	z	Peak-level		Cluster-level	
Dependent and occasional smokers together				**t**	**p (FWE corrected)**	**cluster size**	**p (FWE corrected)**
Left cerebellum	-45	-61	-25	5.641772	0.036016	1	0.017406

Appendix 4: Ethical approval letter (study reported in chapter 2)

UCL RESEARCH ETHICS COMMITTEE
GRADUATE SCHOOL OFFICE

Professor Valerie Curran
Division of Psychology and Language Sciences
UCL

18 June 2013

Dear Professor Curran

Notification of Ethical Approval
Project ID: 4810/001: Investigating the reward processing in cigarette smokers

I am pleased to confirm that your study has been approved by the UCL Research Ethics Committee for the duration of the project i.e. until July 2016.

Approval is subject to the following conditions:

1. You must seek Chair's approval for proposed amendments to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the 'Amendment Approval Request Form'.

The form identified above can be accessed by logging on to the ethics website homepage: http://www.grad.ucl.ac.uk/ethics/ and clicking on the button marked 'Key Responsibilities of the Researcher Following Approval'.

2. It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. Both non-serious and serious adverse events must be reported.

   Reporting Non-Serious Adverse Events
   For non-serious adverse events you will need to inform Helen Dougal, Ethics Committee Administrator (ethics@ucl.ac.uk), within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair of the Ethics Committee will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

   Reporting Serious Adverse Events
   The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information leaflet and/or study protocol.

On completion of the research you must submit a brief report (a maximum of two sides of A4) of your findings/concluding comments to the Committee, which includes in particular issues relating to the ethical implications of the research.

With best wishes for the research.

Yours sincerely

Professor John Foreman
Chair of the UCL Research Ethics Committee

Cc:
Will Lawn, Applicant
Professor Peter Fonagy, Head of Department

UCL Research Ethics Committee, c/o The Graduate School, North Cloisters, Wilkins Building
University College London Gower Street London WC1E 6BT
Tel: +44 (0)20 7679 7844 Fax: +44 (0)20 7679 7043
ethics@ucl.ac.uk
www.ucl.ac.uk/gradschool

Appendix 5: Information sheet (study reported in chapter)

VOLUNTEER INFORMATION SHEET

Title of project: Investigating reward processing in cigarette smokers.

Investigators: Will Lawn, Dr. Tom Freeman, Dr. Celia Morgan, Prof. H.Valerie Curran.

Contact:
Will Lawn, Clinical Psychopharmacology Unit, UCL, Gower Street, London WC1E 6BT.
[redacted]

INFORMATION LEAFLET FOR VOLUNTEERS

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

WHAT IS THE PURPOSE OF THE STUDY AND WHAT WILL BE STUDIED?

We are interested to find out how nicotine dependence and abstinence affect the processing of cigarette and natural rewards (music, chocolate). In this study we will be comparing groups of individuals who are nicotine dependent with occasional smokers, while you are smoking normally and when you are abstinent for 12 hours before the experiment. You will choose to receive one reward over another (e.g. do you want to win points that give you cigarettes or points that give you chocolate). At the end of the task you will 'consume' the rewards that you win, e.g. eating the chocolate, smoking the cigarettes, listening to the music.

BACKGROUND AND BENEFITS OF THE RESEARCH

This study will investigate reward processing in smokers when they have smoked and when they are abstinent; it will help determine how abstinence affects processing of cigarette rewards and natural rewards.

These findings could play a role in determining what maintains nicotine addiction and, in the future, which therapies are good at improving natural reward processing while reducing cigarette reward processing.

WHO CAN TAKE PART IN THE STUDY?

We are inviting cigarette smokers who do not use smoking cessation aids, are not seeking psychological or pharmacological therapy for a mental health problem, speak fluent English, and enjoy eating chocolate, to take part in this study.

HOW WOULD I BE INVOLVED IF I AGREED TO TAKE PART?

If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

If you agree to take part, the experimenter will ask you some brief demographic questions and you will be asked to complete a 30 minute computer task and a few short questionnaires. Subsequently you will have a 25 minute stage where you can smoke some cigarettes, eat chocolates, and listen to music. Altogether this will last for approximately 90 minutes.

You will do the experiment twice, once after you have smoked normally and once after you have been nicotine abstinent for 12 hours. The experimental days will be between 4 and 10 days apart (though usually 7 days apart). The experiment will take place in the Clinical Psychopharmacology Unit labs. You will be paid £7.50 per hour for taking part and you will be paid after the second session. You also have the opportunity to enjoy the other rewards (cigarettes, chocolate, music) you win, but you may not take them home.

WHAT DO I DO IF I WANT TO TAKE PART?

If you want to find out if you are eligible to take part in the study then email or ring Will Lawn [redacted]

You should know that if you do decide to take part, but then decide you do not wish to continue, you can withdraw from the study at any point without giving a reason.

CONFIDENTIALITY

Any information collected about you will be held in accordance with the 1998 Data Protection Act. All the information that is collected about you during the course of the research will be kept strictly confidential. Your results will have your name and any other details about you removed first so that you cannot be recognized from them.

If you require further information please ask Will Lawn

Thank you for reading this leaflet and we hope that you will be able to take part in the study.

You do not have to take part in the study if you do not want to. If you decide to take part, you may withdraw at any time without having to give a reason

Appendix 6: Ethical approval (study reported in chapter 3)

Your application for ethical approval (2014/582) has been conditionally accepted

apache@exeter.ac.uk on behalf of Ethics Approval System [D.M.Salway@exeter.ac.uk]

Actions

To:
Lawn, William
Inbox

Thursday, April 24, 2014 3:10 PM

Ethical Approval system

Your application (2014/582) entitled Reward processing and valuation of cigarette and non-drug rewards in dependent and occasional smokers: an fMRI study has been conditionally accepted

Please visit http://www.exeter.ac.uk/staff/ethicalapproval/

Please click on the link above and select the relevant application from the list. The conditions are as follows:

This application is approved with the following condition:A breach of confidentiality may be necessary if an abnormality is detected during the MRI procedure and so this must be accommodated within the briefing documentation/procedure.Participants' GP details must be collected at the briefing stage, along with participants' permission to contact their GP under the circumstances described above.Please confirm that the above condition will be adhered to by emailing the PREC Chair (C.N.W.Burgess@ex.ac.uk) before commencing data collection.

Appendix 7: Information sheet (study reported in chapter 3)

Reward processing and valuation of cigarette and non-drug rewards in dependent and occasional smokers: an fMRI study

Purpose of Study

The purpose of this study is to investigate the neural correlates of cigarette smokers when they anticipate, receive feedback, make valuations and respond for cigarettes and non-drug rewards (vouchers, music and chocolate). It aims to improve our understanding of what happens when people get addicted to nicotine and how this influences the way people interact with cigarettes and other motivationally relevant rewards. This work is beneficial because it could improve treatments for those trying to quit smoking, especially those treatments involving alternative rewards.

Procedures

If you agree to take part, the experimenter will ask you some brief demographic questions and you will be asked to complete some computer tasks inside and outside of the functional magnetic resonance imaging (fMRI) scanner. In the tasks you will do various things: i) state how much various cigarettes and vouchers are worth to you ii) press a button quickly to win cigarettes and music iii) choose between winning cigarettes and chocolate. If you like, you are given the opportunity to smoke some of the cigarettes and listen to the music after the tasks. You may take some of the cigarettes, the chocolate and the vouchers home with you. The whole study will last for approximately 90 minutes. You will spend approximately 40 minutes in the fMRI scanner. We may also ask some questions about your cigarette smoking up to 6 months after the experiment.

It is important to note that you can withdraw from the experiment at any time without giving a reason and you will be paid for your time.

All data will be stored anonymously using password-encrypted computer files or questionnaires stored in locked drawers. Your name will never be associated with your results.

You will also be asked to provide your GP details in the unlikely scenario that your GP needs to contacted concerning the results from your MRI scan. Anonymity of your MRI results will have to be broken in this unlikely scenario.

Remuneration

You will receive £7.50 per hour for your participation and will also have the opportunity to win vouchers, chocolate, music and cigarettes, which you can choose to keep if you like.

Potential Risks and Ethical Consideration

fMRI scanning is totally harmless as long as you meet various criteria, e.g. not having any metal inside your body, not having a pacemaker, not having a hearing-aid. You will be carefully screened beforehand to make sure you can go in the scanner so it is safe. Some people can get anxious inside the scanner because you will be lying in a small space. There is an emergency button to press if you become anxious and we can stop the experiment at any moment for you to get out.

You will be able to win cigarettes in this study. As you will know, smoking is very bad for your health.

Appendix 8: Ethics amendment approval – ethical approval for a similar, previous study had already been granted (study reported in chapter 4)

amounts of money that can be won in these tasks so this will unlikely 'pressure' participants to take part. We believe these other tasks do not raise any extra ethical considerations.

6) Experimenters will have to place electrodes on the participant's hand prior to recording their galvanic skin response. This is now listed in the information sheet.

7) No extra ethical considerations.

8) No extra ethical considerations.

References:

Bühler, M., Vollstädt-Klein, S., Kobiella, A., Budde, H., Reed, L. J., Braus, D. F., ... & Smolka, M. N. (2010). Nicotine dependence is characterized by disordered reward processing in a network driving motivation. Biological psychiatry, 67(8), 745-752.
Sweitzer, M. M., Geier, C. F., Joel, D. L., McGurrin, P., Denlinger, R. L., Forbes, E. E., & Donny, E. C. (2013). Dissociated Effects of Anticipating Smoking versus Monetary Reward in the Caudate as a Function of Smoking Abstinence. Biological psychiatry.
Audrain-McGovern, J., Paul Wileyto, E., Ashare, R., Cuevas, J., & Strasser, A. A. (2014). Reward and Affective Regulation in Depression-Prone Smokers. Biological Psychiatry.

7 **Other Information** (provide any other information which you believe should be taken into account during ethical review of the proposed changes)
I have included the updated information sheet

Declaration (to be signed by the Principal Researcher)

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendments to be implemented.
- For student projects I confirm that my supervisor has approved my proposed modifications.

[redacted]

Date: 02/10/14

FOR OFFICE USE ONLY:

Amendments to the proposed protocol have been approved by the Research Ethics Committee.

Signature of the REC Chair, Professor John Foreman: [redacted]

Date: 10/10/2014.

Appendix 9: Information sheet (study reported in chapter 4)

Information Sheet for Participants in Research Studies

You will be given a copy of this information sheet.

Title of Project: **The role of dopamine in cognitive and subjective effects of short term tobacco abstinence**

Name Will Lawn

Work Address Clinical Psychopharmacology Unit

Research Department of CEH Psychology

University College London

1-19 Torrington Place

WC1E 7HB

Contact Details [redacted]

We would like to invite Smokers aged 18-50 to participate in this research project.

Details of Study: We would like to invite you to participate in this research project. You should only participate if you want to. Before you decide whether you want to take part, it is important for you to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or you would like more information. This study is being conducted by researchers from the Clinical Psychopharmacology Unit.

Why are we doing this study?

Smoking is the leading cause of preventable death worldwide. Many smokers want to stop but a year after they try, only 5% are successful. Many relapses occur in the first few days after a target quit date. Previous research suggests that activity of a brain chemical called dopamine plays an important role in the symptoms experienced when smokers deprive themselves of cigarettes. We wish to test a specific idea about how

dopamine regulates your motivation to receive different types of reward. To do this, the study uses a single dose of one widely prescribed medication which alters dopamine activity. By taking part you will contribute to the scientific knowledge of tobacco addiction, an area that is vital to public health. If you would like to receive a brief report of the findings of this study when it is completed, please ask the investigator. Please note that this is **not** a smoking cessation study and we will not be investigating changes in, or aiming to influence your *general* smoking behaviour.

What will I have to do?

If you agree to participate in this study you will be asked to come to the Clinical Psychopharmacology Unit, at a time convenient for you. We will then assess your recent smoking behaviour by asking you to breathe through a smoke-analyser. After going through a medical checklist you will be given 2 pills to swallow. One will be either pramipexole or placebo. In order for the experiment to be 'blind', you will not know which drug you have taken. When pramipexole is administered at higher doses it can cause nausea or sickness to occur. Based on previous research in humans this is unlikely to occur. However as a precaution you will swallow an additional pill (domperidone) that prevents nausea and sickness. You will do the experiment twice, once taking pramipexole + domperidone and once taking placebo + domperidone. You will first fill in some questionnaires about your smoking behaviour and mood, and will wait for around 1.5 hours before testing resumes. You will rate your desire to smoke and your mood, complete a number of pen and paper questionnaires, computer **and eye tracking tasks**. One of these tasks will allow you to win cigarettes, music and chocolate. During this task you will have your visual attention and pupil dilation measured. You will then be able to consume the rewards you won in a 25 minute stage after the tasks are over. In addition, some of these tasks will enable you to win extra money (around £4 extra each session) that you will be paid at the end of the experiment. One of the questionnaires asks about your previous illicit drug use. The whole experiment should take about 3.5 hours.

Will I be paid?

You will be paid £7.50 per hour for taking part and you can win around £4 each session from some of the tasks. Each session (there are two sessions) will last approximately 3.5 hours. Therefore you will earn approximately £53 over both sessions plus any money you win from the tasks. You will be paid after the second session.

What are these drugs and are they safe?

Pramipexole is a widely used drug in Parkinson's disease. Clinically, this drug is given at a dose of 1-6 mg per day. When this drug is administered repeatedly at these doses, side effects can occur including nausea, dizziness, and lowered blood pressure. However, you will receive only a single dose of 0.5 mg in order to avoid the occurrence of side effects. If you have a known hypersensitivity to the drug, are breastfeeding, or have decreased kidney function you should **not** participate in this experiment.

Domperidone is a widely used drug used to treat sickness, nausea and stomach upsets in healthy adults and children. The standard dose for treating sickness and nausea in adults is 40mg 3 to 4 times daily. You will be given a single, lower dose of 30mg in order to prevent any sickness or nausea caused by pramixpexole. Adverse effects from taking this drug are highly unlikely, but include lowered sex drive in men, diarrhoea, rash and abnormal body movements. If you have a known hypersensitivity to the drug, are breastfeeding, or have decreased kidney or liver function you should **not** participate in this experiment.

Due to the possibility for drowsiness in response to pramipexole, you should **not** drive or operate machinery on the day of testing once the study has been completed.

How will my data be stored?

All information which is collected about you during the course of the research will be kept strictly confidential and will be securely stored electronically, using a numbered code so that you cannot be identified. Only researchers directly involved in the study will have access to the data. All data will be stored in accordance with the Data Protection Act 1998. The data will be used only for informing the research question in this study and the results of the research will be disseminated in peer-reviewed scientific journals, but you will in no way be identifiable from such publications.

Note – if you have any further questions regarding this study please do not hesitate to contact the researcher above.

This study has been approved by the UCL ethics committee

It is up to you to decide whether or not to take part. If you choose not to participate it will involve no penalty or loss of benefits to which you are otherwise entitled. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

All data will be collected and stored in accordance with the Data Protection Act 1998.

All data will be collected and stored in accordance with the Data Protection Act 1998.

Appendix 10: Ethical approval (study 1 reported in chapter 5)

UCL RESEARCH ETHICS COMMITTEE
GRADUATE SCHOOL OFFICE

Professor Valerie Curran
Research Department of Clinical, Educational and Health Psychology
UCL

12 November 2013

Dear Professor Curran

Notification of Ethical Approval
Project ID: 3325/002: How do different types of cannabis affect users' memory, well-being and experiences of the drug?

Further to receipt of the confirmation from the MHRA that your study is not a CTIMP, I am pleased to confirm that your project has been granted ethical approval by the UCL Research Ethics Committee for the duration of the study i.e. **until September 2016.**

Approval is subject to the following conditions:

1. You must seek Chair's approval for proposed amendments to the study for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the 'Amendment Approval Request Form'.

The form identified above can be accessed by logging on to the ethics website homepage: http://www.grad.ucl.ac.uk/ethics/ and clicking on the button marked 'Key Responsibilities of the Researcher Following Approval'.

2. It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. Both non-serious and serious adverse events must be reported.

   Reporting Non-Serious Adverse Events
   For non-serious adverse events you will need to inform Helen Dougal, Ethics Committee Administrator (ethics@ucl.ac.uk), within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair of the Ethics Committee will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

   Reporting Serious Adverse Events
   The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information leaflet and/or study protocol.

Appendix 11: Information sheet (study 1 reported in chapter 5)

CLINICAL PSYCHOPHARMACOLOGY UNIT
CLINICAL PSYCHOLOGY

VOLUNTEER INFORMATION SHEET
Version 4: 01/05/14

How do different types of cannabis affect users' memory, well-being and experiences of the drug?

What is this study?

You are being invited to participate in a research study. This study aims to increase our understanding of why some types of cannabis may have different effects on the brain, psychological wellbeing and memory.

This study is being conducted by researchers from the Clinical Psychopharmacology Unit at University College London. Before we describe the study and its purpose we would like to make it clear that this is a completely voluntary study and that you will be free to pull out at any time.

Why are we doing this study?

Cannabis contains about 80 chemicals which are unique to the plant and are called 'cannabinoids'. The two most abundant cannabinoids in cannabis are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). High levels of THC are found in strains of cannabis such as 'skunk', which is now the most common type of cannabis available in the UK. Our recent research has found that different types of cannabis may have different effects on people's experience of the drug.

The present study is a controlled laboratory study of the above-mentioned cannabinoids. It aims to investigate how different types of cannabis affect users' brain function, memory, well-being and experiences of the drug.

Who can participate in this study?

We are inviting people aged 18-70 who have used cannabis voluntarily at least twice before without adverse consequences. You must be able to inhale a substance as that is how treatment is being administered. All volunteers should be healthy and not receiving treatment for any mental health problem. Volunteers must also have good spoken English and basic literacy skills, as well as good vision, no colour blindness and no history of psychosis either personally or in their immediate family (i.e. mother, father, siblings). If you are pregnant or are at risk of becoming pregnant you will not be able to take part. If you are afraid of small closed spaces or loud noises you may not be suitable for this study.

What is involved?

The study will involve four sessions. The first of these will be a baseline session (45-60 minutes) in which you will practice some of the tasks and fill out some questionnaires. Next, you will be asked to come for three separate testing days, at least 7 days apart. All volunteers must agree to not use any recreational drug (including cannabis) or alcohol for 24 hours prior to each test day, which will be tested with a urine sample. You will be sent a text message to remind you of this. Females will also be tested for pregnancy from a urine sample on each test day. If your test results suggest that you have used recreational drugs in the last 24 hours, or that you are might be pregnant, you will not be permitted to take part.

On each test day you will be asked to fill out questionnaires about your mood and mental state. You will then be asked to inhale one of 3 treatments via a balloon-like device. The 3 treatments are medical cannabis containing THC, medical cannabis containing THC+CBD, and placebo (cannabis with the active ingredients removed). You will receive two treatments on each of the 3 days. First you will be given a 133.3mg dose of cannabis/placebo, and 90 minutes later you

will be given a second dose of 66.7mg. You will be asked to fill out some further questionnaires about your mood and mental state and do some computer tasks. Some of the tasks will be given to you while you are in an fMRI scanner. On each test day we will collect blood pressure, heart rate, and samples of saliva and urine. These samples will be labelled anonymously and stored securely at -80°C. They will be sent for analysis as soon as possible. After analysis (for levels THC and CBD) all samples will be destroyed.

Each test day will last for about four hours. Most people find the tests quite straightforward and fun to do. Neither you nor the researcher will know on which day you will receive each treatment. You should not drive or operate machinery after each of the test days.

If you agree to take part you will also be asked whether you are happy to be contacted about participation in future related studies. Your participation in the present study will not be affected should you choose to be re-contacted or not.

What are the risks of taking part in this study?

As participants are all experienced cannabis users, no risks are envisaged from the administration of either type of medical cannabis because the THC and/or CBD content will be in similar or lower quantities than those commonly found in street cannabis. You will be familiar with its effects, which include 'stoned' feelings, anxiety, psychosis like effects, increased appetite, drowsiness, euphoria, and increased heart rate.

There are no known effects from exposure to magnetic fields (MRI). However, because MRI involves being placed in a strong magnetic field, there are times when it is not safe to be scanned. For example, in the first three months of pregnancy, or when there are surgical clips inside the brain, or if you have a heart pacemaker fitted. We have a safety questionnaire that you will fill in on the interview / screening day for the study, so that we can be sure that it is completely safe for you to be scanned. In case you have any questions, we will be happy to discuss this with you. We will also check that you are safe to be scanned on the day you come for the scan.

Some individuals undergoing fMRI become anxious being in a confined space, and some people do not like the sound of the scanner when it is in operation. If these reactions happen to you at any time during the procedure, the experiment will be stopped as soon as you tell us that you are uncomfortable.

We will be taking pictures of your brain, and occasionally we will have unexpected findings that none of us suspected. The pictures are reviewed by experienced doctors, called neuroradiologists who specialise in looking at pictures of brain and spine. If there are any unexpected findings that need further tests, he/she will write to your GP in the first instance. The GP will then contact you if further tests are required. This is why your GP details are required in the safety check form.

A doctor will be available for medical cover on the test days.

What are the benefits to me?

You will leave with the knowledge that you have contributed to our understanding of the effects of cannabis and further progress in medical and psychological research. In addition, you will be given a one page summary of results when the study has finished and an information leaflet containing advice for stopping cannabis use.

Will I receive compensation for giving my time?

You will be given a small honorarium of £10 per hour (maximum £130) to compensate you for your time. You will also be given the opportunity to win additional money (maximum £4 extra per testing session).

How will my data be kept?

Your data from this study will be stored electronically using a numbered code so that you cannot be personally identified. Only researchers directly involved in the study have access to the data. All data will be collected and stored in accordance with the Data Protection Act (1998).

Who can I contact for further information?

If you have any further questions please contact:

Dr Rebecca Pope [redacted]

Prof Val Curran [redacted]

It is up to you to decide whether to take part or not; choosing not to take part will not disadvantage you in any way. If you do decide to take part you are still free to withdraw at any time and without giving a reason.

All research projects are reviewed by an ethics committee. This proposal was reviewed and approved by the UCL Research Ethics Committee.

Please discuss the information above with others if you wish or ask us if there is anything that is not clear or if you would like more information.

Appendix 12: Ethical approval (study 2 reported in chapter 5)

UCL RESEARCH ETHICS COMMITTEE
GRADUATE SCHOOL OFFICE

Professor Valerie Curran
Clinical and Educational Health Psychology
UCL

28th March 2014

Dear Professor Curran

Notification of Ethical Approval
Project ID: 5402/001: Investigating the determinants and psychological consequences of high-potency cannabis and ketamine use

In my capacity as Chair of the UCL Research Ethics Committee (REC) I am pleased to confirm that your study has been approved by the UCL REC for the duration of the project i.e. until June 2018.

Approval is subject to the following conditions:

1. You must seek Chair's approval for proposed amendments to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the 'Amendment Approval Request Form'.

The form identified above can be accessed by logging on to the ethics website homepage: http://www.grad.ucl.ac.uk/ethics/ and clicking on the button marked 'Key Responsibilities of the Researcher Following Approval'.

2. It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. Both non-serious and serious adverse events must be reported.

   Reporting Non-Serious Adverse Events
   For non-serious adverse events you will need to inform Helen Dougal, Ethics Committee Administrator (ethics@ucl.ac.uk), within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair of the Ethics Committee will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

   Reporting Serious Adverse Events
   The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information leaflet and/or study protocol.

On completion of the research you must submit a brief report (a maximum of two sides of A4) of your findings/concluding comments to the Committee, which includes in particular issues relating to the ethical implications of the research.
With best wishes for your research.

Yours sincerely

[redacted]

Professor John Foreman
Chair of the UCL Research Ethics Committee

Cc:
Lisa Harvey & Alyssa Joye, Applicants
Professor Peter Fonagy, Head of Department

UCL Research Ethics Committee, c/o The Graduate School, North Cloisters, Wilkins Building
University College London Gower Street London WC1E 6BT
Tel: +44 (0)20 7679 7844 Fax: +44 (0)20 7679 7043
ethics@ucl.ac.uk
www.ucl.ac.uk/gradschool

Appendix 13: Information sheet (study reported in chapter 5)

RESEARCH DEPARTMENT OF CLINICAL, EDUCATIONAL & HEALTH PSYCHOLOGY
UCL PSYCHOLOGY

INFORMATION LEAFLET FOR VOLUNTEERS

Version 1 February 2014

The determinants and psychological consequences of ketamine and high potency cannabis use

Investigators: Lisa, Harvey, Alyssa Joye, Will Lawn, Prof. H.Valerie Curran

Purpose of the study:

To determine the long term effects of high potency cannabis and ketamine use

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

WHAT IS THE PURPOSE OF THE STUDY?

To determine the effects of using different types of recreational drugs upon mental functioning and mood.

SOME BACKGROUND TO THE RESEARCH

Many drugs have long term effects; for instance people who drink lots of alcohol often find their memories are not as good as they were. This can often be affected by factors such as the length of time they have been drinking and the quantity that they drink. The present study aims to find out what the long-term effects of using recreational drugs may be on mental state and cognition.

WHAT WILL BE STUDIED?

We will ask people who *regularly* use ketamine and cannabis a series of questions about their drug use and their psychological well-being. After these, participants will then be asked to complete a series of computer tasks designed to look at attention and memory.

HOW WOULD I BE INVOLVED IF I AGREED TO TAKE PART?

If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

If you agree to participate, on the testing day you will come to the Psychopharmacology Laboratories at UCL or, if you do not live locally, the researchers will come to your home. We will collect a urine sample to test for the drug being studied and to screen for use of other drugs; the results will be kept confidential and the sample disposed of at the end of the testing session. You

Version 2, dated 16/02/07

will be paid for participation upon completing the various research tasks. The full testing session will last approximately 2 hours.

CONFIDENTIALITY

Any information collected about you will be held in accordance with the 1998 Data Protection Act. All the information that is collected about you during the course of the research will be kept strictly confidential. Your results will have your name and any other details about you removed first so that you cannot be identified from them.

If you would like further information please ask the investigator

Thank you for reading this leaflet and we hope that you will be able to take part in the study.

You do not have to take part in the study if you do not want to. If you decide to take part, you may withdraw at any time without having to give a reason.

Contacts:

[redacted]

Clinical Psychopharmacology Unit
Research Dept of Clinical, Educational and Health Health Psychology
University College London Gower Street London WC1E 6BT
[redacted]
www.ucl.ac.uk/clinical-health-psychology

All proposals for research involving human subjects are reviewed by an ethics committee before they can proceed. This proposal was reviewed by the UCL Committee for the Ethics of non-NHS Human Research.

Version 2, dated 16/02/07