EFFECTS OF SMOKING STATUS ON PUNISHMENT SENSITIVITY AND COGNITIVE CONTROL

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Abstract

A hallmark feature of addiction, including nicotine dependence, is persistent drug use despite the adverse consequences of such behaviour. This implies that there may be deficient processing of punishment in dependent individuals. However, despite growing bodies of research investigating both altered reward sensitivity and error monitoring deficits there is a paucity of empirical work investigating sensitivity to punishment in nicotine dependence. The main aim of this thesis was therefore to investigate the effects of satiation level (abstinent/satiated) and smoking history (current/former/never) on behavioural measures of punishment sensitivity. Furthermore, the related phenomenon of loss aversion (the tendency for individuals to be more sensitive to losses compared to gains) was investigated in former smokers alongside a range of self-control indices.

Study 1 assessed the capability of some operant tasks to assess punishment sensitivity in a group of healthy non-smoking participants. A conflict task (in which responding was made under reward only and reward with concurrent punishment conditions) adequately detected punishment-induced suppression of responding and so was used in study 2 alongside a probabilistic reversal learning (PRL) task (in which reward and punishment contingencies were first learned and then reversed) in order to investigate the effects of satiation level on punishment sensitivity in a group of nicotine-dependent participants. Satiated and abstinent smokers did not differ in punishment sensitivity assessed by either task. Study 3 investigated the effects of satiation level and smoking history on punishment sensitivity using a more difficult PRL task. The groups were found not to differ in punishment sensitivity however there was some evidence to suggest that former smokers may have exhibited greater error monitoring during the PRL task compared to satiated smokers. This was coupled with greater post-punishment slowing of reaction times in never and former smokers compared to satiated smokers. The present work does not find significant differences between former and never smokers on the error monitoring or post-punishment slowing measures. However given the direction of findings and given that previous imaging research suggests that former smokers are 'supra-normal', showing greater top-down control than both satiated and never smokers, study 4 compared former smokers that had successfully maintained long term abstinence and never smokers on a range of self-control indices (inhibitory control, performance monitoring, risk taking and loss aversion). Former smokers showed impairments on some of the self-control indices, however levels of loss aversion were found to be greater in former smokers relative to never smokers.

In conclusion, the results presented here demonstrate that sensitivity to punishment is not affected by level of satiation or smoking history. However, the rewards and punishers used were not drug-related and therefore a more specific impairment in punishment sensitivity dependent upon a drug-related context cannot be ruled out. In addition, satiated smokers may be less able to monitor their behaviour compared to former smokers and this may be related to reduced processing following negative feedback. Further work is required in order to establish the mechanism behind this impairment and to ascertain if it contributes to the maintenance of smoking behaviours. Furthermore, loss aversion may be an important factor contributing to the ability of former smokers to maintain long term abstinence. However, longitudinal studies are warranted to determine if high loss aversion predicts or is a consequence of successful abstinence.

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List of Main Abbreviations

ANOVA	Analysis of Variance
BDI	Beck Depression Inventory
BIS/BAS	Behavioural Inhibition System/Behavioural Activation System Scales
BIS-11	Barratt Impulsiveness Scale
CFT	Coin Flip Task
CGT	Cambridge Gambling Task
CO	Carbon Monoxide
CV	Coefficient of Variation
DRL	Differential Reinforcement of Low Rates
DSM	Diagnostic and Statistical Manual of Mental Disorders
DST	Digit Span Task
ERP	Event-Related Potential
fMRI	Functional Magnetic Resonance Imaging
FTND	Fagerstrom Test for Nicotine Dependence
GST	GoStop Task
IGT	Iowa Gambling Task
IWR	Immediate Word Recall
mg	Milligrams
NART	National Adult Reading Test
NDSS	Nicotine Dependence Syndrome Scale
NicVAS	Nicotine-Sensitive Visual Analogue Scales
PRL	Probabilistic Reversal Learning Task
PSS	Post Signal Slowing
PSWQ	Penn State Worry Questionnaire
QSU-Brief	Questionnaire of Smoking Urges – Brief
RARP	Reward and Reward/Punishment Task
RRQ	Rumination-Reflection Questionnaire
RVIP	Rapid Visual Information Processing Task
S.E.M.	Standard Error of the Mean
SMRI	Scott-McIntosh Rumination Inventory
SSD	Stop Signal Delay
SSRT	Stop Signal Reaction Time
VI	Variable Interval
VR	Variable Ratio

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Declaration

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed:

Kevin Allan Butler

Dated: April 2013

Chapter 1   General Introduction

1.1   Overview

The work presented in this thesis examines the effects of satiation level (satiated or abstinent) on punishment sensitivity in dependent smokers. It also compares punishment sensitivity in current, former and never smokers and examines the related phenomenon of loss aversion in former smokers. This introductory chapter outlines key theoretical and empirical evidence from the area of nicotine dependence and punishment sensitivity as well as from related areas such as reward sensitivity and error monitoring in order to establish a background to the research aims and experimental chapters which follow. The chapter is split into three sections. The first section, 'general background', begins with information on tobacco use, the diagnostic criteria for nicotine dependence and the stages of addiction. This is followed by an examination of some relevant theories that help to explain the aetiology of addiction, and a discussion of the factors that drive and protect against relapse. In the next section, 'specific background', the existing empirical work on nicotine dependence and punishment sensitivity and related areas are considered. Finally in the third section, 'experimental aims', the aims of the thesis and the contribution this work hopes to make are presented. Throughout this work the terms 'dependence' and 'addiction' are used interchangeably since both words can be used to describe the loss of control over drug-seeking/taking behaviour. Similarly, the terms 'sensitivity' and 'responsivity' are used interchangeably, both referring to an individual's reaction to a stimulus, reward or punishment.

1.2   General Background

1.2.1   Cigarette Smoking

The most common mode of tobacco administration in England is smoking filtered cigarettes, though hand rolled varieties are becoming ever more popular (National Statistics, Statistics for smoking: England, 2011). Statistics from 2009 suggest that in England approximately 21% of adults aged 16 and over smoke (22% of men and 20% of women) and that the 16-19 and 20-24 year old age groups report the highest prevalence of smoking. In addition, on average current smokers reported smoking an average of 13.1 cigarettes per day (National Statistics, Statistics for smoking: England, 2011).

Smoking prevalence has decreased by 18% since 1980, but despite this cigarette smoking remains a major health and socio-economic problem with tobacco smoking directly responsible for approximately 462,000 hospital admissions in England for 2009/2010 among adults aged 35 and over (that is 5% of all admissions for this period in this age group) and approximately 82,000 deaths in England in 2010 among adults aged 35 and over (that is 18% of all deaths for this age group; National Statistics, Statistics for smoking: England, 2011). This amount of smoking related ill-health and mortality leads to high associated costs that place an economic burden on the country. It has been estimated that smoking cost the NHS £5.2 billion in 2005/2006 which was approximately 5.5% of the total healthcare costs for that period (Allender et al., 2009).

Stopping smoking is remarkably difficult and nicotine dependence is a chronic relapsing condition. In Great Britain during 2008/2009, 75% of current smokers reported having tried to give up smoking at some point in the past. Of the 75% of smokers who have attempted to quit 55% had tried to give up once, 24% had made two attempts and 21% had made three or more quit attempts. In addition, of the smokers who had made these previous quit attempts 22% had quit for a week, 29%

had remained abstinent for six months or more and just 8% had quit for two years or more (National Statistics, Statistics for smoking: England, 2011). Furthermore, unsuccessful quit attempts may be under reported particularly if they last a short time or occurred a long time ago (Berg et al., 2010). Additionally, data from the NHS Stop Smoking Services shows that In England between April 2010 and March 2011 there were 787,527 quit attempts through the service yet by the four week follow up just 383,548 (or 49%) of these attempts were on-going (National Statistics, Statistics for smoking: England, 2011).

In Great Britain during 2008/2009, 67% of current smokers reported wanting to give up smoking (National Statistics, Statistics for smoking: England, 2011). When these individuals were asked why they wanted to give up 83% gave a health reason, 31% gave a financial reason, 22% were worried about harming their children and 16% cited pressure from others. These statistics suggest that current smokers are aware of the negative aspects associated with their smoking such as risk to their own health and the health of others, the expense and the negative social image that others can hold regarding smoking but that nevertheless they continue smoking.

In recent years there has been the introduction of a number of tobacco control policies including a total advertising ban (implemented in stages from February 2003 to July 2005), wider availability of NHS Stop Smoking services and information to individuals attempting to quit and smoke free legislation (implemented in England on 1st July 2007). However, smoking statistics suggest that the introduction of this smoke-free legislation has had little impact on the prevalence of smoking (National Statistics, Statistics for smoking: England, 2011). In addition, in March 2011 the UK government launched its Tobacco Control Plan for England in which it set out ambitions to reduce adult smoking prevalence to 18.5% or less by 2015. This would mean 210,000 fewer smokers nationally. Taken together, these statistics help to illustrate the need for continued research into smoking behaviour particularly research that furthers our understanding of why current smokers continue to smoke

even when they are aware of the negative consequences of doing so and research that has the potential to improve cessation rates.

1.2.2 Measuring Nicotine Dependence and the Stages of Addiction

Nicotine produces the central pharmacological effects of smoking tobacco that lead to addiction (Stolerman and Jarvis, 1995). Nicotine exerts its central effects through activation of nicotinic acetylcholine receptors. These receptors are widely distributed throughout the brain and activation of these receptors located on presynaptic nerve terminals results in the release of neurotransmitters, including dopamine and serotonin (e.g. Toth et al., 1992). It is this facilitation of neurotransmitter release that is thought to underlie the behavioural effects of nicotine. In terms of the pharmacokinetics, nicotine reaches the brain in 10 to 20 seconds following a cigarette puff producing rapid activation of the dopaminergic system underlying behavioural reinforcement effects (Benowitz, 1990, 1996). Peak nicotine plasma levels are reached within 5-9 minutes from the onset of smoking (around the time the cigarette is extinguished) and fall rapidly to approximately half peak levels within about 30-35 minutes. Overnight, nicotine concentration falls to very low levels and regular smokers will typically smoke soon after waking and continue to smoke at regular intervals throughout the day in order to maintain a constant nicotine blood plasma level and avoid withdrawal symptoms and drug craving. So for example, 31% of heavy smokers smoke within five minutes of waking whereas just 3% of light smokers smoke within five minutes of waking (National Statistics, Statistics for smoking: England, 2011). However, in clinical and research settings identifying smokers' level of dependence as opposed to classifying individuals as either heavy or light smokers tends to be more common.

In clinical settings diagnosing and classifying mental disorders is often guided by the signs and symptoms of the disorders regardless of the pathological changes causing them. The most recent set of guidelines was published by the American Psychiatric Association and the World Health Organisation in the Diagnostic and Statistical Manual, Fourth Edition, Text Revision (DSM-IV-TR, American Psychiatric Association,

2000). The DSM-IV-TR classification of mental disorders provides a description of the patterns of behaviour that can be expected with each disorder so that clinicians can compare their patients' behaviours to clear theoretically driven and empirically tested disease criteria. In DSM-IV-TR nicotine dependence is said to manifest when 3 or more symptoms out of a possible total of 7 symptoms are experienced within a 12 month period. These hallmark physiological, psychological and behavioural symptoms are outlined below:

1. Tolerance

Tolerance can manifest as the absence of nausea and dizziness symptoms caused by smoking nicotine containing cigarettes despite substantial amounts of nicotine intake or by any markedly diminished effect of nicotine observed with continued use of the same amount of nicotine. The requirement of more nicotine to produce an effect previously observed at a lower dose also demonstrates tolerance.

2. Time spent using or procuring

Time spent using or procuring can manifest as a great deal of time spent in activities necessary to obtain cigarettes. Spending a great deal of time actually smoking i.e. chain smoking also demonstrates existence of this symptom.

3. Impaired control

Impaired control can manifest as an individual smoking all their cigarettes faster than intended. It is the consumption of nicotine in larger amounts or over a longer period than intended.

4. Unsuccessful quit attempts

Unsuccessful quit attempts can manifest as a persistent desire to quit smoking which is never realised or repeated unsuccessful efforts to quit smoking.

5. Withdrawal

Withdrawal can manifest as a well-defined withdrawal syndrome caused by an

abrupt cessation or a reduced intake of nicotine and is characterised by four or more of the following: irritability, frustration or anger, dysphoria (depressed mood), anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite and insomnia. Nicotine use to alleviate or avoid withdrawal symptoms also demonstrates existence of this symptom.

6. Neglecting other activities

Neglecting other activities can manifest as recreational, social or occupational pursuits being given up or reduced either because more time is spent using or procuring nicotine or because such activities occur in places or with people that prohibit or restrict smoking.

7. Use despite negative consequences

Use despite negative consequences can manifest as continued smoking despite the knowledge that smoking causes problems or despite having a persistent or recurrent problem that is likely to have been caused or exacerbated by smoking. This could be a problem with physical health, social interactions with non-smokers, decreased productivity at work due to increased time spent smoking or something similar.

In research settings, however, the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991; revised from the Fagerstrom Tolerance Questionnaire (FTQ; Fagerstrom, 1978)) is a more useful measure of nicotine dependence because it provides a brief and reliable measure of the severity or level of dependence. The FTND is an established clinical marker of nicotine addiction and association studies using FTND as the primary smoking phenotype have identified genetic variations contributing to nicotine addiction (Kendler et al., 1999; Vink et al., 2005) further supporting this test's use as a trait marker of nicotine addiction. In addition, some commentators have argued that the DSM criteria for nicotine dependence is under-used in research settings and that it has low validity in the prediction of dependence features such as relapse (Baker et al., 2011). Baker et al. suggest that future editions and revisions of the DSM criteria would benefit from the removal of most of the

current criteria and the addition of new criteria such as urge to smoke on typical smoke days and in abstinence, heaviness of smoking, frequency of smoking and latency to smoke after waking some of which can already be assessed with existing measures including the FTND. Despite criticisms of the DSM, the DSM-IV-TR and the FTND provide the current gold standard clinical and research tools for the assessment of nicotine dependence and nicotine dependence severity.

These assessment tools are however essentially descriptive measures and do not explain how nicotine dependence develops, that is the transition from use to loss of control over use. Several stages of substance dependence have been identified and these include the initiation, maintenance, cessation and relapse of drug use (Ogden, 1996, p. 89-107). These stages reflect the level of involvement with substance use such that initiation reflects the transition from non-use to irregular, experimental use and moving from initiation to maintenance reflects transition across a number of stages from experimental use to regular use to harmful/problem use to dependence. Finally, moving from maintenance to cessation and relapse reflects the transition from drug use to abstinence and back to drug use again. Since nicotine dependence is a chronic relapsing condition there can often be several cycles of cessation and relapse. This thesis will focus on the maintenance and cessation stages since it will examine punishment sensitivity in current and former smokers and loss aversion in former smokers. To reflect this focus, the next two sub-sections will highlight some theories of addiction relevant to this thesis and discuss factors that both drive relapse and protect from relapse.

1.2.3   Theories of Addiction

Addiction is at its core a chronic and progressive disease that affects the brain's reward system (Volkow et al., 2010). All addictive drugs cause, either directly or indirectly, transient increases in dopamine in the mesolimbic system specifically in a part of the ventral striatum known as the nucleus accumbens (Di Chiara and Imperato, 1988). For example, using positron emission tomography Brody et al. (2004) found greater reductions in [(11)C]raclopride binding (an indirect measure of

dopamine release) in nicotine dependent smokers after smoking compared to nicotine dependent smokers that had not smoked and similarly Brody et al. (2009) found greater reductions in [(11)C]raclopride binding in nicotine dependent smokers after smoking a regular cigarette compared to nicotine dependent smokers that had smoked a denicotinized cigarette. Originally thought to encode the hedonic impact of a reward, the neurotransmitter dopamine is now thought to play a more complex role in encoding reward and non-reward information such as: saliency of non-rewarding stimuli (Zink et al., 2003), aversive events (Budygin et al., 2012), reward expectation (de la Fuente-Fernandez et al., 2002), the discrepancy between predicted and actual reward (Schultz et al., 1997) and incentive salience or 'wanting' (Robinson and Berridge, 1993; described below).

Various reinforcement mechanisms may contribute to initiation and maintenance of drug use. For example, positive reinforcing effects (i.e. any positive event occurring as a consequence of drug-taking such as cognitive benefit or euphoria) may increase the chances of future drug-taking. The idea that drugs of abuse are addictive because of their positive reinforcing effects particularly the euphoric consequences of dopamine release has previously been proposed (Stewart et al., 1984; Wise and Bozarth, 1987). However, it seems likely that other mechanisms contribute to drug use since nicotine for example has been shown to increase subjective effects that could be described as aversive such as dizziness, dysphoria and disorientation in non-smokers (Foulds et al., 1997; Soria et al., 1996). Smokers are known to experience withdrawal symptoms and negative affect after acute abstinence (e.g. Bidwell et al., 2012). With negative reinforcement the incentive to continue drug use comes from relief of the unpleasant state brought on by withdrawal.

Robinson and Berridge (1993) provided an alternative to the pleasure seeking interpretation of drug use and put forward the theory of incentive-sensitisation. The theory proposes that drug 'wanting' is distinct from drug 'liking' so that even though tolerance to the positive subjective experience of drug taking may develop (e.g. Foltin and Fischman, 1991; Kelly et al., 1991; Perkins et al., 2001; Foltin and Haney, 2004),

the drug is still wanted. According to the incentive-sensitisation theory, drugs of abuse activate the mesolimbic dopamine system just as other natural incentive stimuli (e.g. food) do. Activation of this system by drugs of abuse allows for the attribution of incentive salience to stimuli associated with activation. Incentive salience can be thought of as a psychological process whereby the mental representation of the drug and drug related stimuli are given salience thus making them more 'attention grabbing', attractive and 'wanted'. It is posited that this increased 'wanting' of the drug is what drives repeated drug taking behaviour. Repeated drug use is proposed to lead to incremental and long lasting neuroadaptations of the mesolimbic dopaminergic system thus rendering it hypersensitive (or sensitised) to drugs and stimuli that are associated with the drug (e.g. cigarettes, lighter, matches or particular location where smoking occurs). The theory suggests that to a casual smoker, smoking will become more and more attractive as the neural system becomes progressively sensitised, that 'wanting' becomes craving which ultimately narrows the behavioural repertoire of the smoker. However, Di Chiara (1995) points out a problem of the incentive-sensitisation theory as an explanatory account of addiction. Di Chiara suggests that there cannot be a generalised increase in the reactivity of the dopamine system as a result of sensitisation since if this was the case one would expect a heightened attribution of incentive salience not only to drug and drug related stimuli but also to non-drug rewards and that this is incompatible with what is observed in the addicted state whereby drugs and drug-related stimuli increase motivated behaviour at the expense of other non-drug rewards. The incentive-sensitisation theory would have to imply therefore that there was something special about drug-related activation of the mesolimbic dopamine system and there is some evidence that this may be the case. For example, drugs of abuse facilitate the release of dopamine at concentrations far greater than that caused by natural rewards such as food (e.g. Di Chiara et al., 1997).

In line with the incentive-sensitisation theory of addiction proposing neuro-adaptive changes in the mesolimbic dopaminergic system with repeated drug exposure, Everitt and Robbins (2005) provide evidence of a neural transition from cortical to

striatal control over drug seeking and drug taking behaviour as well as a progression from ventral to more dorsal regions of the striatum. The authors suggest that drug addiction be viewed as the endpoint of a series of stages from initial drug use through to loss of control over this behaviour such that it becomes habitual and ultimately compulsive and that this progressive nature of addiction is represented at the neural level by the aforementioned transitions.

In keeping with a neural-level account of drug addiction, Goldstein and Volkow (2002) propose the Impaired Response Inhibition and Salience Attribution (IRISA) theory of addition. This theory highlights the importance of two frontal areas in addiction, the orbitofrontal cortex and the anterior cingulate cortex. These two areas are neuroanatomically connected to the striatal and limbic midbrain regions already implicated in the addiction process. Furthermore, the IRISA theory suggests that addiction is commonly associated with specific behavioural impairments such as deficits in the ability to track and update the salience of a reinforcer and deficits in inhibitory control that are dependent upon the integrity of these two frontal regions. The behavioural impairments are proposed to manifest in the addicted individual as the overvaluing of drug reinforcers, the undervaluing of alternative reinforcers and the impaired ability to restrain pre-potent behaviours such as drug use. In addition, Goldstein and Volkow (2002) review literature showing that these frontal regions are commonly found to be activated in addicts during intoxication, craving and bingeing, and are deactivated during withdrawal.

Volkow et al. (2003) highlight the importance of an integrated neural model of addiction onto which psychological and behavioural processes can be mapped. They propose that drug addiction is likely to be mediated by functional and/or structural changes in the circuits that are modulated by dopamine and drugs of abuse (Figure 1.1A shows the neuroanatomical proximity of the areas containing the neural circuits implicated in addiction). In doing so, they present a four neural network model (shown in Figure 1.1B) that implicates patterns of neural activity in the brain circuits mediating reward, motivation and drive, memory and learning, and behavioural

monitoring and control in choice and decision making processes. Put simply, the integrative neural network model proposed by Volkow et al. (2003) suggests that addiction occurs because drugs of abuse produce long lasting changes in the neural circuitry that subserves the expected positive feelings, salience attribution and motivation to take drugs (reward circuitry and motivation/drive circuitry), circuitry that is also affected by previous knowledge (memory circuitry). Furthermore, the cognitive decision to take drug (or not) is processed, at least in part, by the prefrontal cortex and the anterior cingulate cortex (control circuit). The brain regions of the control circuitry are proposed to monitor behaviour and implement cognitive control when appropriate; however, Volkow's model suggests that neuroadaptive changes within the control circuitry weaken the brains 'stop' mechanisms so that they are easily overcome and the decision to take drug is made.

More recently Hong and colleagues (2009) used a resting state functional imaging technique to extend the understanding of neural networks in nicotine dependence. They demonstrated that the severity of nicotine dependence (as assessed with the FTND) is inversely associated with the strength of activity between the striatum and the dorsal anterior cingulate suggesting that resting state synchronised activity in this cingulate-striatal circuit may serve as an endophenotype or biomarker for nicotine addiction. One criticism of the work is the relatively mild dependence levels reported in the participants (mean Fagerstrom score of 4.3; maximum possible score is 10) and therefore, it is not known if the results would generalise to those with greater levels of dependence. Despite this weakness, the study provides evidence that nicotine dependence is associated with weaker connectivity between two of the neural networks implicated by Volkow et al. (2003) as playing a major role in decision-making and compulsive drug use. These theories of addiction help to explain the development and maintenance of addiction. The next sub-section will focus on abstinence and relapse.
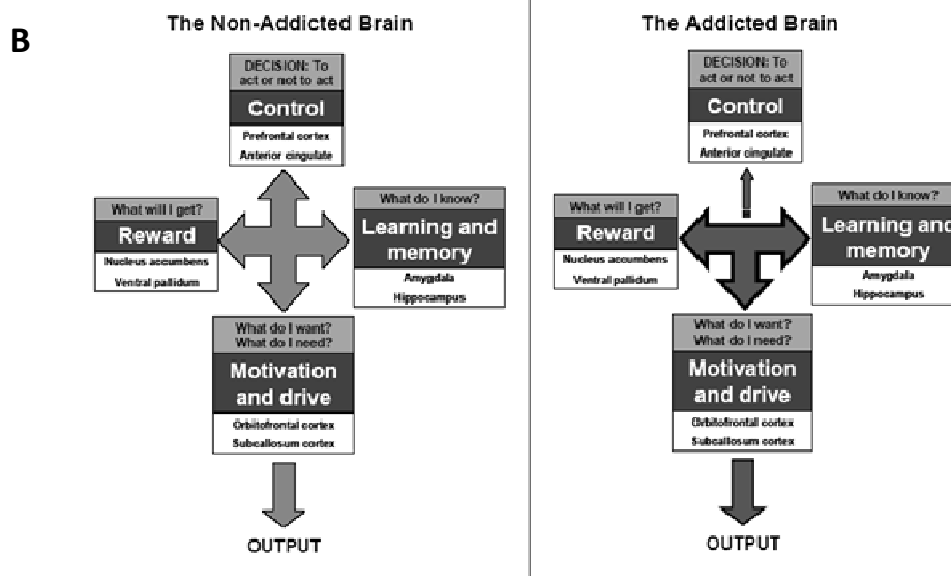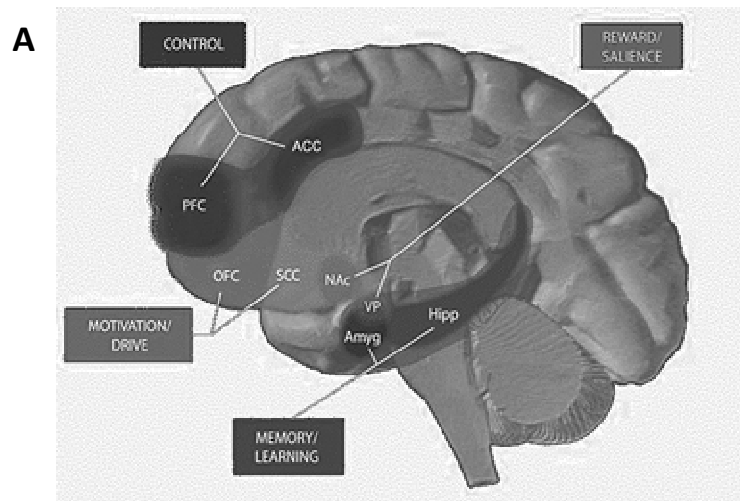
Figure 1.1: The Addicted Brain

A: Neuroanatomical Proximity of Areas Containing Circuits Implicated in Addiction. (Abbreviations: PFC – prefrontal cortex, ACC – anterior cingulate cortex, OFC – orbitofrontal cortex, SCC – subcallosal cortex, NAc – nucleus accumbens, VP – ventral pallidum, Hipp – hippocampus, Amyg – amygdala). Figure adapted from National Institute on Drug Abuse, (2008). B: Difference Between the Addicted and Non-addicted Brain. (The four neural network model of addiction proposed by Volkow et al. (2003) predicts greater activity in the circuits underpinning reward/salience, motivation/drive and memory of learned associations. This overcomes cognitive control normally exerted by prefrontal regions leading to compulsive drug use). Figure adapted from Volkow et al. (2003).

1.2.4 Factors Driving Relapse and the Maintenance of Abstinence

Symptoms of a withdrawal syndrome may be an important driver of relapse particularly at the early stages post-cessation. Evidence suggests that withdrawal symptoms or at least drug off-set effects can begin as quickly as 30 minutes into abstinence from smoking (Hendricks et al., 2006). Studies looking at the time course of withdrawal show that self-report symptoms decline rapidly over the first few days of abstinence and continue to decline across successive weeks (Cummings et al., 1985; Van Zundert et al., 2009). In fact, a review of more than 100 studies suggests that withdrawal symptoms peak within the first week of abstinence and last 2-4 weeks (Hughes, 2007). Therefore, other factors must play a role in relapse particularly at more advanced stages of cessation.

Preclinical models of relapse behaviour have typically focused on three different types of relapse namely: cue-induced, stress-induced and drug-induced relapse. Thus, relapse may be initiated by cues that have acquired incentive motivational properties and encode the availability of drug reward, or by stimuli that trigger activation of the neural circuitry that subserves the processing of stress. Alternatively, the perceptual and sensory qualities or the psychopharmacological effects of the drug itself once ingested in a small amount (a priming dose) may lead to a full relapse. Smoking-related cues for example have been found to increase craving, increase negative mood, decrease positive mood and increase heart rate and blood pressure (Heishman et al., 2010). Cue reactivity (assessed by fMRI changes in response to smoking related cues) has been shown to persist into abstinence (Janes et al., 2009) and incubation of craving (cue induced craving not only persisting but also increasing with abstinence) has also been documented (Bedi et al., 2011). In addition, reactivity to smoking cues prior to quitting may predict relapse vulnerability. Janes et al. (2010) investigated cue reactivity assessed by fMRI changes in response to smoking related cues and attentional bias to smoking related words in 21 dependent smokers prior to making a quit attempt. Individuals who relapsed had shown greater reactivity to smoking related cues and analysis of both the attentional bias task and fMRI data predicted the abstinence/relapse outcome with 79% accuracy. Interestingly, this

study also showed that relapsers had decreased functional connectivity in brain regions involved in cognitive control suggesting that those who could not maintain their abstinence may have had reduced self-control as well as increased cue reactivity.

Self-control has been defined as a key aspect of adaptive decision-making (e.g. Jasinska et al., 2011). Jasinska et al. suggest that self-control allows long-term goals to be pursued by overcoming more automatic and immediate response tendencies that conflict with that goal. Therefore, an effective self-control system must enable an individual to restrain or inhibit their behaviour and to avoid and evaluate certain situations and risks effectively as well as monitoring for goal conflicts or errors in their own actions so that behaviour can be adjusted accordingly. Deficits in self-control are associated with addiction. For example Ersche et al. (2012) found impairments in inhibitory control and abnormalities in frontal-striatal brain circuitry linked to self-control in stimulant-dependent individuals and their first-degree relatives with no history of drug abuse compared to unrelated controls also with no history of drug abuse. Ersche et al. argue that these findings support the notion of an underlying neurocognitive endophenotype for stimulant drug addiction. If diminished self-control is a feature of drug addiction, then enhanced self-control might conceivably contribute to 'relapse resilience' in former addicts. Interestingly, Muraven (2010) showed that smokers who practised tasks requiring self-control (i.e. through completing difficult exercises or avoiding sweet foods) were more successful during a subsequent quit attempt compared to smokers who practised control tasks requiring no self-control. Additionally, Muraven argues that these findings lend support to the self-control strength model (Muraven and Baumeister, 2000) that proposes that practising self-control builds self-control resources. However, one criticism of the Muraven (2010) finding is that it does not reveal which specific aspects of self-control are important for the maintenance of abstinence.

1.2.5 Summary

Cigarette smoking-related ill health and mortality as well as the associated health

care costs place a burden on society. However, cigarette smoking is extremely hard to stop despite smoking statistics suggesting that current smokers are aware of the negative consequences that are associated with continued use. In susceptible individuals nicotine dependence can develop with extended use. At the behavioural level a hallmark feature of dependence is compulsive drug use i.e. the loss of control over use and the continued use despite the negative consequences of use, and these features form part of the current diagnostic criteria for nicotine dependence. At the neural level this is thought to be the consequence of, or at least coincide with, specific neuroadaptations particularly in the midbrain reward/motivation circuitry resulting in enhanced drug 'wanting' and in the frontal control/monitoring circuitry resulting in diminished cognitive control. Moreover, these brain changes give rise to a compromised decision making system that not only reacts strongly to pre-potent stimuli but also exhibits a reduced ability to stop reacting. Furthermore, strengthening the stop or control circuitry may represent one mechanism to help smokers quit and remain abstinent.

1.3   Specific Background

This section of the introduction reviews key empirical evidence regarding punishment sensitivity and addiction with a focus on dependent smokers. Findings from related areas will also be discussed with the aim of highlighting the need for further research on the effects of satiation level (satiated or abstinent) on punishment sensitivity in dependent smokers, for research comparing punishment sensitivity in current, former and never smokers and for research into loss aversion in former smokers. Consequently, this section seeks to justify and set the scene for the aims of the research conducted in this thesis and presented at the end of this introduction.

1.3.1   Nicotine, Smoking, Abstinence from Smoking and Cognition

Various other central affects of nicotine besides the addictive properties have been investigated and these include the ability of nicotine to increase psychomotor activity (Hindmarch et al., 1990) and enhance certain aspects of cognitive function (attention e.g. Wesnes and Warburton, 1984 and memory e.g. Levin et al., 1993). Nicotine

appears to enhance aspects of cognitive function in smokers (Wesnes and Warburton, 1983), non smokers (Foulds et al., 1996) and in populations characterised by cognitive deficits such as Alzheimer's disease (White and Levin, 1999), attention deficit hyperactivity disorder (Potter and Newhouse, 2004), Tourettes syndrome (Howson et al., 2004), schizophrenia (Barr et al., 2008), Parkinson's disease (Kelton et al., 2000) and depression (McClernon et al., 2006). As a result, there is much interest in the development of drugs that target specific nicotinic receptors (e.g. Dunbar et al., 2007) in order to treat a variety of central nervous system disorders. Interestingly, many of the populations in which cognitive deficits are characteristic and in which nicotine has been shown to enhance cognitive performance also demonstrate a higher prevalence of smoking than the normal population and this has led some to postulate that these individuals may be self-medicating (e.g. Bekker et al., 2005; Markou et al., 1998). In addition, as well as nicotine-enhancing aspects of cognition in smokers, abstinence from smoking produces deficits in cognitive performance (Foulds et al., 1996; Wesnes and Warburton, 1983). These deficits in cognitive performance, which can be reversed by the administration of nicotine (e.g. Atzori et al., 2008), can begin early into abstinence (Hendricks et al., 2006) and last several weeks in some smokers (Gilbert et al., 2004). One particular cognitive process of relevance to addiction is decision making.

1.3.2 Decision Making

As suggested previously, addiction may be indexed by a compromised decision making system and in line with this notion brain regions commonly implicated in addiction (i.e. striatum, amygdala, prefrontal cortex) are also implicated as regions involved in decision making (Diekhof et al., 2008). Decision making is a cognitive process concerned with reflecting on the consequence of choice (Bechara, 2005) and thus at its core decision making depends, amongst other things, on reward sensitivity, punishment sensitivity and performance monitoring (i.e. the ability to monitor on-going performance for errors and to integrate information about performance outcomes so that response-consequence associations are learned and updated; a review of performance monitoring aspects of cognitive control is provided

by Alexander and Brown, 2010). Previous work has investigated the effects of drugs of abuse or withdrawal from these drugs on these decision making components. The following sections will outline the existing empirical evidence for the effects of nicotine, smoking and withdrawal on these components.

1.3.3   Reward Sensitivity

Since the involvement of the reward system is so inherent in an understanding of addiction it is perhaps unsurprising that much research has been carried out assessing the effect of nicotine, smoking and withdrawal from smoking on reward sensitivity. As the main focus of this thesis is punishment sensitivity, only a selection of relevant empirical work related to reward sensitivity is outlined below. Evidence from animal studies suggests that nicotine alters the brain's threshold for rewarding brain stimulation. Hustonlyons and Kornetsky (1992) demonstrated how the reward threshold of brain stimulation was lowered by nicotine and that this effect could be blocked by the nicotine receptor antagonist, mecamylamine. It was concluded that nicotine was increasing the sensitivity to rewarding brain stimulation. These findings were confirmed in a study by Kenny and Markou (2006). In this study, it was found that self-administration of 0.03 mg/kg nicotine in rats increased the sensitivity of brain reward systems detected by post-nicotine lowering of reward thresholds. This could be reversed by the nicotinic receptor antagonist dihydro-β-erythroidine. It was found that this nicotine-enhanced sensitivity of brain reward systems was long lasting (persisting for at least 36 days) even after nicotine self-administration had ceased. In contrast, nicotine withdrawal decreases activity of brain reward systems as measured by elevation of intracranial self-stimulation thresholds (Epping-Jordon et al., 1998; Kenny and Markou, 2005). Additionally, behavioural work has shown that nicotine has reinforcement-enhancing properties such that nicotine enhances behaviours that result in the delivery of non-pharmacological reinforcers (Palmatier et al., 2006; Chaudhri et al., 2006; Chaudhri et. al., 2007).

Behavioural evidence from human studies has demonstrated that a single transdermal dose of nicotine enhances responding to non-drug rewards in non-

smokers (Barr et al., 2008). In terms of the smoking and abstinence from smoking literature, overnight abstinent smokers show reduced reward responsiveness compared to both satiated smokers and non-smokers (Powell et al., 2002a) and reward responsiveness can be restored in abstinent smokers after smoking a cigarette (Al-Adawi and Powell, 1997) or after taking a nicotine lozenge (Powell et al., 2004; Dawkins et al., 2006). In addition, smokers that remained abstinent for 10 hours rated happy film clips as less happy than satiated smokers and non-smokers whereas no group differences existed for sad film clips (Dawkins et al., 2007). However, in a follow-up study abstinence blunted responses to both happy and sad film clips (Dawkins and Powell, 2011) suggesting that abstinence may cause a general suppression of normal motivational responses. In line with this, an earlier study found that both non-smokers and smokers that had recently smoked displayed similar levels of interference from reward and threat-related words compared to neutral words in a modified Stroop task whereas there was no effect of word type in abstinent smokers (Powell et al., 2002b). Furthermore, a longitudinal study comparing ad-lib smokers and smokers paid to maintain abstinence at 1 week, 1 month and 3 months showed that reward responsivity in the abstinent group improved from a 12 hour abstinent baseline assessment and that this improvement plateaued between a week and a month of abstinence. In addition reward responsivity did not differ between the groups at any timepoint (Dawkins et al., 2009). Dawkins et al. suggest that performance in the ad-lib smokers was improved from the abstinent baseline as a result of recent nicotine use whereas the improvement in abstinent smokers is consistent with a recovery of appetitive motivational processes. Similarly, Snuggs and Hajek (2012) show elevations in the positive ratings of rewarding events in abstinent smokers after 1 and 4 weeks of abstinence compared to reactions while smoking. Taken together these findings suggest that acute abstinence from smoking is associated with reduced reward sensitivity that can be reversed by nicotine or smoking (however conversely, Kalamboka et al. (2009) found no effect of abstinence on reward responsivity). Furthermore, impaired reward sensitivity found in abstinent smokers appears to recover naturally with continued abstinence.

1.3.4 Punishment Sensitivity

In contrast to reward sensitivity, there have been few studies investigating the effects of nicotine, smoking and withdrawal on punishment sensitivity. The effect of nicotine on punishment sensitivity and on punishment schedules has been investigated in a small number of animal studies. Responding on a punishment schedule can be maintained by concurrent reinforcement and it is well known that drugs can modify operant responses that are both rewarded and punished simultaneously. For example, minor tranquillisers restore responses which are suppressed by punishment, whereas stimulant drugs such as amphetamine further reduce responses that have already been suppressed by punishment but increase operant responding when there is no punishment contingency (Geller and Seifter, 1960).

Morrison (1969) looked at the effects of 0.1 and 0.4mg/kg nicotine on punished behaviour. In the study, 16 rats from various strains and of varying experimental experience lever pressed for water presentation on a variable interval (VI) schedule with a concurrent punishment contingency of electric shock. Despite great individual variation in responding, Morrison found that in most animals nicotine further suppressed responding that was suppressed by the electric shock, though it did increase responding in some animals. Since the effect of nicotine in this study was variable and small in magnitude, Morrison suggested that the conclusions drawn were speculative and that further work should be carried out in a larger, matched sample. However, she also noted that the effect of nicotine resembled in most cases the effects of amphetamine upon punished responding. This finding was replicated by Glowa (1986); although, Furusawa and Tadokoro (1990) demonstrated that nicotine had no effect on conflict behaviour and concluded that more work must be carried out to specify the exact mechanism of action of nicotine if any in punishment schedules.

The only human studies that have looked at the effects of nicotine upon punished responding were those of Bennett and Cherek in the late 1980's and early 1990's. In

the first of these studies (Cherek and Bennett, 1989) the effects of nicotine on a free-operant avoidance schedule (in which absence of lever pressing would result in point loss every 5 seconds and a lever press would postpone point subtractions by 20 seconds) was examined. Three smokers (all of whom had smoked for at least 4 years) were given either placebo, nicotine gum (2, 4 or 8 mg nicotine) or 7, 15 or 30 puffs from a low yield cigarette (0.42mg nicotine) or high yield cigarette (2.14mg nicotine). This study demonstrated that smoking nicotine-containing cigarettes resulted in dose-dependent increases in avoidance responding compared to non-smoking baseline data, but that chewing nicotine-containing gum did not produce any changes in avoidance responding compared to baseline. These results suggested that nicotine administered via cigarettes increases responses that result in the most favourable outcome. The fact that no change in avoidance responding was observed with the nicotine-containing chewing gum was attributed to the different amounts of time the different methods of administration took to alter nicotine concentrations in the body.

In another study (Bennett et al., 1989), nicotine dose-related decreases in punished responding (i.e. an enhanced response to punishers in the form of further suppression) were observed. In this study, Bennett et al. used five smokers and the spirometry method of smoke inhalation to test what effect twenty 60cc puffs of either sham, 1.2 (low yield) or 2.7mg (high yield) nicotine-containing cigarettes would have on punished and unpunished responding compared to a baseline 0.3mg nicotine yield cigarette condition. In these studies, lever pulling was maintained by a variable interval (VI) 20 second schedule of point presentation and suppressed by point subtraction on a variable ratio (VR) 30 schedule (the punishment contingency). The same group extended this work to ten male smokers and the same effect, decreases in punished responding, resulted. However, when the punishment contingency was omitted, no consistent effect of nicotine on non-punished responding was observed (Cherek and Bennett, 1991). These two studies provide evidence that nicotine further suppresses punished responding.

In the last of this series of studies, Bennett and Cherek extended their original study by looking at the effect of nicotine administration or abstinence upon the same avoidance responding task in 6 smokers. The results showed that there were no consistent effects of nicotine abstinence on avoidance responding, two subjects increased, two subjects decreased and two subjects displayed no effect at all on avoidance responding. This study also found that there were inconsistent effects of different doses of nicotine on avoidance responding, with just one subject showing a significant increase in avoidance responding following a 2.7mg nicotine yield cigarette compared to baseline with the other subjects showing minimal changes to their responses (Bennett and Cherek, 1991). It is difficult to explain the variability in these results but it could possibly be that the smokers were poorly matched in terms of their level of nicotine dependence or their lengths of abstinence. Unfortunately, not enough details were reported for firm conclusions to be made. Further studies in humans are required using larger numbers of participants and a greater number of punishment sensitivity measures in order to conclusively see if smoking or abstinence from smoking modulates sensitivity to punishment.

1.3.5 Performance Monitoring

Performance monitoring is essentially a mechanism for monitoring on-going performance so that cognitive control can be implemented when required (Alexander and Brown, 2010). While there is much debate over the precise details of the monitoring system (Alexander and Brown, 2010) several influential models suggest that the monitoring system is associated with activity in an area of the medial prefrontal cortex known as the anterior cingulate cortex. For example, electrophysiological studies using event-related potentials (ERPs) measured during a task giving positive and negative feedback demonstrate that receiving this feedback can alter the ERP trace produced (Mathalon et al., 2003). In fact, there is a characteristic negative deflection observed in an ERP trace upon receiving negative feedback and making an error and the origin of this negative deflection on the ERP trace is the anterior cingulate cortex (Ruchsow et al., 2002; Van Veen and Carter, 2002; Nieuwenhuis et al., 2004 and Hajcak et al., 2006). Holroyd and Coles (2002)

suggest that error detection be thought of in terms of reinforcement learning. They argue that when an error in performance occurs this will generate a negative prediction error (i.e. the difference between actual and expected outcome) which is carried to the anterior cingulate cortex via the midbrain dopamine system and that these error signals can then provide an indication that greater cognitive control is required, resulting in further recruitment of motor, attention or inhibitory mechanisms. In line with this, Bryden et al. (2011) find that the anterior cingulate cortex not only signals errors in reward prediction but is also active on trials subsequent to an error (following an unexpected change in reward outcome) when attention was also found to be increased. This finding has led Bryden et al. to argue that the anterior cingulate cortex may also signal the need for greater neural resources after an error. Interestingly, individual sensitivity to reward or punishment may be related to a correspondingly sensitive error monitoring system (Frank et al., 2005). For example, self-report punishment sensitivity has been linked to functioning of the anterior cingulate cortex (Boksem et al., 2006; Amodio et al., 2008; Balconi and Crivelli, 2010a, 2010b).

Nicotine has been shown to alter activity in the anterior cingulate cortex (e.g. Li et al., 2008 and Kumari et al., 2003). ERP studies have shown that error monitoring is reduced in smokers compared to non-smokers (Franken et al., 2010; Luijten et al., 2011a). For example, Luijten et al. show that smokers have a reduced error-related negativity compared to non-smokers when performing a flanker task in the presence of smoking cues. Similarly, De Ruiter et al. (2009) using functional Magnetic Resonance Imaging showed prefrontal hypoactivity in smokers during receipt of negative feedback on a probabilistic reversal learning task. Interestingly, Nestor et al. (2011) show that former smokers have increased prefrontal activity during error monitoring compared to both current and never smokers. Taken together these studies suggest that there is reduced error processing in smokers, a feature which may contribute to continued smoking despite full knowledge of the adverse consequences of doing so. Furthermore, the Nestor et al. study suggests that elevated cognitive control may be a feature of successful abstinence; however the

direction of causality cannot be inferred from the cross-sectional design used in that study.

1.3.6 The Loss Aversion Bias, Cognitive Control and Addiction

The loss aversion bias is a bias in decision making reflecting the tendency for individuals to be more sensitive to losses compared to gains, typically resulting in individuals rejecting gambles with 50:50 odds unless the amount that can be won is approximately twice the amount that could be lost (Tversky and Kahneman, 1992). The neural basis of loss aversion is beginning to be understood. For example, Tom et al. (2007) find greater frontal cortical sensitivity to increasing losses compared to equivalent increases in gains. Furthermore, Tom et al. suggest that substance abusers may be less loss averse (showing diminished neural sensitivity to losses) compared to healthy populations. In line with this, several commentators have proposed that studies integrating methods and approaches from behavioural economics and cognitive neuroscience may provide greater insights into the nature of substance dependence and its treatment (e.g. Takahashi, 2007; Tom et al., 2007; Chivers and Higgins, 2012; Rosen, 2012).

Besides performance monitoring, attentional biasing has received great attention in theories of cognitive control (Alexander and Brown, 2010). In the context of cognitive control, attentional biasing refers to control of attention towards cues that will drive behaviour, where that behaviour is consistent with the bias. For example, in a choice task an attentional bias in response to loss might drive attention to actual or possible losses and trigger cognitive control so as to drive behaviour away from losses. In line with this, losses have been proposed to orient attention (Yechiam and Hochman, 2012) and furthermore, loss averse individuals have been shown to pay more attention to losses (Janowski and Rangel, 2011). If diminished loss aversion contributes to substance abuse (as postulated by Tom et al., 2007), it is conceivable that elevated loss aversion could contribute to 'relapse resilience' in former addicts. Empirical work in this area is lacking, however.

1.3.7 Summary

Pro-cognitive effects of nicotine are well documented in non-smokers and smokers alike. In addition, cognitive deficits in withdrawal from smoking are similarly well established. The cognitive process of decision making, which concerns itself with the consequence of choice, has here been de-constructed into three sub-components. Perhaps unsurprisingly there has been much research on the effects of nicotine, smoking and withdrawal from smoking on reward sensitivity and this is most likely due to the fact that reward systems are fundamentally involved in addiction. In contrast, not so much research has investigated the effects of nicotine, smoking and withdrawal from smoking on punishment sensitivity despite imaging studies showing reduced frontal cortical activation in response to errors (performance monitoring) in current smokers compared to non-smokers. Several small-scale animal and human studies have been conducted with inconsistent findings. However despite the incongruent findings from previous studies, a common finding from one group in particular (the Bennett and Cherek studies) is that nicotine further suppresses punished responding, a result that is consistent with nicotine increasing punishment sensitivity. The lack of behavioural work is surprising since a hallmark feature of substance dependence is continued drug use despite the negative consequences of continued use and reduced sensitivity to punishment may be predicted to contribute to the maintenance of drug use. Furthermore if smoking is maintained, at least in part, by a reduced sensitivity to punishment, it is conceivable that normalised or enhanced sensitivity to punishment or loss aversion might contribute to successful long-term abstinence from smoking.

1.4   Experimental Aims

1.4.1   Experimental Aims of this Thesis

Smokers continue to smoke despite appreciation of the adverse consequences of doing so. Therefore smokers may have reduced sensitivity to punishment compared to non-smokers. The main aim of this thesis is to provide a behavioural examination of punishment sensitivity in dependent smokers. This includes an investigation of the

effects of both satiation level (satiated and abstinent) and smoking status (current, former and never smokers) on punishment sensitivity. It is hoped that this work will add to existing knowledge regarding the maintenance of drug use. In this respect, the aims of this thesis are not to question existing theories regarding factors that contribute to continued drug use (e.g. alterations in reward system sensitivity, relief of withdrawal symptoms, inhibitory control etc.) but instead to elucidate the potential role that punishment sensitivity may also have. A further aim of this thesis is to compare former and never smokers on a range of self-control measures. Impairments in self-control are associated with addiction and strengthening self-control may be a potential target for addiction treatments. However it is unknown which specific aspects of self-control are most important for maintaining abstinence and this work addresses this question. Ultimately it is hoped that this thesis will lead to a greater understanding of processes that may contribute to the maintenance of drug use and factors that may contribute to successful long-term abstinence. It is further hoped that such an understanding will translate into more efficacious pharmacological or psychological treatments for addiction that lead to improved cessation rates.

1.4.2   Thesis Outline

Chapter 2 will describe the methods used in this thesis although specific methodologies, procedures and statistical techniques used for each study will be described in the appropriate chapters. Chapters 3, 4, 5 and 7 are experimental chapters (described below) and Chapter 6 is a chapter extending analyses of data collected in a previous chapter (also described below). Chapters 3 to 5 mainly focus on punishment sensitivity whereas Chapters 6 and 7 mainly focus on aspects of cognitive/self-control. In Chapter 3, two operant tasks are evaluated for their ability to assess punishment sensitivity in order to see if either would be suitable for future studies assessing punishment sensitivity in smokers. Chapter 4 compares punishment sensitivity in abstinent and satiated smokers and Chapter 5 assesses punishment sensitivity in current smokers (both satiated and abstinent), former smokers and never smokers. Chapter 6 uses reaction time data obtained from tasks used in

Chapter 5 to examine post-punishment slowing and reaction time variability in order to draw conclusions regarding cognitive control in current, former and never smokers and Chapter 7 compares former smokers and never smokers on a range of self-control measures. Specific aims and hypotheses are described in more detail in each chapter. Finally Chapter 8 aims to integrate and discuss the main findings of this thesis in relation to existing knowledge. In addition, this chapter provides a discussion on both the limitations of the current work and directions for future research following on from the current work.

Chapter 2   General Methods

2.1   Overview

This chapter describes the various physiological, subjective, questionnaire, cognitive and behavioural measures used in the experimental chapters that follow. The remaining methodological details for each study are located in the individual methods sections found in each experimental chapter.

2.2   Physiological Measures

2.2.1   Breath Alcohol Test

Breath alcohol was measured using a breathalyser (Lion Alcometer SD-40; Lion Laboratories Ltd., Cardiff, UK). Participants were instructed to provide a breath sample by exhaling at a sustained, constant rate through the mouthpiece. Breath alcohol was recorded in grams per litre (g/L).

2.2.2   Exhaled Carbon Monoxide Test

Exhaled carbon monoxide (CO) was measured using a Smokerlyzer (Bedfont Micro Smokerlyzer; Bedfont Scientific Ltd., Kent, UK). Participants were instructed to hold their breath for 15 seconds before emptying their lungs fully by exhaling slowly through the mouthpiece. Exhaled CO was recorded in parts per million (ppm).

2.3   Drug Use Questionnaires

2.3.1   Fagerstrom Test for Nicotine Dependence

The Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991) is a six item self-report measure assessing tobacco dependence through its behavioural symptoms (e.g. "How soon after you wake up do you smoke your first cigarette?" and "How many cigarettes per day do you smoke?"). The overall score of the FTND ranges between 0-10 with greater scores indicating greater levels of dependence. The FTND has been used extensively in the smoking research literature and as a result it is often

described as the gold standard dependence measure. However, the FTND does not cover all aspects of the dependence syndrome (e.g. escalation of/loss of control over use and unsuccessful quit attempts) and these limitations are also noted in the literature (e.g. Perez-Rios et al., 2009).

2.3.2 Medicinal Drug, Alcohol and Illicit Drug Use Questionnaire

The Medicinal Drug, Alcohol and Illicit Drug Use Questionnaire (MAID) was used as a self-report screening tool to assess participants study inclusion eligibility. The questionnaire consisted of three parts: 1) a question on current herbal, over the counter and prescription medication use, 2) questions about the quantity and frequency of alcohol use over the previous six months assessed using the Alcohol Use Questionnaire (AUQ; Mehrabian and Russell, 1978), 3) questions about life-time illicit drug use and current illicit drug use (over the previous week) assessed using a Drug Use Questionnaire (DUQ; based upon that used by Townshend and Duka, 2005) and including amphetamines, cocaine, MDMA, opiates, hallucinogens and cannabis.

2.3.3 Nicotine Dependence Syndrome Scale

The Nicotine Dependence Syndrome Scale (NDSS; Shiffman et al., 2004) was used to assess tobacco dependence. The scale is based upon the concept of a dependence syndrome and reflects the Diagnostic and Statistical Manual of Mental Disorders (DSM-III and DSM-IV; American Psychiatric Association, 1980, 1994) criteria for dependence. The NDSS is a nineteen item self-report measure, where each item is rated on a five point Likert-type scale ranging from 'not at all true' to 'extremely true'. The NDSS generates an overall dependence score and scores for each of five factors (drive assessing craving and withdrawal symptoms in abstinence as well as compulsion to smoke, priority assessing the tendency to prefer smoking over other reinforcers, tolerance assessing reduced sensitivity to the effects of smoking, continuity assessing the regularity of smoking, and stereotypy assessing if smoking is varied by other things or situations). The current work used the overall score only.

2.4 Mood-Related Questionnaires

2.4.1 Beck Depression Inventory

The Beck Depression Inventory (BDI; Beck et al., 1961; Beck and Steer, 1984) was used to assess depression severity. BDI is a twenty one item self-report measure of depressive symptoms (including affective, behavioural, cognitive, somatic and physical symptoms) within the past week. Participants were required to rate each item from 0-3 in terms of perceived intensity, yielding a score range of 0-63 where higher scores indicate greater depression severity. As a guide scores in the ranges 0-13, 14-19, 20-28 and 29-63 are considered minimal, mild, moderate and severe respectively. BDI correlates well with clinician-rated measures of depression such as the Hamilton Depression Rating Scale (Hamilton, 1980).

2.5 Personality Questionnaires

2.5.1 Barratt Impulsiveness Scale

The Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) was used to assess impulsiveness. BIS-11 is a thirty item self-report measure describing common impulsive or non-impulsive (for the eleven reverse scored items) situations. Participants were required to rate how often these situations occurred for them on a four point Likert-type scale ranging from 'rarely/never' at one extreme to 'almost always/always' at the other. The BIS-11 generates an overall 'impulsiveness' score and three second-order factors (attentional impulsiveness which assesses task focus and intrusive thoughts, motor impulsiveness which assesses the tendency to act on the spur of the moment and perseveration and non-planning impulsiveness which assesses planning, self-control and enjoyment of challenging tasks). The current work used the overall 'impulsiveness' score only.

2.5.2 Behavioural Inhibition System/Behavioural Activation System Scales

The Behavioural Inhibition System/Behavioural Activation System Scales (BIS/BAS; Carver and White, 1994) were used as a subjective assessment of reward and punishment sensitivity. Several theories (e.g. Gray, 1972; 1981) argue that two motivational systems underlie behaviour: a behavioral approach system (BAS) that regulates appetitive motives, in which the goal is to move toward something desired, and a behavioral avoidance (or inhibition) system (BIS) that regulates aversive motives, in which the goal is to move away from something unpleasant. BIS/BAS is a twenty four item self-report measure, where each item is rated on a four point Likert-type scale ranging from 'very true' to 'very false'. Four factors are derived from the BIS/BAS scales; one which assesses overall trait activation of the BIS, and three which assess separate aspects of trait activation of the BAS (reward responsiveness assessing positive responses to the anticipation or occurrence of reward, drive assessing pursuit of desired goals, and fun seeking assessing willingness to approach new things).

2.5.3 Penn State Worry Questionnaire

The Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990) is a sixteen item self-report measure that assesses worry, where each item is rated on a five point Likert-type scale ranging from 'not at all typical of me' to 'very typical of me'. The PSWQ assesses worry in general without focusing on any particular domains of worry but instead focusing on the excessiveness and uncontrollability of worry symptoms. Lower scores on the PSWQ indicate less, or more controlled, worrying.

2.5.4 Rumination-Reflection Questionnaire

The Rumination-Reflection Questionnaire (RRQ; Trapnell and Campbell, 1999) is a twenty four item, two scale self-report measure where each item is rated on a five point Likert-type scale ranging from 'strongly disagree' to 'strongly agree'. The RRQ distinguishes between maladaptive and adaptive components of self-awareness such that twelve items assess ruminative self-focus and twelve items assess self-curiosity

and reflective thinking. Higher scores on each of the scales represent greater rumination and reflection.

2.5.5 Scott-McIntosh Rumination Inventory

The Scott-McIntosh Rumination Inventory (SMRI; Scott and McIntosh, 1999) is a nine item self-report measure, where each item is rated on a seven point Likert-type scale ranging from 'does not describe me well' to 'does describe me well'. The SMRI assesses the extent to which people engage in rumination as a consequence of non-attainment of goals. Specifically, the questionnaire measures three aspects of this type of rumination: distraction which assesses the degree to which people are distracted by ruminative thoughts regarding their goals, Emotionality which assesses the degree to which people experience emotions in connection with ruminative thoughts about failed goal attempts, and motivation which assesses the degree to which people are motivated to do something to reduce ruminative thoughts about failed goal attempts. Higher scores indicate greater levels of rumination.

2.6 Subjective Measures

2.6.1 Nicotine-Sensitive Visual Analogue Scales

The Nicotine-Sensitive Visual Analogue Scales (NicVAS; based on Perkins et al., 1999, 2003; and as used in Jackson et al., 2009 and Nesic et al., 2011a) comprised a set of eleven 100 mm scales anchored at each end by 'not at all' and 'extremely'. The items used were: 'stimulated', 'buzzed', 'impatient', 'alert', 'irritable', 'jittery', 'dizzy', 'relaxed', 'hungrier than usual', 'thirsty' and 'contented'. NicVAS has previously been shown to be sensitive to acute smoking and abstinence from smoking (see Jackson et al., 2009 and Nesic et al., 2011a).

2.6.2 Questionnaire of Smoking Urges – Brief

The Questionnaire of Smoking Urges - Brief (QSU-Brief; Cox et al., 2001) is a ten item self-report measure of craving developed from the thirty two item full version (Tiffany and Drobes, 1991). The QSU-Brief uses a seven point Likert-type scale

ranging from 'strongly agree' to 'strongly disagree' and generates an overall craving score and scores for two further factors (factor 1 - assesses the desire to smoke in anticipation of positive outcomes from smoking and factor 2 - assesses the urge or need to smoke in anticipation of relief from withdrawal). The current work used the overall craving score only.

2.7 Cognitive and Behavioural Measures

2.7.1 Cambridge Gambling Task

The Cambridge Gambling Task (CGT; Rogers et al., 1999) was used to assess decision making under risk outside of a learning context. As such, relevant information was presented to the participants 'up-front' and there was no need to learn or retrieve information over consecutive trials. Participants were presented with an array of 10 boxes coloured red and blue, in varying ratios of red:blue. The participant was required to make a probability judgement on which colour box hid a concealed yellow token and then make a wager based on the confidence of their decision. Wagers were made by betting a proportion of points and the overall aim of the task was to try to accumulate as many points as possible. Wagers were made under two conditions, ascending (where the longer a participant waited the greater the proportion of their points they could bet) and descending (where the longer a participant waited the smaller the proportion of their points they could bet). The CGT outcome measures are: quality of decision making (the proportion of trials where the majority colour was selected), deliberation time (mean decision making latency), risk taking (mean proportion of the current points total bet when the majority colour was selected), overall proportion bet (mean proportion of the current points total bet on all trials, including betting on less likely and equally likely outcomes), risk adjustment (reflecting the tendency to bet a higher proportion of points when the majority of boxes were the colour chosen than when a smaller majority of the boxes were the colour chosen) and delay aversion (reflecting the inability to wait in order to bet larger amounts when bets were presented in ascending order compared to descending order). Risk adjustment was calculated as twice the mean proportion

risked on trials when 9 of the 10 boxes matched the colour chosen plus the mean proportion risked on trials when 8 of the 10 boxes matched the colour chosen, minus the mean proportion risked on trials when 7 of the 10 boxes matched the colour chosen minus twice the mean proportion risked on trials when 6 of the 10 boxes matched the colour chosen, divided by the mean proportion risked over all of these trials. Delay aversion was calculated by subtracting risk taking for ascending trials from risk taking for descending trials. The CGT is part of the CANTAB test battery (Cambridge Cognition Ltd., Cambridge, UK). Figure 2.1 shows a screen-shot of the CGT.

Figure 2.1: Cambridge Gambling Task
Screen-shot of the Cambridge Gambling Task. In this example, the majority box colour is blue. Therefore the yellow token is most likely to be hidden behind a blue box. The colour blue was selected (as indicated by the high-lighting around the box containing the word 'blue') and currently 75 points of the 100 total points can be wagered. The 75 points would rise (in the ascending condition) or fall (in the descending condition) with time so that participants have the opportunity to wager a larger or smaller proportion of their total points.

2.7.2 Coin Flip Task

The Coin Flip Task (CFT; adapted from Fehr and Goette, 2007 and Gachter et al., 2010) was used to assess loss aversion (λ). λ is a bias in decision making under risk

that reflects the tendency for individuals to be more sensitive to losses compared to gains. In the CFT participants were required to decide whether they wanted to accept (that is, play for the chance to win £8) or reject (and receive nothing) a series of 15 wagers. Each wager had odds of 50:50 (a coin flip) and the potential win for each wager was fixed at £8. Only the potential loss varied between wagers from £1 to £15. Participants were told that at the end of the study one of the accepted wagers would be picked at random and played for real. This was done so that the data obtained would reflect real life λ. In reality whereas coin flip wins were honoured with £8, coin flip losses were waivered such that losing participants did not receive either the £8 win or any penalty (however all participants were compensated for their time as described in the methods sections of each experimental chapter). An estimate of λ was calculated from the CFT using the equation: λ = potential gain (£8)/level of acceptable loss (£1 to £15). The CFT was presented as a pen and paper test. Figure 2.2 shows the format of the CFT wagers.

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1.   If the coin turns up heads, then you lose £1;
      If the coin turns up tails, you win £8.

2.   If the coin turns up heads, then you lose £2;
      If the coin turns up tails, you win £8.

3.   If the coin turns up heads, then you lose £3;
      If the coin turns up tails, you win £8.

      ….   ….   ….   ….   ….   ….   ….
      ….   ….   ….   ….   ….   ….   ….

15.   If the coin turns up heads, then you lose £15;
      If the coin turns up tails, you win £8.

Figure 2.2: Coin Flip Task
This shows the format of the Coin Flip Task wagers. Participants were presented with fifteen wagers each with odds of 50:50, a fixed win of £8 and a variable loss ranging £1 to £15. Participants were instructed to select which of the wagers they would accept and which they would reject to play for real money.

2.7.3 Differential Reinforcement of Low Rates Task

An operant conditioning task based on a differential reinforcement of low rates (DRL) schedule (whereby a minimum amount of time must elapse between responses in order for reinforcement to occur and premature responses act to reset this time) was used as a measure of ability to use positive and negative feedback to guide behaviour. Participants were instructed that they could gain points by repeatedly pressing a response button. It was explained that points would be gained if each response occurred after a set period of time had elapsed, however the exact time that had to elapse between responses was not made known to participants. The task consisted of 40 trials. Before each trial participants were presented with a crosshair for 2 seconds and removal of the crosshair from the screen indicated the start of a new trial. For the first 20 trials, 10 points and a smiley face feedback picture where presented for 2 seconds if a response was made after 11 seconds but before the end of the trial (16 seconds). However, if the response was made before 11 seconds or if no response was made by the end of the trial participants would lose 10 points and a sad face feedback picture would be presented for 2 seconds. After either the positive or negative performance feedback a crosshair would be presented followed by the next trial thus resetting the timer so that no points were available until 11 seconds had elapsed. For the last 20 trials the DRL schedule changed such that points were available if a response was made between 13 seconds and the end of the trial (18 seconds). The purpose of changing the schedule was to encourage greater levels of premature responding during the second half of the task, so that participants received more negative feedback. Levels of premature responding were recorded throughout the task as an index of ability to use feedback to guide behaviour. The DRL task was programmed and administered using E-Prime version 1.1 (Psychology Software Tools Inc., Pittsburgh, PA, USA). Figure 2.3 shows the DRL task diagrammatically.
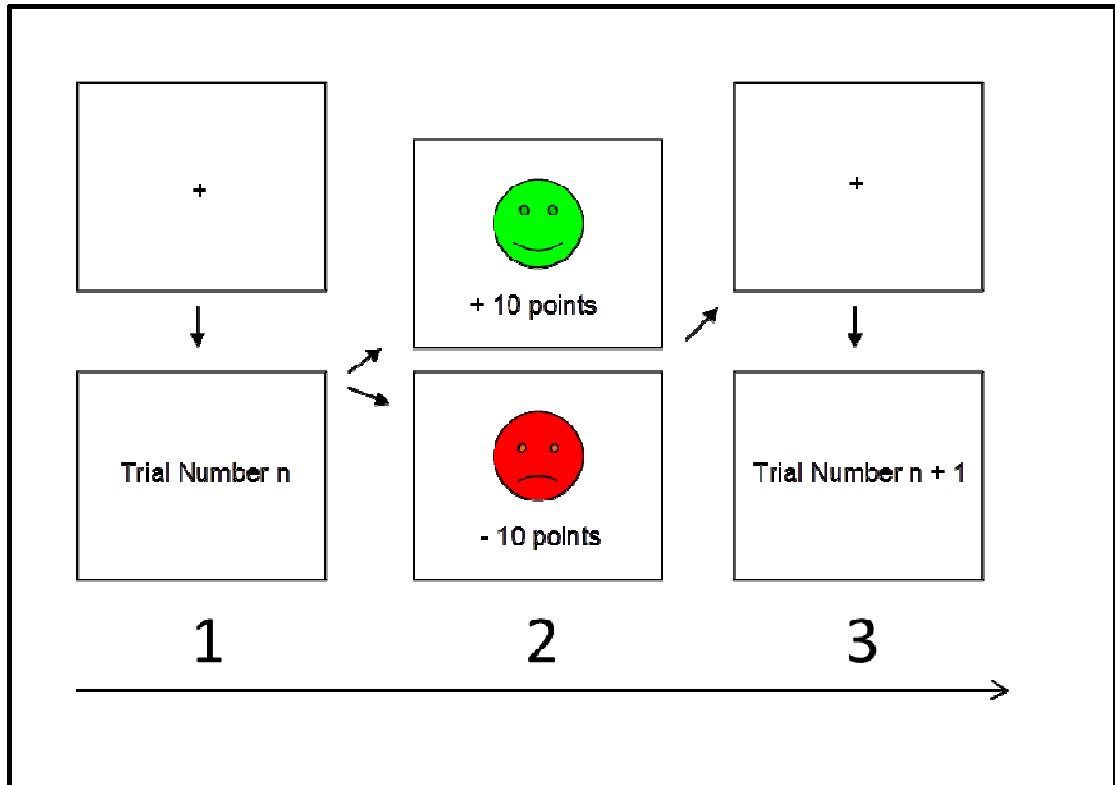
Figure 2.3: Differential Reinforcement of Low Rates Task
1. The inter-trial crosshair changing to a screen with the trial number displayed indicated that the DRL schedule had started. 2. If an appropriate response was made positive performance feedback was displayed. This took the form of a smiling face and point gain. If no response was made or if responding occurred too soon negative performance feedback was displayed. This took the form of an unhappy face and point loss. 3. The inter-trial crosshair changing to a screen with the trial number displayed indicated that the DRL schedule had been reset for the next trial (after negative performance feedback) or restarted for the next trial (after positive performance feedback).

2.7.4 Digit Span Task

The Digit Span Task (DST; based on Wechsler, 1981) is a measure of working memory. Participants were read strings of digits at a rate of one digit per second and were instructed to repeat back the digit string either forwards or in reverse. The test begun with a string of three digits and the string increased in length until the participant committed errors. There were three sequences of digits at each string length and participants had to correctly repeat at least one of the sequences in order to progress to the next string length. Two lists containing the number sequences were created

(one for digit span forward and one for digit span backwards). The digit stimuli for the sequences of digit strings in the lists were selected randomly with replacement from the digits 0-9. The digit span forwards and backwards is the maximum string length that was correctly recalled.

2.7.5   GoStop Task

The GoStop Task (GST; Dougherty et al., 2005) was used to assess response inhibition. In the GST five-digit numbers were presented in black font in rapid sequence to participants. There were 320 trials in total and 160 of these were target trials (where two consecutive numbers matched). Half of the target trials were go trials and half were stop trials. Participants were instructed to make a response as quickly as possible when two consecutive numbers matched (go trials) but to try to withhold from making a response if the matching number changed from black font to red font (stop trials). On stop trials the black font changed to red font at varying intervals (known as the stop signal delay) such that the interval was initially 250 ms but adjusted by 50 ms steps. The stop signal delay increased if participants were successful at inhibiting responding and decreased if participants were unsuccessful at inhibiting responding so that the task finds the delay at which the response inhibition rate is approximately 50% (i.e. the time interval at which processes of response inhibition and response execution are tied). The remaining 160 trials were novel trials (where consecutive numbers didn't match) and participants were instructed not to respond on these trials. The GST outcome measures were: the number of responses made on go, stop and novel trials, the average response latency on go trials, the 50% stop signal delay (SSD; this is the stop signal delay at which participants were able to withhold responding 50% of the time) and the 50% stop signal reaction time (SSRT; this is an estimate of the time required to inhibit a response and is calculated by subtracting the SSD from the mean response latency of trials where inhibition occurred 50% of the time). As well as assessing response inhibition the GST was used to assess performance monitoring. Response reaction times following errors are increased compared to response reaction times that do not follow errors and this increase in reaction time is thought to reflect cognitive processes involved in error

correction (Rabbit, 1966). Post signal slowing (PSS; the reaction time difference between go trials that immediately followed a stop trial and those that do not follow a stop trial) is thought to index a similar process and has previously been used as a measure of performance monitoring in stop-signal tasks (Li et al., 2006). PSS was calculated in addition to the other GST outcome measures. Figure 2.4 shows the GST diagrammatically.
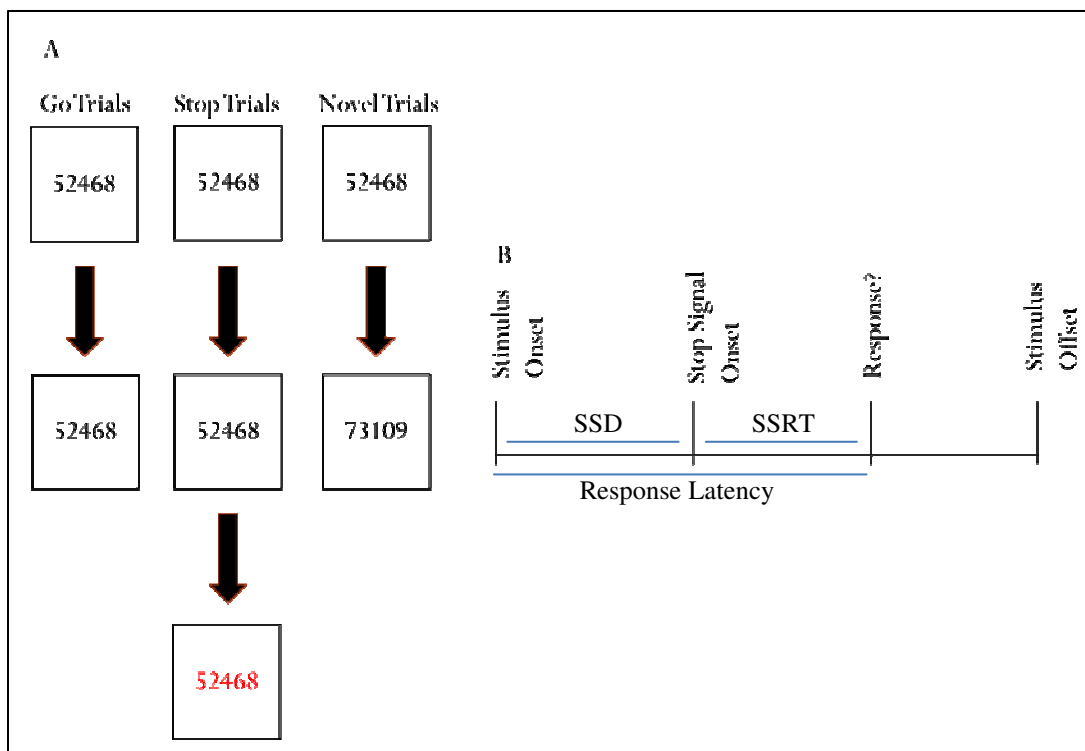
Figure 2.4: GoStop Task
A: Participants were instructed to respond as quickly as possible on go trials, to try to withhold responding on stop trials and not to respond on novel trials. B: The stop signal delay was initially 250 ms adjusting by 50 ms depending on performance. The 50% stop signal delay (SSD) is the stop signal delay at which participants were able to withhold responding 50% of the time and the 50% stop signal reaction time (SSRT) is an estimate of the time required to inhibit a response and is calculated by subtracting the SSD from the mean response latency of trials where inhibition occurred 50% of the time.

2.7.6   Immediate Word Recall Test

The Immediate Word Recall Test (IWR) is a measure of short-term memory. Participants were read a twenty item list of words at a rate of one word every two seconds. Once the list had been read participants were immediately required to recall as many words as possible in any order. Two word lists were created based on those used by Rusted and Warburton (1989) which were matched for number of syllables, word frequency and imagery. The lists were counterbalanced across participants such that each participant received only one of the lists. The IWR score is the number of items recalled.

2.7.7   Iowa Gambling Task

The Iowa Gambling Task (IGT; Bechara et al., 1994) assesses decision making under risk in a learning context. Participants were presented with 4 virtual decks of cards on a computer screen and were instructed that they must select one of the decks on each turn. Participants started with a virtual loan of £2000 game money and were told that the object of the task was to make as much money as possible by the end of the task and that some decks may be better than others to achieve this goal. Each time they chose a card, participants would win some game money. Every so often, however, choosing a card caused participants to lose some money as well as the usual win. Two decks were 'bad decks' and two decks were 'good decks' because over the long run they lead to losses and wins respectively. The 'bad decks' and 'good decks' differed from each other in a number of ways i.e. the reward for selecting the deck on each trial, the amount that was lost on each selection and the number of trials over which losses were distributed. These differences and a screenshot of the IGT are shown in Figure 2.5. The task was complete after 100 deck selections however participants were unaware of this and instructed to keep selecting decks until the task finished. Performance on the IGT was indexed by looking at the number of deck selections across five 20 trial bins and subtracting 'bad deck' selections from 'good deck' selections across these same bins. Performance on the IGT was used to reflect performance monitoring since the task required participants to monitor the feedback of their deck selections across trials and integrate this information to guide

responding. The IGT was administered with PEBL version 0.11 (available from http://pebl.sourceforge.net/battery.html).

Figure 2.5: Iowa Gambling Task
A: This shows a screenshot of the Iowa Gambling Task with an example of the feedback received after a deck selection. B: Table showing the differences between the four decks (two 'good' and two 'bad') on the Iowa Gambling Task.

2.7.8   National Adult Reading Test

The National Adult Reading Test (NART; Nelson, 1982) was used as an estimate of intellectual ability. NART comprises a list of 50 short, irregular words of increasing complexity. Pronunciation of irregular words in the English language cannot be deduced by relying upon the common rules of grapheme-phoneme representation and pronunciation which apply to the majority of regular words. It is therefore supposed that the ability to read irregular words reflects previous familiarity with them (an index of intellectual ability). Participants were required to read aloud each

word and were encouraged to attempt every word even when they were uncertain about the pronunciation. The NART error score (number of words read incorrectly) was recorded.

2.7.9 Probabilistic Reversal Learning Task

The Probabilistic Reversal Learning Task (PRL; based on the task used by Budhani et al., 2006) was used to assess responsivity to negative feedback. This task used 12 line drawings paired together to produce 6 pairs of different stimuli. The stimuli were presented together in these pairs for the duration of the task (280 trials). In order to progress through the task, participants were required to select one stimulus from each pair. One stimulus from each pair was associated with a reward (point gain) and the other with a punishment (point loss). Two different versions of this task were used in the studies that follow and the versions differed only in the reward and punishment contingencies that determined which stimulus would result in point gain or point loss on each trial (the contingencies of the pairs were either 100-0% or 80-20% for one version of the task and 80-20% or 70-30% for the other). Participants were instructed to select the stimulus which they believed was rewarding them on the majority of occasions and to stick with it even if it was occasionally incorrect. However, participants were told to switch responding to the alternate stimulus should they believe that the stimulus was no longer rewarding them on the majority of occasions (and was instead punishing them more often than not). There are two phases to each stimulus pair presentation, an acquisition phase where the stimulus pairs are first encountered (either 20 or 40 trials per pair) and the contingencies of the pairs can be learned, and a reversal phase in which some of the pairs reverse contingency (either 20 or 40 trials per pair) so that a stimulus which was previously rewarded is now punished and vice versa. As in Budhani et al. (2006) there were 2 reversing pairs, 2 non-reversing pairs and 2 dummy pairs (that had an acquisition phase only). In order to increase task difficulty, rather than deal with each stimulus pair serially participants had experience with two different pairs at a time. This was done because serial presentation may have allowed participants to easily calculate that reversals occurred after a set number of trials. In addition, the presence of non-

reversing pairs also meant that participants would not easily know when a reversal would occur. As in Budhani et al. (2006) the main outcome measures are win-shift errors (after a correct response that was rewarded the participant incorrectly shifts to the incorrect response on the subsequent trial - a measure of impulsiveness), lose-stay errors (after an incorrect response that was punished the participant stays with the incorrect response on the subsequent trial - these perseverative errors are a measure of punishment sensitivity) and win-maintenance failures (after a correct response that was punished, the participant fails to maintain the correct response and wrongly shifts to the incorrect response - this over-reaction to false feedback was also a measure of punishment sensitivity). Reaction time data for all PRL responses was also recorded. Additionally, the number of trials taken to reach a learning criterion of 6 consecutive correct responses in acquisition phases was calculated as a measure of contingency learning. Since calculation of the main outcome measures relied upon information from the preceding trial all trials were included in analyses except the very first trial. The PRL task was programmed and administered using E-Prime version 1.1 (Psychology Software Tools Inc., Pittsburgh, PA, USA). Figure 2.6 shows the main outcome measures of the PRL task diagrammatically.
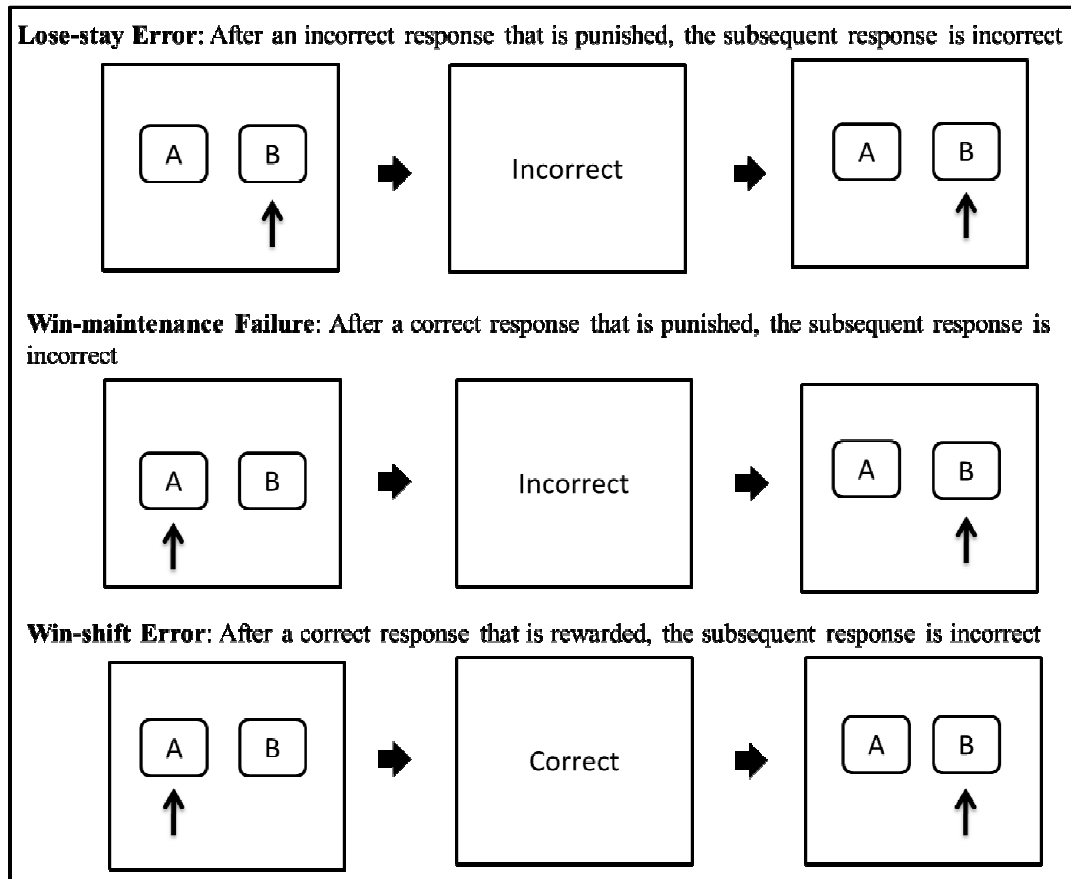
Figure 2.6: Probabilistic Reversal Learning Task
The Probabilistic Reversal Learning Task outcome measures were: lose-stay errors, win-maintenance failures and win-shift errors. In this example stimulus A is the correct stimulus and stimulus B is the incorrect stimulus.

2.7.10 Rapid Visual Information Processing Task

The Rapid Visual Information Processing Task (RVIP; based on Wesnes and Warburton, 1984) was used to assess sustained attention (vigilance). A five minute version of the task was used as has been used previously (e.g. Jackson et al., 2009). Participants were required to monitor a continuous stream of digits, presented at a rate of eighty digits per minute, and to press a response button whenever they saw either three consecutive odd or three consecutive even digits. There were eight such target strings of digits in each one minute block. The number of correct detections of targets ('hits') were recorded within a 1500 ms window following the onset of the third digit in the target sequence. The average latency of correct detections (ms) and the number of false alarms (responses to non-targets) were also recorded. The RVIP

was programmed and administered using E-Prime version 1.1 (Psychology Software Tools Inc., Pittsburgh, PA, USA). Figure 2.7 shows the RVIP diagrammatically.
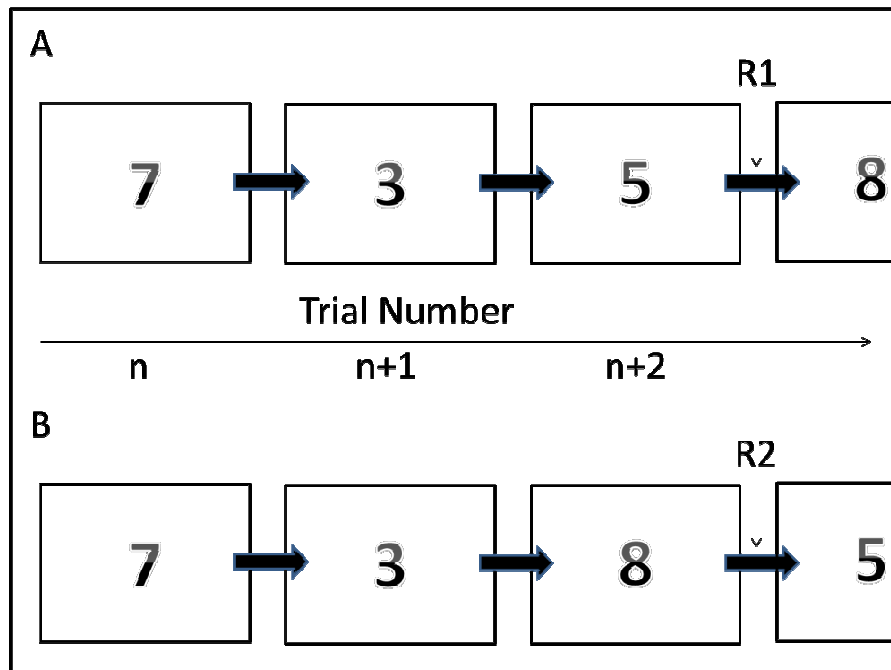
Figure 2.7: Rapid Visual Information Processing Task
A: A response at R1, after 3 consecutive odd or even numbers (targets), was recorded as a 'hit' provided the response was made within 1500 ms of the onset of the third digit in the target sequence. Failure to respond at R1 was classified as a 'miss'. B: A response at R2, when no target has been presented, was recorded as a false alarm.

2.7.11 Reward and Reward/Punishment Task

The Reward and Reward/Punishment Task (RARP; based on Cherek and Bennett, 1991) is an operant conflict task that was used to assess responsivity to reward and punishment. It was explained to participants that they must make responses in order to try to gain as many points as possible. Rules about how to press in order to achieve this goal were not explained to the participant. Points were available on a variable interval 20 second schedule (VI 20). This means that on average, point gain would occur every 20 seconds provided that the participant responded at the appropriate time. In one condition a punishment contingency which stipulated point subtractions on a variable ratio 30 schedule (VR 30) was also used concurrently. This means that

on average point loss would occur for every 30 responses that participants made. In a second condition the punishment contingency was omitted. The outcome measures were the number and rate of responses made during each condition and from this a suppression ratio (number of responses made under conditions of reward/number of responses made under conditions of reward and punishment) was calculated in order to quantify the degree to which punishment suppressed responding. The main difference between RARP and the operant task used by Cherek and Bennett (1991) is that participants made responses with the space bar of a computer keyboard in the RARP whereas participants responded by pulling the lever of a Lindley manipulandum in the older task. Two different versions of this task were used in the studies that follow, a 20 minute and a 10 minute version. The RARP task was programmed and administered using E-Prime version 1.1 (Psychology Software Tools Inc., Pittsburgh, PA, USA). Figure 2.8 shows the RARP in more detail diagrammatically.
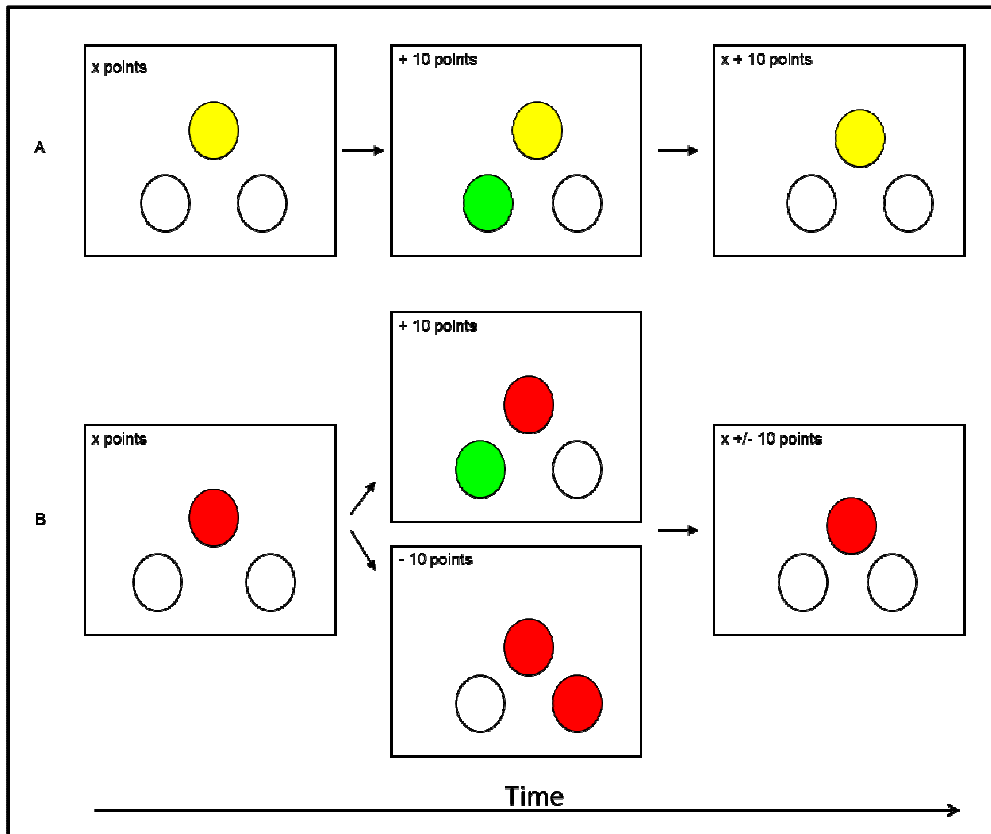
Figure 2.8: Reward and Reward/Punishment Task

A: Reward only condition. A constant yellow light indicated that points could be won on a VI20 schedule. Cumulative points earned were displayed in the top left hand corner in order that participants could visualise their performance at all times. If an appropriate response was made positive performance feedback was displayed. This took the form of a green light being flashed and participants receiving points such that the cumulative points total increased. B: Reward/Punishment condition. A constant red light indicated that points could be won on a VI20 schedule but that points could also be lost on a VR30 schedule. Positive feedback was the same as for the reward only condition or negative feedback in the form of a red light being flashed and participants losing points such that the cumulative points total was updated.

Chapter 3 Effect of Punishment (Negative Feedback) on Responding in Two Operant Tasks in Non-Smokers

3.1 Introduction

Operant conditioning uses reinforcement and punishment to shape or modify behaviour such that a reinforced response will increase in frequency whereas a punished response will decrease in frequency. Bradshaw et al. (1977) for example, demonstrate that the button pressing responses of three participants maintained by monetary reinforcement were suppressed when responding was punished by the loss of money. The current study examined the effect of punishment on the behavioural responses of non-smokers in two operant tasks, a task based on a differential reinforcement of low rates schedule (DRL task) and a conflict task (Reward and Reward/Punishment (RARP) task) based on Cherek and Bennett (1991). The main purpose of the current study was to assess the tasks' suitability for subsequent work that aimed to compare punishment sensitivity in satiated and abstinent smokers.

DRL schedules reinforce responses only when a fixed time has elapsed without an intervening response. Typically, premature responses on DRL schedules re-start the timer so that responders have to wait longer until reinforcement is available. The DRL task used in the current study reinforced responses if a fixed time elapsed without an intervening response and punished premature responses as well as re-starting the timer. Furthermore, half-way through the DRL task used in the current study the minimum time required to elapse without an intervening response increased so as to increase levels of premature responding. Using a similar schedule, Holz et al. (1963) punished all responses made by pigeons maintained by a DRL schedule of food reinforcement. Punishment improved performance on the task in that it reduced the frequency of responses and the increased temporal spacing of responses resulted in more reinforcements and reduced premature responses. Therefore, in the current study levels of premature responding over time were used as an index of punishment sensitivity.

Operant conflict tasks, whereby behavioural responses maintained by reinforcement are then suppressed by a concurrent punishment, are traditionally used for the preclinical assessment of drug effects upon punished responding. Individual sensitivity to the punisher can be established through calculation of a suppression ratio (level of responding during the reward only condition/level of responding during the reward with concurrent punishment condition). The RARP task was based upon the conflict task used by Cherek and Bennett (1991). Cherek and Bennett investigated the effect of administering tobacco smoke from cigarettes containing 0, 0.3, 1.2 and 2.7mg nicotine on punishment sensitivity in 10 male smokers who participated in 20 minute sessions of lever pulling which was maintained by a variable interval 20 second schedule (VI20) of point presentation (points could later be exchanged for money). In one condition, a punishment contingency consisting of point subtraction on a variable ratio 30 schedule (VR30) suppressed responding whereas in a second condition the punishment was omitted. It was found that nicotine enhanced suppression of (i.e. further suppressed) punished responding in a dose dependent manner.

Both operant tasks used in the current study must be long enough to enable learning from the response feedback yet short enough to allow for post-smoking performance levels on more than one task (i.e. a battery of cognitive and behavioral assessments) to be collected as would be the case for future studies. Under these circumstances time is limited by the pharmacokinetics of nicotine. Nicotine reaches the brain in 10 to 20 seconds following a cigarette puff producing rapid activation of the dopaminergic system underlying behavioural reinforcement effects (Benowitz, 1990, 1996). There is some delayed uptake of nicotine to the brain from the blood however nicotine is also distributed extensively to other body tissues with the liver, kidney, spleen and lungs having high affinity for nicotine (Urakawa et al., 1994). In addition, the distribution half-life is short at approximately 8 minutes (Hukkanen et al., 2005). Peak plasma levels of nicotine are reached within about 5-10 minutes after smoking and levels fall rapidly over the next 20-30 minutes (see Figure 3.1; reprinted from Benowitz et al., 1988). This rapid rate of delivery of nicotine and the rapid dissipation

of the acute effects of nicotine in the brain imply that there is a small window of opportunity in which to observe the behavioural effects of nicotine before concentrations fall below behaviourally active levels. Therefore, test batteries that take no longer than approximately 30-40 minutes are often used to study the acute effects of smoking in order to cover the period of maximum effects of nicotine.
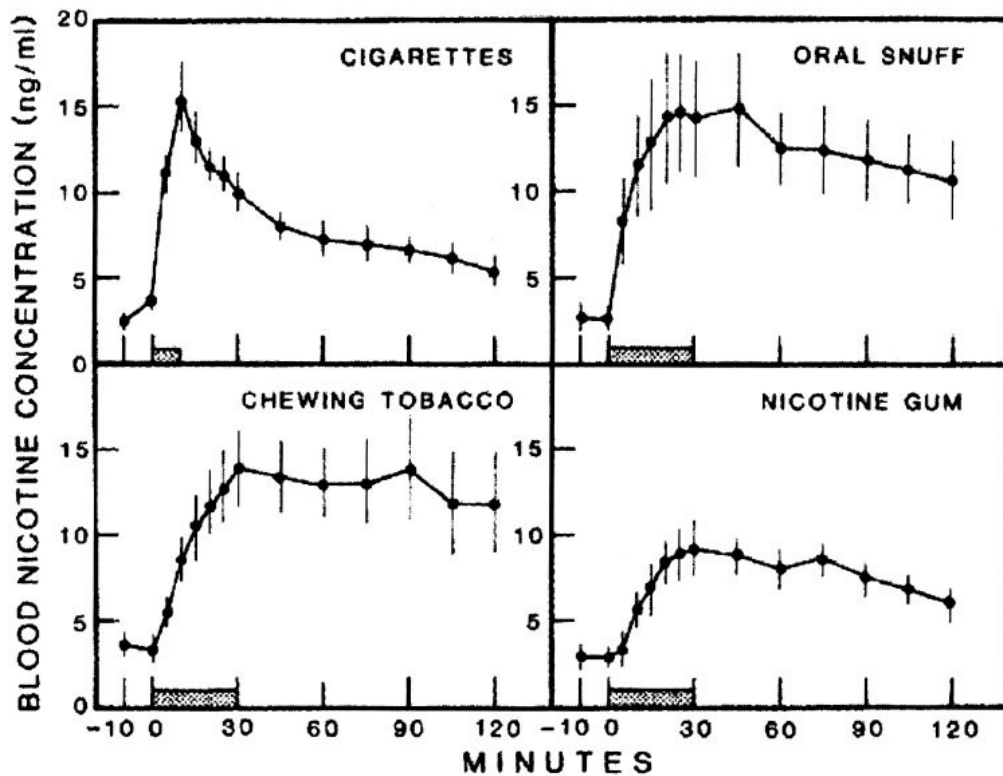
Figure 3.1: Blood Nicotine Concentrations During and After Administration of Nicotine via Different Routes.
(Cigarette smoking for 9 minutes, oral snuff (2.5g), chewing tobacco (average 7.9g) and nicotine gum (two 2mg pieces). The average values for 10 subjects are shown with error bars representing standard error of the mean). This figure was reprinted from Benowitz et al. (1988).

Therefore, the first aim of the current study was to compare directly the ability of two versions of the RARP task to measure individual responsivity to punishment in a non-smoking population. A 20 minute version of RARP similar to that which has been used previously (Cherek and Bennett, 1991) and a shorter 10 minute version that could be used for future studies (alongside other tasks) investigating sensitivity to punishment in satiated and abstinent smokers were compared. The two versions

were compared on outcome measures that are typical of operant conflict methodology (level and rate of responding and suppression of responding by punishment). The second aim of the current study was to pilot the DRL task in order to see if the tasks outcome measure (level of premature responding over time) could provide an adequate index of individual sensitivity to punishment. In line with operant learning theory it was predicted that in the RARP task, levels and rates of responding would be greatest under conditions of reward compared to conditions of reward with concurrent punishment. Furthermore, it was predicted that punishment would suppress responding to the same extent in both the long and short version of the task. It was predicted that in the DRL task levels of premature responding would fall over time, as participants learned from the punishing negative feedback, but that premature responses would increase after the waiting requirement was increased, only to fall again over time as participants used the punishing negative feedback.

In addition to these main aims the current study assessed if RARP task performance was affected by the order in which participants completed the RARP and DRL tasks or the order of the RARP task components (i.e. reward followed by reward/punishment or vice versa). Furthermore, the current study also assessed if gender or age affected performance on the RARP and DRL tasks and additionally the correlation between RARP task suppression ratio and change in levels of premature responding over time on the DRL task (both used to index punishment sensitivity) was investigated.

3.2   Materials and Methods

3.2.1   Participants

Twenty four participants (12 male and 12 female) aged 19-50 years were recruited for the study from the Universities of Brighton and Sussex. In order to meet the inclusion criteria participants were required to be in good health, not be using psychotropic medication or regular medication of any sort (with the exception of oral contraceptives), to be non-smokers and to arrive at the laboratory having not

consumed alcohol for at least 12 hours prior to the testing session. Ethical approval was obtained from the University of Brighton School of Pharmacy and Biomolecular Sciences Research Ethics Committee. All participants gave their written informed consent prior to participation, were free to withdraw from the study at any point and were debriefed at the end of the study. Participants received £3 compensation for their time.

3.2.2 Design

In order to minimise practice effects due to repeating the same schedules present in both versions of the RARP task different participants completed the two different versions of the RARP task. The 20 minute long version of the RARP task was completed by 13 participants and the 10 minute short version was completed by 11 participants. Every participant completed the DRL task. Participants attended the laboratory on one occasion lasting approximately 25 to 35 minutes.

3.2.3 Procedure

Before participation in the study participants were asked about their general health, current medication use and their non-smoking status was confirmed. On arrival at the laboratory, participants were subject to a breath alcohol test (see General Methods, section 2.2.1) in order to ascertain that no recent drinking of alcohol had occurred. Subsequently, participants completed either the long or short duration RARP task (see General Methods, section 2.7.11) to which they had been randomly assigned and the DRL task (see General Methods, section 2.7.3) in a counterbalanced order. The presentation of the reward only and the reward with concurrent punishment components of the RARP task were also counterbalanced. Upon completion of the behavioural tasks all participants were debriefed as to the nature of the study.

3.2.4 Data Analysis

Statistical analysis was conducted on data from all 24 participants using SPSS version 16 (SPSS Inc., Chicago, IL, USA). Participant demographic data was analysed using Chi

Square (for gender) and an independent samples t-test (for age). Dependent samples t-tests were used to determine if there were any differences in the number of responses made under conditions of reward compared to under conditions of reward and punishment for each RARP version. Differences in the rate of responding under conditions of reward compared to under conditions of reward and punishment and differences in the rate of responding between RARP versions were analysed with a 2 (reward and reward/punishment condition) x 2 (long and short version) mixed design analysis of variance (ANOVA).

Suppression ratios (the degree to which punishment was able to suppress responding for reward) were calculated for each participant (using the equation: number of responses made under the reward only condition/number of responses made under the reward and concurrent punishment condition) and an independent samples t-test compared the suppression ratios for both the long and short duration RARP task. Additional independent samples t-tests were used to investigate potential task component order (i.e. reward only component of RARP first followed by reward and punishment component or vice versa), operant task ordering (i.e. RARP task followed by DRL task or vice versa), and gender and age effects on suppression ratio. For this analysis, the suppression ratios from both tasks were pooled (to increase statistical power) and groups were formed from the natural categories (RARP/DRL or DRL/RARP for task order; reward/reward and punishment or reward and punishment/reward for task component order; male or female for gender) or by median split (for age, which resulted in a younger group aged 19-26 years and an older group aged 27-50 years).

Differences in the levels of premature responses across four 10 trial time bins of the DRL were analysed with one-way repeated measures ANOVA with appropriate contrasts (time bins 1 and 2 and time bins 3 and 4 were compared to assess the effect of feedback on premature responding and time bins 2 and 3 were compared to assess the effect of increasing the waiting requirement on premature responding). For each participant, the change in mean percentage of trials with premature

responses was computed between time bins 1 and 2 and between time bins 3 and 4. These change scores were then averaged for every participant to generate a mean percentage change in premature responses score that would index the degree to which punishing feedback reduced premature responding. Independent samples t-tests were used to investigate potential gender and age (groups based on median split as before) effects on the mean change in premature responses.

Finally, the inter-task correlation between RARP task suppression ratio and DRL task change in premature responses was conducted with Pearson's Correlation Coefficient. For this analysis the suppression ratio data from both the long and short versions of the RARP task were combined. All statistical tests were two-tailed with alpha set at $p = 0.05$. In cases where statistical significance was greater than $p = 0.05$ but less than or equal to $p = 0.075$, results have been considered a trend. Where multiple comparisons were required p-values were Bonferroni corrected by multiplying the p-value obtained by the total number of comparisons made (as in Bland and Altman, 1995) this is equivalent to lowering the level of alpha. In addition effect sizes were reported for significant findings. The assumption of normal distribution was assessed using the Kolmogorov-Smirnov test and by visual assessment of histograms of the data produced in the SPSS output. Where data was found to violate the assumption of normality, transformations were applied to the data and the specific transformations are described where they occurred in the appropriate places in the results section. The assumption of homogeneity of variance/sphericity was assessed with Levene's test or Mauchly's test as appropriate however none of the data violated these assumptions and so no adjustment of degrees of freedom or p-value were necessary.

3.3 Results

3.3.1 Demographics

The demographic data for all 24 participants are shown in Table 3.1. All participants completed the DRL task, and the long and short versions of the RARP task were each completed by approximately half of the participants. There was no significant difference in the numbers of male and female participants that carried out the long version of RARP compared to those which carried out the short version of RARP ($X^2(1)$ = 1.51, p = 0.219). Similarly, there was no significant difference in the mean age (natural log transformed) of participants that carried out the long version of RARP compared to those which carried out the short version of RARP (t(22) = -1.48, p = 0.153).

Demographic	RARP Task		DRL Task
	Long	Short	(All Participants)
N	13	11	24
Gender (M/F)	5/8	7/4	12/12
Mean Age in Years (S.E.M.)	25.46 (1.92)	30.09 (2.70)	27.58 (1.65)

Table 3.1: Demographic Data for Participants Completing Long and Short RARP Tasks and the DRL Task.
(Abbreviations: M/F: male/female, S.E.M.: standard error of the mean, RARP: Reward and Reward/Punishment, DRL: Differential Reinforcement of Low Rates).

3.3.2 Responding for Reward and the Effect of Concurrent Punishment

The number of responses made under conditions of reward and conditions of reward and concurrent punishment on each version of the RARP task are shown in Figure 3.2. Participants responded more under conditions of reward compared to conditions of reward and concurrent punishment for both the long (t(12) = 4.85, p < 0.001) and short (t(10) = 4.02, p = 0.002) versions of the RARP task and these significant differences were associated with large effect sizes (r = 0.81 and 0.79 for the long and short version respectively). As the two RARP versions were of different durations

level of responding was not directly compared between the two versions. Instead, performance was compared by rate of responding and suppression ratio.
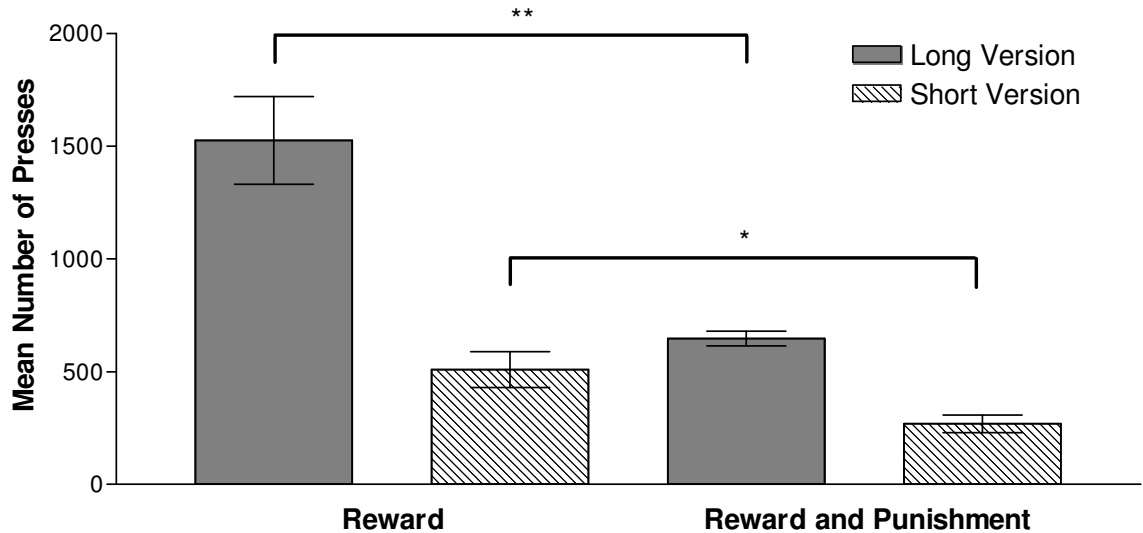
Figure 3.2: Mean Number of Responses for the Reward Only and the Reward and Concurrent Punishment Conditions of the Long and Short Versions of the RARP Task.
(Abbreviations: RARP = reward and reward/punishment. Mean number of responses made under reward > mean number of responses made under reward and concurrent punishment, * = $p < 0.005$ and ** = $p < 0.001$ for the short (n = 11) and long (n = 13) version of the RARP task respectively. Error bars represent standard error of the mean).

Participants had higher rates of responding under conditions of reward compared to conditions of reward and concurrent punishment ($F(1, 22) = 10.63$, $p = 0.004$) and this significant difference was associated with a large effect size (r = 0.57). Overall rates of responding did not differ between the long and short versions of the task ($F(1, 22) = 2.59$, $p = 0.122$). In addition, there was no significant task condition by task length interaction ($F(1, 22) = 1.47$, $p = 0.239$) showing that the difference between rates of responding under conditions of reward compared to conditions of reward and concurrent punishment did not vary between versions of the task. Rates of responding under both conditions and for both versions of the RARP task are shown in Figure 3.3.
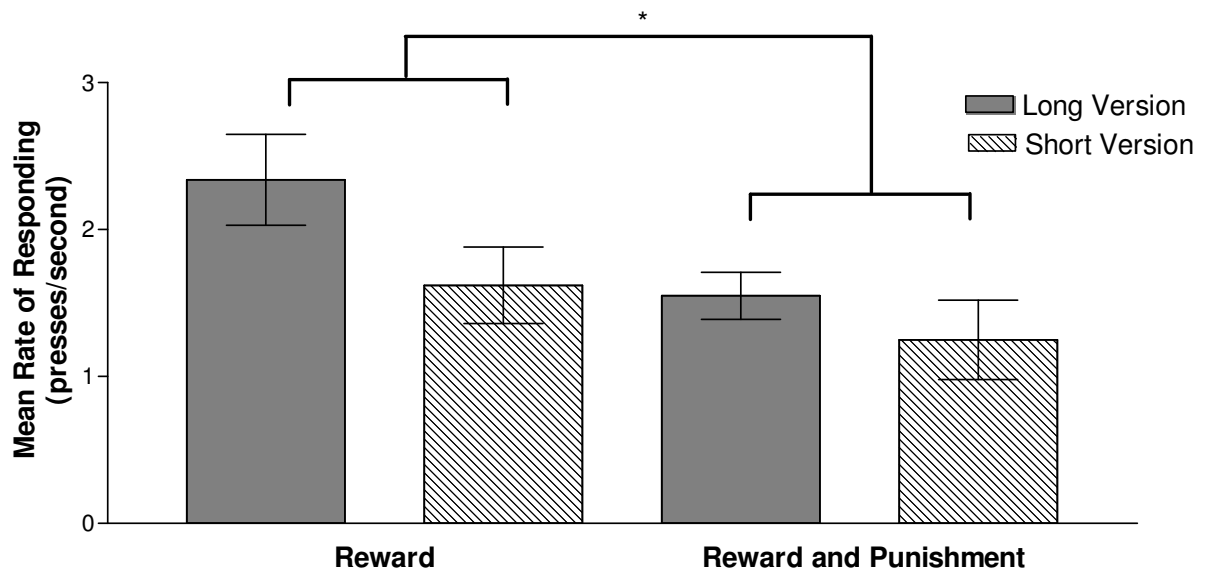
Figure 3.3: Mean Rate of Responding for the Reward Only and the Reward and Concurrent Punishment Conditions of the Long and Short Versions of the RARP Task.
(Abbreviations: RARP = reward and reward/punishment. Mean rate of responding under reward > mean rate of responding under reward and concurrent punishment, * = p < 0.005. Error bars represent standard error of the mean).

3.3.3   Suppression Ratio

Mean suppression ratios (natural log transformed) did not significantly differ between the long and short versions of the RARP task (t(22) = 0.78, p = 0.445). As no significant difference was found, the suppression ratio data from both versions of the RARP task were pooled (to increase statistical power) for analyses investigating potential RARP task component order, gender, age and operant task order effects on the degree to which punishment suppressed responding. Table 3.2 shows the suppression ratios obtained for both versions of the RARP task and suppression ratios obtained after splitting the data by these other task ordering and demographic criteria. Mean suppression ratios (natural log transformed) did not significantly differ between groups based on RARP component order (t(22) = -0.63, p = 0.536), gender (t(22) = -1.18, p = 0.250), age (t(22) = -0.95, p = 0.354) or operant task order (t(22) = 0.05, p = 0.958).

Data Split By:	Suppression Ratio (S.E.M.)	
RARP Version (Long/Short)	2.36 (0.28)	2.10 (0.37)
RARP Component Order (R-RP/RP-R)	2.05 (0.25)	2.44 (0.38)
Gender (Male/Female)	2.02 (0.34)	2.46 (0.30)
Age (Young/Older)	2.06 (0.32)	2.42 (0.32)
Operant Task Order (RARP-DRL/DRL-RARP)	2.24 (0.31)	2.24 (0.34)

Table 3.2: Mean Suppression Ratio for Participants Based on Task Ordering and Demographic Splits.
(Abbreviations: S.E.M.: standard error of the mean, RARP: Reward and Reward/Punishment, R-RP: reward component followed by reward and concurrent punishment component, RP-R: reward and concurrent punishment component followed by reward component, RARP-DRL: Reward and Reward/Punishment task followed by Differential Reinforcement of Low Rates task, DRL-RARP: Differential Reinforcement of Low Rates task followed by Reward and Reward/Punishment task).

3.3.4   Premature Responses Across Time Bins

Figure 3.4 shows the mean percentage of DRL trials in each of four 10 trial time bins with premature responses. The DRL premature response data did not show a normal distribution and transformations of the data did not help correct this. However, the assumption of sphericity was met and Berkovits et al. (2000) argue that when this is the case, the one-way repeated measures ANOVA unadjusted F is robust and offers satisfactory type 1 error control. The mean percentage of trials with premature responses significantly changed across time bins ($F(3, 69) = 5.02$, $p = 0.003$) such that using feedback significantly reduced premature responses between trial 1 and trial 20 (between time bins 1 and 2; $p = 0.018$ Bonferroni corrected) and this was associated with a large effect size ($r = 0.53$). However, once the DRL schedule was changed premature responses significantly increased between trial 21 and trial 30 (time bins 2 and 3; $p = 0.009$ Bonferroni corrected) and this was associated with a large effect size ($r = 0.56$). Finally, using feedback significantly reduced premature

responses between trial 31 and trial 40 (between time bins 3 and 4; p = 0.015 Bonferroni corrected) and this was also associated with a large effect size (r = 0.54).
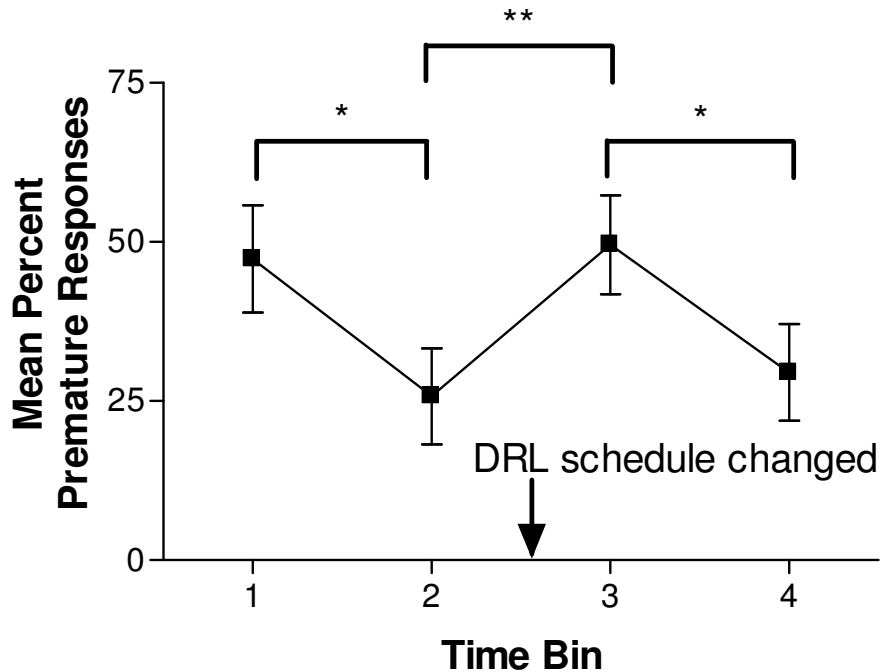
Figure 3.4: Mean Percentage of Trials with Premature Responses in Each of the 10 Trial Time Bins of the DRL Task.
(Abbreviations: DRL = differential reinforcement of low rates. After 20 trials the DRL schedule changed from a DRL-11 to a DRL-13. Mean percentage of trials with premature responses in time bin 1 > in time bin 2, time bin 3 > time bin 4 (* = p < 0.05 for both) and time bin 2 < time bin 3 (** = p < 0.01). Error bars represent standard error of the mean).

3.3.5   Change in Premature Responses

The overall mean percentage change in premature responses (between time bins 1 and 2 and time bins 3 and 4) was -20.83% (4.79 S.E.M.). The mean change scores for each participant were used for analyses investigating potential gender and age effects on the degree to which punishment reduced premature responding and Table 3.3 shows the mean percentage change in premature responses obtained after splitting the data by these demographic selection criteria. Mean percentage change in premature responses did not significantly differ between groups based on age (t(22) = 0.53, p = 0.531) or gender (t(22) = 0.48, p = 0.480).

Data Split By:	Mean Percent Change in Premature Responses (S.E.M.)	
Gender (Male/Female)	-17.35 (8.11)	-24.30 (5.29)
Age (Young/Older)	-23.91 (6.43)	-17.74 (7.27)

Table 3.3: Mean Percentage Change in Premature Responses on the DRL Task. (Abbreviations: S.E.M.: standard error of the mean, DRL: Differential Reinforcement of Low Rates).

3.3.6 Inter-task Correlation

As there was no significant difference between the suppression ratios of the long and short versions of the RARP task these were combined. The mean suppression ratio (natural log transformed) failed to correlate significantly with the mean percentage change in premature responses ($r = 0.23$, $p = 0.291$, $n = 24$).

3.4 Discussion

3.4.1 Main findings

The principal findings of this study are that punishment reduced both the total number of responses and the rate of responding for both the long and short version of the RARP task. This punishment-induced suppression of responding was equivalent for both versions of the task and suggests that the short version of RARP will provide a useful research tool. Additionally, the use of feedback reduced premature responses over time in the DRL task. However, RARP task suppression ratio and the mean change in premature responses did not correlate. The full findings are discussed further in this section.

3.4.2 Demographics

The participants that carried out the two different versions of the RARP task were matched for gender and age. However one limitation of this study was the omission

of recording additional demographic and personality factors that may have influenced performance on the operant tasks (e.g. IQ, education level, previous illicit drug use and individual differences in attention, memory and depression). In addition, self-report measures that may have further validated the two operant tasks as a measure of responsivity to punishment (such as impulsivity, and behavioural inhibition) were not assessed. Future studies using these tasks should seek to address this issue.

3.4.3   Suppression of Responding by Punishment

This study showed that reward (in this case positive feedback and point gain) was able to maintain high levels of responding on the RARP task irrespective of which version was used. In addition, punishment (negative feedback and point loss) suppressed the level of responding on both versions of the task. Therefore, this study supports one of the most basic tenets of operant psychology and the experimental analysis of behaviour – that the frequency of behavioural responding is suppressed by punishment that is received as a consequence of that same responding and is consistent with others showing punishment-induced suppression of responding (e.g. Ayllon and Azrin, 1966; Bradshaw et al., 1977; Cherek and Bennett, 1991). The similar suppression ratio scores for both the long and short versions of the task suggest that punishment controlled levels of responding to the same extent in both versions. Furthermore this finding suggests that the short version of the RARP task adequately assesses punishment induced suppression of responding and would be suited to assessing the effect of acute smoking and abstinence on punished responding in future studies.

3.4.4   Reduction of Premature Responses

Premature responding was encouraged on the DRL task by increasing the waiting time to point reinforcement half-way through the task. This technique of encouraging premature responses is similar to that employed by Besson et al. (2010) in which premature responses were encouraged in rats on a 5-choice serial reaction time task (5-CSRT). The Besson et al. procedure increases the inter-trial interval following

acquisition of the 5-CSRT task thus increasing the delay to reward in much the same way as the current study does for the DRL task. Prior to and after the increase in waiting time on the current task premature responses decreased with time presumably as a result of using feedback to guide responding. This finding is consistent with Holz et al. (1963) that found that punishment reduced premature responses in a similar DRL schedule.

3.4.5   Task Ordering Effects

The suppression ratio for individuals that received the RARP task followed by the DRL task did not differ from the suppression ratio of those that completed the tasks in the opposite order. Similarly, the suppression ratio for individuals that received the RARP task components in the order reward followed by reward with concurrent punishment did not differ from the suppression ratio of those that received the components in the opposite order. This finding is inconsistent with Weiner (1969) and Lefrancois and Metzger (1993) that found that prior exposure to one operant schedule influenced responding in a second. However there are important differences between the current study and these previous studies. The operant schedules operating in the previous studies were very similar with prior exposure to responding on a DRL schedule leading to responding on a subsequent fixed interval schedule looking more like the responding of a DRL schedule. Fixed interval schedules are very similar to DRL schedules, the difference being that premature responses do not reset the time required to wait in order for the reward to become available. Therefore if a DRL schedule is learned and then subsequently changed to a fixed interval schedule, the similarity of these schedules lends itself to the responding remaining DRL-like (Lefrancois and Metzger, 1993). The finding of no effect of operant task order or RARP task component order on suppression ratio in the current study suggests that the DRL schedule is sufficiently different from the RARP schedules and that the schedules governing reward and punishment in the RARP task are sufficiently different from one another so as not to affect responding.

3.4.6 Gender and Age Effects

The finding that male and female participants did not differ in mean suppression ratio or mean change in premature responses suggests that punishing, negative feedback was used equally well for males and females. This finding is consistent with Arenas et al. (1993) that found no gender differences in the escape-avoidance behaviour of mice. However, the finding is inconsistent with human brain-imaging work showing differential brain activity in response to gains and losses in males and females (Kamarajan et al., 2008) and showing reduced variability in the brains response to feedback in female compared to male 'high-risk' adolescents (i.e. those who have been exposed to drugs of abuse prenatally, have suffered some form of postnatal adversity and score highly on behavioural measures of risk taking; Crowley et al., 2009). Differences in the relative sensitivity of behavioural and imaging techniques may account for these inconsistent findings.

The current study also found that younger and older groups of participants did not differ in mean suppression ratio or mean change in premature responses. This suggests that punishing, negative feedback was used equally well for both younger and older groups. However this finding is inconsistent with research showing age-related changes in response to feedback (e.g. Nieuwenhuis et al., 2002; Eppinger et al., 2008; Pietschmann et al., 2008; Wild-Wall et al., 2009) which would suggest that care should be taken in matching for age in future studies evaluating sensitivity to punishment. The discrepancy between the current findings and the previous literature could be due to the method used to create the young and old age groups. In the current study a median split of the age data was used which created groups that were not very highly polarized when compared to the age groups in the previous studies. Furthermore, the previous studies showing age-related differences in response to feedback measured electrophysiological correlates of brain activity in response to feedback and so differences in the relative sensitivity of the methods used may also account for the inconsistency.

3.4.7 Inter-task Correlation

There is a case for the use of both the RARP and DRL tasks for future research investigating smoking and abstinence effects on punishment sensitivity. For example, responding on the tasks is modified by punishing feedback, levels of responding on both operant tasks appear not to be at floor or ceiling (allowing for drug and abstinence effects to either enhance or reduce levels of responding) and both the DRL task and the short version of the RARP task run for an appropriately short duration (so as to be included as part of a test battery). However, the lack of correlation between RARP task suppression ratio and DRL task change in premature responses suggests that the outcome measures from both operant tasks are not assessing the same construct. The RARP task measures levels of responding for reward and assesses the impact of punishment on this level of responding therefore it seems fairly sensible to conclude that this is indeed an index of punishment sensitivity. With the DRL task however, response to rewarding and punishing feedback are not assessed individually. Instead, the task likely provides a measure of general ability to learn from feedback including punishing negative feedback. In addition DRL tasks, without punishment, have previously been used to assess impulsive responding in both laboratory animal and human studies (e.g. in rats: Peterson et al., 2003; Lovic et al., 2011; and in humans: Gordon, 1979; McClure and Gordon, 1984; Avila et al., 2004 and Stewart et al., 2006) and the task is also likely to assess the ability to estimate time accurately. Therefore, change in premature responses on the DRL task may reflect a composite of all of these things and as a consequence, the RARP task may be a more suitable assessment tool for punishment sensitivity in future studies.

3.4.8 Strengths and Limitations

There are several strengths and limitations to this study. The number of participants in the study was quite low. However, strong and robust effects of punishment on levels of responding were found. The median split method used for investigating the potential effect of age on punishment sensitivity did not result in two polarized groups and as such group differences that may have been found in more polarized

groups may not have been observed in this study. Had a larger sample size been tested more polar groups could have been created by removing those aged in the mid-range. Alternatively, larger sample sizes may have been more suited to age-behaviour correlation analysis. The collection of more demographic data with which to match participants and to assess as factors that may influence punished responding would have been useful. The assessment of impulsivity for example (using a subjective self-report measure or behavioural tasks) would have allowed examination of the effects of various subtypes of impulsivity on punished responding. It could be argued that positive and negative feedback without monetary outcomes (as was used by the operant tasks in this study) may not have been incentive enough to motivate behaviour. This however, does not appear to be the case as positive feedback and point gain effectively maintained high levels of responding and negative feedback and point loss appeared to function well as a punisher in the RARP task. Also, in the DRL task use of positive and negative feedback over time reduced premature responses. In addition, Paulus et al. (2003) also used point gain and loss in a task designed to assess decision making under risk and found brain activation of the insula for risky versus safe decisions. Since there was activation of the insula, an area often associated with reward and punishment processing, during a task that used points as opposed to monetary outcomes it is suggested that point gain and point loss must share at least some of the underlying neural substrates required for the processing of monetary incentive and loss.

3.4.9 Conclusions

In summary, this study has provided evidence that a short 10 minute version of the RARP task is capable of assessing the effect of punishment (point loss) to suppress responding and that it does this equally as well as a longer 20 minute version of the task. This finding appears quite robust, with punishment-induced suppression of responding being associated with a large effect size and remaining unaffected by prior operant task experience, task component order and participant gender or age. In addition, the use of feedback over time reduced premature responses on the DRL task. Together these findings suggest that the short version of the RARP task and the

DRL task could be used for future psychopharmacological studies. However, the lack of correlation between the two operant tasks calls into question the specificity of what the DRL task is actually measuring. Therefore the next study, investigating the acute effects of smoking and abstinence from smoking on punishment sensitivity, used the short version of the RARP task. This version of the task is particularly well suited to such a study since consideration of the pharmacokinetics of inhaled nicotine stipulates a requirement for short test batteries in order to satisfactorily pick up acute drug effects.

3.5   Executive Summary of Main Findings

- Punishment suppressed responding in both the long and short versions of the RARP task.

- The long and short versions did not differ in the level of punishment induced suppression of responding suggesting that both versions assess punishment sensitivity equally well.

- Feedback reduced premature responding in the DRL task.

- The lack of correlation between RARP suppression ratio and DRL premature responding, in combination with a theoretically driven appreciation of what the DRL task measures, suggests that the RARP task may better index punishment sensitivity.

- The short version of the RARP task was used to investigate punishment sensitivity in satiated and abstinent smokers in the next chapter.

Chapter 4   The Effect of a Smoking Manipulation on Punishment Sensitivity in Dependent Smokers

4.1   Introduction

The effect of abstinence from smoking on reward sensitivity has previously been investigated. Abstinent smokers show reduced reward sensitivity compared to both satiated smokers and non-smokers (Powell et al., 2002a) and reward sensitivity can be restored in abstinent smokers after smoking a cigarette (Al-Adawi and Powell, 1997) or after taking a nicotine lozenge (Powell et al., 2004; Dawkins et al., 2006). Fewer studies have systematically investigated the effect of smoking and abstinence from smoking on punishment sensitivity. Therefore, the current study aimed to compare satiated and abstinent smokers on a number of punishment sensitivity measures.

There are several reasons to investigate punishment sensitivity in satiated and abstinent smokers. For example, impaired punishment sensitivity is well documented in a variety of psychiatric populations (such as schizophrenia e.g. Kim et al. (2009) and depression e.g. Must et al. (2006)) and investigators of such impairments often consider the potential contribution of psychotropic medication exposure on task performance. However, the satiated or abstinent status of participants that smoke who may be involved in these studies could potentially confound the experimental data. Therefore consideration of punishment sensitivity in both satiated and abstinent smokers may benefit those obtaining data in this related field of research. In fact this may be particularly useful as an unusually large proportion of individuals with diagnoses of these psychiatric conditions are known to smoke (Lawrence et al., 2009). Also, despite a growing awareness of an altered response to error in drug users compared to non-users (e.g. Franken et al., 2010; Luijten et al., 2011a) little is known about punishment sensitivity in satiated compared to abstinent drug users. Furthermore, de Ruiter et al. (2009) showed reduced brain activity in response to punishment in smokers compared to non-smokers however the contribution of smoking or abstinence was not investigated.

Effects of abstinence on punishment sensitivity might be expected because abstinence effects are observed on reward sensitivity (Powell et al., 2002a) and the processing of reward and punishment is achieved by distinct but overlapping neurochemical (dopamine; see review by Schultz, 2007) and neuroanatomical (fronto-striatal-limbic circuitry; e.g. Camara et al., 2008) substrates. Abstinence from smoking may cause a general suppression of normal motivational responses. In line with this Powell et al. (2002b) found that both non-smokers and smokers that had recently smoked displayed similar levels of interference from reward- and threat-related words compared to neutral words in a modified Stroop task whereas there was no effect of word type in abstinent smokers. In addition, abstinence has been shown to blunt responses to both happy and sad film clips (Dawkins and Powell, 2011). Furthermore, abstinence is associated with deficits in aspects of cognition (e.g. sustaining attention (Wesnes and Warburton, 1983) and working memory (Mendrek et al., 2006)) that may be required for learning from both positive and negative feedback. These previous findings are consistent with abstinence from smoking reducing punishment sensitivity.

Previous preclinical and human studies using a variety of different operant tasks and investigating nicotine/smoking- and abstinence-induced changes in punishment sensitivity has culminated in inconsistent results (showing increases, decreases and no effect on levels of punished responding and avoidance behaviour; e.g. Morrison, 1969; Glowa, 1986; Bennett et al., 1989; Cherek and Bennett, 1989; Furusawa and Tadokoro, 1990; Bennett and Cherek, 1991; Cherek and Bennett, 1991). Amongst these disparate findings a common outcome from one group in particular (the Bennett and Cherek studies) is that nicotine further suppresses punished responding, a result that is consistent with nicotine increasing punishment sensitivity. The inconsistencies in the previous research may in part be due to the small size of the studies or the use of differing operant tasks from one study to the next. A further limitation of this previous work is the use of just one measure of punishment sensitivity per study.

The present study aimed to address these limitations by investigating the effects of smoking and remaining abstinent on punishment sensitivity in a larger sample than has previously been tested using two operant tasks (Reward and Reward/Punishment (RARP) task and a Probabilistic Reversal Learning (PRL) task) that provided a number of punishment sensitivity measures. In line with the idea that abstinence from smoking causes a general suppression of normal motivational responses it was hypothesised that abstinent smokers would be less sensitive to punishment than satiated smokers. In addition to this main aim this study explored the relationships between RARP task and PRL task punishment sensitivity measures and the relationships between these punishment sensitivity measures and subjective behavioural inhibition. In addition, the relationships between all the RARP and PRL task behavioural measures and smoking-related demographic data were explored as were the relationships between these behavioural measures and subjective impulsiveness.

The RARP task (based on that used by Cherek and Bennett, 1991) assessed the level and rate of responding for reward and the impact of punishment on this reinforced responding. Punishment sensitivity was indexed by calculation of a suppression ratio (level of responding during the reward only condition/level of responding during the reward with concurrent punishment condition) as in Chapter 3. The PRL task (based on that used by Budhani et al., 2006) indexed punishment sensitivity with lose-stay errors (perseveration with the incorrect response in the face of punishment) and win-maintenance failures (inappropriate shifts in responding after punishing false feedback). As it was hypothesised that abstinent smokers would be less sensitive to punishment than satiated smokers it was predicted that abstinent smokers would have smaller suppression ratios and make more perseverative errors (lose-stay errors) and fewer shifts after receiving false feedback (win-maintenance failures) compared to satiated smokers. In addition the PRL task recorded response reaction times and win-shift errors (inappropriate shifts from the correct, rewarded response to the incorrect response) that may index impulsiveness to some degree. It was predicted that reaction times following punishment would be slower than following

correct, rewarded responses (a post-punishment slowing effect thought to reflect post-punishment processing; Rabbitt, 1966 and Laming, 1979) and it was predicted that abstinent smokers would have reduced post-punishment processing (smaller post-punishment slowing) compared to satiated smokers.

4.2 Materials and Methods

4.2.1 Participants

Thirty healthy smokers (14 male and 16 female) aged 18-36 years were recruited for the study from the Universities of Brighton and Sussex. In order to meet the inclusion criteria participants were required to be in good health, not be using psychotropic medication or regular medication of any sort (with the exception of oral contraceptives) and to score ≥ 5 on the Fagerstrom Test for Nicotine Dependence (FTND). In addition, all participants were required to arrive at the laboratory having not consumed alcohol for at least 12 hours and having not smoked for at least 3 hours prior to the testing session and to have refrained from the use of illicit drugs for at least 1 week. Ethical approval was obtained from the University of Brighton School of Pharmacy and Biomolecular Sciences Research Ethics Committee. All participants gave their written informed consent prior to participation, were free to withdraw from the study at any point and were debriefed at the end of the study. Participants received £12 compensation for their time.

4.2.2 Design

The study used a between subjects design in order to avoid practice effects arising from repeating behavioural tasks. Each participant attended the laboratory on one occasion and took part in a test session lasting approximately 1 hour and 30 minutes. All participants were asked to bring one of their own cigarettes and were told that they would be asked to smoke at some point during the study. Participants were randomly assigned to either a smoke or a no-smoke group but were not told which group they were assigned to or at which point during the study they would be

smoking. This was done in an attempt to reduce smoking/abstinence-related performance expectancies in participants.

4.2.3 Procedure

Before participation in the study, participants were asked about their general health, current medication use, smoking behaviour/nicotine dependence, alcohol and illicit drug use by completing screening questionnaires consisting of the FTND (see General Methods, section 2.3.1) and the Medicinal Drug, Alcohol and Illicit Drug Use Questionnaire (MAID; see General Methods, section 2.3.2). On arrival at the laboratory, participants were subject to a breath alcohol test (see General Methods, section 2.2.1) and an exhaled carbon monoxide (CO) test (see General Methods, section 2.2.2) in order to ascertain that no recent drinking of alcohol or cigarette smoking had occurred. Participants were excluded for a breath alcohol reading greater than 0 g/L and for an exhaled CO level above 15 ppm. Exhaled CO levels of 15ppm may initially appear to be a relatively high threshold, however it should be noted that the minimum length of abstinence from smoking required was also relatively short at just 3 hours. Therefore, by setting the threshold at this level it would be unlikely that participants who had smoked up to the 3 hour limit would be excluded in error.

Participants were then asked to complete a batch of personality and mood questionnaires consisting of the Barratt Impulsiveness Scale (BIS; see General Methods, section 2.5.1), the Behavioural Inhibition System/Behavioural Activation System Scales (BIS/BAS; see General Methods, section 2.5.2) and the Beck Depression Inventory (BDI; see General Methods, section 2.4.1). All participants then completed Nicotine-Sensitive Visual Analogue Scales (NicVAS; see General Methods, section 2.6.1) and those in the smoke group completed the brief version of the Questionnaire of Smoking Urges (QSU-brief; see General Methods, section 2.6.2). All participants then completed an immediate word recall test (IWR; see General Methods, section 2.7.6) after which the smoke group were asked to smoke one of their own brand cigarettes. During this same period, those in the no-smoke group sat with a time out

period. After smoking (or not), all participants completed a second exhaled CO test and a second NicVAS. The computerised test battery (programmed and administered using E-Prime version 1.1 (Psychology Software Tools Inc., Pittsburgh, PA, USA) and presented to participants on a laptop computer in a quiet, neutral environment) consisting of the 10 minute RARP task (see General Methods, section 2.7.11) and the PRL task (see General Methods, section 2.7.9) followed. The test battery took no longer than 20-25 minutes to complete in order to capture performance within the narrow window before the rapid drop off in plasma nicotine levels (Benowitz, 1988). Once the computerised tasks were completed participants completed a final NicVAS and a final exhaled CO test. Those in the smoke group completed a second QSU-brief and were then debriefed whereas those in the no-smoke group completed their first QSU-brief and were asked to smoke one of their own brand cigarettes before returning to complete their second QSU-brief before being debriefed. The no-smoke group were asked to smoke at the end of the study so that they would not leave the laboratory in a withdrawn state. Furthermore the main reason for the different procedures in terms of the QSU-brief was so that the no-smoke group would have a task to complete once they had actually smoked a cigarette at the end of the study and this approach was chosen in an attempt to reduce smoking/abstinence-related performance expectancies in participants.

4.2.4 Data Analysis

Statistical analysis was conducted on data from all thirty participants (15 smoke group and 15 no-smoke group) using SPSS version 18 (SPSS Inc., Chicago, IL, USA). Participant demographic data was analysed using Chi Square (for gender) and independent samples t-tests (for age, personality, mood, general cognitive and smoking related demographics). Physiological (exhaled carbon monoxide levels) and subjective effects (NicVAS) of smoking were examined using 3 (time point) x 2 (group) mixed design ANOVA's followed by appropriate post-hoc t-tests. As craving scores were obtained at different time points for the smoke and no-smoke groups craving over time was examined for each group separately with dependent samples t-tests. However, post-smoke craving in the smoke group was compared to pre-smoke

craving in the no-smoke group with an independent samples t-test since this reflected craving in both groups immediately after completion of the test battery. For RARP task data, the effect of punishment to suppress both number of responses and response rate was examined with dependent samples t-tests for each group and group differences in suppression ratio (calculated as: number of responses made under conditions of reward/number of responses made under conditions of reward and punishment) were examined with an independent samples t-test.

For the PRL task, each participant was required to have learned the correct stimulus for each pair at acquisition in order for their data to be included in analysis of PRL errors. Therefore a learning criterion of 6 consecutive correct responses in the acquisition phases of the PRL task was imposed for each stimulus pair (a method used previously by Budhani et al. (2006)) whereby participants had to achieve at least 6 consecutive correct responses with each stimulus pairing before data was included for analysis. All participants met this 6 consecutive correct trials criterion and the mean number of trials taken to reach this criterion provided a measure of learning speed. The number of trials taken to reach this criterion was compared across groups with an independent samples t-test. PRL errors were compared across groups at acquisition, reversal and in total using either independent samples t-tests or Mann-Whitney U tests where data was not normally distributed and transformation of the data could not correct this. Irrespective of smoking group, PRL errors were compared across task phase (acquisition versus reversal) and across task contingencies (100-0% versus 80-20%) using dependent samples t-tests or Wilcoxon signed-ranks tests where data was not normally distributed and transformation of the data could not correct this. For PRL reaction time data, reaction times following correct, rewarded responses and reaction times following punished responses were compared across the groups using a 2 (group) x 2 (response outcome) mixed design ANOVA. In addition, mean post-punishment slowing was calculated (mean reaction time following punished responses minus mean reaction time following correct and rewarded responses) for each group.

Finally, for analyses of relationships between behavioural measures, subjective measures and smoking-related demographics the groups were collapsed and Pearson's Correlation Coefficient was used. All statistical tests were two-tailed with alpha set at p = 0.05. In cases where statistical significance was greater than p = 0.05 but less than or equal to p = 0.075, results have been considered a trend. Where multiple comparisons were required p-values were Bonferroni corrected by multiplying the p-value obtained by the total number of comparisons made (as in Bland and Altman, 1995) this is equivalent to lowering the level of alpha. In addition effect sizes were reported for significant findings. The assumption of normal distribution was assessed using the Kolmogorov-Smirnov test and by visual assessment of histograms of the data produced in the SPSS output. Where data was found to violate the assumption of normality, transformations were applied to the data and the specific transformations are described where they occurred in the appropriate places in the results section. The assumption of homogeneity of variance/sphericity was assessed with Levene's test or Mauchly's test as appropriate. Adjusted degrees of freedom and p-values are reported for t-tests where variances were not equal and Greenhouse-Geisser corrected degrees of freedom and p-values are reported for violations of sphericity.

4.3   Results

4.3.1   Demographics

The demographic data for the smoke and no-smoke groups are shown in Table 4.1. There were no significant differences in the numbers of male and female participants (X^2 (1) = 0.54, p = 0.464) or the mean age of participants in each group (t(28) = 0.24, p = 0.813). Additionally, there were no significant differences between the groups in terms of general cognitive ability (IWR performance, t(28) = 0.65, p = 0.518) personality (BIS total score, t(28) = 0.95, p = 0.350; BIS/BAS subscale scores: BAS Drive, t(28) = 0.10, p = 0.918, BAS Fun Seeking, t(28) = 0.18, p = 0.855, BAS Reward Responsiveness, t(28) = -0.66, p = 0.516, BIS, t(23.47) = -1.71, p = 0.101) or mood (BDI, t(28) = -0.25, p = 0.804).

In terms of smoking related demographic data, there were no significant differences between the groups in level of dependence (FTND score, $t(28) = -0.32$, $p = 0.755$), number of cigarettes smoked per day ($t(28) = -0.84$, $p = 0.409$), the number of years that participants had been smoking for ($t(28) = -0.33$, $p = 0.742$) and length of abstinence at the start of the study ($t(28) = -0.10$, $p = 0.919$). The mean number of cigarettes smoked per day for all participants was 15.27 (0.87 S.E.M.) and the mean FTND score for all participants was 6.27 (0.21 S.E.M.). The mean length of abstinence prior to arriving at the laboratory was 9 hours 24 minutes (range: 3-20 hours).

	Smoke Group	No-Smoke Group
Demographic	Mean (S.E.M.)	Mean (S.E.M.)
N	15	15
Gender (M/F)	6/9	8/7
Mean Age (years)	23.27 (1.43)	22.87 (0.88)
IWR (words recalled)	8.40 (0.40)	8.07 (0.32)
BIS (total score)	76.00 (3.04)	72.47 (2.14)
BIS/BAS - BAS Drive	10.53 (0.40)	10.47 (0.51)
BIS/BAS - BAS Fun Seeking	13.07 (0.49)	12.93 (0.53)
BIS/BAS - BAS Reward Responsiveness	16.00 (0.54)	16.47 (0.47)
BIS/BAS – BIS	18.33 (0.56)	20.13 (0.89)
BDI	10.13 (1.46)	10.87 (2.53)
FTND Score	6.20 (0.24)	6.33 (0.35)
Cigarettes/day	14.53 (1.26)	16.00 (1.22)
Years of Smoking	7.07 (1.31)	7.60 (0.93)
Abstinence at Start (mins)	558.00 (78.36)	570.00 (87.10)

Table 4.1: Demographic Data for Participants in the Smoke and No-Smoke Groups. (Abbreviations: S.E.M.: standard error of the mean, M/F: male/female, IWR: Immediate Word Recall, BIS: Barratt Impulsiveness Scale, BIS/BAS: Behavioural Inhibition Scale/Behavioural Activation Scale, BIS/BAS – BIS: Behavioural Inhibition Subscale, BDI: Beck Depression Inventory, FTND: Fagerstrom Test for Nicotine Dependence).

4.3.2 Physiological Effects of Smoking

Mean exhaled CO levels changed over time during the study ($F(2, 56) = 57.06$, $p < 0.001$) and there was a time by group interaction ($F(2, 56) = 83.65$, $p < 0.001$). The

smoke and no-smoke groups CO levels did not differ at baseline ($t(28) = -1.27$, $p = 0.639$ Bonferroni corrected) but the smoke group had higher exhaled CO levels at time point 2 (immediately before the test battery) compared to the no-smoke group ($t(28) = 2.72$, $p = 0.033$ Bonferroni corrected, $r = 0.46$). Exhaled CO levels remained higher in the smoke group at time point 3 (at the end of the study prior to the no-smoke group smoking) compared to the no-smoke group ($t(28) = 2.68$, $p = 0.036$ Bonferroni corrected, $r = 0.45$). Figure 4.1 shows these exhaled CO data.
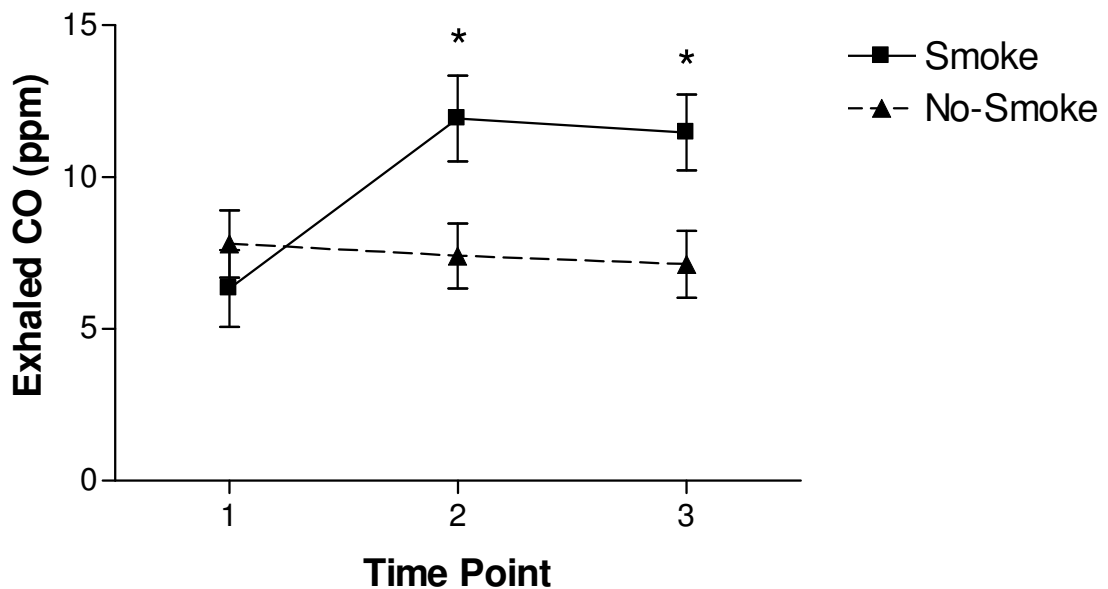
Figure 4.1: Mean Exhaled Carbon Monoxide (CO) for the Smoke and No-Smoke Groups Across Time.
(Abbreviations: CO: carbon monoxide, ppm: parts per million. Time point 1 = baseline, time point 2 = before test battery (after smoke group smoked), time point 3 = end of study (before no-smoke group smoked). * = $p < 0.05$ for smoke group compared to no-smoke group at the corresponding time point. Error bars represent standard error of the mean).

4.3.3   Subjective Effects of Smoking

The smoke and no-smoke group differed across time in subjective ratings of 'buzzed' ($F(2, 56) = 8.27$, $p = 0.001$) and 'dizzy' $F(2, 56) = 4.83$, $p = 0.012$). Ratings of 'buzzed' were significantly greater in the smoke group immediately before the test battery

compared to the no-smoke group (t(20.73) = 3.41, p = 0.009 Bonferroni corrected, r = 0.60) but not at any other time point (baseline: t(28) = 1.11, p = 0.834 Bonferroni corrected; end of the study: t(28) = -0.32, p = 1.000 Bonferroni corrected). Similarly, ratings of 'dizzy' were significantly greater in the smoke group immediately before the test battery compared to the no-smoke group (t(14.26) = 3.48, p = 0.012 Bonferroni corrected, r = 0.68) but not at any other time point (baseline: t(14.75) = 2.55, p = 0.066 Bonferroni corrected; end of the study: t(28) = 0.28, p = 1.000 Bonferroni corrected). The groups also differed across time in ratings of 'hungrier than usual' (F(1.46, 40.90) = 5.60, p = 0.013) however post-hoc t-tests failed to reveal any significant differences in ratings between the groups at any time point and post-hoc repeated measures ANOVA for each group individually failed to reveal any significant changes in ratings across time. The data plot for the 'hungrier than usual' data suggested that towards the end of the study hunger increased in the smoke group whereas it decreased in the no-smoke group.

Overall the smoke group had greater ratings of 'dizzy' and 'contented' and smaller ratings of 'impatient' compared to the no-smoke group (F(1, 28) = 6.78, p = 0.015, r = 0.44; F(1, 28) = 5.12, p = 0.032, r = 0.39; F(1, 28) = 4.34, p = 0.046, r = 0.37 respectively). Also, overall ratings of 'buzzed' and 'stimulated' changed across time (F(2, 56) = 3.94, p = 0.025; F(2, 56) = 4.80, p = 0.012 respectively) such that ratings of 'buzzed' increased between baseline and immediately before the test battery (p = 0.019 Bonferroni corrected, r = 0.44) and ratings of 'stimulated' increased between baseline and the end of the study (p = 0.013 Bonferroni corrected, r = 0.49). Figure 4.2 shows the 'buzzed', 'dizzy', 'hungrier than usual', 'contented', 'impatient' and 'stimulated' data. There were no effects on the remaining subjective rating scales of the NicVAS ('irritable', 'jittery', 'thirsty', 'alert' and 'relaxed') and these data are shown in Table 4.2.
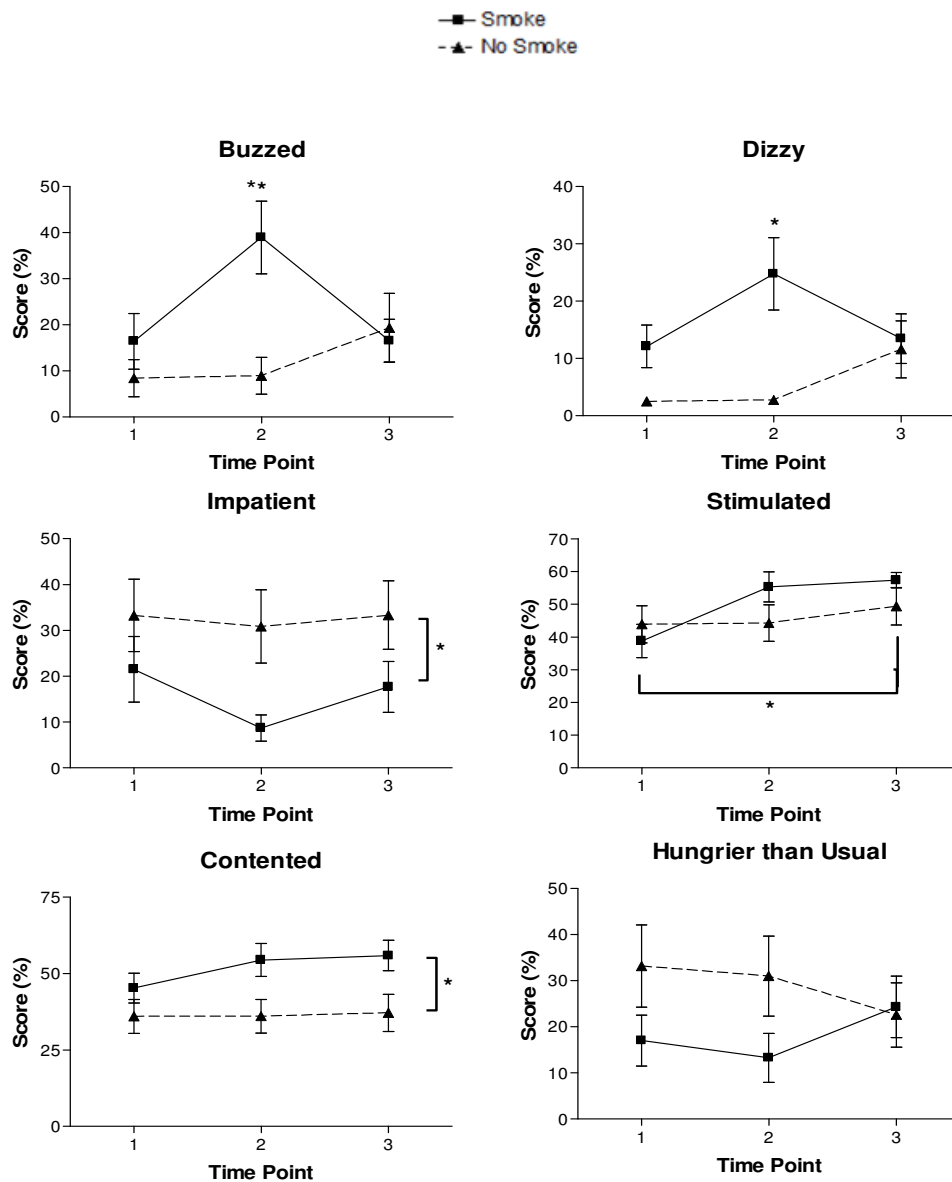
Figure 4.2: Subjective Visual Analogue Scale Ratings Across Time for the Smoke and No-Smoke Groups.

(Time point 1 = baseline, time point 2 = before test battery (after smoke group smoked), time point 3 = end of study (before no-smoke group smoked). A: Ratings of 'buzzed'. ** = smoke group > no-smoke group at time point 2, $p < 0.01$ B: Ratings of 'dizzy'. * = smoke group > no-smoke group at time point 2, $p < 0.05$ C: Ratings of 'impatient'. * = smoke group < no-smoke group, $p < 0.05$ D: Ratings of 'stimulated'. * = time point 1 < time point 3, $p < 0.05$ E: Ratings of 'contented'. * = smoke group > no smoke group, $p < 0.05$ F: Ratings of 'hungrier than usual'. Significant time x group interaction, $p < 0.05$. Error bars represent standard error of the mean).

NicVAS Rating (%)	Smoke Group Mean (S.E.M.)	No-Smoke Group Mean (S.E.M.)
Alert T1	48.87 (4.18)	47.27 (5.69)
Alert T2	59.07 (3.96)	46.00 (5.22)
Alert T3	53.93 (5.22)	49.40 (4.77)
Irritable T1	14.60 (4.40)	15.27 (5.16)
Irritable T2	7.40 (2.13)	15.67 (5.36)
Irritable T3	16.07 (3.29)	14.80 (4.03)
Jittery T1	14.13 (4.36)	20.00 (5.93)
Jittery T2	16.60 (5.91)	20.27 (5.98)
Jittery T3	12.33 (3.21)	13.67 (5.55)
Relaxed T1	46.60 (4.63)	44.53 (6.43)
Relaxed T2	58.67 (5.26)	44.07 (5.91)
Relaxed T3	57.73 (4.84)	44.67 (5.40)
Thirsty T1	33.67 (5.43)	33.60 (6.12)
Thirsty T2	41.73 (6.61)	33.20 (6.47)
Thirsty T3	38.40 (6.18)	37.93 (7.58)

Table 4.2: Subjective Visual Analogue Scale Ratings Across Time for the Smoke and No-Smoke Groups.
(Abbreviations: S.E.M.: standard error of the mean, NicVAS: Nicotine-Sensitive Visual Analogue Scales, T1: baseline, T2: before test battery (after smoke group smoked), T3: end of study (before no-smoke group smoked)).

For the smoke group craving scores were significantly higher before smoking (median: 4.40, IQR: 0.80) compared to after smoking (median: 2.70, IQR: 1.80; z = -3.21, p < 0.001, r = -0.59). Similarly, for the no-smoke group craving scores were significantly higher before smoking (median: 4.60, IQR: 2.40) compared to after smoking at the end of the study (median: 1.40, IQR: 1.40; z = -3.41, p < 0.001, r = -0.62). As craving scores for each group were obtained at different time points the most meaningful comparison of craving between groups is immediately after completion of the test battery (that is after smoking had occurred for the smoke group and before the no-smoke group smoked at the very end of the study). This

analysis revealed that craving in the smoke group (mean: 2.85, 0.28 S.E.M.) was significantly lower than craving in the no-smoke group (mean: 4.14, 0.33 S.E.M.; $t(28)$ = -2.98, p = 0.006, r = 0.49).

4.3.4 Effect of Punishment in the RARP Task

Both the smoke group and the no-smoke group responded more under conditions of reward (mean: 590.47 presses, 61.50 S.E.M.; mean: 735.20 presses, 111.20 S.E.M. for the smoke group and no-smoke group respectively) compared to conditions of reward with concurrent punishment (mean: 299.20 presses, 26.20 S.E.M., $t(14)$ = 5.66, p < 0.001 , r = 0.83; mean: 300.93 presses, 30.28 S.E.M., $t(14)$ = 4.73, p < 0.001 , r = 0.78 for the smoke and no-smoke group respectively).

Similarly, both the smoke group and the no-smoke group had a higher rate of responding under conditions of reward (mean: 1.83 presses/second, 0.19 S.E.M.; mean: 2.31 presses/second, 0.35 S.E.M. for the smoke group and the no-smoke group respectively) compared to conditions of reward with concurrent punishment (mean: 1.35 presses/second, 0.19 S.E.M., $t(14)$ = 2.49, p = 0.026, r = 0.55; mean: 1.51 presses/second, 0.20 S.E.M., $t(14)$ = 3.79, p = 0.002, r = 0.71 for the smoke and no-smoke group respectively).

4.3.5 RARP Suppression Ratio

Suppression ratios for the smoke group and the no-smoke group did not significantly differ ($t(28)$ = -0.78, p = 0.440). Figure 4.3 shows these suppression ratio data.

Figure 4.3: Mean Suppression Ratio for the Smoke and No-Smoke Groups.
(Error bars represent standard error of the mean).

4.3.6   PRL Task Trials to Criterion

The mean number of trials (natural log transformed) taken to reach the learning criterion of 6 consecutive correct responses in the acquisition phases of the PRL task did not significantly differ between the smoke group (mean: 8.28 trials, 0.38 S.E.M.) and the no-smoke group (mean: 7.72 trials, 0.26 S.E.M.; t(28) = 1.18, p = 0.250).

4.3.7   Acquisition, Reversal and Total PRL Errors

The smoke group and the no-smoke group did not differ in the number of win-shift errors (*U* = 103.00, z = -0.42, p = 0.713), lose-stay errors (*U* = 73.00, z = -1.71, p = 0.106) or win-maintenance failures (natural log transformed; t(28) = 0.97, p = 0.339) in acquisition phases of the PRL task. Similarly, the smoke and the no-smoke group did not differ in the number of win-shift errors (*U* = 111.00, z = -0.07, p = 0.967), lose-stay errors (natural log transformed; t(28) = 0.79, p = 0.437) or win-maintenance failures (*U* = 97.50, z = -0.64, p = 0.539) in reversal phases of the PRL task.

Furthermore, the smoke and the no-smoke group did not differ in the total number of win-shift errors (natural log transformed; t(28) = 0.05, p = 0.960), lose-stay errors (natural log transformed; t(28) = 1.14, p = 0.264) or win-maintenance failures (natural log transformed; t(28) = 1.10, p = 0.281). PRL task error data are shown in Table 4.3.

PRL Errors	Smoke Group Mean (S.E.M.)	No-Smoke Group Mean (S.E.M.)
Acquisition Errors		
Lose-stay Errors #	1.00 (3.00)	0.00 (1.00)
Win-maintenance Failures	2.93 (0.50)	2.27 (0.33)
Win-shift Errors #	0.00 (3.00)	1.00 (2.00)
Reversal Errors		
Lose-stay Errors	9.00 (2.31)	6.00 (0.79)
Win-maintenance Failures #	2.00 (2.00)	2.00 (2.00)
Win-shift Errors #	1.00 (2.00)	1.00 (2.00)
Total Errors		
Lose-stay Errors	11.40 (2.87)	7.07 (0.90)
Win-maintenance Failures	5.20 (0.82)	4.00 (0.52)
Win-shift Errors	3.13 (0.89)	2.40 (0.43)

Table 4.3: Acquisition, Reversal and Total Errors in the PRL Task for the Smoke and No-Smoke Group.
(Abbreviations: S.E.M.: standard error of the mean, PRL: Probabilistic Reversal Learning; # = median and interquartile range shown instead of mean and standard error of the mean for data that was analysed using non-parametric tests).

4.3.8 PRL Errors in Acquisition Versus Reversal

As the number of errors made by both groups was low and there were no group differences in the number of errors made, errors in acquisition were compared to errors in reversal irrespective of group. For win-shift errors, the number of errors in acquisition (median: 0.50, IQR: 2.00) did not significantly differ from the number of errors in reversal (median: 1.00, IQR: 2.00, z = -1.00, p = 0.319). However for lose-stay errors, the number of errors in acquisition (median: 1.00, IQR: 2.25) was significantly less than the number of errors in reversal (median: 5.00, IQR: 4.25, z = -4.48, p <

0.001, r = -0.82). Whereas for win-maintenance failures, the number of errors in acquisition (median: 2.00, IQR: 2.25, mean: 2.60) was significantly greater than the number of errors in reversal (median: 2.00, IQR: 2.00, mean: 2.00, z = -2.16, p = 0.033, r = -0.39).

4.3.9 PRL Errors by Contingency

As the number of errors made by both groups was low and there were no group differences in the number of errors made, errors in 100-0% trials were compared to errors in 80-20% trials irrespective of group. For win-shift errors, the number of errors in 100-0% trials (median: 1.00, IQR: 2.00) did not significantly differ from the number of errors in 80-20% trials (median: 1.53, IQR: 3.00, z = -0.82, p = 0.413). However for lose-stay errors, the number of errors in 100-0% trials (mean: 2.77, 1.01 S.E.M.) was significantly less than the number of errors in 80-20% trials (mean: 6.47, 0.84 S.E.M., natural log transformed, t(29) = -6.83, p < 0.001, r = 0.79). Similarly for win-maintenance failures, the number of errors in 100-0% trials (median: 0.00, IQR: 0.00) was significantly less than the number of errors in 80-20% trials (median: 4.60, IQR: 3.50, z = -4.79, p < 0.001, r = -0.87).

4.3.10 PRL Reaction Times

The groups did not differ in overall reaction time (natural log transformed, F(1, 28) = 0.10, p = 0.752). There was a trend for longer reaction times following punished responses compared to reaction times following correct, rewarded responses (a post-punishment slowing) irrespective of group (natural log transformed, F(1, 28) = 3.71, p = 0.064). The groups did not differ in this post-punishment slowing or in reaction times following correct, rewarded responses or following punished responses (natural log transformed, F(1, 28) = 1.05, p = 0.315). Table 4.4 shows the post-punishment slowing of each group and the reaction time data.

	Smoke Group	No-Smoke Group
PRL Reaction Times	Mean (S.E.M.)	Mean (S.E.M.)
Overall RT (ms)	1136.03 (57.24)	1166.66 (60.88)
RT following CR (ms)	1116.62 (50.63)	1109.02 (48.27)
RT following P (ms)	1155.44 (66.630	1224.30 (85.11)
Post-Punishment Slowing (ms)	38.82 (29.94)	115.27 (65.74)

Table 4.4: PRL Reaction Times and Post-Punishment Slowing for the Smoke and No-Smoke Group.
(Abbreviations: S.E.M.: standard error of the mean, PRL: Probabilistic Reversal Learning, RT: reaction time, CR: correct and rewarded response, P: punished response, ms: milliseconds).

4.3.11 Correlation Between RARP and PRL Punishment Sensitivity

Suppression ratio did not significantly correlate with natural log transformed total win-maintenance failures (p = 1.000 Bonferroni corrected) or natural log transformed total lose-stay errors (p = 0.132 Bonferroni corrected).

4.3.12 Correlation Between BIS/BAS BIS and Punishment Sensitivity

BIS/BAS BIS subscale score did not significantly correlate with natural log transformed total lose-stay errors (p = 1.000 Bonferroni corrected) and natural log transformed total win-maintenance failures (p = 1.000 Bonferroni corrected). However, there was a trend towards a significant negative correlation between BIS/BAS BIS subscale score and suppression ratio (r = -0.43, p = 0.057 Bonferroni corrected, n = 30), and the scatterplot for this correlation is shown in Figure 4.4.

4.3.13 Correlation Between Nicotine Dependence and Behavioural Measures

FTND score did not significantly correlate with suppression ratio (p = 1.000 Bonferroni corrected), natural log transformed total lose-stay errors (p = 1.000 Bonferroni corrected), natural log transformed total win-maintenance failures (p = 1.000 Bonferroni corrected) and natural log transformed total win-shift errors (p = 1.000 Bonferroni corrected).

4.3.14 Correlation Between Years of Smoking and Behavioural Measures

Years of smoking did not correlate with suppression ratio (p = 1.000 Bonferroni corrected), natural log transformed total lose-stay errors (p = 0.168 Bonferroni corrected) and natural log transformed total win-maintenance failures (p = 0.096 Bonferroni corrected). However, years of smoking significantly correlated with natural log transformed total win-shift errors (r = 0.54, p = 0.008 Bonferroni corrected, n = 30). The scatterplot for this correlation is shown in Figure 4.5.

4.3.15 Correlation Between Impulsiveness and Behavioural Measures

BIS total score did not significantly correlate with suppression ratio (p = 0.912 Bonferroni corrected), natural log transformed total lose-stay errors (p = 0.240 Bonferroni corrected), natural log transformed total win-maintenance failures (p = 0.276 Bonferroni corrected) or natural log transformed total win-shift errors (p = 1.000 Bonferroni corrected).
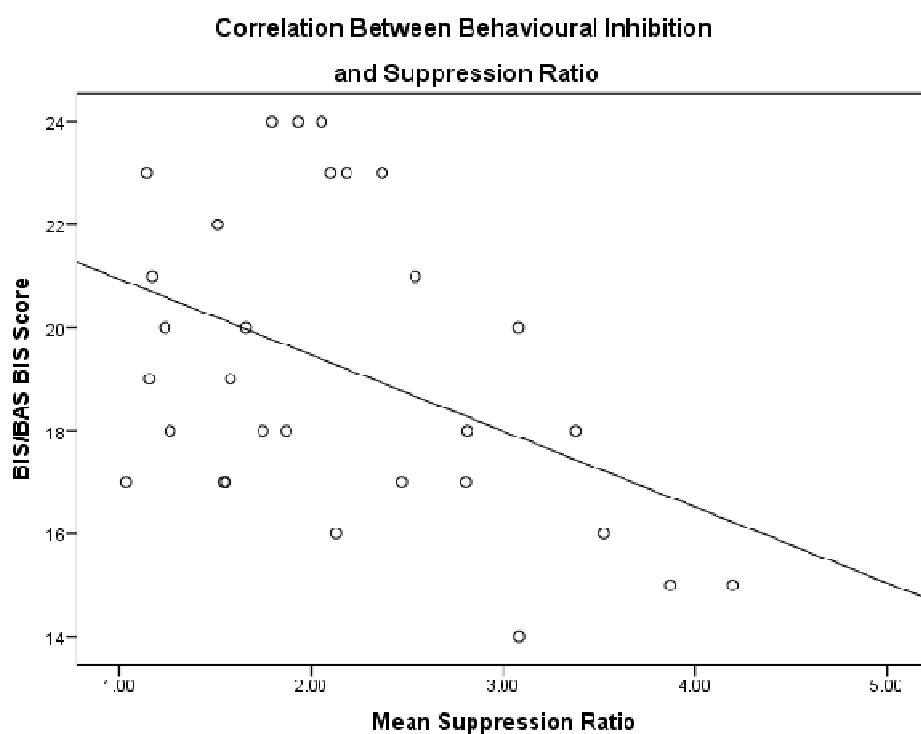
Figure 4.4: Correlation Between BIS/BAS BIS Subscale and Suppression Ratio.
(r = -0.43, p = 0.057 Bonferroni corrected, n = 30)
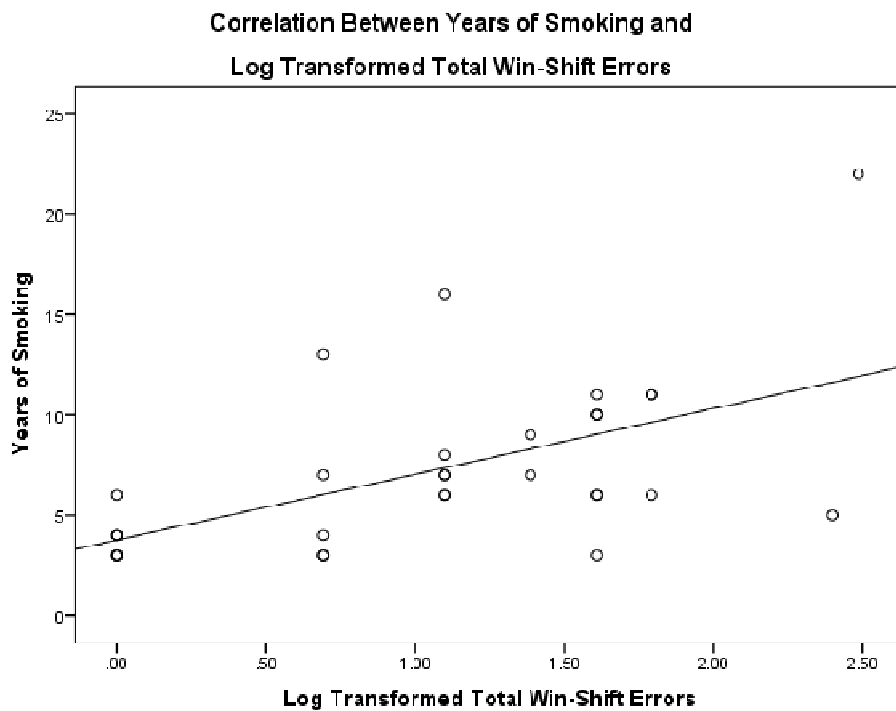
Figure 4.5: Correlation Between Years of Smoking and Log Transformed Total Win-shift Errors.
(r = 0.54, p = 0.008 Bonferroni corrected, n = 30).

4.4   Discussion

4.4.1   Main Findings

The main aim of this study was to compare punishment sensitivity in satiated and abstinent smokers. In this study the performance of abstinent smokers that either smoked a cigarette or remained minimally deprived were compared on two behavioural tasks that assessed punishment sensitivity – a conflict task and a probabilistic reversal learning task that both used point gain and point loss as rewards and punishment. Contrary to the prediction that abstinent smokers would be less sensitive to punishment, satiated and abstinent smokers did not significantly differ in their behavioural responses to punishment on either task. Additionally, it was found that the groups did not differ in post-punishment slowing, and irrespective

of smoking group win-shift errors, a measure of impulsiveness, correlated with years of smoking. The findings of this study are discussed below.

4.4.2   Punishment Sensitivity

The number of responses and the rate of responding on the RARP task were greater under conditions of reward compared to conditions of reward with concurrent punishment for both the smoke and no-smoke group. Punishment suppressed responding on the RARP task to the same degree in both groups as shown by the non-significant difference in RARP suppression ratio. There was also no significant difference between the groups in PRL task errors that index punishment sensitivity (lose-stay errors and win-maintenance failures) at acquisition or reversal phases of the task, or in total.

4.4.3   Comparisons with Other Studies

Taken together these findings suggest that there are no group differences in punishment sensitivity assessed with either the RARP task or the PRL task. This finding does not support the idea that abstinence from smoking causes a general suppression of normal motivational responses that may be predicted from previous research (e.g. Powell et al., 2002b; Dawkins and Powell, 2011). However, abstinence from smoking may not always lead to a general motivational suppression but instead may be associated with motivational suppression to positively valenced stimuli only (Dawkins et al., 2007). Indeed, there is strong evidence to suggest that despite reward and punishment processing being achieved by overlapping neural substrates, there are also distinct neurochemical (e.g. serotonin; see review by Cools et al., 2008) and neuroanatomical (e.g. Wrase et al., 2007) substrates for the processing of punishment compared to reward. Therefore, it does not necessarily follow that because smoking/abstinence modulates reward sensitivity (e.g. Dawkins et al., 2006) that smoking/abstinence should modulate punishment sensitivity.

In terms of previous research that has used operant methods to investigate punishment sensitivity, the current finding of no group differences is in line with

some of the previous studies suggesting that administration of nicotine has no effect on conflict behaviour. For example Furusawa and Tadokoro (1990) investigated, in gerbils, the effect of nicotine (0.1, 0.3 and 1mg/kg) on lever pressing for food on a fixed ratio schedule and a concurrent fixed ratio schedule of electric shock punishment. Nicotine, at all doses, had no effect on conflict behaviour. It is important to note however that this study did not assess conflict behaviour in dependent animals. In human studies there have been inconsistent findings in the previous work. Cherek and Bennett (1989) examined in smokers the effects of nicotine (either as 2, 4 or 8mg gum or 7, 15 or 30 puffs of a 0.42mg low yield or 2.14mg high yield cigarette) on a free-operant avoidance schedule in which absence of lever pressing would result in point loss every 5 seconds and a lever press would postpone point subtractions by 20 seconds. This study demonstrated that smoking nicotine-containing cigarettes resulted in dose dependent increases in avoidance responding compared to non-smoking baseline data (inconsistent with our data), but that chewing nicotine containing gum did not produce any changes in avoidance responding compared to baseline. The discrepancy in this study was attributed to the different amounts of time the different routes of administration take in altering nicotine concentrations in the body. However, the current finding is more in line with the nicotine gum data and would suggest that there may be an alternative reason as to why smoking induced changes in avoidance behaviour in this older study. Interestingly, Bennett and Cherek (1991) did not replicate this effect of smoking on the same avoidance responding task in a slightly larger group of smokers. The results of this latter study showed that there were no consistent effects of smoking or abstinence on avoidance responding. In fact Bennett and Cherek reported just one subject that showed a significant increase in avoidance responding following smoking of a 2.7mg nicotine yield cigarette compared to baseline. It is difficult to reconcile the differences Bennett and Cherek found between their studies in terms of the effects of smoking on avoidance responding. It could be that the smokers used were poorly matched in terms of their level of nicotine dependency or their lengths of abstinence, unfortunately however, not enough details were reported for firm conclusions to be made.

The current finding is in contrast to some other studies that provide evidence that punishment sensitivity can be modulated through smoking/nicotine administration and abstinence. For instance, Morrison (1969) found that 0.1 and 0.4mg/kg nicotine further suppressed responding that was already being suppressed by electric shock in rats that were lever pressing for water presentation on a variable interval schedule. The effect of nicotine in this study was varied and small in magnitude, probably due to the small number of rats tested and also that the animals had varying experimental experience and were from different strains. Similarly, Glowa (1986) investigated the effects of nicotine on schedule controlled responding in the mouse. Here, 0.003-10.0mg/kg nicotine affected punished responding that was maintained by a fixed interval schedule of food presentation. The punishment in this case was a fixed ratio schedule of electric shock and it was found that suppression of responding was a function of the nicotine dose. In human studies Bennett et al. (1989) showed smoking dose-related decreases in punished responding. In this study the spirometry method of smoke inhalation was used in five smokers to test what effect twenty 60cc puffs of either sham, 1.2 (low yield) or 2.7mg (high yield) nicotine containing cigarettes would have on punished and unpunished responding compared to a baseline 0.3mg nicotine yield cigarette condition. In these studies, lever pulling was maintained by a variable interval schedule of point presentation and suppressed by point subtraction on a variable ratio schedule. The same group extended this work into 10 male smokers and the same effect, decreases in punished responding, resulted. However, when the punishment contingency was omitted, no consistent effect of smoking on non-punished responding was observed (Cherek and Bennett, 1991). These two human studies do however provide evidence that nicotine acted to further suppress punished responding, a finding somewhat at odds with the current work. However, it is important to bear in mind the low numbers tested in these previous studies and the fact that the current work used multiple measures of punishment sensitivity unlike the previous studies. Together this may lend greater support to the current finding that satiated and abstinent smokers do not differ in punishment sensitivity.

The inconsistent findings in past literature, with some studies showing that nicotine and smoking increase avoidance behaviour and further suppress punished behaviour and other studies showing no effects, may be an indication that any effects of smoking on punishment sensitivity are dependent upon other factors such as impulsivity. This idea may be supported by evidence of reduced punishment sensitivity in individuals self-reporting greater levels of impulsiveness (Potts et al., 2006) and suggests that reduced punishment sensitivity may be characteristic of populations in which impulsivity features. However, the current study was not designed to investigate how individual differences in impulsivity modulate punishment sensitivity.

4.4.4   PRL Learning Criterion

In addition to finding no significant differences in the PRL errors that index punishment sensitivity there were a number of other findings with this task. There was no significant difference between the groups in the mean number of trials taken to reach the 6 consecutive correct trial criterion when learning the stimulus contingencies during acquisition trials suggesting that both groups were able to learn the tasks stimulus contingencies and that the rate of learning was the same for both the smoke and no-smoke groups.

4.4.5   Win-shift Errors

There were no significant group differences in win-shift errors at acquisition or reversal phases, or in total. This suggests that impulsive behaviour may not have differed between the two groups. This finding is at odds with research suggesting that acute nicotine increases impulsive action (Kirshenbaum et al., 2011) and impulsive choice (Kolokotroni et al., 2011). However the current study was not designed to investigate impulsiveness and win-shift errors have not previously been used to quantify impulsive behaviour (although intuitively a measure of shifting away from a correct, rewarded stimulus to an alternative stimulus indexes some form of

impulsiveness). Furthermore, impulsivity is not a unitary construct (Evenden, 1999) and it is unclear which aspects of impulsivity win-shift errors may index.

4.4.6   Errors in Reversal as a Measure of Cognitive Flexibility

The lack of group differences in errors in reversal phases of the task (where the correct and incorrect stimuli are reversed for some of the stimulus pairings) suggests that there are no group differences in cognitive flexibility. This finding is at odds with that of Nesic et al. (2011b) which found that recent smoking impaired flexibility in smokers with similar levels of dependence to those in the current study but not in smokers with a lower degree of dependency. However, Nesic et al. used a more complex attentional set-shifting task to assess flexibility which may have been more sensitive at picking up differences in cognitive flexibility. In contrast, and in line with the current study Mancuso et al. (1999) found that nicotine patch had no effect on the flexibility of smokers who were abstinent for two hours prior to testing and like the current study cognitive flexibility was assessed with a reversal learning task.

4.4.7   Effect of Task Phase and Contingency

As the number of PRL errors made by participants were low and no group differences were found, the groups were collapsed and differences in the number of errors made across the task phases (acquisition and reversal) and across the task contingencies (100-0% and 80-20%) were investigated. Differences in PRL errors were found between the acquisition and reversal phases irrespective of group. Firstly, a greater number of win-maintenance failures occurred in acquisition compared to reversal. Win-maintenance failures occur when participants respond to false feedback by switching from the correct choice to the incorrect choice and as such as the task progresses participants will become more certain which choice is correct and more familiar with receiving false feedback both of which would act to reduce errors of this type. Therefore, making fewer win-maintenance failures in reversal compared to in acquisition likely reflects a performance monitoring process i.e. the integration over time of previous trial-to-trial reinforcement history. Secondly, more lose-stay errors were found in reversal compared to acquisition. Lose-stay errors occur when

participants perseverate with an incorrect choice despite receiving feedback indicating that those choices are incorrect. It is suggested that lose-stay errors are higher in reversal because in reversal participants have to deal with reversing stimulus pairs (i.e. a stimulus that was previously correct becoming incorrect). Therefore, lose-stay errors occur in reversal as a result of either choosing the wrong stimulus and not adapting appropriately to negative feedback (as is the case with lose-stay errors in acquisition trials) or because of an inability to withhold responding for a previously correct choice. Therefore, one limitation of lose-stay errors as a measure of punishment sensitivity is that these errors may also reflect the inability to withhold responding for previous correct choices, a measure of inhibitory control.

Irrespective of group, PRL errors differed according to contingency (trials containing 100-0% pairs versus trials containing 80-20% pairs). Trials containing 80-20% pairs had greater numbers of lose-stay errors and win-maintenance failures than the trials containing 100-0% pairs. Lose-stay errors are likely to be greater in the 80-20% trials because of greater uncertainty with trials of this type (because of the presence of false feedback). For example receiving punishment on 80-20% trials may either be because the choice was incorrect (requiring a switch in responding to the correct stimulus on the subsequent trial) or because the choice was correct but false feedback was given (thus requiring no such switch). It is this uncertainty which increases perseverative errors in 80-20% trials. There were no win-maintenance failures in the 100-0% trials as the feedback given was always true and by definition win-maintenance failures occur when participants fail to maintain responding for the correct choice after receiving false feedback about the previous choice (i.e. being told the correct choice was incorrect) therefore, it is unsurprising that there was a greater number of these errors in 80-20% trials as trials of this type did contain false feedback.

4.4.8 PRL Reaction Times and Post-Punishment Slowing

There were no differences between the smoke and no-smoke group in overall reaction time or mean reaction time following correct, rewarded responses or

following punished responses. There was a trend towards slower reaction times following punishment that likely reflects a post-punishment or post-error slowing effect (Rabbitt, 1966; Laming, 1979). There was no group difference in post-punishment slowing suggesting that the smoke and no-smoke groups did not differ in post-punishment processing. However, it should be noted that mean post-punishment slowing in the abstinent smokers was nearly three times that of satiated smokers and that the lack of a significant difference may be attributable to large variability in the reaction time data.

4.4.9 Demographics

The participants that were randomly allocated to either the smoke or no-smoke groups were well matched for gender and age and on a range of personality and mood questionnaires. In addition, participants from both groups were well matched on short-term memory performance assessed with immediate word recall. In terms of smoking characteristics of participants, both groups were matched for level of dependence (assessed with the FTND), the number of cigarettes smoked per day and the number of years that the participants had been a smoker. Importantly, the mean FTND score for all participants was 6.27 indicating a moderate level of dependence and the duration of abstinence at the beginning of the study was equal for both groups. One limitation of the current study was the omission of recording additional factors upon which to match participants that may have influenced behavioural performance (e.g. education level, IQ and individual differences in attention) and future studies should address these omissions.

4.4.10 Smoking Manipulation

The smoking manipulation was validated by an increase in CO levels following cigarette smoking and CO levels remained higher in the smoke group for the remainder of the study. Significant subjective effects provided additional evidence of the effectiveness of the smoking manipulation. For example, smoking a cigarette was associated with increases in subjective ratings of 'buzzed' and 'dizzy' and similar subjective effects have been found in previous studies (Jackson et al., 2009; Nesic et

al., 2011a). Further evidence that the smoking manipulation was effective was that craving (assessed with the QSU-brief) was reduced by smoking, and that levels of craving were therefore lower in the smoke group compared to the no-smoke group when completing the behavioural tasks.

4.4.11 Correlation Between BIS/BAS BIS and RARP Suppression Ratio

This study explored the relationships between RARP task and PRL task punishment sensitivity measures and the relationships between these punishment sensitivity measures and subjective behavioural inhibition. In addition, the relationships between all the RARP and PRL task behavioural measures and smoking-related demographic data were explored as were the relationships between these behavioural measures and subjective impulsiveness. Bonferroni corrections were applied for multiple correlations and although this procedure is very good at controlling for type one errors (false positives) it can be considered conservative and increase the probability of type two errors (false negatives) particularly for small increases in the number of correlations made (Curtin and Schulz, 1998). For this reason the correlation that approached significance as well as the correlation that reached the significance threshold are discussed further. However, interpretation of the correlational analyses should be made with caution as in general this type of analysis may be more appropriate for larger sample sizes.

The negative correlation between the BIS/BAS BIS subscale score and RARP suppression ratio that approached significance is at first glance surprising because high scores on the BIS subscale of the BIS/BAS reflect greater activation of the inhibition or avoidance system which is associated with greater punishment sensitivity. Larger suppression ratios also reflect greater punishment sensitivity so a positive correlation might easily have been predicted. However, it is important to remember that self-report measures and behavioural measures of the same constructs do not always correlate as expected. Furthermore, whereas the BIS/BAS can be considered a measure of trait inhibition/avoidance (punishment sensitivity), RARP suppression ratio is a state measure of punishment sensitivity and whether

state and trait punishment sensitivity share common underlying processes is not established.

4.4.12 Correlation Between Win-shift Errors and Years of Smoking

There was a positive correlation between years of smoking and win-shift errors. Win-shift errors occur when a participant shifts from a correct, rewarded response to an incorrect response and therefore may reflect behavioural impulsiveness. Causation cannot be determined through correlation however one possibility is that those that had smoked for the longest time had done so because they were more impulsive and this could have been because more impulsive individuals find it more difficult to quit smoking. VanderVeen et al. (2008) showed for example that those with greater impulsivity had greater increases in craving and anxiety during a 48 hour abstinence period. These increases could explain why higher impulsive individuals struggle to remain abstinent. Another study that supports this hypothesis investigated the link between impulsivity and increased susceptibility to relapse. In this study, rats that had been screened for impulsivity with the 5-choice serial reaction time task were subsequently trained to self-administer cocaine under a 'seeking-taking' chained schedule whereby responses on a seeking lever resulted in presentation of a taking lever. Responding upon the taking lever resulted in cocaine reinforcement. After stable responding was established an intermittent punishment schedule was introduced whereby presses on the seeking lever resulted in the random presentation of either the taking lever or a mild footshock. The result of this study indicated that footshock punishment led to a decrease in cocaine seeking and that removing the footshock punishment 7 days later resulted in a relapse in responding on the seeking lever. High and low impulsive rats both reinstated this cocaine seeking response after a single phase of punishment. However, a second phase of punishment resulted in only high impulsive rats reinstating seeking responses suggesting that impulsivity that predates drug abuse increases the susceptibility to relapse (Economidou et al., 2009). However, it is important to note that the smokers in the current study were not attempting to quit and that previous quit attempts, if any, were not recorded.

The correlation might also suggest that those that had smoked for the longest had become more impulsive perhaps due to smoking-induced neuroadaptations in regions responsible for reward processing or impulsive behaviour. Nicotine induced neuroadaptations are documented (see review by D'Souza and Markou, 2011) and acute nicotine has been shown to increase impulsive action (Kirshenbaum et al., 2011) and impulsive choice (Kolokotroni et al., 2011) however further work is required in order to see if extended nicotine use leads to a more impulsive phenotype.

4.4.13 Strengths and Limitations

This study was not without its limitations. One limitation was that point gain and point loss was used for reward and punishment respectively as opposed to a monetary outcome or winning and losing cigarettes. Participants may have been more motivated by these latter rewards and punishers. However, the fact that participants worked for points, that subtraction of points on the RARP task was able to sufficiently suppress responding and that loss of points on the PRR was capable of producing switches in responding indicates that points acted effectively as rewards and punishment. Another limitation of the study was that the number of errors generated in the PRL task was low. Future studies could use a PRL task where it is harder to determine the correct and incorrect stimulus from a pair (i.e. using a task containing 70-30% pairs). This increased task difficulty (uncertainty) might increase the number of errors generated and improve task sensitivity. A further limitation is that the correlations reported here were based on low numbers and so replication of these in future work would increase confidence in conclusions drawn from them.

Contrary to the hypothesis abstinent smokers were not found to be less sensitive to punishment than satiated smokers. Participants were minimally deprived having been asked not to smoke for a minimum of 3 hours (although the actual mean abstinence levels were much higher than this, some of the participants were only 3 hours into abstinence). Therefore the possibility remains that participants in the no-

smoke group may not have been abstinent for long enough for effects on punishment sensitivity to be observed. Future work using longer abstinence periods would avoid this potential limitation.

Despite these limitations, there were also several strengths to the current work. The groups were well matched on demographic measures and mean FTND scores indicated that the groups were moderately dependent. However the possibility still remains that group differences may have been found had participants with higher levels of dependence been tested. In addition, this study is one of the largest to investigate smoking and abstinence-induced effects upon punishment sensitivity and unlike many older studies that used single measures of punishment sensitivity the current work used multiple, independent measures of punishment sensitivity.

4.4.14 Conclusions

In conclusion, this study found that there were no differences in punishment sensitivity between satiated and abstinent smokers as assessed using two different operant tasks. Furthermore, there were no group differences in post-punishment slowing suggesting that post-punishment processing did not differ across the groups. The study also found that irrespective of group win-shift errors, a measure of impulsiveness, were associated with years of smoking.

4.5   Executive Summary of Main Findings

• Punishment suppressed responding in both abstinent and satiated smokers.

• The degree to which punishment suppressed responding did not differ between abstinent and satiated smokers suggesting that these groups did not differ in punishment sensitivity.

• Satiated and abstinent smokers did not differ in the number of lose-stay errors or win-maintenance failures also suggesting that these groups did not differ in punishment sensitivity.

• Satiated and abstinent smokers did not differ in post-punishment slowing suggesting that post-punishment processing was similar across the groups.

• Win-shift errors, a measure of impulsiveness, were associated with years of smoking. This suggests that either extended smoking leads to increases in impulsiveness or that increased impulsiveness leads to individuals smoking for longer.

Chapter 5   Investigating Punishment Sensitivity in Current, Former and Never Smokers

5.1   Introduction

Previous research suggests that abstinence from smoking may be related to suppression of normal motivational responses (e.g. Powell et al., 2002b; Dawkins and Powell, 2011). In line with this abstinent smokers show reduced reward sensitivity compared to both satiated smokers and non-smokers (Powell et al., 2002a) and reward sensitivity can be restored in abstinent smokers after smoking a cigarette (Al-Adawi and Powell, 1997) or after taking a nicotine lozenge (Powell et al., 2004; Dawkins et al., 2006). However previous research on the effects of smoking and abstinence from smoking on punishment sensitivity has been equivocal, with different groups (both animal and human studies) finding increases, decreases and no effects on avoidance behaviour or similar operant indices (e.g. Morrison, 1969; Glowa, 1986; Cherek and Bennett, 1989; Furusawa and Tadokoro, 1990; and Bennett and Cherek, 1991).

The previous study (Chapter 4) found no differences in punishment sensitivity between satiated and abstinent smokers on two different operant tasks: a conflict task and a probabilistic reversal learning (PRL) task. However a number of limitations to this study were identified. Firstly the smokers were only minimally deprived, having been asked to abstain from smoking for a minimum of 3 hours prior to the testing session. Therefore the possibility remains that differences in punishment sensitivity may have been observed if recent smoking had been compared to greater durations of abstinence. Secondly the number of errors generated by participants on the PRL task, which were used to calculate the punishment sensitivity indices, were low thus calling into question the ability of the task to discriminate punishment sensitivity between the groups. The current study aimed to address these limitations by investigating punishment sensitivity in a smoking condition and in an overnight abstinent condition. Furthermore, punishment sensitivity was assessed using lose-stay errors (perseverative errors in the face of negative feedback) and win-

maintenance failures (inappropriate shifts after unexpected negative feedback) on a PRL task in which the correct and incorrect stimuli were rewarded and punished on the basis of either an 80-20% or a 70-30% contingency (as opposed to the 100-0% and 80-20% contingencies used in the previous study). It was anticipated that the increased frequency of false feedback in the new task would make the task more difficult by increasing the uncertainty over which stimulus was correct and that this increased uncertainty would increase the number of errors that participants generated on the task.

In addition to investigating punishment sensitivity in satiated and abstinent smokers the current study included a group of never smokers so that the influence of chronic cigarette smoking on punishment sensitivity could be examined with reference to a non-smoking control group. Evidence suggests that chronic exposure to drugs of abuse is associated with insensitivity to punishment. For example cocaine experienced rats will continue with cocaine seeking responses even when the seeking responses are punished (Pelloux et al., 2007). In human studies chronic cocaine users display elevated levels of perseverative responding in the face of monetary loss compared to controls (Ersche et al., 2008). Furthermore, neuroimaging research has shown that dependence is associated with reduced neural activity in response to errors and punishment (e.g. in cocaine users: Franken et al., 2007; and in smokers: Franken et al., 2010; Luijten et al., 2011a; de Ruiter et al., 2009). de Ruiter et al. (2009) found a reduced neural response to punishment in smokers compared to non-smokers in a PRL task similar to that used in the current study but an in-depth analysis of the behavioural reaction to negative feedback in smokers (similar to the work in cocaine users; Ersche et al., 2008) is lacking and the current study will address this issue.

Insensitivity to negative consequences may explain, at least in part, why dependent populations persist with drug use despite knowledge of the negative consequences (e.g. health, social and financial) that can occur with use, and further to this improved punishment sensitivity in former smokers may represent a mechanism by which

abstinence is maintained. In line with this suggestion former smokers have been shown to have an enhanced neural response to error compared to both current smokers and never smokers (Nestor et al., 2011) and furthermore punishment sensitivity has been shown to be related to error monitoring (Boksem et al., 2006, 2008; Amodio et al., 2008; Balconi and Crivelli, 2010a, 2010b). Therefore, the current study also included a former smoker group for comparison purposes.

The main aim of this study was to compare punishment sensitivity in satiated, abstinent, former and never smokers using a PRL task. In line with previous research it was predicted that abstinent smokers would be less sensitive to punishment (making more lose-stay errors and fewer win-maintenance failures) compared to satiated smokers. In addition, consistent with the view that drug dependence is associated with insensitivity to punishment it was predicted that current smokers irrespective of their satiation/withdrawal state would be less sensitive to punishment (making more lose-stay errors and fewer win-maintenance failures) compared to never smokers. Furthermore consistent with the suggestion that increased error monitoring is characteristic of successfully abstaining former smokers (Nestor et al., 2011) it was hypothesised that former smokers would have greater sensitivity to punishment (fewer lose-stay errors and more win-maintenance failures) compared to current smokers.

In addition to the punishment sensitivity measures, the PRL task also assesses win-shift errors which are thought to reflect impulsiveness. In line with previous work showing increased impulsiveness in smokers compared to non-smokers (e.g. Bernow et al., 2011) it was predicted that the current smoker groups would make more errors of this type. Group differences in the change in PRL task errors from acquisition to reversal phases of the task were also investigated. Change in lose-stay errors across the task phases might index cognitive flexibility and change in win-maintenance failures across the task phases might index feedback monitoring. In line with research suggesting that smoking is associated with deficits in cognitive flexibility (Martin et al., 2000; Kalmijn et al., 2002) it was predicted that the change in lose-stay errors in

reversal compared to acquisition would be greater for current smokers compared to never smokers. Furthermore, former smokers were predicted to have a greater change in win-maintenance failures from acquisition to reversal compared to current smokers in line with evidence of greater monitoring in this group (Nestor et al., 2011). Participants also performed a Rapid Visual Information Processing (RVIP) task as a cognitive control task that is sensitive to nicotine effects (e.g. Wesnes and Warburton, 1984; Jackson et al., 2009) and a range of self-report mood and personality measures.

5.2   Materials and Method

5.2.1   Participants

Sixty healthy participants (30 current smokers, 15 former smokers and 15 never smokers) aged 18-38 years were recruited for the study from the Universities of Brighton and Sussex and from the local community. Current smokers were defined as those who had smoked at least 10 cigarettes per day for at least 1 year. Former smokers were defined as those who had a pre-quit smoking level of at least 10 cigarettes per day and had not smoked for at least 6 months. Never smokers were defined as those who had not smoked more than 5 cigarettes in their lifetime. All current smokers were asked to arrive at the laboratory having not smoked since 11pm the previous night (overnight abstinence). In addition, in order to meet the inclusion criteria all participants were required to be in good health, not be using psychotropic medication or regular medication of any sort (with the exception of oral contraceptives) and were required to arrive at the laboratory having not consumed alcohol for at least 12 hours and to have refrained from the use of illicit drugs for at least 1 week. Ethical approval was obtained from the University of Brighton School of Pharmacy and Biomolecular Sciences Research Ethics Committee. All participants gave their written informed consent prior to participation, were free to withdraw from the study at any point and were debriefed at the end of the study. Participants received £12 compensation for their time.

5.2.2 Design

This study used a between subjects design comparing the performance of current, former and never smokers. Upon arrival current smokers were randomly assigned to either a satiated or abstinent group in a single blind design. This created the following 4 experimental groups: satiated smokers (n = 15), abstinent smokers (n = 15), former smokers (n =15) and never smokers (n = 15). In order to reduce any potential smoking/abstinence-related performance expectancies all smokers were told that they would smoke at some point during the session but not when. Those in the satiated smokers group smoked before the test battery and those in the abstinent group smoked at the end of the session so that they did not leave the laboratory in a withdrawn state. Each participant attended the laboratory on one occasion and took part in a test session lasting approximately 1 hour and 30 minutes.

5.2.3 Procedure

Before participation in the study, participants were asked about their general health, current medication use, smoking behaviour/nicotine dependence, alcohol and illicit drug use by completing screening questionnaires consisting of the Fagerstrom Test for Nicotine Dependence (FTND; see General Methods, section 2.3.1) and the Medicinal Drug, Alcohol and Illiciit Drug Use Questionnaire (MAID; see General Methods, section 2.3.2). On arrival at the laboratory, all participants were subject to a breath alcohol test (see General Methods, section 2.2.1) and an exhaled carbon monoxide (CO) test (see General Methods, section 2.2.2) in order to ascertain that no recent drinking of alcohol or cigarette smoking had occurred. Participants were excluded for a breath alcohol reading greater than 0 g/L and for an exhaled CO level above 10 ppm.

Participants were then asked to complete a batch of personality and mood questionnaires consisting of the Barratt Impulsiveness Scale (BIS; see General Methods, section 2.5.1), the Behavioural Inhibition System/Behavioural Activation System Scales (BIS/BAS; see General Methods, section 2.5.2), the Beck Depression

Inventory (BDI; see General Methods, section 2.4.1), the Rumination and Reflection Questionnaire (RRQ; see General Methods, section 2.5.4) and the Scott-McIntosh Rumination Inventory (SMRI; see General Methods, section 2.5.5). Current smokers also completed the Nicotine Dependence Syndrome Scale (NDSS; see General Methods, section 2.3.3). Participants then completed the National Adult Reading Test (NART; see General Methods, section 2.7.8) and an immediate word recall test (IWR; see General Methods, section 2.7.6). Participants completed the computerised test battery (programmed and administered using E-Prime version 1.1 (Psychology Software Tools Inc., Pittsburgh, PA, USA) and presented to participants on a laptop computer in a quiet, neutral environment) consisting of a PRL task (the version with the 80-20% and 70-30% contingency pairs; see General Methods, section 2.7.9) and a RVIP task (see General Methods, section 2.7.10) presented in a counterbalanced order. Current smokers randomly assigned to the satiated condition smoked one of their own cigarettes immediately before completing the test battery and those randomly assigned to the abstinent condition did not. Instead, smokers in the abstinent condition smoked one of their own cigarettes at the very end of the study. Breath CO level recordings were repeated before the test battery (after the satiated smoker group had smoked) and after the test battery. Nicotine-Sensitive Visual Analogue Scales (NicVAS; see General Methods, section 2.6.1) were completed upon arrival at the laboratory, immediately before the test battery (after the satiated smoker group had smoked) and after the test battery. Craving was assessed in the current smoker groups using the brief version of the Questionnaire of Smoking Urges (QSU-brief; see General Methods, section 2.6.2). The QSU-brief was completed upon arrival at the laboratory, immediately before the test battery (after the satiated smoker group had smoked) and at the very end of the testing session (after the abstinent smoker group had also smoked).

5.2.4   Data Analysis

Statistical analysis was conducted on data from all sixty participants (15 satiated smokers, 15 abstinent smokers, 15 former smokers and 15 never smokers) using SPSS version 18 (SPSS Inc., Chicago, IL, USA). Participant demographic data was analysed

using Chi Square (for gender) and one-way analysis of variance (ANOVA) or Kruskal-Wallis test where data was not normally distributed and transformations could not correct this (for age, years of education, self-report personality and mood, NART score, IWR and smoking-related demographics). Significant group differences in these demographics were followed up with post-hoc pairwise comparisons. Where smoking-related demographics applied to the two current smoker groups only group differences were analysed using independent samples t-tests.

The physiological effects of smoking (exhaled CO levels) were examined using a 3 (time point) x 4 (group) mixed design ANOVA followed by three separate post-hoc ANOVA's to examine group differences at each time point. Significant group differences were then followed up with post-hoc pairwise comparisons. For the effects of smoking on craving (QSU-brief) and the subjective effects of smoking (NicVAS) the majority of data was not normally distributed and transformations could not correct this. In the minority of cases where parametric assumptions were met (NicVAS 'alert', 'relaxed' and 'thirsty') a 3 (time point) x 4 (group) mixed design ANOVA was performed. Significant interactions were followed up by separate repeated measures ANOVA's for each group along with post-hoc pairwise comparisons. In all other cases non-parametric Wilcoxon signed-ranks tests were used to compare baseline scores with scores obtained immediately before the test battery (i.e. after smoking in the smoke group) for each group separately. In addition, for the craving measure an extra comparison was made between baseline scores and scores obtained at the end of the study, again for each group separately. Also, craving scores were compared using a Mann-Whitney U test between abstinent and satiated smokers immediately before the test battery as a manipulation check.

For RVIP the mean number of hits, the mean number of false alarms and the mean hit latency were compared between groups using one-way ANOVA followed by post-hoc pairwise comparisons. Additionally, the RVIP data was divided into five 1 minute time bins (each time bin contained 80 trials and 8 targets). The mean number of hits between the first and last time bin were compared for each group separately using

Wilcoxon signed-ranks tests as the data was not normally distributed and transformations could not correct this.

For the PRL task, each participant was required to have learned the correct stimulus for each pair at acquisition in order for their data to be included in analysis of PRL errors. Therefore a learning criterion of 6 consecutive correct responses in the acquisition phases of the PRL task was imposed for each stimulus pair (a method used previously by Budhani et al. (2006)) whereby participants had to achieve at least 6 consecutive correct responses with each stimulus pairing before data was included for analysis. All participants met this 6 consecutive correct trials criterion and the mean number of trials taken to reach this criterion provided a measure of learning speed. The number of trials taken to reach this criterion was compared across groups for each contingency (80-20% and 70-30% contingency pairs) using one-way ANOVA or Kruskal-Wallis where data was not normally distributed and transformations could not correct this. PRL errors (lose-stay errors, win-maintenance failures and win-shift errors) were compared across groups for each contingency in both acquisition and reversal using one-way ANOVA or Kruskal-Wallis where data was not normally distributed and transformations could not correct this. Significant findings were followed up with either post-hoc pairwise comparisons or Mann-Whitney U tests where appropriate. For all PRL error types change from acquisition to reversal, irrespective of contingency, was computed (calculated as the total number of errors made in reversal minus the total number of errors made in acquisition). As the change score data for each error type was not normally distributed and transformations could not correct this, the change scores were analysed across groups using Kruskal-Wallis followed by post-hoc Mann-Whitney U tests.

All statistical tests were two-tailed with alpha set at $p = 0.05$. In cases where statistical significance was greater than $p = 0.05$ but less than or equal to $p = 0.075$, results have been considered a trend. Where multiple comparisons were required p-values were Bonferroni corrected by multiplying the p-value obtained by the total number of comparisons made (as in Bland and Altman, 1995) this is equivalent to

lowering the level of alpha. In addition effect sizes were reported for significant findings. The assumption of normal distribution was assessed using the Kolmogorov-Smirnov test and by visual assessment of histograms of the data produced in the SPSS output. Where data was found to violate the assumption of normality, transformations were applied to the data and the specific transformations are described where they occurred in the appropriate places in the results section. The assumption of homogeneity of variance/sphericity was assessed with Levene's test or Mauchly's test as appropriate. Significant Levene's tests indicating violation of the assumption of homogeneity of variance was addressed by using Welch's robust test of equality of means. Significant Mauchly's tests indicating violation of the assumption of sphericity was addressed by using Greenhouse-Geisser corrected degrees of freedom and p-values.

5.3   Results

5.3.1   Demographics

Table 5.1 shows the demographic data for the satiated, abstinent, former and never smoker groups. There was no significant difference in the mean age of each group $(F(3, 56) = 1.29, p = 0.287)$, a trend towards a significant difference in the mean number of years of education in each group $(F(3, 56) = 2.63, p = 0.059$; the means show that the current smoker groups had fewest years of education followed by former and then never smokers) and a significant difference in the number of males and females in each group $(X^2 (3) = 17.13, p = 0.001)$ with the ratio of males to females approximately 1:1, 3:1, 1:6 and 1:6 in satiated, abstinent, former and never smokers respectively. Additionally, the groups did not differ in mean number of NART errors $(F(3, 56) = 0.46, p = 0.709)$ or number of words recalled in the IWR $(F(3, 56) = 1.66, p = 0.187)$.

Demographic	SS Mean (S.E.M.)	AS Mean (S.E.M.)	FS Mean (S.E.M.)	NS Mean (S.E.M.)
N	15	15	15	15
Gender (M/F) **	8/7	11/4	2/13	2/13
Mean Age (years)	22.20 (1.05)	24.87 (1.72)	25.80 (1.50)	24.20 (0.95)
Years of Education	15.33 (0.49)	15.93 (0.78)	16.67 (0.61)	17.60 (0.48)
NART Errors	14.80 (0.92)	14.13 (1.24)	13.00 (1.33)	14.53 (1.13)
IWR (words recalled)	7.07 (0.64)	7.53 (0.51)	7.80 (0.54)	8.73 (0.49)
BIS (total score)	72.27 (1.55)	75.80 (2.16)	68.87 (3.87)	65.53 (2.69)
BIS/BAS - BAS Drive #	11.00 (4.00)	11.00 (4.00)	11.00 (2.00)	11.00 (3.00)
BIS/BAS - BAS Fun Seeking #	14.00 (3.00)	11.00 (3.00)	13.00 (3.00)	12.00 (3.00)
BIS/BAS - Reward Responsiveness #	17.00 (4.00)	17.00 (3.00)	18.00 (4.00)	17.00 (2.00)
BIS/BAS – BIS *	19.73 (1.05)	18.93 (0.80)	22.80 (0.81)	20.67 (0.86)
BDI *	7.13 (1.11)	7.13 (1.15)	6.60 (1.34)	3.73 (0.87)
RRQ Rumination *	3.39 (0.19)	3.33 (0.19)	3.91 (0.13)	3.04 (0.20)
RRQ Reflection	3.47 (0.19)	2.95 (0.19)	3.37 (0.28)	2.74 (0.27)
SMRI Distraction	14.53 (0.93)	14.47 (0.77)	15.00 (0.74)	12.93 (1.11)
SMRI Emotionality	10.27 (1.14)	10.93 (0.94)	11.47 (1.21)	10.53 (0.62)
SMRI Motivation	14.53 (1.03)	13.93 (1.40)	14.53 (1.17)	16.87 (0.72)

Table 5.1: Demographic Data for Satiated, Abstinent, Former and Never Smokers.
(Abbreviations: SS: satiated smokers, AS: abstinent smokers, FS: former smokers, NS: never smokers, S.E.M.: standard error of the mean, M/F: male/female, NART: National Adult Reading Test, IWR: Immediate Word Recall, BIS: Barratt Impulsiveness Scale, BIS/BAS: Behavioural Inhibition Scale/Behavioural Activation Scale, BIS/BAS – BIS: Behavioural Inhibition Subscale, BDI: Beck Depression Inventory, RRQ: Rumination-Reflection Questionnaire, SMRI: Scott-McIntosh Rumination Inventory; # = median and interquartile range shown instead of mean and standard error of the mean for data that was analysed using non-parametric tests, * = significant group difference $p < 0.05$, ** = significant group difference $p < 0.005$).

In terms of personality and mood, the groups did not differ in mean scores obtained on the BIS/BAS behavioural activation subscales (drive ($H(3) = 0.73$, $p = 0.868$), fun seeking ($H(3) = 5.01$, $p = 0.173$) or reward responsivity ($H(3) = 4.07$, $p = 0.257$)), RRQ reflection subscale ($F(3, 56) = 2.09$, $p = 0.112$) or SMRI subscales (distraction ($F(3, 56) = 1.00$, $p = 0.398$, emotionality ($F(3, 56) = 0.27$, $p = 0.846$) or motivation ($F(3, 56) = 1.37$, $p = 0.262$). Differences between the groups in BIS total score approached significance ($F(3, 56) = 2.66$, $p = 0.057$; the means show that the current smoker groups had the greatest BIS scores followed by former and then never smokers). There was a significant difference in the BIS/BAS BIS subscale scores ($F(3, 56) = 3.56$, $p = 0.020$). Pairwise comparisons revealed that former smokers had greater BIS/BAS BIS subscale scores than satiated (Bonferroni corrected, $p = 0.051$, $r = 0.40$) and abstinent (Bonferroni corrected, $p = 0.009$, $r = 0.54$) smokers but not never smokers (Bonferroni corrected, $p = 0.282$). There was also a significant difference between the groups in RRQ rumination subscale scores ($F(3, 56) = 4.01$, $p = 0.012$). Pairwise comparisons revealed that former smokers had greater rumination scores than never smokers (Bonferroni corrected, $p = 0.003$, $r = 0.60$) but not satiated (Bonferroni corrected, $p = 0.135$) or abstinent (Bonferroni corrected, $p = 0.078$) smokers. In addition there was a significant difference between groups on BDI score (natural log transformed; $F(3, 56) = 3.30$, $p = 0.027$). Pairwise comparisons revealed that never smokers scored significantly less on the BDI compared to satiated (Bonferroni corrected, $p = 0.027$, $r = 0.44$) and abstinent (Bonferroni corrected, $p = 0.027$, $r = 0.44$) but not former smokers (Bonferroni corrected, $p = 0.120$).

5.3.2   Smoking-related Demographics

In terms of smoking related demographic data, satiated, abstinent and former smokers did not differ in the mean number of cigarettes smoked per day (pre-quit levels for former smokers; $F(2, 42) = 1.39$, $p = 0.261$) or the mean age at which they started smoking ($F(2, 42) = 0.87$, $p = 0.428$). However, there was a significant difference in the mean number of years for which these groups had smoked ($F(2, 42) = 3.52$, $p = 0.039$). Pairwise comparisons showed that abstinent smokers had smoked for longer than satiated smokers (Bonferroni corrected, $p = 0.038$, $r = 0.44$) but not

former smokers (Bonferroni corrected, p = 0.078). In addition, satiated and abstinent smokers did not differ in mean dependence levels assessed with either the FTND (t(28) = -0.42, p = 0.681) or NDSS (overall score; (t(28) = 0.69, p = 0.498). These smoking-related demographics are shown in Table 5.2 alongside the mean number of months former smokers had been abstinent and for never smokers the mean number of lifetime cigarettes.

Smoking-Related Demographic	SS	AS	FS	NS
	Mean (S.E.M.)	Mean (S.E.M.)	Mean (S.E.M.)	Mean (S.E.M.)
Cigarettes per Day #	14.20 (1.20)	15.47 (0.76)	13.07 (1.06)	-
Age Started Smoking (years)	15.73 (0.86)	14.4 (0.35)	14.93 (0.84)	-
Years of Smoking *	5.47 (0.80)	9.33 (1.53)	5.93 (0.90)	-
FTND Score	4.87 (0.40)	5.07 (0.27)	-	-
NDSS (Overall Score)	0.24 (0.17)	0.07 (0.16)	-	-
Duration of abstinence (months)	-	-	20.47 (4.38)	-
Lifetime Cigarettes	-	-	-	1.47 (0.55)

Table 5.2: Smoking-related Demographics for Satiated, Abstinent, Former and Never smokers.
(Abbreviations: SS: satiated smokers, AS: abstinent smokers, FS: former smokers, NS: never smokers, S.E.M.: standard error of the mean, FTND: Fagerstrom Test for Nicotine Dependence, NDSS: Nicotine Dependence Syndrome Scale; # = pre-quit levels for former smokers, * = significant group difference p < 0.05).

5.3.3 Physiological Effects of Smoking

Mean exhaled CO levels changed over time during the study (F(2, 112) = 64.38, p < 0.001) and overall CO levels differed between the groups (F(3, 56) = 113.20, p < 0.001). There was a time by group interaction (F(6, 112) = 95.11, p < 0.001). Post-hoc ANOVA's revealed that the groups were significantly different at baseline (F(3, 29.22)

= 25.14, p = 0.003, Bonferroni corrected), before the test battery (F(3, 29.28) = 80.87, p = 0.003, Bonferroni corrected) and after the test battery (F(3, 28.60) = 84.72, p = 0.003, Bonferroni corrected). Pairwise comparisons for each time point showed that at baseline both satiated smokers and abstinent smokers had greater breath CO levels than both former and never smokers (all p values = 0.004, Bonferroni corrected). Before the test battery the breath CO levels of satiated smokers were greater than the breath CO levels of abstinent, former and never smokers (all p values = 0.005, Bonferroni corrected). Additionally breath CO levels of abstinent smokers were greater than former and never smokers at this time point (all p values = 0.005, Bonferroni corrected). The same pattern of results was seen after the test battery (all p values = 0.005, Bonferroni corrected). Effect sizes for the pairwise comparisons described above ranged from r = 0.77 to r = 0.97. These data are shown in Figure 5.1.
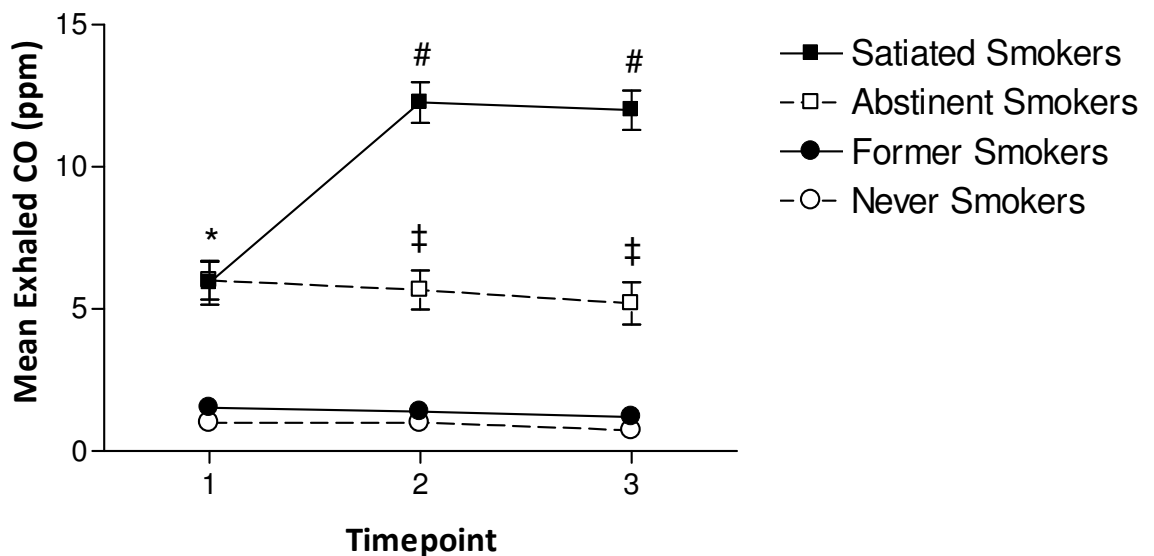
Figure 5.1: Mean Exhaled Carbon Monoxide (CO) Across Time for Satiated, Abstinent, Former and Never Smokers.
(Abbreviations: CO: carbon monoxide, ppm: parts per million. Time point 1 = baseline, time point 2 = before test battery, time point 3 = after test battery. * = satiated and abstinent smokers > former and never smokers, all p values < 0.005. # = satiated smokers > all other groups, all p values < 0.01 and ‡ = abstinent smokers > former and never smokers but < satiated smokers, all p values < 0.01. . Error bars represent standard error of the mean).

5.3.4 Subjective Effects of Smoking

Table 5.3 shows the NicVAS data obtained at baseline, immediately before and after the test battery for every group. The groups differed across time in ratings of 'alert' ($F_{(4.23, 78.97)}$ = 3.70, p = 0.007) and 'relaxed' ($F_{(5.25, 98.02)}$ = 12.08, p < 0.001). Ratings of 'alert' changed across time for satiated smokers ($F_{(2, 28)}$ = 14.29, p = 0.004 Bonferroni corrected) but not for abstinent ($F_{(1.02, 14.30)}$ = 1.23, p = 1.000 Bonferroni corrected), former ($F_{(1.15, 16.13)}$ = 0.36, p = 1.000 Bonferroni corrected) or never ($F_{(1.01, 14.13)}$ = 0.38, p = 1.000 Bonferroni corrected) smokers. Pairwise comparisons revealed that ratings of 'alert' increased from baseline to immediately before (Bonferroni corrected p = 0.002, r = 0.78) and after (Bonferroni corrected p = 0.002, r = 0.74) the test battery for satiated smokers. Ratings of 'relaxed' changed across time for satiated ($F_{(2, 28)}$ = 18.86, p = 0.004 Bonferroni corrected) and abstinent ($F_{(1.34, 18.71)}$ = 13.90, p = 0.004 Bonferroni corrected) smokers but not for former ($F_{(1.13, 15.84)}$ = 6.34, p = 0.080 Bonferroni corrected) or never ($F_{(1.04, 14.49)}$ = 3.16, p = 0.380 Bonferroni corrected) smokers. Pairwise comparisons revealed that ratings of 'relaxed' increased from baseline to immediately before (Bonferroni corrected p = 0.002, r = 0.81) and after (Bonferroni corrected p = 0.010, r = 0.66) the test battery in satiated smokers. Whereas in abstinent smokers ratings decreased from baseline to before (Bonferroni corrected p = 0.014, r = 0.64) and after (Bonferroni corrected p = 0.002, r = 0.73) the test battery.

Furthermore, between baseline and immediately before the test battery satiated smokers showed increases in ratings of 'buzzed' (z = -3.41, p = 0.004 Bonferroni corrected, r = -0.62), 'dizzy' (z = -3.29, p = 0.004 Bonferroni corrected, r = -0.60) and 'contented' (z = -3.41, p = 0.004 Bonferroni corrected, r = -0.62). In addition, satiated smokers showed decreases in ratings of 'irritable' (z = -3.18, p = 0.004 Bonferroni corrected, r = 0.58) and 'impatient' (z = -2.84, p = 0.012 Bonferroni corrected, r = -0.52) between the same time points. In contrast, between the same time points abstinent smokers showed increases in ratings of 'irritable' (z = -3.30, p = 0.004 Bonferroni corrected, r = -0.60) and impatient (z = -3.30, p = 0.004 Bonferroni corrected, r = -0.60) and decreases in ratings of 'contented' (z = -3.04, p = 0.004

Bonferroni corrected, r = -0.56). For ratings of 'stimulated' between these time points both satiated smokers and former smokers showed increases (z = -3.07, p = 0.004 Bonferroni corrected, r = -0.56 and z = -2.55, p = 0.032 Bonferroni corrected, r = -0.47 respectively). There were no significant differences in ratings of 'jittery', 'hungrier than usual', or 'thirsty' between baseline and before the test battery for any group.

For the satiated smoker group craving scores were significantly higher at baseline (i.e. before smoking; median: 4.70, IQR: 1.40) compared to immediately prior to the test battery (i.e. after smoking; median: 2.00, IQR: 0.80; z = -3.41, p = 0.002 Bonferroni corrected, r = -0.62) and compared to the end of the study (median: 3.00, IQR: 1.70; z = -3.41, p = 0.002 Bonferroni corrected, r = -0.62). Whereas in the abstinent smoker group craving scores significantly increased from baseline (median: 4.70, IQR: 1.30) to immediately prior to the test battery (median: 5.50, IQR: 1.30; z = -2.99, p = 0.002 Bonferroni corrected, r = -0.55) and were significantly higher at baseline compared to after smoking had occurred in this group at the end of the study (median: 1.80, IQR: 0.90; z = -3.41, p = 0.002 Bonferroni corrected, r = -0.62). Craving scores immediately before the test battery were significantly higher in abstinent smokers compared to satiated smokers (U = 4.50, z = -4.49, p < 0.001, r = -0.82).

NIcVAS Rating (%)	SS Mean (S.E.M.)	AS Mean (S.E.M.)	FS Mean (S.E.M.)	NS Mean (S.E.M.)
Alert T1	40.50 (5.38)**‡‡	48.10 (5.93)	47.10 (4.76)	55.20 (4.04)
Alert T2	66.90 (2.61)	45.70 (5.57)	50.03 (4.32)	54.73 (3.94)
Alert T3	60.47 (5.59)	54.67 (5.19)	50.93 (5.74)	58.13 (4.26)
Buzzed T1 #	4.00 (4.00)**	3.00 (5.50)	2.00 (9.00)	3.00 (4.00)
Buzzed T2 #	76.00 (37.00)	2.00 (4.00)	5.00 (8.00)	3.00 (5.00)
Buzzed T3 #	16.00 (48.00)	3.50 (16.00)	7.00 (15.00)	10.00 (20.00)
Contented T1 #	36.00 (29.50)**	50.00 (38.00)**	50.00 (37.00)	61.00 (30.00)
Contented T2 #	71.00 (24.00)	48.00 (36.50)	49.00 (38.00)	59.00 (28.00)
Contented T3 #	66.00 (19.00)	33.00 (40.00)	43.00 (20.50)	50.00 (9.00)
Dizzy T1 #	3.00 (10.50)**	1.00 (2.00)	2.50 (8.00)	3.00 (3.50)
Dizzy T2 #	28.50 (60.00)	2.00 (3.00)	3.00 (8.00)	2.00 (5.00)
Dizzy T3 #	12.00 (24.00)	4.00 (10.50)	8.50 (12.50)	4.00 (24.00)
HTU T1 #	3.00 (16.00)	5.00 (55.00)	3.00 (22.00)	2.00 (6.00)
HTU T2 #	4.00 (9.00)	29.00 (57.00)	8.00 (18.00)	2.00 (5.50)
HTU T3 #	7.50 (10.50)	30.00 (49.00)	9.00 (17.00)	8.00 (13.00)
Impatient T1 #	38.00 (75.00)*	4.00 (37.00)**	9.50 (18.00)	4.00 (7.50)
Impatient T2 #	8.00 (14.00)	20.00 (32.00)	9.00 (21.00)	4.00 (8.50)
Impatient T3 #	18.50 (13.00)	31.00 (43.00)	6.00 (32.00)	9.00 (30.00)
Irritable T1 #	24.00 (70.50)**	8.00 (15.00)**	4.00 (11.50)	2.00 (4.00)
Irritable T2 #	6.00 (10.00)	14.00 (21.00)	6.00 (19.00)	2.00 (4.00)
Irritable T3 #	7.50 (12.00)	23.50 (31.00)	6.00 (19.50)	6.00 (44.00)
Jittery T1 #	7.00 (54.50)	3.00 (17.00)	3.00 (7.50)	3.00 (5.00)
Jittery T2 #	18.00 (26.00)	3.50 (17.00)	4.00 (7.50)	3.00 (7.00)
Jittery T3 #	7.50 (24.00)	4.00 (28.00)	4.00 (14.00)	4.00 (18.00)
Relaxed T1	39.97 (5.64)**‡	51.63 (6.24)*‡‡	53.93 (4.77)	52.73 (4.09)
Relaxed T2	72.97 (3.87)	42.80 (5.53)	52.70 (4.46)	51.60 (3.82)
Relaxed T3	58.63 (4.63)	34.87 (5.56)	40.37 (3.88)	44.73 (3.23)
Stimulated T1 #	30.00 (33.00)**	40.00 (21.00)	50.00 (26.00)*	50.00 (16.00)
Stimulated T2 #	58.00 (19.00)	39.00 (26.00)	50.00 (23.50)	50.00 (14.00)
Stimulated T3 #	59.00 (15.50)	50.00 (31.00)	57.00 (35.00)	53.00 (12.00)
Thirsty T1	29.63 (5.53)	30.17 (7.42)	32.30 (6.93)	28.87 (7.53)
Thirsty T2	45.90 (6.36)	30.47 (7.28)	31.20 (6.77)	28.30 (7.38)
Thirsty T3	33.83 (6.76)	30.37 (7.30)	28.03 (7.50)	24.27 (5.69)

Table 5.3: Subjective Ratings Across Time for Satiated, Abstinent, Former and Never Smokers.

(Abbreviations: SS: satiated smokers, AS: abstinent smokers, FS: former smokers, NS: never smokers, NicVAS: Nicotine-Sensitive Visual Analogue Scales S.E.M.: standard error of the mean, HTU: hungrier than usual, T1: baseline, T2: before test battery, T3: after test battery. # = median and interquartile range shown instead of mean and standard error of the mean for data that was analysed using non-parametric tests. Significant difference between T1 and T2 * = $p < 0.05$, ** = $p < 0.005$; significant difference between T1 and T3 ‡ = $p < 0.05$, ‡‡ = $p < 0.005$).

5.3.5   RVIP Task

The mean number of target hits decreased between the first and the last time bin of the RVIP task for abstinent (z = -3.25, p = 0.004 Bonferroni corrected, r = -0.59), former (z = -2.46, p = 0.048 Bonferroni corrected, r = -0.45) and never (z = -3.44, p = 0.004 Bonferroni corrected, r = -0.63) smokers but not for satiated smokers (z = -0.32, p = 1.000 Bonferroni corrected). Figure 5.2 shows the hit data for each group at these two time bins.

In addition, there was a significant difference between the groups in the mean number of target hits (F(3, 56) = 4.41, p = 0.007). Pairwise comparisons revealed that satiated smokers had fewer hits than never smokers (p = 0.003 Bonferroni corrected, r = 0.61) but not former smokers (p = 0.108 Bonferroni corrected) whilst there was a trend for fewer hits in satiated smokers compared to abstinent smokers (p = 0.063 Bonferroni corrected). However there were no group differences in mean hit latency (F(3, 56) = 2.26, p = 0.091). Further, there was a significant difference between the groups in the mean number of false alarms (natural log transformed, F(3, 56) = 5.91, p = 0.001). Pairwise comparisons revealed that the satiated smokers had more false alarms than abstinent (p = 0.015 Bonferroni corrected, r = 0.46), former (p = 0.036 Bonferroni corrected, r = 0.46) and never (p = 0.003 Bonferroni corrected, r = 0.53) smokers. Table 5.4 shows the mean number of hits, false alarms and mean hit latency for each group.
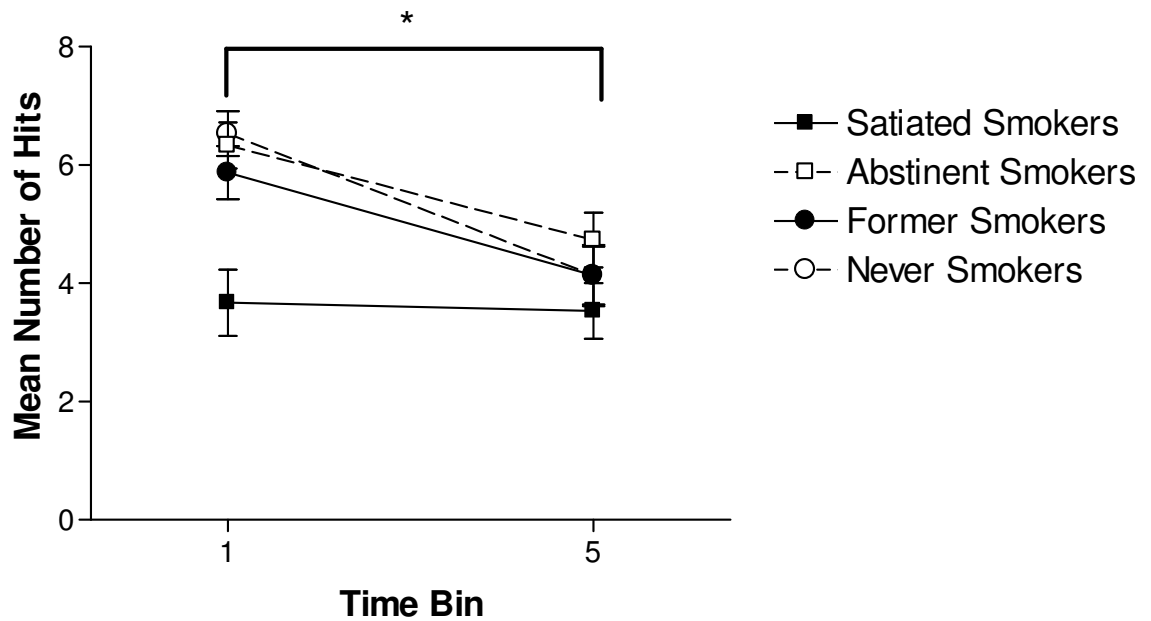
Figure 5.2: Mean Number of Hits in the First and Last Time Bin of the Rapid Visual Information Processing Task.

(* = Fewer hits in last time bin compared to first time bin for abstinent (p < 0.005), never (p < 0.005) and former (p < 0.05) smokers but not satiated smokers. Error bars represent standard error of the mean).

RVIP Task	SS	AS	FS	NS
	Mean (S.E.M.)	Mean (S.E.M.)	Mean (S.E.M.)	Mean (S.E.M.)
Number of Hits *	19.53 (1.22)	25.13 (1.94)	24.60 (1.73)	27.93 (1.69)
Hit Latency (ms)	519.01 (10.96)	500.47 (11.20)	494.78 (17.24)	471.74 (11.29)
Number of False Alarms ‡	13.53 (4.20)	4.40 (1.15)	4.73 (0.90)	3.07 (0.80)

Table 5.4: Rapid Visual Information Processing Task Data for Satiated, Abstinent, Former and Never Smokers.

(Abbreviations: SS: satiated smokers, AS: abstinent smokers, FS: former smokers, NS: never smokers, RVIP: Rapid Visual Information Processing, S.E.M: standard error of the mean. * = significant difference between SS and NS (p < 0.005), ‡ = significant difference between SS and AS (p < 0.05), SS and FS (p < 0.05) and SS and NS (p < 0.005)).

5.3.6 PRL Learning Criterion

The groups did not differ in the mean number of trials taken to reach 6 consecutive correct responses in acquisition of 80-20% contingency pairs (H(3) = 4.00, p = 0.260) or 70-30% contingency pairs (reciprocal transformed data, F(3, 56) = 0.01, p = 0.998). Table 5.5 shows the number of trials taken to reach the 6 consecutive correct response learning criterion.

5.3.7 PRL Lose-stay Errors

In acquisition groups did not differ in the number of lose-stay errors with either 80-20% contingency pairs (H(3) = 4.32, p = 0.224) or 70-30% contingency pairs (H(3) = 1.06, p = 0.789). Similarly in reversal groups did not differ in the number of lose-stay errors with 80-20% contingency pairs (H(3) = 2.11, p = 0.556) or 70-30% contingency pairs (F(3, 56) = 0.50, p = 0.681). Table 5.5 shows the number of lose-stay errors by group for 80-20% and 70-30% pairs at acquisition and reversal.

5.3.8 PRL Win-maintenance Failures

In acquisition groups did not differ in the number of win-maintenance failures in acquisition with either 80-20% contingency pairs (H(3) = 4.92, p = 0.178) or 70-30% contingency pairs (H(3) = 2.82, p = 0.426). Similarly in reversal groups did not differ in the number of win maintenance failures with either 80-20% contingency pairs (H(3) = 2.64, p = 0.452) or 70-30% contingency pairs (H(3) = 2.48, p = 0.487). Table 5.5 shows the number of win-maintenance failures by group for 80-20% and 70-30% pairs at acquisition and reversal.

5.3.9 PRL Win-shift Errors

In acquisition groups did not differ in the number of win-shift errors with 70-30% contingency pairs (H(3) = 0.97, p = 0.815). However the groups did differ with 80-20% contingency pairs (H(3) = 8.68, p = 0.030). Post-hoc comparisons revealed that there was a trend for fewer win-shift errors in never smokers compared to abstinent smokers (U = 63.50, z = -2.44, p = 0.060 Bonferroni corrected) and that never smokers made fewer win-shift errors than former smokers (U = 54.00, z = -2.82, p = 0.015

Bonferroni corrected, r = - 0.51) but not satiated smokers (U = 80.50, z = -1.72, p = 0.393 Bonferroni corrected). In reversal groups did not differ in the number of win-shift errors with 70-30% contingency pairs (H(3) = 1.61, p = 0.656). However the groups did differ with 80-20% contingency pairs (H(3) = 8.07, p = 0.041). Post-hoc comparisons revealed that never smokers made fewer win-shift errors than satiated and abstinent smokers (U = 59.00, z = -2.58, p = 0.033 Bonferroni corrected r = -0.47 for both) but not former smokers (U = 74.50, z = -1.95, p = 0.201 Bonferroni corrected). Table 5.5 shows the number of win-shift errors by group for 80-20% and 70-30% pairs at acquisition and reversal.

PRL Task	SS Mean (S.E.M.)	AS Mean (S.E.M.)	FS Mean (S.E.M.)	NS Mean (S.E.M.)
Trials to 6 CCR 80-20 #	7.67 (2.00)	7.33 (1.67)	9.00 (2.33)	8.00 (2.67)
Trials to 6 CCR 70-30	10.93 (1.04)	10.36 (0.77)	11.69 (1.56)	11.18 (1.26)
LSE Acq 80-20 #	1.00 (2.00)	2.00 (3.00)	1.00 (2.00)	1.00 (2.00)
LSE Acq 70-30 #	3.00 (5.00)	3.00 (6.00)	3.00 (3.00)	2.00 (6.00)
LSE Rev 8o-20 #	4.00 (6.00)	3.00 (4.00)	3.00 (1.00)	2.00 (3.00)
LSE Rev 70-30	5.73 (0.95)	6.80 (1.06)	7.73 (1.57)	6.80 (0.91)
WMF Acq 80-20 #	1.00 (2.00)	1.00 (2.00)	2.00 (4.00)	2.00 (3.00)
WMF Acq 70-30 #	3.00 (5.00)	3.00 (3.00)	4.00 (4.00)	2.00 (3.00)
WMF Rev 80-20 #	2.00 (1.00)	1.00 (3.00)	1.00 (4.00)	1.00 (2.00)
WMF Rev 70-30 #	3.00 (3.00)	2.00 (3.00)	2.00 (4.00)	2.00 (3.00)
WSE Acq 80-20 # *	0.00 (1.00)	1.00 (4.00)	1.00 (2.00)	0.00 (0.00)
WSE Acq 70-30 #	1.00 (3.00)	1.00 (3.00)	0.00 (4.00)	0.00 (2.00)
WSE Rev 80-20 # ‡	1.00 (2.00)	1.00 (2.00)	0.00 (1.00)	0.00 (0.00)
WSE Rev 70-30 #	1.00 (1.00)	1.00 (1.00)	0.00 (1.00)	0.00 (2.00)

Table 5.5: Probabilistic Reversal Learning Task Data for Satiated, Abstinent, Former and Never Smokers.
(Abbreviations: SS: satiated smokers, AS: abstinent smokers, FS: former smokers, NS: never smokers, PRL: Probabilistic Reversal Learning, CCR: consecutive correct responses, LSE: lose-stay error, WMF: win-maintenance failure, WSE: win-shift error, Acq: acquisition trials, Rev: reversal trials, 80-20 and 70-30 refer to the pair contingencies, S.E.M.: standard error of the mean. # = median and interquartile range shown instead of mean and standard error of the mean for data that was analysed using non-parametric tests. * = significant difference between NS and FS (p < 0.05), ‡ = significant difference between NS and SS (p < 0.05) and NS and AS (p < 0.05)).

5.3.10 Change in PRL Errors from Acquisition to Reversal

As the number of PRL errors split by contingency (80-20% and 70-30%) were low, group differences in the change in number of PRL errors from acquisition to reversal were investigated irrespective of contingency. The groups did not differ in the change in lose-stay errors or win-shift errors from acquisition to reversal (H(3) = 0.37, p = 0.944 and H(3) = 1.01, p = 0.805 for lose-stay and win-shift respectively). However, the groups did differ in the change in win-maintenance failures from acquisition to reversal (H(3) = 10.49, p = 0.011). Post-hoc comparisons revealed that the change in win-maintenance failures from acquisition to reversal was significantly greater for former smokers compared to satiated smokers (U = 46.50, z = -2.77, p = 0.020 Bonferroni corrected, r = -0.51). In addition, before correction for multiple comparisons there was a trend for change in win-maintenance failures from acquisition to reversal to be greater in former smokers compared to abstinent smokers (U = 66.00, z = -1.95, p = 0.052) and never smokers (U = 70.00 , z = -1.78, p = 0.075) and for the change in win-maintenance failures from acquisition to reversal to be significantly larger in never smokers compared to satiated smokers (U = 64.50, z = -2.03, p = 0.041). However applying correction for multiple comparisons adjusted the p-values further from the threshold for significance (p = 0.208, 0.300 and 0.164 respectively). These data are represented graphically in Figure 5.3.
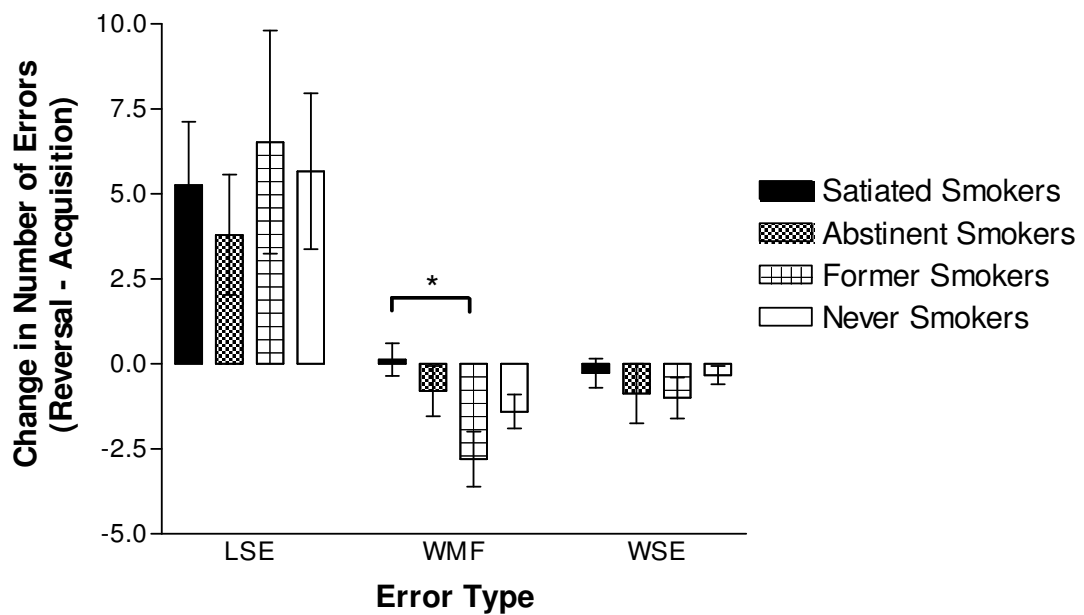
Figure 5.3: Change in Probabilistic Reversal Learning Task Errors from Acquisition to Reversal in Satiated, Abstinent, Former and Never Smokers.
(Abbreviations: LSE: lose-stay errors, WMF: win-maintenance failures, WSE: win-shift errors. * = significant difference between former smokers and satiated smokers (p < 0.05). Error bars represent standard error of the mean).

5.4   Discussion

5.4.1   Main Findings

The main aim of this study was to compare punishment sensitivity in satiated, abstinent, former and never smokers. To do this a probabilistic reversal learning task was used allowing measurement of two punishment sensitivity indices (lose-stay errors and win-maintenance failures). The main findings were that there were no group differences in lose-stay errors or win-maintenance failures in acquisition or reversal for 80-20% or 70-30% contingency pairs suggesting that punishment sensitivity did not differ between the groups in this task. However, the groups did differ on some baseline mood and personality questionnaires as well as in the number of PRL win-shift errors (a measure of impulsiveness) in directions presumed inherent in group membership. In addition group differences were also found in

change in win-maintenance failures from acquisition to reversal and this may reflect a feedback monitoring process. The results are discussed more fully below.

5.4.2 Punishment Sensitivity in Satiated and Abstinent Smokers

There were no group differences in the number of lose-stay errors or win-maintenance failures in the PRL task. This finding suggests that punishment sensitivity does not differentiate the groups, at least not in the current task. The finding of no significant differences in punishment sensitivity between satiated and abstinent smokers is in keeping with the results of the previous study (Chapter 4) that found no difference in punishment sensitivity between satiated and minimally deprived smokers in two behavioural tasks. The current finding is also supported by some of the inconsistent past literature investigating the effect of smoking on punishment sensitivity (e.g. Bennett and Cherek, 1991). Previous research showing a lack of interference from reward and threat-related words on Stroop performance in abstinence but not in satiated smokers and non-smokers (Powell et al., 2002b) and showing that abstinence from smoking blunts responses to both happy and sad film clips (Dawkins and Powell, 2011) suggests that abstinence from smoking may lead to a general suppression of normal motivational responses. The current finding of no significant differences in punishment sensitivity between satiated and abstinent smokers does not support this hypothesis. One important difference between the current work and this past research was that the aversive stimuli in these previous studies (sad film clips and threat-related words) were likely to evoke greater emotional responses than the negative feedback used in the present study. However this is unlikely to account for the discrepancy as the use of more emotionally charged stimuli would be expected to motivate responses to a greater degree than the relatively mildly aversive negative feedback used presently. In any case, the aversive stimuli of the past and present work were qualitatively different and processing of these stimuli may therefore rely upon distinct neural substrates. A future experiment using a PRL task with more emotionally charged stimuli as rewards and punishers would clarify if this was the case.

5.4.3 Punishment Sensitivity in Current Smokers and Non-smokers

The fact that smoking persists despite knowledge of the serious adverse consequences suggests that smokers may be insensitive to negative consequences. However the present finding of no differences in punishment sensitivity between the current smoker groups and the never-smoker group does not support this hypothesis. Previous research has shown that smokers have reduced brain activity in response to punishment and error compared to non-smokers (de Ruiter et al., 2009; Franken et al., 2010; and Luijten et al., 2011a) however behavioural data from these same studies have been equivocal. For example, Franken et al. (2010) found a trend towards increased errors in smokers compared to non-smokers and Luijten et al. (2011) found decreased post-error slowing of reaction times in smokers compared to non-smokers both using an Eriksen Flanker task, a task typically used to assess response inhibition. More comparable with the current work de Ruiter et al. (2009) used a probabilistic reversal learning task that was similar to the task used presently. De Ruiter et al. report that no significant differences in mean reaction time were found and that smokers earned significantly less than non-smokers on the task. Overall money earned is a general guide to task performance but without a breakdown of error-types as in the current study it cannot be determined if smokers made more perseverative errors (which might indicate an insensitivity to punishment and/or impaired inhibitory control), if they over-reacted to false feedback (which might indicate increased sensitivity to punishment) or if shifted away from correct, rewarded stimuli more often (which might indicate that they were more impulsive).

Previous work that has investigated error-types similar to the current study and in drug dependent populations has shown that chronic cocaine users displayed increased perseverative responding compared to healthy non-drug taking controls but that chronic amphetamine users, chronic opiate users and former drug users did not (Ersche et al., 2008). Ersche et al. argue that the different pharmacological profiles of cocaine, amphetamine and opiates may explain the divergent findings. In addition the former drug user group were a heterogeneous population with respect to previous drug use (consisting of former stimulant users, former opiate users and

those previously dependent upon both stimulants and opiates) making it difficult to draw firm conclusions regarding perseveration in a homogeneous group of former users. Nevertheless the finding in the present study, that current smokers do not have increased perseverative responding compared to never smokers, is more in line with the amphetamine and opiate users result from Ersche et al. than it is with the cocaine users result and differences in the pharmacological profile of nicotine and cocaine might account for this. However differences in the relative dependence levels of chronic drug users and differences in the PRL tasks used (i.e. Ersche et al. used a single reversing pair with false feedback determined by an 80-20% contingency that reversed after 40 trials) make direct comparisons across studies difficult.

One explanation for the lack of significant group differences on PRL punishment sensitivity measures is that smokers may not exhibit a general behavioural deficit in punishment sensitivity but instead have a more specific impairment in processing punishment in the context of drug use. For example, cocaine seeking in rats has been shown to persist even under aversive conditions but only in those rats with an extended history of cocaine administration and not in those with limited cocaine self-administration experience. However, rats with an extended history of sucrose self-administration do not continue to persist with sucrose seeking behaviour under the same aversive conditions (Vanderschuren and Everitt, 2004; Pelloux et al., 2007). Vanderschuren and Everitt also show that this persistent cocaine seeking in the face of adversity was not due to impaired fear conditioning suggesting that the compulsive drug seeking behaviour was not due to a general deficit in punishment sensitivity but that the deficit was context dependent. Building on the current work, future studies could try embedding smoking-related cues into the PRL task or use drug related rewards and punishers to motivate behaviour as these types of manipulation may be more sensitive at detecting altered punishment sensitivity in smokers.

5.4.4 Change in Win-maintenance Failures from Acquisition to Reversal

As was discussed for the previous study (Chapter 4, section 4.4.7) win-maintenance failures occur when participants respond to false feedback by switching from the correct choice to the incorrect choice. As the PRL task progresses participants will not only become more certain which stimulus of any given pair is the correct stimulus to choose but also increasingly accustomed to the degree of false feedback associated with that pair. Therefore, making fewer win-maintenance failures in reversal compared to acquisition may reflect some kind of performance or feedback monitoring process (i.e. the integration over time of previous trial-to-trial reinforcement history). Interestingly the difference in the number of win-maintenance failures from acquisition to reversal (now referred to as the win-maintenance change) was significantly different between the groups. Former smokers had a significantly larger win-maintenance change compared to satiated smokers (and before correction for multiple comparisons there was also a trend for a greater win-maintenance change in former smokers compared to both abstinent and never smokers and for never smokers to have a significantly greater win-maintenance change compared to satiated smokers). This pattern of results suggests that non-smokers have greater feedback monitoring than current smokers and specifically that the greatest level of feedback monitoring occurred in former smokers with the poorest monitoring in satiated smokers. This finding is in line with Nestor et al. (2011) that found significantly greater neural activity in prefrontal cortical regions during error monitoring on a response inhibition task in former smokers compared to current smokers that had recently smoked. Further Nestor et al. showed that former smokers also had greater activity during error monitoring than never smokers. The Nestor et al. findings provide evidence of increased top-down control in former smokers and this may be a particularly important characteristic for long-term successful abstinence. The present results do not show a significant difference between former and never smokers however in general the pattern of findings is in keeping with the Nestor et al. work. The current work may further the findings of Nestor et al. by suggesting that former smokers show improved monitoring compared to recent smokers in a situation requiring flexibility

(i.e. when stimulus-outcome associations are changing) and future work should seek to discover if this is a requirement for successful long-term abstinence.

5.4.5 Cognitive Flexibility

The lack of group differences in lose-stay errors in reversal phases of the PRL task (where the correct and incorrect stimuli are reversed for some of the stimulus pairings) and the lack of group differences in the change in lose-stay errors from acquisition to reversal suggests that there were no group differences in cognitive flexibility. As in the previous study (Chapter 4) the finding that satiated and abstinent smokers did not differ in cognitive flexibility is at odds with Nesic et al. (2011b) which found that recent smoking impaired flexibility in smokers with similar levels of dependence to those in the current study but not in smokers with a lower degree of dependency. However, Nesic et al. used a more complex attentional set-shifting task to assess flexibility which may have been more sensitive at picking up differences in cognitive flexibility than the PRL task. In contrast, and in line with the current study Mancuso et al. (1999a) found that nicotine patch had no effect on the flexibility of smokers who were abstinent for two hours prior to testing and like the current study cognitive flexibility was assessed with a reversal learning task.

While there are a number of studies reporting impairments in cognitive flexibility in stimulant, opiate, cannabis and poly-drug users (e.g. Ornstein et al., 2000; Lundqvist, 2005; Verdejo-Garcia et al., 2005, 2006) few studies have assessed cognitive flexibility in dependent smokers. Martin et al. (2000) and Kalmijn et al. (2002) suggest that smoking may be associated with cognitive inflexibility however Rotheram-Fuller et al. (2004) found no difference in cognitive flexibility between smokers and non-smokers on the Wisconsin Card Sorting Task. The current finding adds to this literature and suggests that current smokers do not differ from non-smokers in cognitive flexibility assessed with a reversal learning task.

5.4.6 Win-shift Errors

There were significant differences in win-shift errors between the groups but only for the easier 80-20% contingency. Win-shift errors result from a shift from the correct response to the incorrect response after positive feedback and as such reflect impulsiveness or increased exploratory behaviour. The results show that never smokers generally made fewer win-shift errors compared to the other groups suggesting that they were less impulsive. This finding is unsurprising because as a group the never smokers might be considered to be particularly non-impulsive (the fact that this group smoked less than 1.5 cigarettes on average in their lifetime suggests that this may be so).

Furthermore, current smokers made more win-shift errors in reversal compared to never smokers suggesting greater levels of impulsiveness in current smokers. This finding is supported by studies showing that both self-report impulsivity-like traits and behavioural assessments of impulsivity are associated with smoking (e.g. Reynolds et al., 2007; Fields et al., 2009; Spillane et al., 2010; Bernow et al., 2011; and see review by Mitchell, 2004). For example, Bernow et al. (2011) found that smokers scored higher on self-report impulsiveness, venturesomeness and novelty seeking compared to never smokers. Typically behavioural studies of impulsivity have assessed inhibition (impulsive action) or delay aversion (impulsive choice) aspects of impulsivity (Mitchell, 2004) however the nature of a win-shift error appears qualitatively more similar to the self-report impulsivity-like traits assessed in Bernow et al. (2011).

The lack of a significant difference in win-shift errors between satiated and abstinent smokers may be at odds with research suggesting that acute nicotine increases impulsive action (Kirshenbaum et al., 2011) and impulsive choice (Kolokotroni et al., 2011) however impulsivity is not a unitary construct (Evenden, 1999) and although it remains unclear which aspects of impulsivity win-shift errors index, as discussed above, they appear qualitatively more similar to self-report impulsivity-like traits.

5.4.7 RVIP Task

Abstinent, former and never smokers showed a deterioration in the mean number of RVIP hits over time whereas satiated smokers did not show this vigilance decrement. This suggests that smoking improved vigilance and is in line with previous studies showing this effect and that the RVIP is sensitive to nicotine manipulations (e.g. Wesnes and Warburton 1983, 1984; Wesnes et al., 1983). However, overall RVIP performance in satiated smokers was poorer than the other groups with fewer hits than never smokers and no effect of smoking on reaction times. These latter findings are not consistent with previous literature showing smoking and nicotine induced improvements on these measures (e.g. Parrott and Winder, 1989; Parrott and Craig, 1992; Foulds et al., 1996) however negative results have also been reported (Herbert et al., 2001) and despite nicotine improving vigilance Mancuso et al. (1999b) report no effect of nicotine on RVIP reaction time. In line with the present finding Tong et al. (1977) showed that there was a vigilance decrement in non-smokers and abstinent smokers but not in satiated smokers. In addition non-smokers generally performed better than smokers however this study used a much longer 60 minute auditory vigilance task.

In addition to vigilance, the RVIP task may be considered to index other cognitive processes such as executive control (i.e. maintaining and updating information in working memory and response inhibition following non-target stimuli) and in line with this the false alarms measure has previously been used to assess inhibitory control (e.g. Jackson et al., 2011). Acute nicotine has been found to increase impulsive action (e.g. Kirshenbaum et al., 2011; Kolokotroni et al., 2011) and the finding that satiated smokers made more false alarms than the other groups in the current study supports this.

5.4.8 General Demographics

The groups were well matched in terms of age, years of education, (IQ) NART score, short term memory (words recalled on the IWR) and a number of self-report personality questionnaires. The ratio of male to female participants differed between

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groups with approximately equal males and females in the satiated smoker group, more males in the abstinent group and more females in the former and never smoker groups. Therefore, it is possible that gender differences contributed to the significant win-maintenance change result. However behavioural evidence for gender effects on performance monitoring is lacking. Furthermore one study assessing brain activity during error monitoring in children suggests that girls and boys had comparable brain activity in response to errors (Torpey et al., 2012). Unfortunately it was not appropriate to include gender as a factor in the win-maintenance change analysis as the data was not normally distributed and was analysed with non-parametric statistics.

The groups also differed on a number of mood and personality measures and although these group differences may have contributed to the current findings/lack of findings it was considered inappropriate to include these variables as covariates in the analyses for a number of reasons. Firstly baseline differences and differences which are inherent in group membership cannot be 'controlled for' by covariate analysis (Lord, 1967, 1969; Miller and Chapman, 2001) and secondly there was an abundance of non-normally distributed data which meant that there was no suitable non-parametric statistic for such an analysis anyway. The theoretical contributions that these differences made are however discussed below.

The groups differed on the BDI with both current smoker groups scoring higher than never smokers. It is possible that this difference contributed to the lack of significant differences in punishment sensitivity between the groups. However, this is considered an unlikely explanation as altered sensitivity to punishment and increased perseverative responding have previously been reported in depression (e.g. Must et al., 2006; Steele et al., 2007). Therefore an increase in BDI scores might be predicted to drive a difference between the current smokers and the never smoker group (such as increased lose-stay errors), a result that is not found. Although the BDI scores of current smokers were significantly higher than never smokers, when the standard cut-offs for clinical significance are applied BDI scores from all groups fall within the

no-minimal depression range. Furthermore, the fact that higher scores were seen in both abstinent and satiated smokers suggests that this may be part of an inherent difference between current and never smokers.

Former smokers had greater self-report punishment sensitivity (BIS subscale of the BIS/BAS) compared to satiated and abstinent smokers. However, this was not accompanied by behaviourally measured increases in punishment sensitivity on the PRL task. The BIS subscale of the BIS/BAS has been associated with both behavioural inhibition and behavioural avoidance (see Amodio et al., 2008 for discussion) and it is possible that former smokers perceive themselves to be more inhibited and avoidant as a result of having been able to successfully abstain from smoking. Punishment sensitivity assessed with the BIS subscale of the BIS/BAS has previously been shown to be related to the magnitude of electrophysiological correlates of performance monitoring (Boksem et al., 2006, 2008; Amodio et al., 2008; Balconi and Crivelli, 2010a, 2010b). These error-related neural signals are thought to be the product of prediction-error signals that are generated in the midbrain by worse than expected outcomes (Holroyd and Coles, 2002). The medial prefrontal cortex is then thought to use these signals to guide action selection in the context of previous action-outcome associations (Rushworth et al., 2004). The association between self-report punishment sensitivity and these error-related signals may suggest that the higher self-report punishment sensitivity found in former smokers in the current study might influence the win-maintenance change finding of improved feedback monitoring in former smokers compared to satiated smokers. However most studies showing the association between the error-related neural signals and punishment sensitivity used conflict tasks and not reinforcement learning tasks and in addition these studies did not investigate if variation in the error-related neural signals, as a function of punishment sensitivity, were accompanied by error-induced behavioural adjustments (Unger et al., 2012). One study that did use a probabilistic learning task found that greater punishment sensitivity resulted in impaired learning on the task and larger feedback-related error signals irrespective of whether the feedback received by the participant was veridical (Unger et al., 2012). The Unger et al. study

suggests that although self-report punishment sensitivity is associated with larger error-related neural signals this does not necessarily facilitate feedback-based learning and means that the higher BIS scores seen in former smokers in the current study might not translate to improved feedback monitoring and integration of previous trial by trial feedback across trials. However, the probabilistic learning task used by Unger et al. did not include a reversal phase as with the task in the current study. Therefore it remains a possibility that greater punishment sensitivity could facilitate learning or integration of previous trial by trial feedback in situations requiring greater flexibility or where there may be increased conflict over response actions (i.e. when response-outcome contingencies are reversed).

Items included on the BIS subscale of the BIS/BAS focus on anxiety in response to threatening situations such as: 'I worry about making mistakes' and 'I feel pretty worried or upset when I think or know somebody is angry at me'. Furthermore, BIS activation has been linked to anxious rumination and worry (see both Juhasz et al., 2010 and Unger et al., 2012 for discussion). Therefore it is unsurprising that the former smoker group also score more highly on a measure of rumination.

There was a trend towards a significant group difference in self-report impulsiveness (BIS) with current smokers having higher scores in general. This is in line with previous research showing increased impulsiveness in smokers compared to non-smokers (e.g. Bernow et al., 2011). Differences in impulsivity could have contributed to the present findings as impulsive individuals assessed with the same self-report measure as in the current study have been shown to be less sensitive to punishment and have a smaller neural response to error than low impulsive individuals (e.g. Potts et al., 2006). However, it should be reiterated that the difference was only a trend.

5.4.9   Smoking-related Demographics

In terms of smoking-related demographics the current smoker groups and the former smoker group were well matched in terms of cigarettes smoked per day (pre-quit levels for former smokers) and the age at which smoking started. Abstinent smokers

had been smokers for longer than satiated smokers although these groups did not differ in terms of dependence level (assessed by the FTND and the NDSS). However, it remains a possibility that differences in the levels of chronic exposure to cigarette smoking may have contributed to the lack of significant differences in punishment sensitivity. Such an effect may be due to different degrees of neuroadaptation resulting from differences in the amount of repeated nicotine exposure although similar dependence levels between the groups may suggest otherwise. Future work should aim to match particpants on all smoking-related demographics in order to avoid this potential confound.

In terms of dependence levels, the current smoker groups had a mean FTND score of approximately 5 indicative of mild to moderate dependence. It is uncertain if the results reported here would generalise to more dependent smokers and future work could investigate the possibility that punishment sensitivity is altered in smokers with higher levels of dependence.

5.4.10 Smoking Manipulation

The smoking manipulation was validated by an increase in CO levels in the satiated smoker group after smoking compared to at the same time point for the abstinent group. Significant subjective effects and reduced craving similar to those found previously (e.g. Jackson et al., 2009; Nesic et al., 2011a) provided further evidence of the effectiveness of the smoking manipulation. In addition, the lack of a vigilance decrement in the satiated group on the RVIP task also suggests that the smoking manipulation was effective.

5.4.11 Strengths and Limitations

This study has a number of strengths and limitations. The groups were well defined such that all satiated and abstinent smokers smoked at least 10 cigarettes per day and had been a smoker for at least 12 months. All former smokers had pre-quit smoking levels of at least 10 cigarettes per day and had not smoked for at least 6 months and all never smokers had smoked no more than 5 cigarettes in their lifetime

and had not smoked in the last 12 months. However, in terms of dependence levels the current smoker groups had a mean FTND score of approximately 5 which is indicative of only mild to moderate dependence. A further limitation was that the smoking-related demographic data relied upon self-report measures which in turn relied upon the quality and accuracy of participant recall. In addition whereas the groups were well matched on some demographics significant differences between the groups in gender, BDI, behavioural inhibition, rumination, and years of smoking in current smokers, remain another limitation.

There was a great deal of evidence to suggest that the smoking manipulation worked as desired and some aspects of the previous study design were improved upon such as including smokers that had undergone an overnight abstinence instead of a 3 hour minimal deprivation. However, in terms of the PRL task used error rates were low. The inclusion of a more difficult PRL task did not result in a large increase in the number of errors as was expected. Similar error rates in the current study compared to the previous study could be due to the ability of healthy participants to increase cognitive effort when the task demands were harder. Nevertheless, the inclusion of just one task to assess punishment sensitivity, in favour of adding a control task, may be another limitation to the current work.

5.4.12 Conclusions

The lack of significant group differences in any of the PRL task errors assessing punishment sensitivity does not support the hypothesis that current smokers have a general deficit in their behavioural reaction to negative feedback. Additionally satiated and abstinent smokers do not appear to differ in punishment sensitivity. Therefore this result does not support the hypothesis that abstinent smokers have a general suppression of normal motivational processes. The win-shift data suggest that never smokers show low (and current smokers show high) impulsiveness and the finding with win-maintenance failures when comparing reversal to acquisition suggests that former smokers may have greater feedback monitoring compared to satiated smokers in situations requiring cognitive flexibility and future studies should

ascertain if this is an important feature of former smokers in terms of their ability to successfully remain abstinent over long periods.

5.5   Executive Summary of Main Findings

- Satiated and abstinent smokers did not differ in the number of lose-stay errors or win-maintenance failures suggesting that these groups did not differ in punishment sensitivity.

- Neither of the current smoker groups differed from the never smokers in the number of lose-stay errors or win-maintenance failures suggesting that these groups did not differ in punishment sensitivity.

- Win-shift errors were lowest in never smokers and highest in current smokers in line with the notion that this error type measures impulsiveness.

- The lack of group differences in lose-stay errors in reversal and change in lose-stay errors from acquisition to reversal suggests that the groups did not differ in a simple measure of behavioural flexibility.

- The change in the number of win-maintenance failures from acquisition to reversal was greater in former smokers compared to satiated smokers and suggests that feedback monitoring in situations requiring behavioural flexibility may be better in former smokers compared to recent smokers.

- Former smokers self-report greater punishment sensitivity than current smokers.

Chapter 6   Post-Punishment Slowing and Intra-Individual Variability in Reaction Time in Current, Former and Never Smokers

6.1   Introduction

In Chapter 5 the behavioural response to punishment in satiated and abstinent current smokers, former smokers and never smokers was investigated. This chapter aimed to extend these findings by analysing the reaction time data obtained on the Rapid Visual Information Processing (RVIP) task and the Probabilistic Reversal Learning (PRL) task. There were three main aims to these analyses: 1) to assess post-punishment slowing of reaction time in the PRL task across groups, 2) to investigate group differences in intra-individual variability in a simple measure of reaction time (RVIP task), and 3) to investigate intra-individual variability in reaction time following punished responses compared to reaction time following correct, rewarded responses (from the PRL task) across the groups. The rationale for these analyses and the predictions made are outlined below.

Post-punishment slowing of reaction time refers to the phenomenon whereby healthy individuals typically show slowed reaction time immediately following feedback indicating that an error has been made (Rabbitt, 1966; Laming, 1979). A performance monitoring account for post-punishment slowing proposes that slowing of reaction time is a mechanism for maintaining response accuracy and results from an increase in subsequent response caution as a consequence of engagement of cognitive control (Botvinick et al., 1999, 2001; Dutilh et al., 2012a). The performance monitoring account is supported by studies showing that the degree of slowing is correlated to electrophysiological measures of error monitoring thought to originate in the anterior cingulate cortex (error related negativity and positivity; Gehring et al., 1993; Hajcak et al., 2003; Debener et al., 2005; Holroyd et al., 2005).

Luijten et al. (2011a) examined error monitoring in smokers and found diminished error processing indexed by reduced error related negativity and positivity, and reduced post-error slowing in minimally deprived smokers compared to never

smokers. No studies have directly investigated error monitoring as a function of abstinent/satiated state however a number of studies suggest that deficits in error processing are a common feature of substance abuse (see Olvet and Hajcak et al., 2008 for discussion) and it has been suggested that deficits in error processing may contribute to the persistence of addictive behaviours (e.g. Franken et al., 2007, 2010). Therefore for the current analysis it was predicted that current smokers, regardless of their abstinent/satiated state, would show reduced slowing of reaction time following negative feedback compared to never smokers. Furthermore the finding from Chapter 5, of a greater change in win-maintenance failures from acquisition to reversal in former smokers compared to satiated smokers, was interpreted as an increased ability to integrate previous trial to trial feedback. The ability to integrate feedback over time is thought to be an integral part of how the performance monitoring system guides action selection (Rushworth et al., 2004) and so suggests that former smokers may have enhanced error processing. In line with this Nestor et al. (2011) found greater neural activity during error monitoring in former smokers compared to both current smokers that had recently smoked and never smokers. Therefore, for the current analysis it was predicted that former smokers would show the greatest slowing of reaction time following negative feedback compared to all other groups.

Intra-individual variability in reaction time, also known as reaction time inconsistency, reflects the transient within-person changes that occur in reaction time over the course of a sequence of trials. Evidence suggests that intra-individual variability in reaction time is related to cognitive control (West et al., 2002; Smallwood et al., 2008; Ode et al., 2011; Jackson et al., 2012). For example Smallwood et al. (2008) found that variability in reaction time predicts deficient response inhibition and Ode et al. (2011) found that variability in reaction time was related to lower scores on a self-report trait measure of self-control. As impairments in cognitive control are reliably found in substance abusing populations (Goldstein and Volkow, 2011), greater intra-individual variability in reaction time might be predicted in drug users compared to non-users.

For the current analysis, given that there is evidence of deficits in cognitive control in smokers compared to non-smokers (e.g. Luijten et al., 2011b), it was predicted that intra-individual variability in a simple measure of reaction time (RVIP task) would be greater in current smokers (regardless of their satiated/abstinent status) compared to never smokers. Increased intra-individual variability in reaction time in abstinent smokers compared to satiated smokers has previously been reported (Kollins et al., 2009, 2012). This finding is consistent with the idea that intra-individual variability correlates negatively with cognitive control since impairment in aspects of cognitive control seen in smokers are exacerbated in the early stages of withdrawal (e.g. Pettiford et al., 2007; Harrison et al., 2009). Therefore for the current analysis it was also predicted that abstinent smokers would show the greatest reaction time variability of all groups. Regarding former smokers, no previous studies have investigated intra-individual variability of reaction time in this group. Furthermore whereas some research suggests that impairments in cognitive control may persist into long term abstinence (e.g. Neuhaus et al., 2006) other work suggests that enhancement of some aspects of cognitive control may characterise successful abstinence in former smokers (e.g. Nestor et al., 2011). This work therefore aims to add to this debate by evaluating the intra-individual variability in reaction time in former smokers and comparing it to both current and never smokers.

Liu et al. (2012) showed increased variability in reaction time, during a cocaine Stroop task, for cocaine related stimulus trials but not for neutral trials in cocaine users but not controls. This finding may suggest that situations requiring cognitive control could exacerbate increases in intra-individual variability in reaction time in groups characterised by reduced cognitive control. Therefore for the current analysis intra-individual variability in PRL task reaction time was calculated for reaction times following correct, rewarded responses and reaction times following punished responses separately. The variability between these post-punished and post-correct, rewarded reaction times were then compared across groups. The reason for this was that performance monitoring accounts predict that cognitive control would be engaged more following negative feedback (Botvinick et al., 1999, 2001; Dutilh et al.,

2012a). It was predicted that current smokers would show greater intra-individual variability in reaction time in trials following punishment compared to those following a correct, rewarded response whereas never smokers would not. Once again, analysis using the former smokers would add to the debate regarding the cognitive control 'strength' of this group.

6.2   Method

6.2.1   General Procedure

This chapter used the reaction time data obtained from the RVIP and PRL tasks used in Chapter 5 (see Chapter 2 General Methods, sections 2.7.9 and 2.7.10 for a full description of these tasks) in order to compare post-punishment slowing (PRL task data) and intra-individual variability in reaction time in satiated and abstinent current smokers, former smokers and never smokers (RVIP task and PRL task data).

6.2.2   Participants and Study Procedure

Only brief information is provided here as a more detailed description of the study populations, the study procedure and full group demographics can be found in the methods and results sections of Chapter 5 (see sections 5.2 and 5.3). Thirty current smokers completed the RVIP and PRL tasks. Current smokers were defined as those who had smoked at least 10 cigarettes per day for at least 1 year. Dependence levels were mild to moderate with Fagerstrom Test for Nicotine Dependence (FTND) scores of approximately 5. All current smokers were asked to arrive at the laboratory having not smoked since 11pm the previous night (overnight abstinence). Half of the smokers remained abstinent whereas the other half smoked one of their own cigarettes prior to completing the RVIP and PRL tasks. Fifteen former smokers completed the RVIP and PRL tasks. Former smokers were defined as those who had a pre-quit smoking level of at least 10 cigarettes per day and had not smoked for at least 6 months however the mean duration of abstinence was much greater than this at approximately 20 months. Fifteen never smokers completed the RVIP and PRL

tasks and never smokers were defined as those who had not smoked more than 5 cigarettes in their lifetime.

6.2.3 Pre-Processing of PRL Task Reaction Time Data

For each participant reaction times were recorded for each stimulus choice on the PRL task. These reaction times were extracted from the raw data files generating two data distributions per participant: 1) reaction times following correct and rewarded responses and 2) reaction times following punished responses. Before assessment of post-punishment slowing and computation of intra-individual variability the data distributions were inspected for outliers. Extremely fast or slow latencies on the PRL task may reflect various sources of error. For example fast responses could be caused by accidental stimulus selections and slow responses could be caused by attentional lapses (particularly as the PRL task was self-paced). Outliers were removed based upon the following criteria: 1) reaction times faster than 250ms were removed (allowing at least 100ms for the motor component and at least 150ms for the decision component as has been suggested by previous research in a choice task (Hultsch et al., 2002)) and 2) the mean and standard deviation were computed separately for each group (satiated, abstinent, former and never smokers) and reaction times slower than the mean plus 3 times the standard deviation of the mean were removed. This method of identifying outliers resulted in removal of less than 10% of the 10395 and 5708 observations from the two reaction time data distributions (reaction times following correct, rewarded responses and reaction times following punished responses respectively) that were obtained from all 60 participants. In terms of the reaction time variability literature, a similar method of identifying outliers has been used previously (e.g. Bunce et al., 2004) and resulted in removal of a comparable proportion of observations. Bunce et al. (2004) also point out that since removing outliers reduces variability this procedure represents a conservative approach for investigation of variability.

6.2.4 Calculation of Post-Punishment Slowing in the PRL Task

Dutilh et al. (2012b) argue that traditional methods for assessing post-punishment slowing (i.e. calculating difference scores for mean post-punishment reaction times and mean post-correct reaction times across every trial of the task used) are open to spurious results since levels of task fatigue and motivation may fluctuate across trials of the task. Dutilh et al. explain how increased fatigue and decreased motivation as the task progresses would lead to more task errors and therefore more post-punishment reaction times being taken towards the end of tasks. However it was considered that the PRL task used in the current work likely avoided this potential confound because the changing pairs of stimuli throughout the task may act to increase task engagement. Furthermore, negative false feedback provided by the task was randomly spaced across trials. In line with this, participant generated errors and the trials from which post-punishment reaction times were extracted were fairly evenly distributed across the task.

Therefore, the degree of post-punishment slowing was investigated by calculating a post-punishment slowing score for each participant. This score was calculated using the following equation: mean reaction time following punished responses – mean reaction time following correct, rewarded responses (thus, positive values indicated slowing of reaction times after punishment). Group means for post-punishment slowing scores were then calculated and compared across groups.

6.2.5 Procedure for Analysis of Intra-Individual Variability in PRL Reaction Time Data

As with other studies (e.g. Liu et al., 2012) the primary measure of intra-individual variability in reaction time data used was the coefficient of variation (CV). This was calculated as the ratio of the standard deviation to the mean ($CV = \sigma/\mu$). CV was calculated for each participant for both of the reaction time distributions (reaction times following correct, rewarded responses and reaction times following punished responses) from which group means were then calculated. Unlike standard deviation, which can only be understood in the context of the mean of the data, CV is

independent of the unit in which the measurement has been taken and assesses the dispersion of data whilst controlling for any differences in the mean of the data.

In addition to the coefficient of variation ex-Gaussian fitting of the reaction time data was explored. Since reaction time data is commonly positively skewed, Gaussian summary statistics may inaccurately describe variability. Modelling reaction time distributions with an ex-Gaussian curve may be more appropriate (Hohle, 1965; Ratcliff, 1979; Heathcote et al., 1991). The ex-Gaussian distribution is composed of a Gaussian (normal) distribution in the initial portion of the distribution curve and an exponential distribution on the latter portion of the distribution curve. This type of distribution has been shown to create a better fit than traditional Gaussian distributions for reaction time data (Ratcliff, 1979; Luce, 1986; Heathcote et al., 1991). The ex-Gaussian distribution can be described using three parameters: mu, the mean of the Gaussian component; sigma, the standard deviation of the Gaussian component; and tau, a single value that describes both the mean and the standard deviation of the exponential component. Ex-Gaussian analyses allow group differences in reaction time distributions to be described in greater detail than the CV method. Changes in variability within the normal portion (i.e. changes in sigma) or within the tail of the distribution (i.e. changes in tau) can be differentiated. Furthermore differences in the reaction time distributions between groups can to be separated into distributional shifting (i.e. a change in mu) or distributional skewing (i.e. a change in tau). Interestingly some researchers have speculated that inferences about different cognitive processes can be made from changes in reaction time distributions such that changes in the Gaussian component have been argued to reflect more stimulus driven, automatic processes and changes in the exponential component more analytic, attention demanding processes (e.g. Hohle, 1965; Logan, 1990, 1992). However other researchers caution this approach due to the lack of evidence (e.g. Matzke and Wagenmakers, 2009) and have suggested that a cognitive interpretation is unnecessary as the purpose of ex-Gaussian analysis is to provide a good description of the data that goes beyond measuring the central tendency of reaction time data collected over a number of trials (Heathcote et al., 1991).

For the present analysis ex-Gaussian parameters were estimated for both of the reaction time distributions (reaction times following correct, rewarded responses and reaction times following punished responses) for each participant with the quantile maximum likelihood technique described by Heathcote et al. (2002) and using the QMPE v.2.18 open source program developed by the same group. Individual participant ex-Gaussian parameter estimates were used to calculate group means. In addition, probability density plots for both reaction time distributions were created as a means of visualising variability in the reaction time distributions for each group. These plots were generated by firstly splitting the reaction time distributions obtained into time bins and making frequency counts of the number of reaction time occurrences in each time bin for each participant. Next the probability density for each participant was calculated by dividing the number of reaction time occurrences in each time bin by the total number of reaction time observations. Means were then calculated for each group for each time bin and these values were plotted.

6.2.6 Procedure for Analysis of Intra-Individual Variability in RVIP Data

Intra-individual variability in RVIP hit latency data was investigated using the CV method described above. Therefore CV was calculated for each participant using the standard deviation and mean of their RVIP hit latencies (using: $CV = \sigma/\mu$) and group mean CV was then calculated from these values. Ex-Gaussian fitting of the RVIP hit latency data was not explored as there is a requirement for at least 40 reaction time data points per participant in order to accurately estimate the mu, sigma and tau parameters (Heathcote et al., 2002; Brown and Heathcote, 2003) and the number of RVIP hit latencies per participant was short of this requirement.

6.2.7 Data Analysis

Statistical analysis was conducted on data from all sixty participants (15 satiated smokers, 15 abstinent smokers, 15 former smokers and 15 never smokers) using SPSS version 18 (SPSS Inc., Chicago, IL, USA). The degree of post-punishment slowing in the PRL task was compared between groups using one-way ANOVA followed by post-hoc pairwise comparisons. Group differences in the intra-individual variability (CV) in RVIP

hit latency were also compared with one-way ANOVA. Group differences in the intra-individual variability measures (CV, mu and sigma) across the two reaction time distributions in the PRL task were investigated using 2 (feedback type) x 4 (group) mixed design ANOVA's followed by post-hoc paired samples t-tests where appropriate. The intra-individual variability measure tau was not normally distributed and transformation could not correct this. Therefore comparisons were made between the two reaction time distributions for each group separately using Wilcoxon signed-ranks tests. In addition group differences in each of the two reaction time distributions were analysed using Kruskal-Wallis tests followed by post-hoc Mann-Whitney U tests.

All statistical tests were two-tailed with alpha set at $p = 0.05$. In cases where statistical significance was greater than $p = 0.05$ but less than or equal to $p = 0.075$, results have been considered a trend. Where multiple comparisons were required p-values were Bonferroni corrected by multiplying the p-value obtained by the total number of comparisons made (as in Bland and Altman, 1995) this is equivalent to lowering the level of alpha. In addition effect sizes were reported for significant findings. The assumption of normal distribution was assessed using the Kolmogorov-Smirnov test and by visual assessment of histograms of the data produced in the SPSS output. Where data was found to violate the assumption of normality, transformations were attempted in order to correct but where this was ineffective non-parametric tests were used. The assumption of homogeneity of variance was assessed with Levene's test however no violations of the assumption of homogeneity of variance were found.

6.3   Results

6.3.1   Post-Punishment Slowing in the PRL Task

The groups significantly differed in mean post-punishment slowing scores ($F_{(3, 56)} = 5.57$, $p = 0.002$). Pairwise comparisons revealed that both former and never smokers

had greater slowing than satiated smokers (p = 0.006 Bonferroni corrected, r = 0.60 and p = 0.018 Bonferroni corrected, r = 0.47 respectively) but that abstinent and satiated smokers did not significantly differ (p = 0.156 Bonferroni corrected). Additionally, former smokers did not significantly differ from abstinent or never smokers (p = 0.750 and p = 1.000 respectively; both Bonferroni corrected) and never smokers did not differ from abstinent smokers (p = 1.000 Bonferroni corrected). Figure 6.1 shows the mean post-punishment slowing score data for the four groups.
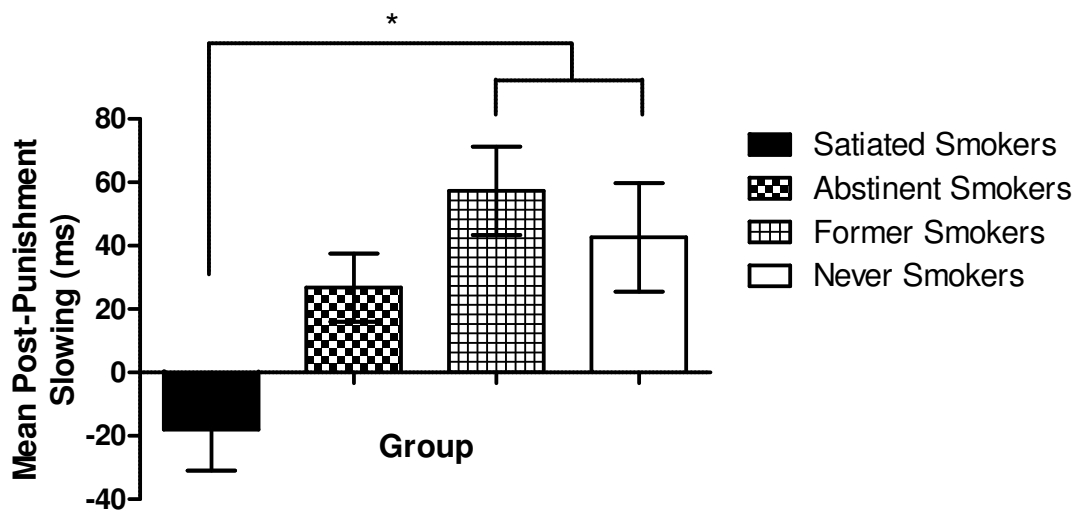
Figure 6.1: Mean Post-Punishment Slowing in Satiated, Abstinent, Former and Never Smokers.
(Abbreviations: ms: milliseconds; * = significant greater post-punishment slowing in former smokers and never smokers compared to satiated smokers (p < 0.01). Error bars represent standard error of the mean).

6.3.2 Intra-Individual Variability in RVIP Hit Latencies

The groups did not differ in the mean CV of their hit latencies on the RVIP task ($F_{(3, 56)}$ = 2.23, p = 0.095). Figure 6.2 shows this mean CV data for the four groups.
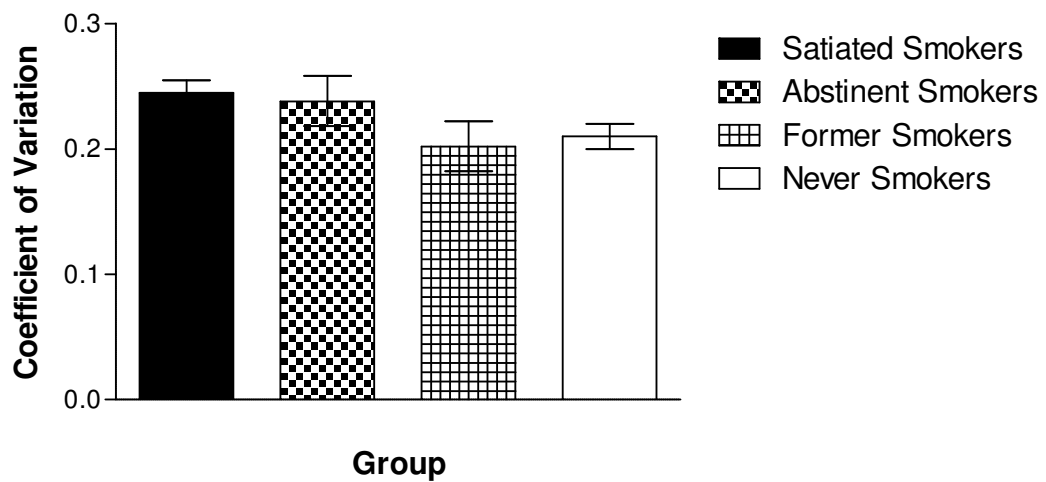
Figure 6.2: Mean Coefficient of Variation in Rapid Visual Information Processing Hit Latencies for Satiated, Abstinent, Former and Never Smokers.
(Error bars represent standard error of the mean).

6.3.3 Intra-Individual Variability in PRL Reaction Time: Coefficient of Variation

Irrespective of group, mean CV was significantly greater for the distribution of reaction times on trials that followed punished responses compared to the distribution of reaction times on trials that followed correct, rewarded responses ($F_{(1, 56)}$ = 65.08, $p < 0.001$, $r = 0.73$). The groups did not differ in overall variability ($F_{(3, 56)}$ = 2.41, $p = 0.076$). However the difference in variability following correct, rewarded responses compared to punished responses varied across the groups ($F_{(3, 56)}$ = 4.99, $p = 0.004$) such that variability following punished responses was significantly greater compared to variability following correct, rewarded responses in former smokers ($t_{(14)}$ = -6.03, $p = 0.004$ Bonferroni corrected, $r = 0.85$) and never smokers ($t_{(14)}$ = -5.99, $p = 0.004$ Bonferroni corrected, $r = 0.85$) but not in satiated or abstinent smokers ($t_{(14)}$ = -2.20, $p = 0.180$, $t_{(14)}$ = -1.99, $p = 0.264$ respectively; all Bonferroni corrected). Figure 6.3 shows the mean CV data for both reaction time distributions across group.

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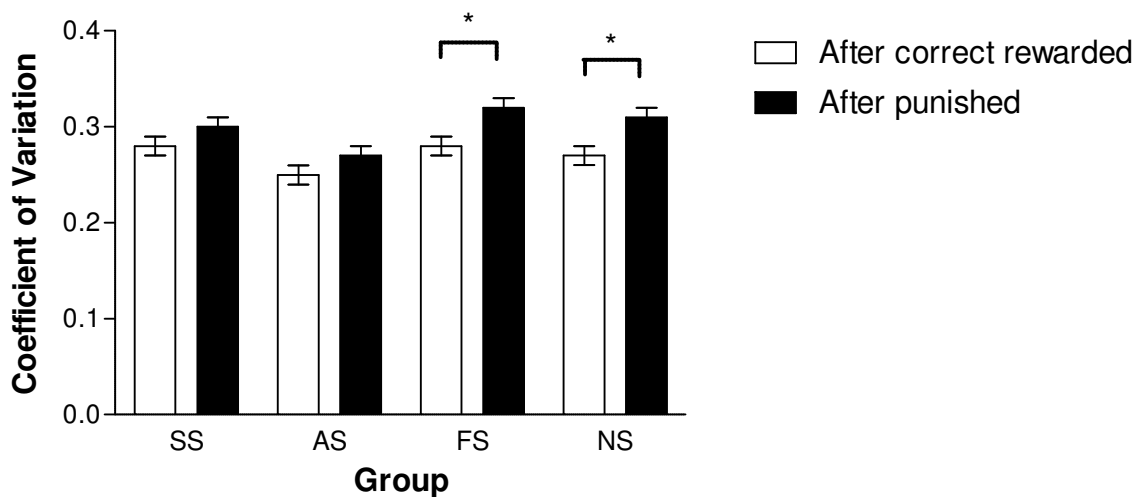
Figure 6.3: Coefficient of Variation for the Probabilistic Reversal Learning Reaction Time Distributions in Satiated, Abstinent, Former and Never Smokers.
(Abbreviations: SS: satiated smokers, AS: abstinent smokers, FS: former smokers, NS: never smokers, After correct rewarded: distribution of reaction times on trials after correct, rewarded responses, After punished: distribution of reaction times on trials after punished responses. * = significantly greater variability following punished responses compared to following correct, reward responses in former and never smokers p < 0.005. Error bars represent standard error of the mean).

6.3.4 Intra-Individual Variability in PRL Reaction Time: Ex-Gaussian Parameters

The ex-Gaussian parameter estimate for mu, sigma (the mean and standard deviation of the Gaussian portion of the reaction time distributions respectively) and tau (reflecting the mean and standard deviation of the exponential component) for both reaction time distributions were investigated across group and the data is shown in Table 6.1. In addition probability density plots (which are used to visualise the distributions) are shown in Figure 6.4.

Irrespective of group, mean mu was significantly smaller for the reaction time distribution that followed punished responses compared to that which followed correct, rewarded responses ($F_{(1, 56)} = 6.72$, $p = 0.012$, $r = 0.33$). The groups did not significantly differ in overall mu ($F_{(3, 56)} = 0.67$, $p = 0.575$) and the difference in mu for the reaction time distribution that followed correct, rewarded responses

compared to punished responses did not vary across the groups (F(3, 56) = 4.38, p = 0.727).

	SS	AS	FS	NS
After CR	Mean (S.E.M)	Mean (S.E.M)	Mean (S.E.M)	Mean (S.E.M)
Mu	870.32 (44.11)	893.21 (26.19)	851.65 (48.90)	927.92 (36.71)
Sigma	227.50 (13.66)	230.20 (6.41)	209.80 (13.53)	222.09 (16.53)
Tau #	173.25 (153.17)	24.16 (15.99)	189.68 (107.66)	218.95 (64.29)
After P				
Mu	816.05 (47.69)	850.95 (39.26)	839.02 (49.84)	897.81 (36.90)
Sigma	213.62 (13.04)	222.48 (13.78)	230.15 (19.19)	236.37 (23.08)
Tau #	208.71 (123.98)	90.29 (138.84)	248.61 (159.35)	266.79 (74.29)

Table 6.1: Ex-Gaussian Parameter Estimates for the Probabilistic Reversal Learning Reaction Time Distributions in Satiated, Abstinent, Former and Never Smokers.
(Abbreviations: SS: satiated smokers, AS: abstinent smokers, FS: former smokers, NS: never smokers, S.E.M: standard error of the mean, After CR: distribution of reaction times on trials after correct, rewarded responses, After P: distribution of reaction times on trials after punished responses. # = median and interquartile range shown instead of mean and S.E.M where non-parametric statistics were used).

Irrespective of group, there were no significant differences in mean sigma between reaction time distributions that followed punished responses compared to those which followed correct, rewarded responses (F(1, 56) = 0.18, p = 0.676). The groups did not significantly differ in overall sigma (F(3, 56) = 0.11, p = 0.953) and the difference in sigma for the reaction time distribution that followed correct, rewarded responses compared to punished responses did not vary across the groups (F(3, 56) = 1.15, p = 0.339).

A

B
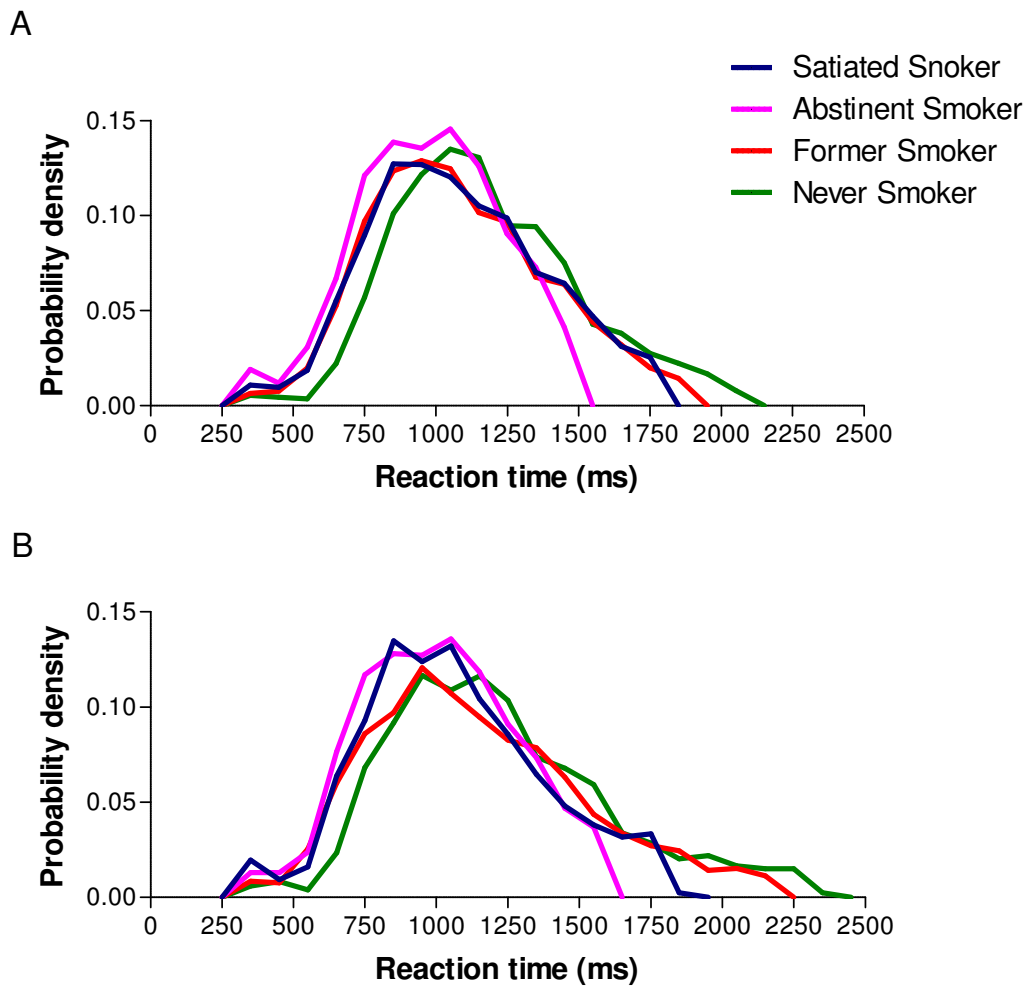
Figure 6.4: Probability Density Plots for the Probabilistic Reversal Learning Reaction Time Distributions in Satiated, Abstinent, Former and Never Smokers.
(A: Distribution of reaction times on trials after correct, rewarded responses. B: Distribution of reaction times on trials after punished responses. Abbreviations: ms: milliseconds).

In addition, abstinent, former and never smokers all had a significantly greater mean tau for the reaction time distribution that followed punished responses compared to that which followed correct, rewarded responses (z = -3.41, p = 0.004 Bonferroni corrected, r = -0.62; z = -2.78, p = 0.012 Bonferroni corrected, r = -0.51 and z = -2.56, p = 0.032 Bonferroni corrected, r = -0.47 respectively). However there was no significant difference in satiated smokers (z = -1.76, p = 0.332 Bonferroni corrected).

For the distribution of reaction times following correct, rewarded responses there was a significant difference between the groups in mean tau (H(3) = 28.41, p = 0.002 Bonferroni corrected). Post-hoc comparisons revealed that abstinent smokers had a significantly smaller mean tau compared to all three other groups (U = 19.00, z = -3.88, p = 0.003, r = -0.71; U = 10.00, z = -4.25, p = 0.003, r = -0.78 and U = 5.00, z = -4.46, p = 0.003, r = -0.81 for satiated, former and never smokers respectively, all Bonferroni corrected). Similarly, for the reaction times following punished responses distribution there was a significant difference between the groups in mean tau (H(3) = 21.20, p < 0.001). Pairwise comparisons revealed that abstinent smokers had significantly smaller tau compared to former and never smokers (U = 26.00, z = -3.59, p = 0.003, r = -0.66 and U = 18.00, z = -3.92, p = 0.003, r = -0.72 for former and never smokers respectively, all Bonferroni corrected). There was a trend towards abstinent smokers having a smaller tau compared to satiated smokers (U = 57.00, z = -2.30, p = 0.063 Bonferroni corrected).

6.4   Discussion

6.4.1   Main Findings

The analyses undertaken here sought to investigate post-punishment slowing and intra-individual variability in reaction time in satiated, abstinent, former and never smokers. Predictions were made in line with established associations of these measures with cognitive control and where possible the findings are discussed with reference to these associations. The main findings were that former and never smokers showed significantly greater post-punishment slowing than satiated smokers and that the groups did not differ in variability in a simple measure of reaction time (RVIP hit latencies) assessed with the CV. Additionally both former and never smokers showed significantly greater reaction time variability assessed with the CV in trials that followed punished responses compared to trials that followed correct, rewarded responses whereas satiated and abstinent smokers did not. The ex-Gaussian analysis

of reaction time variability found that following punished responses as compared to correct, rewarded responses former, never and abstinent smokers, but not satiated smokers, had greater variability in the tail of the reaction time distribution (increased tau). Furthermore, the size of the reaction time distribution tail was generally smaller in abstinent smokers (smaller tau) compared to the other groups and the normal component of the reaction time distribution was shifted to the left (smaller mu) after punished responses compared to after correct, rewarded responses for all groups. These findings are discussed in more detail below.

6.4.2 Post-Punishment Slowing of Reaction Time

The performance monitoring account of post-punishment slowing proposes that slowing is a consequence of increased recruitment and implementation of cognitive control (Botvinick et al., 1999, 2001; Dutilh et al., 2012a). In line with this, the degree of post-punishment slowing is correlated with electrophysiological measures of error monitoring thought to originate in the anterior cingulate cortex (Gehring et al., 1993; Hajcak et al., 2003; Debener et al., 2005; Holroyd et al., 2005). Therefore the finding that never and former smokers showed a significantly greater degree of post-punishment slowing than satiated smokers suggests that there may be an underlying impairment in cognitive control related to error processing in the satiated smoker group compared to the never and former smoker group. Although this finding is in keeping with other research showing that reduced error processing may be characteristic of substance dependent populations (e.g. Franken et al., 2007, 2010; and see Olvet and Hajcak et al., 2008 for discussion) it is unclear why the same result was not found with the abstinent smoker group.

The degree of post-punishment slowing in abstinent smokers was not found to differ significantly from either satiated smokers or never or former smokers. This finding is inconsistent with Luijten et al. (2011a) that found reduced post-error processing measured with electrophysiological correlates of error monitoring and a reduced post-error slowing in abstinent smokers that were minimally deprived (1 hour abstinence) compared to never smokers. The reason for the inconsistency of the

current result with the previous work is unclear particularly as the minimally deprived smokers in the Luijten et al. (2011a) study smoked a similar number of cigarettes per day and had similar dependence levels (assessed with the Fagerstrom Test for Nicotine Dependence) as did the smokers in the current work. The abstinent smokers included in the current analysis were abstinent to a much greater extent (over-night abstinence) than those in the Luijten et al. (2011a) study but this is considered unlikely to have inflated post-punishment slowing in former smokers in the current work as over the short term larger impairments of cognitive control would be expected with increased duration of abstinence (i.e. in over-night abstinent smokers compared to 1 hour abstinent smokers).

In terms of the numerical differences in post-punishment slowing, the satiated smokers could be differentiated from the other groups as they did not show slowing of their reaction time following punishment whereas the other three groups all slowed, albeit it to varying degrees, after punishment. The recency of smoking in the satiated smoker group may explain why post-punishment slowing was impaired in this group. Worse than expected outcomes (i.e. receiving punishment when reward was expected) generate a negative prediction error signal (Schultz et al. 1997; Hollerman and Schultz, 1998). This error signal is thought to be carried by midbrain dopamine neurones to the anterior cingulate which is thought to integrate recent reinforcement history so that behaviour can be adjusted if necessary (Holroyd and Coles, 2002; Rushworth et al., 2004; Holroyd and Coles, 2008; Chase et al., 2011). Negative prediction errors lead to pauses or a depression in phasic firing of dopamine neurones (Bayer et al., 2007). Interestingly, error signals can be disrupted pharmacologically (e.g. Zirnheld et al., 2004; De Bruijn et al., 2004; De Bruijn et al., 2006; Wardle et al., 2012). Furthermore, nicotine self-administration in chronically exposed rats has been shown to enhance burst firing activity in dopamine neurones (Caille et al., 2009). Therefore it is speculated that satiated smokers displayed impaired post-punishment slowing due to nicotine induced masking of the phasic dopamine dip that follows worse than expected outcomes. This masking might be expected to disrupt integration of reinforcement history (performance monitoring) in

satiated smokers and this prediction may be supported to some extent by the finding in Chapter 5 that numerically all groups except the satiated smokers make fewer win-maintenance failures in reversal phases of the reversal learning task compared to acquisition (see results section, Chapter 5). Interestingly Wardle et al. (2012) find a similar reduction in post-punishment slowing in healthy participants administered 20mg of d-amphetamine.

Former smokers were expected to have significantly greater post-punishment slowing compared to all groups in accordance with evidence suggesting that error monitoring is enhanced in this population compared to both current and never smokers (Nestor et al., 2011) however despite displaying the greatest degree of slowing numerically, former smokers were not significantly different from the other groups with the exception of satiated smokers. This is in line with the finding in Chapter 5 that was interpreted in terms of performance monitoring (that former smokers made significantly fewer win-maintenance failures than satiated smokers in reversal phases of the PRL compared to acquisition phases but that former smokers were not significantly different from any other groups). The Chapter 5 finding along with the current post-punishment slowing finding both contrast with the Nestor et al. (2011) work and this is likely due to behavioural measures being used in the former and imaging in the latter.

6.4.3 Variability in RVIP Hit Latency

This study found that satiated, abstinent, former and never smokers did not significantly differ in the variability of their RVIP hit latencies. Therefore, the predictions made that current smokers would show increased variability compared to never smokers and that abstinent smokers would show the greatest variability of all groups were not supported. Although it is interesting to note that numerically the direction of the variability results were that the two current smoker groups had greater variability than the two non-smoker groups. The predictions were made on the basis that there is a negative association between cognitive control and reaction time variability (West et al., 2002; Smallwood et al., 2008; Ode et al., 2011; Jackson et

al., 2012) and that cognitive control impairments have been reported in smokers compared to non-smokers (e.g. Luijten et al., 2011b) and in addition greater intra-individual variability in reaction time has previously been reported in abstinent smokers compared to satiated smokers (Kollins et al., 2009, 2012). It is unclear why the current findings are inconsistent with these previous studies. In Kollins et al. (2009) smokers smoked at least 15 cigarettes per day and were abstinent over-night and in Kollins et al. (2012) smokers smoked at least 10 cigarettes per day and were abstinent for 24 hours. Both of these studies assessed reaction time variability in a continuous performance task not unlike the RVIP task used here. Perhaps the biggest difference between these studies and the current work is that they used a within subjects design with participants attending for both a satiated and abstinent session whereas a between subjects design was used to assess variability here.

The fact that no significant differences were found between current smokers and never smokers in reaction time variability may suggest that the current smokers tested for the current work did not show impairments in cognitive control. Indeed, not all studies investigating aspects of cognitive control in smokers have found differences compared to non-smokers (e.g. Dinn et al., 2004; Monterosso et al., 2005; Reynolds et al., 2007) however it is worth bearing in mind that for the satiated smokers tested here there is evidence for increased false alarms on the RVIP and reduced levels of post-punishment slowing both of which may indicate reduced cognitive control in this group. Therefore the lack of a significant difference between satiated and never smokers is somewhat surprising.

6.4.4 Variability Following Different Feedback

The CV data for the two PRL reaction time distributions show that there was increased intra-individual variability in reaction times following punished responses compared to reaction times following correct, rewarded responses for former and never smokers but not abstinent and satiated smokers. This finding directly opposes the prediction made that current smokers would show greater intra-individual variability in these circumstances whereas never smokers would not. This prediction

was based on the suggestion that situations requiring cognitive control may exacerbate increases in intra-individual variability in reaction time in groups characterised by reduced cognitive control. For example, Liu et al. (2012) showed that cocaine users had increased variability in reaction time during a cocaine Stroop task for cocaine related stimulus trials but not for neutral trials whereas controls did not. There are a number of possible reasons why the results were not as expected.

Firstly as reaction times were expected to slow following punishment those individuals that showed the greatest post-punishment slowing would have a greater number of long duration responses in their reaction time distributions following punishment. Therefore, this could have masked an increase in variability by a group that was not demonstrating a slowing of response times following punishment. Examination of the ex-Gaussian findings shows that there was a significantly greater tau found in abstinent, former and never smokers for reaction times following punished responses compared to reaction times following correct, rewarded responses. This means that the increased variability found in former and never smokers in the CV data was driven by an increased tail to the distribution and suggests that for abstinent, former and never smokers there was an increased probability of a longer duration response being made after punished responses compared to after correct, rewarded responses. It is worthwhile noting that it is these same three groups which showed a degree of post-punishment slowing (where as satiated smokers did not). This supports the idea that the post-punishment slowing effect found in former and never smokers masked the increased variability that would otherwise have been observed in the current smoker groups. It is speculated that since the abstinent smoker groups post-punishment slowing was not numerically as great as the former and never smokers that this is why an increase in variability is not seen in the CV data.

A second possibility as to the unexpected findings might be down to differences between the PRL task used here and the cocaine Stroop task used by Liu et al. (2012). The original prediction was that those who were more impaired in cognitive control

would show the greatest variability when cognitive control was required however, in the Liu et al. study the cocaine users needed to engage cognitive control on trials with cocaine stimuli whereas the control particpants had no need to do this. Whereas for the current work, the performance monitoring account of post-punishment slowing proposes that engagement of cognitive control follows trials that provide negative feedback (Botvinick et al., 1999, 2001; Dutilh et al., 2012a) therefore this suggests that it is the former and never smokers (i.e. those with the greatest post-punishment slowing) that engaged cognitive control to the greatest extent.

6.4.5   Tail of the Distribution in Abstinent Smokers

The ex-Gaussian data also showed that the abstinent smoker group had a significantly smaller tau compared to the other groups indicating a smaller number of long duration responses in this group. This reduced variability is surprising given the previous findings of increased variability in this group compared to satiated smokers (Kollins et al., 2009, 2012), the negative relationship between cognitive control and intra-individual variability in reaction time (West et al., 2002; Smallwood et al., 2008; Ode et al., 2011; Jackson et al., 2012) and given that impairment in aspects of cognitive control in abstinence have been reported (e.g. Pettiford et al., 2007; Harrison et al., 2009).

One possible explanation of this finding is that abstinent smokers in the current study were motivated to perform the task consistently more quickly than the other groups. Upon admission to the study, current smokers were all told that they would smoke at some point during the experimental session but were not told when this would occur. Therefore it is speculated that the abstinent smokers, knowing that they were yet to smoke, performed the task consistently more quickly in order to finish the task and "move on" to their smoking opportunity. Indeed, craving levels, assessed in the abstinent smokers suggested a great urge to smoke in this group (see results section in Chapter 5) supporting the idea that there was drive/motivation to complete the task quickly. Other studies have shown that intra-individual variability in reaction time can be manipulated using motivating/goal directed feedback (Garrett et al.,

2012). Therefore the current finding suggests that it is important to take participants current motivational states into account when assessing intra-individual variability in reaction time.

6.4.6 Distribution Skewing and Shifting

As mentioned previously abstinent, former and never smokers had a significantly greater tau for reaction times following punished responses compared to reaction times following correct, rewarded responses. In addition decreased mu was observed uniformly across the groups for reaction times following punished responses compared to reaction times following correct, rewarded responses. Whereas increases in tau (the tail of the distribution) skew the reaction time distribution and reflect changes in variability, changes in mu (the mean of the normal component of the distribution) reflect a shift of the distribution. It is somewhat surprising that mu decreased after punished responses compared to correct, rewarded responses as it might be expected that longer reaction times in general would follow punishment. However the reaction time distributions appear to suggest that this is not the case and that increased reaction time following punishment was driven by changes in the latter portion of the distribution (i.e. increases in tau) even when the distribution was shifting to the left (i.e. decreasing mu).

Interestingly some researchers have speculated that inferences about different cognitive processes can be made from changes in reaction time distributions. Changes in the exponential component (tau) are thought to be more analytic, attention demanding processes (e.g. Hohle, 1965; Logan, 1990, 1992). This interpretation fits with the current finding that changes in tau are associated with the presentation of punishment. However, changes in mu have been argued to reflect more perceptual and automatic processes (e.g. Hohle, 1965; Logan, 1990, 1992). It is not clear what a change in mu in the current work represents however it should also be noted that some researchers caution the approach of assigning cognitive processes to the ex-Gaussian parameters (e.g. Matzke and Wagenmakers, 2009).

6.4.7 Strengths and Limitations

There are a number of strengths and limitations to this work. The use of both Gaussian and ex-Gaussian approaches to analysing the PRL task reaction time distributions can be considered a strength as it increases the level of detail in which variability can be scrutinized. Unfortunately the same level of detail could not be applied to the RVIP task as the number of available latencies did not permit such an analysis. Regarding the PRL task, trials containing different pairs of stimuli were interleaved. The task was designed in this way so as to increase task difficulty but this meant that participants had to deal with multiple pairs of stimuli at any given point and it is possible that interleaving pairs of stimuli in this way could have caused interference in post-punishment slowing from one pair to the other. In addition, since the number of errors on the PRL task were low, the majority of punishments received by participants were task generated false feedback. Therefore, it is unknown if the findings presented here would generalise to a situation in which veridical negative feedback were available more frequently.

6.4.8 Conclusions

The main findings from these analyses were that former and never smokers showed significantly greater post-punishment slowing than satiated smokers. It was suggested that nicotine may disrupt the prediction error signal indicating that an outcome worse than expected has occurred however additional evidence is required to confirm this hypothesis. Furthermore, contrary to predictions the groups did not differ in variability in a simple measure of reaction time (RVIP hit latencies) assessed with the CV. Additionally both former and never smokers showed significantly greater reaction time variability assessed with the CV in trials that followed punished responses compared to trials that followed correct, rewarded responses whereas satiated and abstinent smokers did not. Ex-Gaussian analysis of reaction time variability found that following punished responses as compared to correct, rewarded responses former, never and abstinent smokers, but not satiated smokers, had greater variability in the tail of the reaction time distribution (increased tau). Since greater post-punishment slowing was also found in these groups it was argued

that slowed reaction times following punishment were driving the increased variability seen in former and never smokers. The size of the reaction time distribution tail was generally smaller in abstinent smokers (smaller tau) compared to the other groups and it was suggested that this was caused by an increased motivation to complete the task quickly and reach the smoking opportunity. Finally, the normal component of the reaction time distribution was shifted to the left (smaller mu) after punished responses compared to after correct, rewarded responses for all groups but it is unclear what this might signify.

6.5   Executive Summary of Main Findings

- Former and never smokers showed significantly greater post-punishment slowing compared to satiated smokers. This suggests there was impaired error processing in satiated smokers.

- The groups did not differ in intra-individual variability in a simple measure of reaction time (RVIP hit latencies).

- Former and never smokers showed significant greater reaction time variability in trials that followed punished responses compared to trials that followed correct, rewarded responses whereas satiated and abstinent smokers did not.

- Ex-Gaussian analysis of reaction time variability found that following punished responses as compared to correct, rewarded responses former, never and abstinent smokers, but not satiated smokers, had greater variability in the tail of the reaction time distribution (increased tau). Increased tau was therefore likely to be driving the overall increase in variability seen in former and never smokers. Increased tau implies more longer duration responses were made therefore increased variability may be related to greater post-punishment slowing in these groups.

- The size of the reaction time distribution tail was generally smaller in abstinent smokers (smaller tau) compared to the other groups and this may have been due to the desire to smoke as soon as possible.

- The normal component of the reaction time distribution was shifted to the left (smaller mu) after punished responses compared to after correct, rewarded responses for all groups.

Chapter 7   Self-Control in Former Smokers that have Successfully Maintained Long Term Abstinence

7.1   Introduction

Nicotine dependence is a chronic relapsing condition with the risk of relapse during the first year after quitting estimated to be between 60-90% however long term success is strengthened by longer durations of abstinence (Krall et al., 2002). Therefore the ultimate goal of psychological and pharmacological treatment approaches must be to help former smokers achieve protracted abstinence. To achieve this aim a greater understanding of factors that drive relapse and those which may lead to 'relapse resilience' (i.e. factors that may protect an individual against relapse) is needed. This study will focus on the latter.

As deficits in self-control are associated with addiction (Ersche et al., 2012) increased self-control might conceivably contribute to 'relapse resilience'. Self-control has been defined as a key aspect of adaptive decision-making (e.g. Jasinska et al., 2011). Jasinska et al. suggest that self-control allows long-term goals to be pursued by overcoming more automatic and immediate response tendencies that conflict with that goal. Therefore, an effective self-control system must enable an individual to inhibit their behaviour, evaluate situations and risks effectively, as well as monitoring for goal conflicts or errors in their own actions so that behaviour can be adjusted accordingly.

Studies investigating self-control in smokers have typically focused on detecting which aspects of self-control are impaired in smokers compared to non-smokers (e.g. Luijten et al., 2011a, 2011b) and in detecting which aspects of self-control impairment are exacerbated by withdrawal (e.g. Pettiford et al., 2007; Harrison et al., 2009). Although this approach hints at possible self-control deficits that maintain smoking an alternative approach, that investigates the self-control profile of former smokers that have successfully maintained long term abstinence, may highlight which aspects of self-control are important for protracted abstinence. This may provide

more appropriate self-control 'targets' through which cessation outcomes can be improved. Fewer studies have taken this approach, indeed Hester et al. (2010) point out that despite studies providing evidence that impairment in executive function is exacerbated in the early stages of withdrawal little evidence exists for how and to what extent the brain may recover following protracted abstinence.

Studies that have looked at self-control with a greater focus on former smokers have suggested that the ability to remain abstinent may, at least in part, be due to individual differences in self-control (Katz and Singh, 1986a, 1986b). In addition Spinella (2003) found that former smokers scored intermediate ratings on the Frontal Systems Behaviour Scale subscales of apathy, disinhibition and executive dysfunction relative to smokers (who rated the greatest dysfunction) and to non-smokers (who rated the lowest levels of dysfunction) suggesting that there may be some recovery of executive function with prolonged levels of abstinence. However, in an electrophysiological study Neuhaus et al. (2006) reported that dysfunctional frontal lobe activation observed in smokers compared to never smokers was also present in former smokers that had, on average, been abstinent for approximately 12 years. There have been limited longitudinal studies examining the trajectory of executive control function with prolonged abstinence and to date these studies do not continue beyond 3 months follow-up. Data indicate that inhibitory control does not improve after 3 months of abstinence compared to the performance of continuing smokers in a satiated state (Dawkins et al., 2009). However baseline inhibitory control has been shown to predict relapse/non-relapse outcome (Krishnan-Sarin et al., 2007; Powell et al., 2010) and in line with this Janes et al. (2010) found that relapsers had elevated fMRI reactivity to smoking-related images and reduced functional connectivity in areas associated with cognitive control.

Furthermore, Nestor et al. (2011) found reduced neural activity in current smokers and former smokers following prolonged abstinence (mean: 84.8 weeks abstinent) during inhibitory control performance providing further evidence that inhibitory control does not improve with abstinence. However, the same former smokers

showed greater error related neural activation compared to both current and never smokers in a number of key areas implicated in cognitive control. Nestor et al. argue that this 'supra-normal' response in former smokers provides evidence for elevated top-down control, specifically involving error/performance monitoring that may have evolved from the practise that these processes receive as the ex-smoker monitors their behaviour during prolonged periods of abstinence.

Unlike the Nestor et al. (2011) work which was based upon neural activation findings there is a lack of evidence for enhanced monitoring measured behaviourally in former smokers compared to never smokers. Former smokers were found to have a significantly greater change in win-maintenance failures from the acquisition phase to the reversal phase of a probabilistic reversal learning task, a measure thought to reflect some aspect of performance monitoring (see Chapter 5), and a significantly greater post-punishment slowing on this task (see Chapter 6) compared to satiated smokers. Although they had numerically the greatest change and slowing scores compared with all other groups former smokers did not significantly differ from never smokers on these measures. Interestingly though, with regard to the speculation by Nestor et al. that practise may have enhanced monitoring, the self-control strength model predicts that self-control may be improved with practise (Muraven and Baumeister, 2000). In addition, Muraven (2010) showed that smokers that practised tasks requiring self-control (i.e. completing difficult exercises or avoiding sweet foods) were more successful during a subsequent quit attempt than smokers who practised control tasks requiring no self-control. However the Muraven (2010) finding does not reveal which specific aspects of self-control may be the most important for the maintenance of abstinence.

On the basis that some aspects of self-control may be enhanced in former smokers through practise of self-control that is achieved by maintaining long term abstinence, as may be alluded to by the self-control strength model (Muraven and Baumeister, 2000) and the findings of Muraven (2010) and Nestor et al. (2011), it was predicted that some aspects of self-control in former smokers would be elevated above levels

found in never smokers. Therefore the current study aimed to compare former smokers that had achieved successful long term abstinence and never smokers on several aspects of self-control (inhibitory control, performance monitoring, risk taking and attentional control) in order to establish if former smokers showed 'supra-normal' performance in any of these processes. Any such enhancement would suggest that this specific aspect of self-control was associated with the ability to maintain long term abstinence and so highlight a potential target for therapeutic intervention in those finding it difficult to remain abstinent. Importantly, a current smoker group was not included in the study as it would be unknown which of these would go on to successful abstinence.

For the current study inhibitory control and performance monitoring were assessed using the GoStop Task (GST; Dougherty et al., 2005). Given that some previous studies have shown that inhibitory control is impaired in smokers compared to non-smokers (e.g. Spinella, 2002; Luijten et al., 2011b), that inhibitory control does not improve over 3 months of abstinence (Dawkins et al., 2009) and that reduced neural activity was found in current smokers and in former smokers following prolonged abstinence compared to never smokers (Nestor et al., 2011) it was predicted that former smokers would show poorer inhibitory control performance compared to never smokers. Regarding performance monitoring, smokers have been reported to show impaired error monitoring (e.g. Franken et al., 2010; Luijten et al., 2011a) and in addition neural imaging data suggests that former smokers show enhanced error monitoring compared to never smokers. This finding would therefore predict greater performance monitoring in the current study in former smokers compared to never smokers. However behaviourally there is little evidence of enhancement and therefore this would predict intact, but not enhanced, levels of performance monitoring in former smokers compared to never smokers.

The current study assessed decision making under risk using the Cambridge Gambling and Iowa Gambling Tasks (CGT, Rogers et al., 1999; IGT, Bechara et al., 1994). These two tasks were chosen so that general risk taking performance could be dissociated

from risk taking performance that required learning and performance monitoring across a number of trials. Given that some studies have found poorer gambling performance in smokers compared to non-smokers (e.g. Xiao et al., 2008; Businelle et al., 2009) and that successful smoking cessation may be associated with reduced risk taking in the face of stress (Schepis et al., 2011) it was predicted that former smokers would show better decision making performance than never smokers, particularly on the IGT where there are increased cognitive demands associated with learning from performance feedback. In addition, the current study also assessed loss aversion with the Coin Flip Task (CFT; adapted from Fehr and Goette, 2007; and Gachter et al., 2010). Loss aversion reflects a bias in decision making that reflects the tendency for individuals to be more sensitive to losses compared to gains and this bias typically results in individuals rejecting gambles with 50:50 odds unless the amount that can be won is approximately twice the amount that could be lost (Tversky and Kahneman, 1992). The theory behind loss aversion originates in the field of behavioural economics and It has been proposed that applying behavioural economic principles to the study of substance dependence may provide greater insights into its nature and treatment (e.g. Takahashi, 2007; Tom et al., 2007; Chivers and Higgins, 2012; Rosen, 2012) however empirical studies are lacking. Since loss aversion can be enhanced through paying more attention to losses (Janowski and Rangel, 2011) it was predicted that exercising self-control during the maintenance of abstinence would lead to former smokers showing greater loss aversion than never smokers.

7.2   Materials and Methods

7.2.1   Participants

Fifteen former smokers (7 male and 8 female) and 15 never smokers (7 males and 8 female) aged 19-39 years were recruited for the study from the Universities of Brighton and Sussex. In order to meet the inclusion criteria participants were required to be in good health, and not be using psychotropic medication or regular medication of any sort (with the exception of oral contraceptives). Former smokers

were required to have pre-quit smoking levels of at least 10 cigarettes per day and to have been abstinent for at least 12 months. Never smokers were required not to have smoked more than 5 cigarettes in their lifetime, and not to have smoked in the last 12 months. In addition, all participants were required to arrive at the laboratory having not consumed alcohol for at least 12 hours and to have refrained from the use of illicit drugs for at least 1 week. Ethical approval was obtained from the University of Brighton, School of Pharmacy and Biomolecular Sciences Research Ethics Committee. All participants gave their written informed consent prior to participation, were free to withdraw from the study at any point and were debriefed at the end of the study. Participants received £12 compensation for their time. In addition, there was the chance to win a further £8 during the testing session (on the CFT; see General Methods, section 2.7.2).

7.2.2 Design

This study used a between subjects design comparing performance of a group of never smokers and a group of former smokers on behavioural tasks assessing inhibitory control, performance monitoring, risk taking and loss aversion. Each participant attended the laboratory on one occasion and took part in a test session lasting approximately 1 hour and 20 minutes.

7.2.3 Procedure

Before participation in the study, participants were asked about their smoking history, general health, current medication use, and alcohol and illicit drug use by completing a screening questionnaire consisting of the Medicinal Drug, Alcohol and Illicit Drug Use Questionnaire (MAID; see General Methods, section 2.3.2). On arrival at the laboratory, participants were subject to a breath alcohol test (see General Methods, section 2.2.1) and an exhaled carbon monoxide (CO) test (see General Methods, section 2.2.2) in order to ascertain that no recent drinking of alcohol or cigarette smoking had occurred. Participants were excluded for a breath alcohol reading greater than 0 g/L and for an exhaled CO level above 5 ppm.

Participants were then asked to complete a batch of personality questionnaires consisting of the Behavioural Inhibition System/Behavioural Activation System Scales (BIS/BAS; see General Methods, section 2.5.2), the Beck Depression Inventory (BDI; see General Methods, section 2.4.1), the Rumination and Reflection Questionnaire (RRQ; see General Methods, section 2.5.4) and the Penn State Worry Questionnaire (PSWQ; see General Methods, section 2.5.3). They then completed the National Adult Reading Test (NART; see General Methods, section 2.7.8), an Immediate Word Recall (IWR; see General Methods, section 2.7.6) and a Digit Span Task (DST; see General Methods, section 2.7.4). Following these questionnaire and baseline measures, participants completed a computerised test battery consisting of tasks that assessed inhibitory control (GST; see General Methods, section 2.7.5), performance monitoring (GST), risk taking (CGT; see General Methods, section 2.7.1, and IGT; see General Methods, section 2.7.7) and loss aversion (CFT; see General Methods, section 2.7.2). The tasks in the main battery were presented in the same order for all participants. All computerised tasks were presented to the participant on a laptop computer in a quiet, neutral environment.

7.2.4   Data Analysis

Statistical analysis was conducted on data from all thirty participants (15 never smokers and 15 former smokers) using SPSS version 18 (SPSS Inc.; Chicago, IL, USA). Demographic data was analysed using Chi Square (for gender) and independent samples t-tests (for age and years of education). Group differences in physiological (exhaled carbon monoxide levels), personality (BIS/BAS, BDI, RRQ and PSWQ), and cognitive (NART, IWR, digit span) measures were examined using independent samples t-tests or Mann-Whitney U tests where data was not normally distributed and transformation of the data could not correct this.

GST performance (number of novel responses, number of go responses, number of stop responses, go latency, stop latency, SSRT, and SSD) of never smokers and former smokers was compared using independent samples t-tests or Mann-Whitney U tests where data was not normally distributed and transformation of the data could not

correct this. In addition, the magnitude of post signal slowing (calculated as the difference between latencies on go trials that immediately followed a stop trial and latencies on go trials that did not immediately follow a stop trial) was compared between the groups using an independent samples t-test.

Group differences in IGT total deck selections, final score, and general IGT performance (calculated as the difference between mean total advantageous deck selections and mean total disadvantageous deck selections) were analysed using independent samples t-tests or Mann-Whitney U tests where data was not normally distributed and transformation of the data could not correct this. In addition, deck selections across the five 20 trial blocks of the IGT were compared for never smokers and former smokers using a 5 (block) x 2 (group) mixed design ANOVA for each deck. Where significant main effects of block were found these were followed up with pair-wise comparisons (contrast between block 1 and block 5 only), and significant block x group interactions were investigated using two separate repeated measures ANOVAs (one for each group) and associated pair-wise comparisons (again, contrasting blocks 1 and 5 only). General IGT performance was also compared across the five 20 trial blocks between never smokers and former smokers. However, since data at 3 of the 5 blocks was not normally distributed and since no single transformation could correct the distributions, general IGT performance was analysed by comparing block 1 with block 5 using the non-parametric Wilcoxon signed-ranks test (both block 1 and block 5 were not normally distributed) in order to establish whether there was any change in performance across time. Next, independent samples t-tests (or Mann-Whitney U tests where data was not normally distributed) were used in order to establish whether the groups differed in performance across blocks. These analyses began at block 1 and proceeded only until a significant group difference was observed, in order to limit the number of comparisons and therefore the magnitude of Bonferroni correction required.

CGT (Quality of Decision Making, Deliberation Time, Risk Taking, Risk Adjustment, Delay Aversion, and Overall Proportion Bet) and CFT (loss aversion (λ)) performance

of never smokers and former smokers was compared using independent samples t-tests or Mann-Whitney U tests where data was not normally distributed and transformation of the data could not correct this. For the loss aversion measure (λ) it is possible to calculate the real world amount that each group was willing to gamble by rearranging the equation λ = potential gain (£8)/level of acceptable loss (£1-£15) to level of acceptable loss = potential gain/λ, and these values have been calculated for illustrative purposes for never smokers and for former smokers.

All statistical tests were two-tailed with alpha set at p = 0.05. In cases where statistical significance was greater than p = 0.05 but less than or equal to p = 0.075, results have been considered a trend. Where multiple comparisons were required p-values were Bonferroni corrected by multiplying the p-value obtained by the total number of comparisons made (as in Bland and Altman, 1995) this is equivalent to lowering the level of alpha. In addition effect sizes were reported for significant findings. The assumption of normal distribution was assessed using the Kolmogorov-Smirnov test and by visual assessment of histograms of the data produced in the SPSS output. Where data was found to violate the assumption of normality, transformations were applied to the data and the specific transformations are described where they occurred in the appropriate places in the results section. Where transformations did not correct data adequately non-parametric alternatives were used. The assumption of homogeneity of variance/sphericity was assessed with Levene's test or Mauchly's test as appropriate. Adjusted degrees of freedom and p-values are reported for t-tests where variances were not equal and Greenhouse-Geisser corrected degrees of freedom and p-values are reported for violations of sphericity.

Finally, exploratory post-hoc analyses were performed for all dependent measures described above based on splitting the former smokers into two separate sub-groups based on selected information regarding their smoking histories (number of quit attempts and duration of abstinence). The rationale for these supplementary analyses and the procedure for dividing the former smokers into sub-groups are

described at the end of the main results section. In all cases, group comparisons were made using independent samples t-tests, or Mann-Whitney U tests where data was not normally distributed and transformation of the data could not correct this. Due to the large number of comparisons and for the sake of clarity only the comparisons that significantly differentiated the former smoker sub-groups are reported in full. As the sample sizes for the former smoker sub-groups are small, effect sizes have not been calculated. Due to the exploratory nature of these analyses Bonferroni corrections for multiple comparisons have not been applied.

7.3 Results

7.3.1 Demographics

The demographic data for the never smoker and former smoker groups are shown in Table 7.1. There were no significant differences in the numbers of male and female participants (X^2 (1) = 0.00, p = 1.000) or the mean age of participants (t(28) = -0.28., p = 0.781) in each group. Furthermore, there was no significant difference in years of education between both groups (t(28) = 1.88, p = 0.070). Smoking related demographic data including the mean number of lifetime cigarettes smoked by never smokers; and the mean number of pre-quit years of smoking, the mean number of pre-quit cigarettes per day, the mean duration of abstinence and the mean number of quit attempts for former smokers, along with the percentage of former smokers that reported having quit with one attempt and the percentage that reported having used a cessation aid of any kind, are shown in Table 7.1.

7.3.2 Physiological Measures

The groups did not significantly differ in their exhaled carbon monoxide levels upon admission to the study (U = 93.00, z = -0.90, p = 0.445).

	Never Smokers	Former Smokers	
General Demographics	Mean (S.E.M.)	Mean (S.E.M.)	Range
N	15	15	-
Gender (Male/Female)	7/8	7/8	-
Mean Age (Years)	26.40 (1.25)	27.00 (1.74)	-
Years of Education	17.13 (0.58)	15.57 (0.60)	-
Smoking Related Demographics			
Lifetime Cigarettes	1.67 (0.48)	-	-
Pre-quit Years of Smoking	-	7.50 (1.46)	2-23
Pre-quit Cigarettes per Day	-	20.67 (2.92)	10-40
No. Quit Attempts	-	3.20 (1.24)	1-20
% Quit with 1 Attempt	-	46.67	-
% Use of Cessation Aid	-	26.67	-
Duration of Abstinence (months)	-	47.17 (12.34)	12-168

Table 7.1: General and Smoking Related Demographic Data for Never and Former Smokers.
(Abbreviations: S.E.M.: standard error of the mean).

7.3.3 Personality Measures

Never smokers and former smokers scores did not differ significantly on any of the personality measures used: BISBAS subscales (BAS Drive, t(28) = 0.58, p = 0.568; BAS Fun Seeking, t(28) = -0.80, p = 0.433; BAS Reward Responsiveness, t(23.19) = 0.77, p = 0.450; BIS, U = 101.00, z = -0.48, p = 0.642), BDI (U = 81.00, z = -1.32, p = 0.194), RRQ subscales (Rumination, t(28) = -0.21, p = 0.838; Reflection, t(28) = 0.88, p = 0.388) and PSWQ (t(28) = 0.34, p =0.738).

7.3.4 Cognitive Measures

Similarly, groups did not differ on any of the baseline cognitive measures used: NART errors (t(28) = 0.96, p = 0.347), IWR (t(28) = 1.44, p = 0.161) and DST (forwards, t(28) = -1.50, p = 0.144; backwards, t (28) = 0.14, p = 0.890).

The data from the physiological, subjective and cognitive measures are presented together in Table 7.2.

	Never Smokers	Former Smokers
Physiological Measures	Mean (S.E.M.)	Mean (S.E.M.)
Exhaled CO (ppm) #	1.00 (2.00)	2.00 (2.00)
Subjective Measures		
BIS/BAS - BAS Drive	11.40 (0.57)	10.87 (0.73)
BIS/BAS - BAS Fun Seeking	11.80 (0.56)	12.53 (0.73)
BIS/BAS - BAS Reward Responsiveness	17.00 (0.50)	16.27 (0.81)
BIS/BAS – BIS #	22.00 (4.00)	22.00 (6.00)
BDI #	4.00 (6.00)	5.00 (4.00)
RRQ Rumination	3.03 (0.16)	3.08 (0.18)
RRQ Reflection	3.31 (0.19)	3.04 (0.24)
PSWQ	46.53 (3.13)	45.07 (3.01)
Cognitive Measures		
NART Errors	14.73 (0.69)	13.73 (0.79)
IWR (words recalled)	8.07 (0.52)	6.93 (0.59)
Digit Span Forwards	7.33 (0.30)	8.00 (0.32)
Digit Span Backwards	5.73 (0.33)	5.67 (0.35)

Table 7.2: Physiological, Subjective and Cognitive Data for Never and Former Smokers.

(Abbreviations: S.E.M.: standard error of the mean, CO: carbon monoxide, ppm: parts per million, BIS: Barratt Impulsiveness Scale, BIS/BAS: Behavioural Inhibition Scale/Behavioural Activation Scale, BIS/BAS – BIS: Behavioural Inhibition Subscale, BDI: Beck Depression Inventory, RRQ: Rumination Reflection Questionnaire, PSWQ: Penn State Worry Questionnaire, NART: National Adult Reading Test; IWR: Immediate Word Recall; # = median and interquartile range shown instead of mean and standard error of the mean for data that was analysed using non-parametric tests).

7.3.5   GST: Inhibitory Control

The never and former smoker groups did not differ on most of the GST performance measures: the number of go responses (log transformed reversed scores; $t(28) = 0.43$, $p = 0.669$), the number of stop responses (log transformed reversed scores; $t(28) = -0.78$, $p = 0.443$), the go Latency ($t(28) = -0.41$, $p = 0.683$), the stop Latency ($t(28) = 0.16$, $p = 0.877$), the SSRT ($t(28) = 1.18$, $p = 0.247$) and the SSD ($t(28) = 0.53$, $p = 0.602$). The former smokers made significantly more novel responses compared to never smokers ($U = 49.50$, $z = -2.75$, $p = 0.005$, $r = -0.50$). This data is presented in Table 7.3.

	Never Smokers	Former Smokers
GoStop Task Outcome Measure	Mean (S.E.M.)	Mean (S.E.M.)
Novel Responses /160 # *	0.00 (1.00)	2.00 (2.00)
Go Responses /80	69.67 (2.38)	69.53 (2.71)
Stop Responses /80	35.13 (2.62)	33.27 (2.92)
Go Latency (ms)	546.25 (38.56)	570.16 (43.32)
Stop Latency (ms)	460.81 (30.62)	454.04 (30.72)
SSRT	88.57 (29.33)	38.06 (31.11)
SSD	373.33 (41.65)	346.67 (28.65)

Table 7.3: GoStop Task Inhibitory Control Data for Never and Former Smokers.
(Abbreviations: S.E.M.: standard error of the mean, ms: milliseconds, SSRT: stop signal reaction time, SSD: stop signal delay; # = median and interquartile range shown instead of mean and standard error of the mean for data that was analysed using non-parametric tests. * = significant group difference $p < 0.01$).

7.3.6 GST: Performance Monitoring

All participants demonstrated a positive post signal slowing effect. That is; slower latencies on go trials that followed stop trials compared to latencies on go trials that did not follow stop trials. However, there were no group differences in the magnitude of this post signal slowing effect ($t(28) = -0.78$, $p = 0.441$). This data is presented in Table 7.4.

	Never Smokers	Former Smokers
GoStop Task Monitoring	Mean (S.E.M.)	Mean (S.E.M.)
Post Signal Slowing (ms)	45.64 (6.74)	54.46 (9.05)

Table 7.4: GoStop Task Monitoring Data for Never and Former smokers.
(Abbreviations: S.E.M.: standard error of the mean, ms: milliseconds).

7.3.7 IGT: Decision Making Under Risk - Overall Performance

Overall, there was no group difference in IGT final score ($U = 112.00$, $z = -0.02$, $p = 0.992$) or in general IGT performance (assessed as the difference score between mean total advantageous deck selections and mean total disadvantageous deck selections; $t(28) = 1.42$, $p = 0.166$). Never and former smokers also did not differ in

the mean number of total selections from each deck: decks 1 and 2 (disadvantageous; t(28) = -0.83, p = 0.411 and t(28) = -1.42, p = 0.166 respectively) and decks 3 and 4 (advantageous; t(28) = 0.55, p = 0.956 and t(28) = 1.30, p = 0.205 respectively). These data are presented in Table 7.5.

Iowa Gambling Task Outcome Measure	Never Smokers Mean (S.E.M.)	Former Smokers Mean (S.E.M.)
Total Deck 1 Selections	12.2 1.46)	13.67 (0.98)
Total Deck 2 Selections	28.67 (4.01)	36.01 (3.31)
Total Deck 3 Selections	30.47 (6.19)	27.33 (3.45)
Total Deck 4 Selections	28.67 (3.56)	22.93 (2.62)
Final Score #	1700.00 (1025.00)	1700.00 (1050.00)
Overall Adv. - Disadv. Deck Selections	18.27 (38.36)	0.53 (29.37)

Table 7.5: Iowa Gambling Task Data for Never and Former Smokers.
(Abbreviations: S.E.M.: standard error of the mean, Adv: advantageous, Disadv: disadvantageous; # = median and interquartile range shown instead of mean and standard error of the mean for data that was analysed using non-parametric tests).

7.3.8 IGT: Decision Making Under Risk – Deck Selections Across Blocks

Figure 7.1 (A-C) shows the mean number of deck selections across the five 20 trial blocks of the IGT for both groups combined (Figure 7.1A), the never smoker group (Figure 7.1B) and the former smoker group (Figure 7.1C). For deck 1 the number of selections varied across blocks (F(4, 112) = 7.61, p < 0.001), such that deck 1 was chosen significantly more often at block 1 compared to block 5 (p < 0.001, r = 0.68). This indicates that the disadvantageous nature of this deck was learned (see Figure 7.1A). As indicated previously, the former smokers and never smokers did not differ in the number of overall deck 1 selections made (F (1, 28) = 0.70, p = 0.411), however there was a significant difference between the former smokers and never smokers in the number of deck 1 selections made across the blocks (F(4, 112) = 3.88, p = 0.005). Post-hoc repeated measures ANOVAs (one for each group and with block as factor) showed that the number of deck 1 selections made by never smokers changed across

blocks (F(4, 56) = 11.58, p = 0.002 Bonferroni corrected) such that deck 1 was chosen significantly more often at block 1 compared to block 5 (p < 0.001, r = 0.90) (see Figure 1B). In contrast, the number of deck 1 selections made by former smokers did not differ across blocks (F(4, 56) = 1.39, p = 0.496 Bonferroni corrected) (see Figure 7.1C), indicating that never smokers learned that deck 1 was a disadvantageous deck whereas former smokers did not.

For deck 2 there was no significant difference in the number of deck selections across the five blocks (F(2.76, 77.34) = 1.83, p = 0.152; see Figure 7.1A). There was also no significant difference in the total number of deck 2 selections made by former smokers compared to never smokers (F(1, 28) = 2.02, p = 0.166), and there was no difference between the two groups in the number of deck 2 selections made at each of the five blocks (F(2.76, 77.34) = 0.93, p = 0.424) (see Figures 7.1B and 7.1C for never smokers and former smokers respectively).

For deck 3 there was a trend towards a difference in the number of deck selections made across the five blocks (F(3.03, 84.73) = 2.43, p = 0.070) (see Figure 7.1A). Pairwise comparisons revealed that deck 3 was chosen significantly more often at block 5 compared to block 1 (p = 0.012, r = 0.45) indicating that overall the fact that this was an advantageous deck was learned. It should be noted that this finding only approaches significance; it is reported here for completeness and must be treated with caution. In addition, there was no significant difference in the total number of deck 3 selections made by former smokers compared to never smokers (F(1, 28) = 0.20, p = 0.662), and there was no difference between the two groups in the number of deck 3 selections made at each of the five blocks (F(3.03, 84.73) = 1.31, p = 0.278) (see Figures 7.1B and 7.1C).

Finally, the number of deck 4 selections made did not vary across the five blocks of the task (F(4, 112) = 1.53, p = 0.198) (see Figure 7.1A). The total number of deck 4 selections made by former smokers compared to never smokers was not significantly different (F(1, 28) = 1.68, p = 0.205), and nor was there a difference between former

smokers and never smokers in the number of deck 4 selections made at each of the five blocks (F(4, 112) = 0.16, p = 0.956) (see Figures 7.1B and 7.1C).

7.3.9 IGT: Decision Making Under Risk – General Performance Across Blocks

IGT general performance (difference scores between advantageous decks and disadvantageous decks) was greater at block 5 compared to block 1 (z = -2.37, p = 0.017, r = -0.43). This indicates that generally the card contingencies had been learned. In terms of group differences, there was no significant difference between former smokers and never smokers at block 1 (U = 108.50, z = -0.17, p = 1.000 Bonferroni corrected). However for block 2 never smokers had significantly higher difference scores between advantageous decks and disadvantageous decks compared to former smokers (t(28) = 2.56, p = 0.032 Bonferonni corrected, r = 0.44). This suggests that never smokers learned the deck contingencies earlier than former smokers. These data are represented graphically in Figure 7.1D.

7.3.10 CGT: Decision Making Under Risk

Never smokers and former smokers did not differ on any of the CGT performance measures: Quality of Decision Making (U = 111.00, z = -0.07, p = 0.954), Deliberation Time (log transformed; t(20.895) = -1.09, p = 0.290), Risk Taking (t(28) = 0.58, p = 0.566), Risk Adjustment (t(28) = -0.80, p = 0.431), Delay Aversion (t(28) = -0.80, p = 0.346) and Overall Proportion Bet (t(28) = 0.67, p = 0.508). The results are shown in Table 7.6.
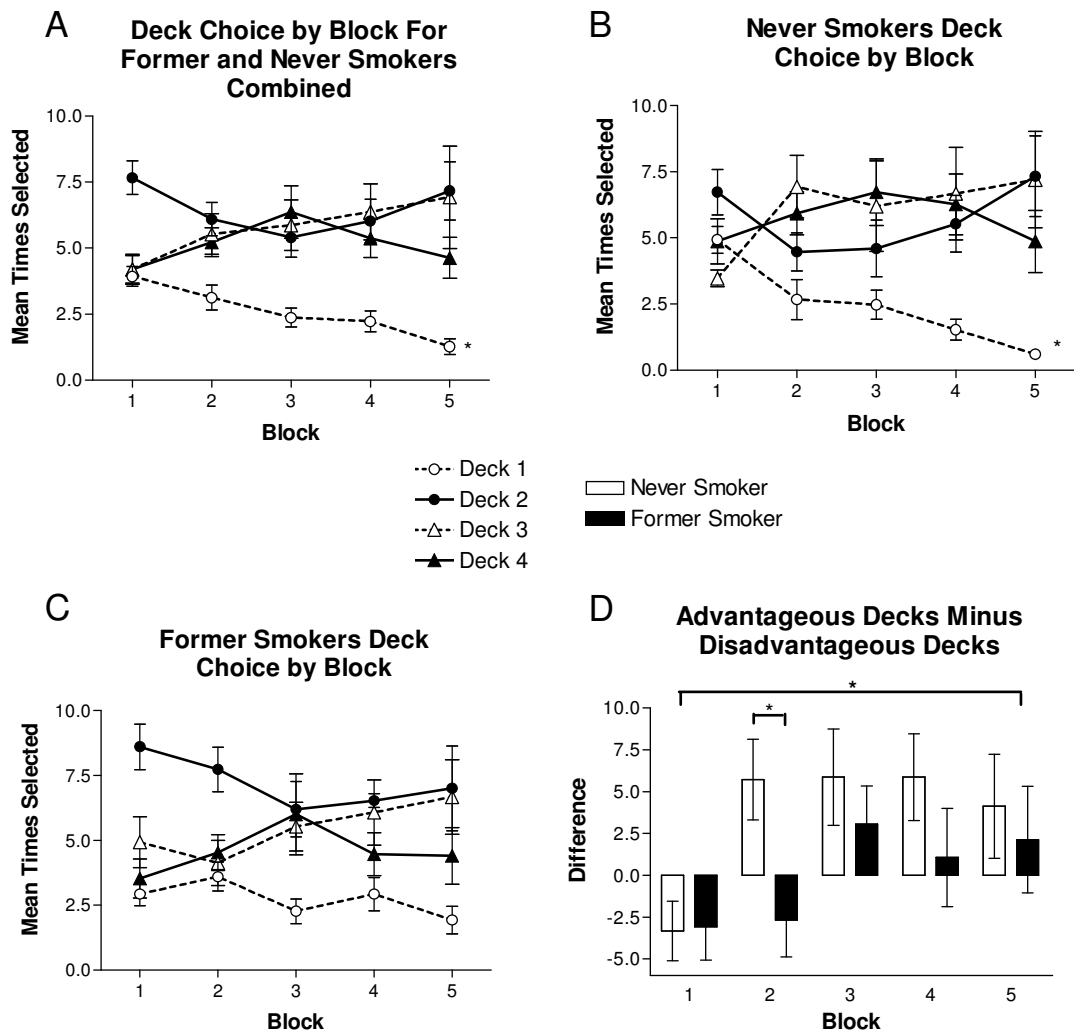
Figure 7.1: Iowa Gambling Task Deck Selections and Advantageous Decks Minus Disadvantageous Decks By Block for Former and Never Smokers.
(A-C: *p<0.001 vs. Block 1 D: *p<0.05. Error bars show standard error of the mean).

7.3.11 CFT: Loss Aversion

Former smokers had greater loss aversion than never smokers. This difference was statistically significant and represents a medium effect size (log transformed; $t(28) = -2.48$, $p = 0.019$, $r = 0.42$). On a gamble where the odds were 50:50, this equates to a willingness in never smokers to risk losing up to an average of £4.47 in order to obtain a potential win of £8 whereas former smokers were only willing to risk losing

up to £2.37 on average for the same potential win of £8. The loss aversion data is presented in Figure 7.2.

Cambridge Gambling Task Outcome Measure	Never Smokers Mean (S.E.M.)	Former Smokers Mean (S.E.M.)
Quality of Decision Making #	1.00 (0.13)	0.95 (0.03)
Deliberation Time (ms)	1834.97 (92.74)	2200.63 (242.63)
Risk Taking	0.54 (0.04)	0.51 (0.04)
Risk Adjustment	1.49 (0.22)	1.76 (0.26)
Delay Aversion	0.12 (0.04)	0.17 (0.03)
Overall Proportion Bet	0.5 (0.04)	0.47 (0.03)

Table 7.6: Cambridge Gambling Task Data for Never and Former Smokers.
(Abbreviations: S.E.M.: standard error of the mean, ms: milliseconds; # = median and interquartile range shown instead of mean and standard error of the mean for data that was analysed using non-parametric tests).
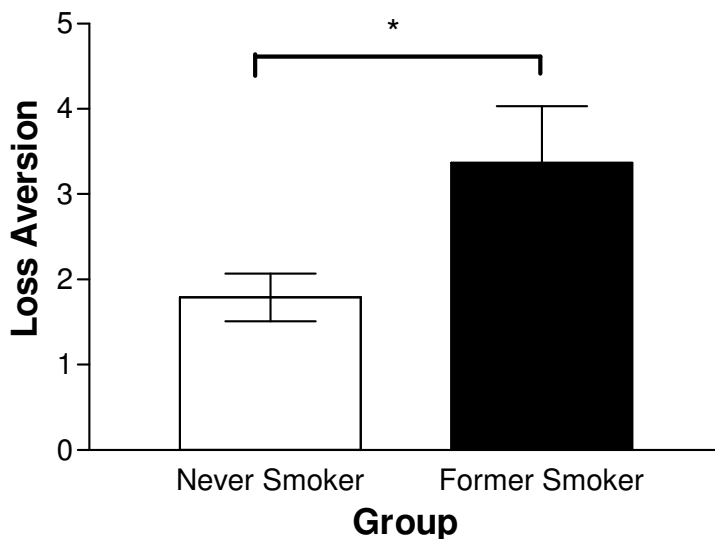
Figure 7.2: Loss Aversion in Never and Former Smokers.
(* = $p < 0.05$. Error bars show standard error of the mean).

7.4　Supplementary Analyses

The data ranges for the smoking-related demographics for former smokers (see Table 7.1) illustrate the huge amount of variation in terms of smoking-related histories within the population of former smokers that were tested in this study. This suggests that sub-populations within the former smoker group may exist and justifies additional post-hoc analyses which are described below.

7.4.1　Former Smoker Group Split by Number of Quit Attempts

By chance, approximately half of the former smokers (n = 7) tested maintained long term abstinence (at least 12 months) with just one quit attempt. The remainder (n = 8) subjectively reported taking 2-20 quit attempts. There is a case for suggesting that former smokers who have achieved long term abstinence on one attempt (with no relapses) may have greater control over the pre-potent 'bottom-up' driven processes that can lead to relapse compared to those former smokers that required several attempts to do so. Thus, this justifies re-analysing the main dependent measures based upon number of quit attempts. To this end the former smoker group was split by number of quit attempts resulting in two sub-groups: former smokers with 1 quit attempt (FS1Qt, n = 7) and former smokers with > 1 quit attempt (FS1+Qt, n = 8).

There were no significant differences between FS1Qt and FS1+Qt on any of the GST, IGT, CGT, or CFT measures.

7.4.2　Former Smoker Group Split by Duration of Abstinence

Whereas the risk of relapse during the first year after quitting is estimated to be between 60-90%, former smokers who are able to maintain abstinence for at least 2 years have a risk of relapse of just 2-4% over the succeeding years dropping to less than 1% annually after 10 years of abstinence (Krall et al., 2002). Additionally, Vangeli et al. (2010) found that after 2 or more years of abstinence just 7% of 357 former smokers that took part in a postal survey thought that they would ever return to smoking. By chance, approximately half of the former smokers (n = 8) tested had remained abstinent for 12-24 months (mean = 17.19 months). The remainder (n = 7)

subjectively reported remaining abstinent for > 24 months (mean = 81.43 months). Little is known about why smoking relapse after 2 years of abstinence becomes less likely and this justifies re-analysing the main dependent measures based upon duration of abstinence. To this end, the former smoker group was split by duration of abstinence resulting in two sub-groups: former smokers with 12-24 months of abstinence (FS_{Short}, n = 8) and former smokers with > 24 months of abstinence (FS_{Long}, n = 7).

IGT final score was significantly lower for FS_{Short} (median: 1425.00, IQR: 768.75) compared to FS_{Long} (median: 2300.00, IQR: 775.00; U = 6.50, z = -2.49, p = 0.010), suggesting that former smokers who had been abstinent for the longest duration performed better on the IGT. In addition, a comparison between number of deck 1 selections between FS_{Short} (mean: 15.38, S.E.M. 1.41) and FS_{Long} (mean = 11.71, S.E.M. 0.99) approached significance (t(13)=2.06, p=0.060) meaning that there was a trend for fewer disadvantageous deck 1 selections in former smokers who had been abstinent for the longest duration.

There were no other differences between FS_{Short} and FS_{Long} on any of the other IGT, GST, CGT, or CFT measures.

7.5   Discussion

7.5.1   Main Findings

This study compared former smokers who were able to successfully maintain long term abstinence with never smokers on a range of self-control indices. The main findings were that the former smokers in this study exhibited greater loss aversion (CFT) relative to never smokers, that one of the measures of inhibitory control used here (GST novel responses) and decision making under risk in which learning and monitoring of the on-going task performance are required for optimal performance (IGT) both differentiated the former smokers from the never smokers, while a

measure of risk taking that did not require learning across trials (CGT) and a measure of performance monitoring (GST post signal slowing) did not differentiate the two groups.

7.5.2 Greater Loss Aversion in Former Smokers

This is the first study to identify greater loss aversion in former smokers. Participants were asked to decide for a range of gambles which they would accept and which they would reject. All gambles had a 50:50 chance of paying out £8 and differed only in the amount that could be lost. From the participants choices loss aversion was computed as the ratio of acceptable loss to possible gain. The mean loss aversion in never smokers was found to be 1.79 (range: 0.53-4.00) this value is consistent with the notion that individuals reject gambles unless the amount that can be won is approximately twice the amount that could be lost (Tversky and Kahneman, 1992) and is comparable to values of loss aversion found in previous studies (e.g. Schmidt and Traub, 2002; Tom et al., 2007; He et al., 2010). For former smokers however, the value of loss aversion found was 3.37 (range: 1.14-8.00). In a choice situation loss aversion is the selection of a course of action that avoids possible losses even at a cost of missing opportunities for gain therefore increased loss aversion indicates greater sensitivity to losses and negative consequences compared to gains. A limitation of the current work is that loss aversion was assessed across one domain and it remains unclear why an individual that is loss averse in choice situations regarding money would also be loss averse in other situations. However, assuming that this is the case loss aversion may contribute to the ability of former smokers to successfully maintain long term abstinence.

The finding of increased loss aversion in long term abstainers could be explained either by pre-quit levels predicting individuals most likely to reach longer durations of abstinence or by the gradual enhancement of loss aversion throughout the duration of abstinence. Further work by way of a longitudinal study will be required in order to elucidate which of these hypotheses is correct. There are theoretical reasons to expect either of these two accounts. For example it has been estimated that for

every 10% increase in the price of cigarettes, smoking rates will fall by between 2.5% and 5% (Chaloupka et al., 2002) and intuitively it would be predicted that price would reduce smoking to a greater degree in individuals higher in loss aversion. Alternatively, those high in loss aversion may be more sensitive to the negative health consequences of smoking relative to their 'expected gain' achieved through continuation of smoking. Future work could investigate whether loss aversion is associated with an increase in uptake of healthier choices when information regarding the health outcomes of options is available and the relationship between loss aversion, increases in taxation and levels of cigarette consumption in smokers. The alternative hypothesis that loss aversion increases through abstinence is supported by the self-control strength model which proposes that practising self-control builds self-control resources (Muraven and Baumeister, 2000). Also Sangthong et al. (2012) showed that longer durations of abstinence were associated with better health behaviours in general and this may be further evidence that self-control builds with abstinence although this is correlational and so directionality cannot be inferred.

It is speculated that loss aversion may be increased through practice. Janowski and Rangel (2011) showed that loss averse individuals paid more attention to losses than less loss averse individuals and conversely those who paid most attention to losses were more loss averse. This finding is particularly interesting as the authors suggest that it may be possible to modulate loss aversion through manipulation of attention to losses. If future studies confirm that loss aversion is indeed associated with the ability to remain abstinent the Janowski and Rangel work might offer a simple mechanism of artificially enhancing loss aversion that could be implemented therapeutically in individuals finding it difficult to maintain abstinence.

7.5.3 Impaired Inhibitory Control in Former Smokers

This study did not detect behavioural differences between never and former smokers on the classical inhibitory control measures from the GST. However a significantly greater number of novel responses were made by former smokers compared to

never smokers. Novel responses on this task are errors of commission since all participants are instructed not to respond when successive five digit numbers do not match. Ordinarily, these commission errors can be used as a guide to participant understanding of the task instructions. For example, a large number of commission errors may indicate that the participant had not understood instructions about when they should and shouldn't be responding and as such this would invalidate the other task response measures. The larger number of novel responses made by former smokers in this case is however unlikely due to a lack of understanding of task instructions since the mean number of responses was just 3.80 out of a possible 160 responses. However, this number of errors does significantly differ from that of never smokers (mean: 0.80) and one likely explanation is that it represents poorer inhibitory control in the former smokers (i.e. responding when one should be withholding such a response). Commission errors on other response based tasks i.e. rapid visual information processing and continuous performance tasks have similarly been interpreted in terms of inhibitory control (e.g. Dougherty et al., 1999; Nesic et al., 2011a).

The finding that former smokers who have achieved long term abstinence are impaired in inhibitory control is in keeping with the sparse literature on the topic. Dawkins et al. (2009) show that continuous performance task errors do not change over 3 months for 33 smokers that maintained abstinence for 3 months and for 31 continuing smokers. Additionally, performance on an anti-saccade task where participants must inhibit the reflexive urge to look towards a target that appears suddenly was unchanged in the abstaining group but improved in the smoking group at 3 months. In addition, Nestor et al. (2011) found reduced neural activity in current smokers and former smokers following prolonged abstinence (mean: 84.8 weeks abstinent, approximately 20 months) compared to never smokers during Go/No-Go inhibitory control performance. Interestingly, Go/No-Go performance like that used in Nestor et al. (2011) and novel responses may assess a different kind of inhibitory control compared to the classical measure of inhibitory control of GST/stop-signal

tasks as the latter reflect how fast a response is inhibited once the response has already been initiated.

The current finding of increased novel responses in former smokers with a mean duration of abstinence of 47.2 months together with the previous studies described above suggest that inhibitory control deficits do not improve with abstinence. Longitudinal studies going beyond 3 months follow-up and using a wider range of inhibitory control measures are needed to further test this emerging hypothesis.

7.5.4 Intact Performance Monitoring in Former Smokers

Performance monitoring is a mechanism for monitoring on-going performance so that response competition and errors can be detected (Ullsperger et al., 2001; Alexander and Brown, 2010). The performance monitoring system is widely acknowledged to be located in the vicinity of the anterior cingulate cortex in the medial frontal cortex although other areas are also known to be involved (e.g. bilateral anterior insula and lateral prefrontal cortex; Ullsperger et al., 2001; Taylor et al., 2007). The system is required to evaluate behavioural progress in the context of current goals so that behaviour can be adjusted if necessary and to detect conflict between competing alternatives so that attentional resources can be allocated efficiently resulting in the correct course of action being taken (Ullsperger et al., 2001; Rushworth et al., 2004; Taylor et al., 2007). A number of studies have shown impaired neural responses in smokers compared to non-smokers in response to actual errors (Franken et al., 2010; Luijten et al., 2011a) and errors that are yet to be experienced (Chiu et al., 2008) and there is evidence that reaction time slowing following an error is impaired in current smokers compared to non-smokers (Luijten et al., 2011a). Interestingly Nestor et al. (2011) found enhanced neural activation during error monitoring on a Go/No-Go task in former smokers with long term abstinence compared to both current and never smokers. However behavioural work suggests that former smokers may show elevated feedback monitoring on a probabilistic reversal learning task and elevated slowing of reaction time after

punishment compared to satiated smokers but not compared to never smokers (see Chapter 5 and 6).

The current study assessed performance monitoring behaviourally using post signal slowing in the GST. Post signal slowing is the difference between the mean response latency made on go trials that follow stop trials and the mean response latency made on go trials that did not follow stop trials. As such the post signal slowing indexes how task related feedback (i.e. the stop signal) adjusts behavioural responding. This method has been used to assess performance monitoring using an inhibitory control task before where decreased post signal slowing was found in a cocaine dependent group compared to controls (Li et al., 2006). All participants in the current study demonstrated a positive post signal slowing effect (slower latencies on go trials that followed stop trials compared to go latencies that did not follow stop trials) and there were no group differences in the magnitude of this effect. This result implies an intact performance monitoring system in former smokers when assessed behaviourally. On the other hand, the Nestor et al. (2011) neural activation data predicts an enhanced monitoring system in former smokers and future work should try to reconcile these behavioural and imaging findings by applying both approaches to the same population.

7.5.5   Risk Taking With and Without a Learning Requirement

The CGT can be considered to assess decision making under risk outside of a learning context since all the information required to make an informed decision is available on screen for each trial (Rogers et al., 1999). The groups did not differ on any of the CGT outcome measures suggesting that they did not differ in terms of their general risk taking. On the IGT however, which assesses decision making under risk when learning and monitoring of performance feedback are required across trials in order for optimal performance levels to be achieved (Bechara et al., 1994), group differences were found. Former smokers showed poorer learning than never smokers on the disadvantageous deck (deck 1) across the five 20 trial blocks of the task and were also slower to learn the deck contingencies, having a smaller performance score

(difference between advantageous and disadvantageous deck selections) at the second 20 trial block compared to never smokers. These IGT findings suggest that, compared to never smokers, former smokers were worse at decision making under risk when learning and monitoring of performance feedback were required. This group difference cannot be accounted for by differences in working memory as the groups were matched for digit span performance. Similarly, group differences in performance monitoring are unlikely to account for this finding as no differences were found on the post signal slowing measure of the GST. The group difference in inhibitory control may account for the IGT findings as reduced inhibitory control in former smokers may have led this group to continue with selections from a deck that they had experienced high reward from even in the face of a high probability of losses. Increased loss aversion in the former smokers should be questioned in the light of these IGT findings since loss averse individuals might be expected to learn the advantageous decks from the disadvantageous decks more quickly. However elevated loss aversion may not be observed in all situations and former smokers simply might not have been averse to losing game money that had no real world value. If reduced inhibitory control in former smokers was causal in finding differences between the groups in IGT performance it might be expected that it would have also caused group differences on the CGT. However the increased cognitive demands of the IGT over the CGT, particularly an increased working memory load, due to the learning requirement in this task may have acted to make the inhibitory control deficit more apparent. In line with this suggestion increased working memory load has previously been shown to impair inhibitory control performance (Mitchell et al., 2002; Hester and Garavan, 2005).

Another point regarding the lack of group differences on the CGT is to highlight the similarity between CGT and CFT wagers. These are similar in that all the information required is given up-front. In the CFT, the amount that can be won and the odds of winning/losing are fixed and the level of acceptable loss is varied systematically whereas in the CGT each of these factors is varied to provide a general index of risk taking. The finding that risk taking behaviour on CGT did not differ between former

and never smokers suggests a degree of specificity in the loss aversion finding in that the former smokers were not simply behaving in a general over-cautious manner compared to the never smokers but instead exhibited a more specific enhancement in their sensitivity to loss compared to gains.

7.5.6   Sub-Populations within the Former Smoker Group

The former smoker group may not have been a homogeneous group. This is evident from the wide range in values reported in the pre-quit smoking demographics and for the relapse/abstinence histories obtained from participants in this group. When splitting the former smoker group by the number of quit attempts those that had succeeded in long term abstinence after just one quit attempt did not significantly differ on any of the main outcome measures compared to those that had taken more than one attempt to do so. However when splitting the former smoker group by duration of abstinence it was found that the IGT final score was significantly lower in former smokers that had been abstinent for 12-24 months compared to former smokers that had been abstinent for more than 24 months. This difference may have been driven by greater disadvantageous deck (deck 1) selections in the 12-24 month abstinent group compared to the longer duration abstinent group as this approached significance. Although based on a very small sample, this finding suggests that better decision making under risk (requiring learning and monitoring of performance across a number of trials) is associated with duration of abstinence. If this result is replicated in a larger sample it would be highly desirable to distinguish whether longer durations of abstinence led to improved performance or if greater performance predicts the ability to remain abstinent for longer durations. Splitting the former smokers up in this way resulted in no group differences in inhibitory control or in loss aversion and so the mechanism by which greater IGT performance was achieved is unclear.

7.5.7   Strengths and Limitations

This study has a number of limitations. The sample size is small and since this is the first study to find elevated loss aversion in former smokers, replication of this result

would be highly desirable. This is also the case for the supplementary analyses which should be interpreted with extreme caution as the sample sizes are even smaller. Indeed, the analyses are really only discussed as preliminary findings because the idea that self-control may be different in various sub-populations of former smokers is an important concept. For example, assessing self-control in various sub-populations of former smokers may highlight specific areas of self-control that contribute to the maintenance of abstinence and may also highlight particular sub-populations that have self-control deficits and where specific self-control enhancing therapies would be best targeted. There is therefore the need for follow up with larger studies. Another limitation is that former smokers were not asked about their reasons for quitting and theoretically this could have implications for the results found. For example, if all the former smokers tested cited financial reasons for giving up smoking, there is the possibility that a greater loss aversion bias existed within this population prior to quitting. Indeed, the financial status of participants was not recorded and this factor could have influenced their loss aversion scores. Additionally, this study relied upon self-report of the number of cigarettes smoked in the lifetime for never smokers and a range of pre-quit smoking, relapse and abstinence demographics for the former smokers. Some of these self-report measures may have been easier to recall compared to others i.e. having made just one quit attempt versus several. In addition, what may have constituted a quit attempt for one individual may not have been considered a 'proper' quit attempt in another. Additionally it is an unknown as to whether any of the former smokers in the current study (that are considered to have successfully maintained abstinence) will relapse into smoking in the future.

However, this study also has a number of strengths. Former smokers and never smokers were well matched on a range of demographics thus controlling for these factors. In addition the groups were well characterised; all former smokers that took part in the study had smoked at least 10 cigarettes per day pre-quit and had not smoked for at least 12 months and all never smokers had smoked no more than 5 cigarettes in their lifetime.

7.5.8 Conclusions

This study shows that indices of self-control can differentiate never smokers and former smokers and that former smokers show impairment in aspects of self-control even after long durations of abstinence. In line with predictions made, former smokers showed reduced inhibitory control compared to never smokers and intact performance monitoring. However contrary to prediction, former smokers showed poorer performance on a gambling task that required learning across a number of trials. In addition, it is suggested that loss aversion may be an important factor contributing to the ability of former smokers to maintain long term abstinence. Although longitudinal studies are warranted to determine if elevated loss aversion predicts or is a consequence of successful long term abstinence. Furthermore, future studies should try to account for the various sub-populations of former smokers that may exist so that results are not confounded by factors such as reasons given for quitting, pre-quit smoking characteristics or relapse and abstinence histories. This approach may lead to identification of self-control 'targets' that may be of benefit to sub-populations that find it difficult to maintain long term abstinence.

7.6   Executive Summary of Main Findings

- Former smokers made significantly more novel responses (errors of commission) on the GoStop Task compared to never smokers suggesting that former smokers had reduced inhibitory control.

- Former and never smokers did not significantly differ on a measure of performance monitoring from the GoStop Task. This suggests that former smokers have intact but not enhanced performance monitoring.

- Former and never smokers did not significantly differ in risk taking on the Cambridge Gambling Task, a measure of decision making under risk that is not dependent upon learning from or monitoring of feedback across trials.

- Former smokers showed impaired learning of advantageous and disadvantageous decks on the Iowa Gambling Task, a measure of decision making under risk that requires learning from and monitoring of feedback across trials in order for optimal performance to be achieved, compared to never smokers.

- Former smokers were significantly more loss averse than never smokers suggesting that increased loss aversion may be an important factor contributing to the ability of former smokers to maintain long term abstinence.

- Former smokers that had been abstinent for 12-24 months had poorer Iowa Gambling Task performance than those which had maintained abstinence for greater than 24 months. This suggests that improved decision making under risk is associated with greater durations of abstinence.

Chapter 8   General Discussion

8.1   Aims

There were two overall aims to this thesis. Firstly to add to the current understanding of processes that may contribute to the maintenance of nicotine dependence and secondly to add to the current understanding of factors that may contribute to successful long-term abstinence in former smokers. To do this a number of studies and analyses that initially examined the effects of smoking status, that is satiation level (satiated or abstinent) and smoking history (current, former and never smokers), on punishment sensitivity were conducted followed by an examination of loss aversion and various aspects of self-control in former smokers.

8.2   Main Findings

Before discussing the theoretical implications and limitations of this work it is necessary to first outline the main findings which have been discussed in detail in Chapters 3-7.

8.2.1   Effect of Punishment (Negative Feedback) on Responding in Two Operant Tasks in Non-Smokers (Chapter 3)

An operant conflict task of two durations (RARP task) and an operant waiting task (DRL task) were assessed for their suitability to measure punishment sensitivity. The short version of the RARP task was considered to be the most appropriate measure for future use. This was because punishment was found to supress responding on the short task equally well as it did for the longer version. Additionally as acute effects of smoking were to be assessed on the task the short duration was considered ideal to use alongside another task and yet still detect the acute effects of smoking that are known to be short acting.

8.2.2 The Effect of a Smoking Manipulation on Punishment Sensitivity in Dependent Smokers (Chapter 4)

The RARP task and a PRL task (with 100-0% and 80-20% contingency pairs) were used to assess punishment sensitivity in satiated and abstinent smokers. The groups could not be differentiated on any of the punishment sensitivity indices. In addition satiated and abstinent smokers did not differ in post-punishment slowing of reaction time.

8.2.3 Investigating Punishment Sensitivity in Current, Former and Never Smokers (Chapter 5)

Punishment sensitivity was investigated in satiated and abstinent current smokers, former smokers and never smokers using a PRL task (with 80-20% and 70-30% contingency pairs). Once again, the groups could not be differentiated on any of the punishment sensitivity indices. However, the change in win-maintenance failures from acquisition phases of the PRL to reversal phases was significantly greater in former smokers compared to satiated smokers suggesting that feedback monitoring in former smokers may be better than that of satiated smokers in situations requiring behavioural flexibility.

8.2.4 Post-Punishment Slowing and Intra-Individual Variability in Reaction Time in Current, Former and Never Smokers (Chapter 6)

The former smokers along with the never smokers showed significantly greater post-punishment slowing of reaction time compared to satiated smokers suggesting reduced post-error processing in satiated smokers. However the groups did not differ in reaction time variability (assessed using a simple measure of reaction time) that has previously been reported to be associated with reduced cognitive control. The abstinent, former and never smoker groups (i.e. the groups that showed at least some degree of slowing after punishment) had increased variability in the tail of their reaction time distributions following punished responses compared to following correct, rewarded responses. In addition, the mean of the normal component of the reaction time distributions was shifted to the left following punished responses

compared to following correct, rewarded responses suggesting that slowing of mean reaction time following punishment is not driven by slowing of all responses but by an increased frequency of long duration responses.

8.2.5 Self-Control in Former Smokers that have Successfully Maintained Long Term Abstinence (Chapter 7)

Former smokers and never smokers were compared on a range of self-control indices. Former smokers made more errors of commission on a GST suggesting that they had poorer inhibitory control than never smokers on this measure. However former smokers could not be differentiated from never smokers on a measure of performance monitoring from the GST. Former smokers also showed impaired risk taking but only when learning from and monitoring of task feedback was required across several trials (i.e. IGT but not CGT performance was able to differentiate the groups). Additionally former smokers were significantly more loss averse than never smokers, and former smokers that had been abstinent for greater than 24 months had better IGT performance than those that had been abstinent for 12-24 months.

8.3 Theoretical Implications

The individual findings were considered within the relevant discussion sections of each chapter, this section will explore the wider theoretical implications that relate to this thesis as a whole.

8.3.1 The Maintenance of Drug Use

The aim of this thesis was not to question existing theories regarding factors that contribute to continued drug use (e.g. alterations in reward system sensitivity, relief of withdrawal symptoms, inhibitory control etc.) but to provide a behavioural examination of punishment sensitivity in dependent smokers. It was hoped that an investigation into the effects of smoking status (that is satiation level and smoking history) on punishment sensitivity would provide an improved understanding of how, if at all, this factor might contribute to the maintenance of drug use.

One theory suggested by the literature is that abstinence may suppress normal motivational responses and that smoking can reverse this deficit (e.g. Powell et al., 2002b; Dawkins and Powell, 2011) and that this may contribute to continued drug use. However whilst this may be the case for appetitive or rewarding motivational responses (e.g. Powell et al., 2002a) evidence for blunted reactivity to negatively toned motivational stimuli is less convincing (e.g. Dawkins et al., 2007). The findings from Chapters 4 and 5 suggest that there is not a reduced responsivity to punishment in abstinent smokers compared to satiated smokers, at least not when assessed with operant conflict and PRL tasks.

Furthermore, it was considered that in dependent smokers insensitivity to negative consequences might drive, at least in part, continued smoking despite knowledge of the negative consequences that can occur with use. As such a reduced sensitivity to punishment was predicted in current smokers compared to non-smokers. This finding would have been in line with several strands of research including reduced error monitoring in current smokers compared to non-smokers (Luijten et al., 2011a), reduced neural activation in response to punishment in smokers compared to non-smokers (de Ruiter et al., 2009) and evidence of resistance to punishment/increased perseverative errors in cocaine users compared to non-users (Ersche et al., 2008). However, the findings of Chapter 5 do not support a general deficit in punishment sensitivity in current smokers, at least not assessed with the PRL task. It may be that a more specific deficit in punishment sensitivity that exists in a drug-related context can further elucidate mechanisms that contribute to compulsive drug use in the face of negative consequences.

Findings from Chapters 5 and 6 of this thesis found that satiated smokers had particular problems processing punishment information. Although only significantly different from former smokers, satiated smokers were the only group that did not reduce win-maintenance failures from acquisition to reversal in Chapter 5. In Chapter 6, although only significantly different from former and never smokers, satiated smokers were the only group to show no degree of post-punishment slowing. Acute

nicotine has been shown to increase impulsive choice and impulsive action (e.g. Kirshenbaum et al., 2011; Kolokotroni et al., 2011) and this may be coupled with a reduced ability to use feedback to guide behaviour. This hypothesis is tempered however by the lack of a significant difference between satiated and abstinent smokers.

8.3.2 Successful Long-Term Abstinence

A secondary aim was to add to an understanding of factors that contribute to successful long term abstinence. Findings from Chapters 5 and 6 suggest that former smokers may have integrated feedback across several trials more effectively than satiated smokers and that this was coupled with a greater degree of post-punishment slowing in former smokers compared to satiated smokers. Taken together this might suggest that former smokers had better performance monitoring than satiated smokers. The finding is difficult to interpret given the lack of differences between other relevant groups but may point to an important distinction between current smokers in their 'normal' satiated state and those that can successfully maintain abstinence.

Enhanced self-control in former smokers might conceivably contribute to 'relapse resilience' in former smokers. However there is some debate over the extent to which former smokers recover some aspects of cognitive control with extended abstinence. Neuhaus (2006) for example reports a long lasting frontal lobe dysfunction in former smokers whereas Nestor et al. (2011) report that enhanced brain activation during error monitoring in former smokers compared to current smokers and never smokers represents 'supra-normal' error monitoring processes that may be characteristic of successful abstinence. Furthermore, Nestor et al. speculate that this 'supra-normal' response may have developed through the practise that monitoring behaviour may have received during abstinence. This speculation is supported by the self-control strength model (Muraven and Baumeister, 2000) that suggests that self-control can be strengthened through practise.

The behavioural findings from Chapters 5 and 6 are at odds with the neuroimaging finding of Nestor et al. (2011) since former smokers are found to have greater monitoring and post-punishment slowing than satiated smokers but do not significantly differ from never smokers. The different methods used to obtain these findings likely account for the discrepancy and a future imaging study comparing current, former and never smokers on the PRL task could determine if this is the case.

Chapter 7 hoped to add to the debate about recovery of cognitive control in former smokers by comparing former and never smokers on a range of self-control indices. In light of the self-control strength model it was predicted that at least one aspect of self-control would be greater in former smokers compared to never smokers. However, given the behavioural findings of Chapters 5 and 6 that contrasted with the Nestor et al. (2011) imaging work it was expected that performance monitoring would not be greater in former smokers compared to never smokers. Similarly, given that inhibitory control does not improve over 3 months of abstinence (e.g. Dawkins et al., 2009) this aspect of self-control was predicted not be greater in former smokers compared to never smokers. Therefore better decision making under risk and greater loss aversion were predicted in former smokers. The findings of this study suggested that former smokers were impaired on a measure of inhibitory control and decision making under risk where learning from and monitoring of feedback was required across several trials compared to never smokers. A performance monitoring measure and risk taking that was not in a learning context could not dissociate the groups. However loss aversion was found to be significantly greater in former smokers compared to never smokers. This pattern of results suggests that some aspects of self-control may not recover after smoking is stopped even after long durations of abstinence however it should be noted that no current smokers were tested with which to draw comparison. Furthermore, this study highlights loss aversion as a candidate target that may be associated with successful long-term abstinence. However longitudinal studies will need to elucidate if elevated loss aversion predicts or is a consequence of successful abstinence. Furthermore, former smokers that had been abstinent for greater than 24 months had better

performance on decision making under risk, in a task that required learning from and monitoring of feedback across several trials, compared to former smokers that had been abstinent for 12-24 months. Again, the cross-sectional design of the study means that it cannot be determined if better decision making under risk predicts or is a consequence of long-term successful abstinence.

8.4 Limitations

While the research presented in this thesis has many strengths the conclusions that can be drawn are limited by several factors. Strengths and limitations of each study were addressed in the relevant section of each chapter however some general limitations will be discussed below.

8.4.1 Population

Due to recruitment of participants from two universities in the south east of England, the majority of the sample population were young Caucasians that were healthy and well educated. Therefore, the sample population may not be fully representative of current, former and never smokers in the general population and thus the findings and conclusions may not generalise to the wider population. Similarly, criteria for current, former and never smokers although theoretically driven may have resulted in groups that were not representative. The dependence level of current smokers, for example, was generally moderate (assessed with the FTND) and so the generalizability to more dependent smokers is unknown.

8.4.2 Methodological Considerations

There were a number of general methodological limitations to consider. Firstly, behaviours measured in an artificial laboratory environment may not reflect 'real-world' behaviours. This may be particularly true for studies like those of the current work where the stakes associated with task success and failure do not mirror those in the 'real-world', or where task decision making and subsequent consequences are made and received over a matter of minutes whereas 'real-world' decisions and consequences are made and received over different time frames (Levitt and List,

2006, 2007). In addition there could be other reasons why laboratory measures might not map on to 'real-world' behaviours, for example participants may have pre-conceived ideas about what the experimenter desires and so may adjust their behaviour accordingly (Orne, 1962).

A further limitation was that a within-subjects design was not employed for studies investigating the effect of satiation level on punishment sensitivity. A between-subjects design was used because this approach prevented practise effects from interfering with task performance. The number of errors made on the PRL tasks were low and it is likely that with practise on the task these errors may have been even lower. However, the between-subjects design employed does not allow for a direct comparison of individual performance under both abstinent and satiated conditions. Therefore further studies using a within-subjects design are required to replicate the lack of effect of satiation level on punishment sensitivity found in the current work.

Another limitation is that phase of the menstrual cycle in female participants was not considered. There is some evidence to suggest that natural modulation of hormone levels can influence performance on cognitive tasks that are thought to be dependent on the prefrontal cortex (e.g. Hatta and Nagaya, 2009).

Finally, the cross-sectional nature of the work presented in this thesis mean that causal inferences cannot be made.

8.4.3   Statistical Considerations

There are some statistical issues to be considered. Firstly, Bonferroni correction was applied throughout for multiple comparisons. However, this correction method is a very conservative method to control the familywise error rate leading some to question the appropriateness of this correction for exploration of five or less planned post-hoc comparisons (Roberts and Russo, 1999). Secondly, although the studies investigating the effects of satiation level on punishment sensitivity were larger than their predecessors (e.g. Bennett et al., 1989; Bennett and Cherek, 1991; Cherek and

Bennett, 1989, 1991) an alternative explanation for finding no significant effect is that the studies presented here were not sufficiently powered (Cohen, 1992). Studies that lack statistical power may increase the probability of both false negative and false positive findings (Christley, 2010).

8.5   Future Research

Possible future studies were suggested throughout this thesis. However, taking all of the findings of this thesis into account it is suggested that there would particularly be merit in pursuing the two following studies.

Firstly, the finding that sensitivity to punishment was not affected by level of satiation or smoking history does not rule out a more specific impairment in punishment sensitivity dependent upon a drug-related context, this is because the tasks assessing punishment sensitivity in the current studies used non-drug related rewards and punishers. A study of this nature would add to the current understanding of factors that contribute to nicotine dependence. Furthermore preclinical evidence suggests that a specific impairment in punishment sensitivity may exist in those with extended cocaine use (Vanderschuren and Everitt, 2004; Pelloux et al., 2007). Therefore, a study that aims to address if there is impaired punishment sensitivity in smokers under these more specific circumstances is proposed for future work.

Secondly, given the finding that loss aversion is greater in former smokers compared to never smokers and that a longer duration of abstinence was associated with better IGT performance, a longitudinal study is proposed for future work. This study would determine if these self-control indices predict long-term abstinence or result from long-term successful abstinence as might be predicted from the self-control strength model (Muraven and Baumeister, 2000). Furthermore this study would add to existing longitudinal work that to date has not gone beyond 3 months follow up and has concentrated mainly on inhibitory control measures (e.g. Dawkins et al., 2009). Moreover, this study would also add to the debate over the extent to which former

smokers can 'recover' aspects of cognitive control (e.g. Neuhaus et al., 2006; Nestor et al., 2011).

8.6   Conclusion

In conclusion, this thesis aimed to add to the current understanding of processes that may contribute to the maintenance of nicotine dependence and to add to the current understanding of factors that may contribute to successful long-term abstinence in former smokers. In order to do this firstly the effect of satiation level and smoking history on punishment sensitivity was examined and secondly former and never smokers were compared on several self-control indices. The findings of this thesis suggest that a general deficit in punishment sensitivity is unlikely to contribute to the maintenance of smoking however a more specific deficit of impaired punishment sensitivity in a drug-related context cannot be ruled out. In addition, former smokers may have better performance monitoring than satiated smokers. Further work is required in order to establish the mechanism behind this and to ascertain if it contributes to the maintenance of smoking behaviours. Furthermore compared to never smokers, former smokers showed impairments on a measure of inhibitory control and in decision making under risk when learning from and monitoring of trial by trial feedback was required. However, the former smokers had greater loss aversion than never smokers. Elevated loss aversion may predict or be a consequence of successful long-term abstinence but further longitudinal studies are required to confirm this.

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