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REWARD RESPONSIVITY AND THE DEVELOPMENT OF DEPENDENCE

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Abstract

Different theories have been proposed to explain the development of nicotine dependence. Some theories suggest that nicotine has direct reinforcing properties, either positive or negative. That is, nicotine is self-administered because it produces pleasure or positive affect or because it alleviates aversive symptoms associated with withdrawal and/or other nondrug aversive states (e.g., depression). Another possibility is that nicotine has indirect reinforcing properties; that is, nicotine can act as an enhancer of other reinforcers and, as such, it can affect responsivity to reward. This possibility was investigated in the present research. Specifically, it was hypothesised that reward responsivity would decrease in withdrawal; the difference between responsivity in withdrawal and satiation (smoking status) would increase with higher levels of dependency. The effects of smoking status and dependence on affect were also examined. Five experiments tested these hypotheses using a behavioural and a subjective measure of reward responsivity and a subjective measure of affect. There was no evidence for an effect of status on reward responsivity. The behavioural data indicated that withdrawal impacted task performance independently of responsivity to task-contingent reward. Some aspects of pleasure/reward (measured subjectively) were reduced, however, in high dependence smokers. In addition, withdrawn smokers showed reduced positive affect, and high dependence smokers showed increased negative affect, providing support for nicotine's direct reinforcing properties. Strong support for the indirect reinforcing properties of nicotine, measured behaviourally and subjectively, in humans was not found.

CHAPTER 1

NICOTINE REINFORCEMENT AND THE DEVELOPMENT OF NICOTINE DEPENDENCE

OVERVIEW

This chapter outlines key theories and relevant empirical evidence in the area of nicotine reinforcement and nicotine dependence. Initially, the chapter presents some background information on tobacco dependence, including formal diagnostic criteria. Next, there is an examination of positive and negative reinforcement theories that have been put forward to explain the aetiology of dependence; empirical evidence in support of these theories is presented. The final section focuses on empirical evidence highlighting the importance of indirect mechanisms of nicotine reinforcement and their contribution to the development of dependence. This sets the background and purpose of Study 1.

Throughout this document, the terms addiction and dependence are used interchangeably because both are experienced subjectively as *loss of control*. That is, behaviour continues despite volitional attempts to abstain or moderate drug use. Similarly, the terms *responsiveness* and *responsivity* are used interchangeably, both meaning reaction/response to a stimulus.

1.1 Background

Tobacco smoking is a worldwide public health problem. Despite widespread knowledge of the harmful effects of smoking, it remains a huge problem in society. This highlights the powerful motivational drive for drug reward. A report on nicotine addiction concluded that cigarette smoking is a manifestation of nicotine addiction that is comparable with addiction to “hard” drugs like heroin and cocaine (Royal College of Physicians, 2002). Nicotine

produces the acute central pharmacological effects of smoking that lead to addiction (Stolerman & Jarvis, 1995). Nicotine is also harmful directly; it is a potent neurotoxin and was widely used as an insecticide in the past. Tobacco smoke inhalation is the most highly optimised vehicle for nicotine administration. Nicotine reaches the brain in about 7 seconds after the first puff, akin to the effects achieved via intravenous injection, and it reaches a peak at around the time the cigarette is extinguished (Ashton & Stepney, 1982). Overnight, nicotine concentrations fall to the levels seen in nonsmokers. Hence, the regular smoker will typically smoke a cigarette soon after waking, and he/she will continue to smoke at regular intervals (every hour or less) throughout the day in order to maintain a roughly constant blood plasma level of nicotine.

Thirty percent of boys and 36% of girls are regular smokers by the age of 15 (Royal College of Physicians, 2002). Nearly three quarters of adult daily smokers in the United States became daily smokers before the age of 20 (United States Department of Health and Human Services, 1994a). Tobacco abuse is a disorder with a paediatric age of onset and a very quick transition from recreational to compulsive drug use (Kessler et al., 1997). Once dependence is established, the majority of smokers will then continue to smoke for nearly 40 years (Royal College of Physicians, 2002). Cigarette smoking curtails the expected lifespan by 7 years among men and 6 years among women (Royal College of Physicians, 2002). It costs the NHS over £1.5 billion per year (Parrott, Godfrey, Raw, West, & McNeill, 1998). No other single avoidable cause of disease accounts for such large proportion of deaths and hospital admissions.

As a result of the foregoing, a great deal of research has been geared towards understanding smoking behaviour. One key concept that has emerged is that of nicotine dependence. Nicotine dependence is though to develop through the actions of nicotine on reward mechanisms. The next sections review the concept of nicotine dependence and outline the ways in which nicotine is thought to produce dependence.

1.2 Nicotine Dependence

1.2.1 Formal Diagnostic Systems and Criteria of Nicotine Dependence

Formal diagnostic systems provide the "gold standard" for identifying and classifying disorders. They are primarily useful as clinical tools. The most recent set of diagnostic guidelines published by the American Psychiatric Association and the World Health Organisation is the Diagnostic and Statistical Manual, Fourth Edition, Text Revision (DSM-IV-TR, American Psychiatric Association, 2000). This system relies on a syndromal (i.e., cluster of symptoms) approach to diagnosing substance-use disorders generally and nicotine-use disorders specifically. In DSM-IV-TR, features of nicotine dependence manifest in three or more symptoms out of a total of seven, with at least three symptoms having been experienced within the same 12-month period. The symptoms, detailed below, encompass most of the salient physiological, psychological, and behavioural features of nicotine dependence.

Tolerance can manifest in one of two ways: (1) by the absence of nausea, dizziness, and other characteristic symptoms despite using "substantial amounts" of nicotine, or (2) by a markedly diminished effect observed with continued use of the same amount of nicotine, or requiring more nicotine to produce an effect previously observed at a lower dose.

Withdrawal can also be manifested in one of two ways: (1) Cessation of nicotine use produces a well-defined withdrawal syndrome (described below), or (2) nicotine is used (delivered by smoking or other means) to reduce, relieve, or avoid withdrawal symptoms. Nicotine withdrawal is precipitated by the abrupt cessation or reduction of use of nicotine after a prolonged period (at least several weeks) of daily use. It is characterised by four or more of the following: dysphoria or depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty concentrating, restlessness, decreased heart rate, and increased appetite.

Impaired control is evident when individuals use nicotine in larger amounts, or over a longer period, than was intended. People may find that they have used up their cigarettes faster than originally intended.

Unsuccessful quit attempts: A persistent desire and/or repeated unsuccessful efforts to quit smoking. For example, less than 20% of those who embarked on a course of treatment succeeded in abstaining for as long as 1 year (Hughes et al., 1992); only around 3% succeeded in quitting using will power alone (Parrott et al., 1998).

Time spent using/procuring: A great deal of time is spent in (1) activities necessary to obtain cigarettes or other nicotine-containing products or (2) smoking or using other nicotine-containing products. Chain-smoking may be one example of spending a great deal of time in using the substance.

Neglect activities: Social, occupational, or recreational activities are given up or reduced because such activities occur in places or with people who restrict or prohibit smoking.

Use despite negative physical consequences: Continue smoking or other nicotine use despite knowledge of having a persistent or recurrent physical problem that is likely to have been caused or exacerbated by smoking or other nicotine use. For example, around 50% of lung cancer patients resumed smoking after undergoing surgery (Stolerman & Jarvis, 1995).

1.2.2 Onset and Prevalence of Nicotine Dependence

Scientists assumed that nicotine dependence has a slow onset and occurs only after prolonged daily use of tobacco. However, they never established that daily use of nicotine is necessary for dependence to begin. The first symptoms of nicotine dependence can appear within days to weeks of the onset of occasional use, often before the onset of daily smoking (e.g., Baker, 1994; DiFranza et al., 2000). Stanton (1995) reported on the 1-year prevalence of nicotine dependence in a sample of 18-year-olds. Of the total sample (N = 937), 321 (34.3%) reported having smoked daily for at least 1 month during the prior year. Over half of the daily smokers (56.4%) met criteria for dependence (1-year prevalence). Thus, more than half of adolescent smokers showed significant signs of nicotine dependence (Colby, Tiffany, Shiffman, & Niaura, 2000). Kandel, Chen, Warner, Kessler, and Grant (1997) studied nicotine dependence in a sample of 87,915 adults. They divided the sample in four age groups: 18- to 25-year-olds, 26- to 34-year-olds, 35- to 49-year-olds, and equal or more than 50-year-olds and found that dependence prevalence increased with each successive age category.

The evidence so far indicates the persistent and compulsive nature of nicotine dependence. The different theories that have been proposed to explain the aetiology of dependence will be discussed next.

1.3 Theories of Addiction

The DSM-IV-TR provides the gold standard for identifying and classifying dependence. However, it is essentially descriptive, and it does not give an account of why dependence develops.

Variaties of approach to the development and modification of addictive behaviours have been described, including those guided by moral and medical frameworks (Marlatt, Baer, Donovan, & Kivlahan, 1988). From the perspective of the moral model, addiction is a sign of weak character. Addicts are responsible for both acquiring and solving their addiction problems, and they are urged to exercise greater will power to overcome their sins. The moral model has little support in the contemporary addiction literature, but it was predominant during the period of Prohibition in the United States, that is, between 1919 and 1933 (Strug, Priadarsini, & Hyman, 1986). The medical/disease model of addiction was developed as an alternative to the victim-blaming orientation of the moral model. Advocates of the disease model hypothesised an underlying progressive disease process resulting in physical dependency. Disease models of addiction suggest that individuals are not responsible either for the aetiology of, or the solution to, their addiction. Thus, disease models stop short of explaining how and why many people overcome their addiction without treatment or professional assistance (Perry, 1985). Other approaches, and the one taken in this thesis, focus on addiction as a motivational/behavioural problem (Di Chiara, 1995; Schuster & Johanson, 1973). As such, addiction develops as the result of a maladaptive interaction between nicotine and the motivational and behavioural systems that form the basis for normal behaviours.

Within this conceptual framework, drug-seeking behaviour is viewed as operant behaviour in the sense that it is behaviour controlled by the reinforcing consequences of drug self-administration. Reinforcers (e.g., drugs) are salient stimuli, events, or consequences that strengthen behaviour (e.g., drug seeking and drug taking). They can be primary (unconditioned) reinforcers, that is, reinforcers that require no training to be effective, or secondary (conditioned) reinforcers, that is, stimuli that acquire their reinforcing properties through learning (i.e., by pairing a stimulus with a primary reinforcer).

An important premise of behavioural theories of addiction is that initially neutral environmental stimuli, through repeated pairings with incentive stimuli (associative learning or classical conditioning), acquire the properties of these incentive stimuli. As a result, they become secondary reinforcers or conditioned reinforcers that acquire conditioned response-eliciting properties. Moreover, conditioned reinforcers can carry over motivational properties and elicit conditioned motivational states, further enhancing the incentive value of stimuli. Thus, if smoking produces pleasure (unconditioned reinforcement) and cigarettes become conditioned stimuli that predict pleasure, then the sight of the cigarette alone should make the individual engage in goal-directed behaviour (drug seeking and drug taking) in order to experience pleasure. Thus, smoking is an operant behaviour in that it is controlled by its consequences, that is, the rewarding effects of smoking.

The hypothesis that dependence is a behavioural problem mediated by conditioning has gained gradual acceptance. Scientists believe that reinforcers strengthen behaviour (e.g., drug seeking and drug taking) either because of the state they induce (positive reinforcement) or because of the state they alleviate

(negative reinforcement). Nicotine, for example, can act as a positive reinforcer because it induces pleasure or positive affect. However, it can also act as a negative reinforcer because it alleviates withdrawal. The majority of researchers that view drugs as reinforcers utilized infrahuman subjects (e.g. Goldberg, Spealman, & Goldberg, 1981; Corrigal & Coen, 1989). Recently, there have been attempts to view human dependence within the conceptual framework of behavioural theories. Some authors stress the importance of positive reinforcement in the development and maintenance of addiction (Stewart, De-Wit, & Eikelboom, 1984; Wise & Bozarth, 1987; Robinson & Berridge, 1993), whereas others stress the importance of negative reinforcement (Eissenberg, 2004; Poulos, Hinson, & Siegel, 1981; Siegel, 1983).

1.3.1 Positive Reinforcement

1.3.1.1 Drugs are Self-Administered because of the State they Induce

According to positive reinforcement theories, drugs are self-administered because of the state they induce, that is, pleasure or positive affect.

Stewart et al. (1984) argued that the reinforcing properties of drugs (incentive) generate appetitive motivational states that maintain compulsive drug use. Appetitive motivational states are the desire to experience the effect(s) of a previously experienced psychoactive substance. This is the 1992 UNDCP/WHO Expert Committee definition of craving. Researchers showed that craving contributes significantly to continued drug use (Tiffany, 1992; Tiffany & Drobes, 1991; Tiffany & Carter, 1998). Wise and Bozarth (1987) suggested that the shared ability of rewarding drugs to activate psychomotor stimulation and produce approach behaviour is what makes them addictive. They implicated the mesolimbic dopamine (DA) system as the neurological

substrate underpinning incentive motivational drug-seeking and drug-taking behaviour. However, unlike natural incentives, such as food, drugs have no naturally occurring primary incentive properties that elicit drug-specific approach and consummatory behaviour. Thus, as researchers, we cannot manipulate the reinforcing properties of drugs through the induction of some deprivation state in nondependent organisms.

1.3.1.2 Positive Reinforcement and the Role of Learning

Stewart et al. (1984) and Wise and Bozarth (1987) further argued that initially neutral environmental stimuli, through repeated pairings with the drug (associative learning or classical conditioning), acquire the motivational properties of the drug. Thus, they elicit a positive affective motivational state that resembles the state produced by the drug itself. In turn, these conditioned incentive stimuli (secondary reinforcers) are capable of evoking "drug-like" positive, hedonic effects that directly stimulate renewed responding. Thus, positive reinforcement produces conditioned appetitive motivational states (i.e., craving) that sustain drug use.

1.3.1.3. Nicotine and Positive Reinforcement

According to positive reinforcement theories, a drug's capacity to elicit hedonically positive effects determines its abuse liability. Although nicotine is an important drug of abuse, in a review of the evidence for its positive hedonic effects Gilbert (1995) concluded that "with few exceptions, nicotine has consistently failed to increase pleasantness and euphoria in experimental studies" (p. 114). In a recent review, Kalman and Smith (2005) found only weak evidence for mood effects of nicotine, which appear to be relatively small and

subtle. They concluded that the evidence that the subjective effects of nicotine directly mediate its reinforcing effects is quite modest.

Few studies have indicated that nicotine can produce positive subjective effects, depending on route of administration as well as nicotine dose. Pomerleau and Pomerleau (1992, 1994) found elevations in ratings of “high”, “buzz”, and “rush” from high nicotine yielding cigarettes versus ultra low nicotine cigarettes. In a recent study, however, Dar, Kaplan, Shaham, and Frenk (2007) challenged the results of Pomerleau and Pomerleau. Dar et al. argued that the results of Pomerleau and Pomerleau were biased due to the experimental instructions (e.g., define buzz as pleasurable rather than unpleasurable). Therefore, they cannot be taken as evidence that smoked nicotine is euphoriant to smokers. But other studies, more sound methodologically, showed that acute nicotine administered through smoking produced dose-related increases in drug liking in smokers (Soria et al., 1996) as well as euphoria and elation in smoking participants (Barrett, Boileau, Okker, Pihl, & Dagher, 2004). Furthermore, intravenous nicotine administration in 16 active cigarette smokers increased self-reported feelings of high, rush, and drug liking (Stein et al., 1998). However, using a slower administration route (subcutaneous injection), researchers documented an absence of mood effects in smokers (Foulds et al., 1997). Finally, although some researchers reported significant positive mood effects with intravenous nicotine (Chausmer, Smith, Kelly, & Griffiths, 2003; Harvey et al., 2004; Jones & Griffiths, 2003), the smokers in those studies were past or current users of other drugs. This precludes generalisation to the general population of smokers because injections of saline can be reinforcing in such participants (Powell, 1995).

With the exception of the studies mentioned above, many researchers assessing the positive effects of smoking on mood used smokers deprived of nicotine. Since withdrawal occurs rapidly after cessation of smoking and is associated with deficits in mood, it is difficult to determine to what extent any effects of nicotine simply reflect withdrawal relief (West, 1993).

Results from studies with smokers as well as nonsmokers have not indicated positive effects of smoking on mood. For example, smoking a high nicotine cigarette produced more unpleasant feelings than a nicotine-free cigarette did. There was no increase in pleasant feelings following either the smokers' usual brand or a high-nicotine cigarette (Gilbert, Meliska, Williams, & Jensen, 1992). Furthermore, although both cigarettes and nasal nicotine spray produced increased dizziness, neither produced increased mood, that is, relaxation (Perkins et al., 1994). Nicotine gum (4mg) did not produce any mood improvement in nonsmokers (Heishman, Snyder, & Henningfield, 1993).

Intravenous nicotine increased anxiety over placebo in nonsmoking Alzheimer's patients, and a moderate dose of nicotine increased ratings of tension, depression, and confusion over a lower dose in healthy nonsmoking volunteers (Newhouse et al., 1990). In addition, nicotine produced decreases in the Profile of Mood States Questionnaire and subjective effects that could be described as aversive, such as increased tension and confusion (Perkins et al., 1993, 1994). Finally, nicotine worsened mood in nonsmokers and caused unpleasant symptoms, such as dizziness, dysphoria, and arm pain (Foulds et al., 1997). Acute nicotine administered through smoking produced disorientation in nonsmokers (Soria et al., 1996).

Thus, the evidence suggests that, in its usual dose range, nicotine use does not cause intoxication or intense euphoria, that is, it does not act as a positive reinforcer. The fact that nicotine does not intoxicate does not make it less addicting, but it may explain why medical bodies and governments have not generally recognised tobacco use as a form of drug addiction.

1.3.1.4 Incentive-Sensitization and Addiction

Stewart et al. (1984) and Wise and Bozarth (1987) maintained that it is the subjective pleasurable or hedonic effects that maintain compulsive drug use. However, this notion has come under scrutiny. Robinson and Berridge (1993) in particular, argued against a pleasure-seeking interpretation and advanced an incentive-sensitisation theory of addiction. According to this theory, addictive drugs (and other incentive stimuli) share the ability to enhance mesotelencephalic DA neurotransmission. One psychological function of this neural system is to attribute "incentive salience" to the perception and mental representation of events associated with the activation of this system. Incentive salience is a psychological process that transforms the perception of stimuli imbuing them with salience, making them attractive, "wanted", incentive stimuli that can ultimately guide behaviour. The authors suggested that repeated drug use produces incremental neuroadaptations of the DA system rendering it increasingly hypersensitive or "sensitized" to drugs and drug-associated stimuli; thus, causing excessive incentive salience to be attributed to the act of drug taking and to stimuli associated with drug taking. As a result, with repeated drug use, drug taking and drug-associated stimuli become more and more attractive. As drug-associated stimuli become more and more able to control behaviour, the neural system that mediates wanting becomes progressively

sensitized. Wanting evolves into craving, which manifests behaviourally as compulsive drug seeking and drug taking. The crucial point here, and the disagreement of Robinson and Berridge with Stewart et al. and Wise and Bozarth, is that it is not the pleasure or "liking" associated with drug taking that motivates continued drug use but sensitization-induced excessive wanting that is independent of liking.

In criticism of the incentive-sensitization theory, Di Chiara (1995) argued that if rewards act on a common dopaminergic mechanism and sensitization of the DA system produces a general increase in the incentive salience of rewarding stimuli, then one would expect a heightened attribution of incentive salience not only to drug-related stimuli but also to all rewarding stimuli. This is incompatible with the addictive state whereby drug-related stimuli increase incentively motivated behaviour in the expense of natural rewards (e.g. food).

In sum, although according to positive reinforcement theories of addiction (Stewart et al., 1984; Wise & Bozarth, 1987) drugs are self-administered because they induce pleasure, with few exceptions (e.g., Barrett et al., 2004; Soria et al., 1996; Stein et al., 1998), it is not clear that benefits attributed to nicotine use, such as improved mood, are real. Many perceived benefits are actually attributable to the negatively reinforcing properties of nicotine, that is, the relief of nicotine withdrawal symptoms and/or the alleviation of other nondrug aversive states, for example, anxiety and/or depression. Negative reinforcement will be discussed next.

1.3.2 Negative Reinforcement

1.3.2.1 Drugs are Self-Administered because of the State they Alleviate

Wikler (1948), who conducted research on opiates, was among the first to emphasise the negative reinforcing properties of addictive drugs. According to Wikler, addictive drugs sustain drug-seeking and drug-taking behaviour because they alleviate aversive symptoms of withdrawal, rather than because they produce a pleasurable state. Negative reinforcement theories of addiction emphasise that the aversive state associated with withdrawal is a principal motivation for the addict to use a drug. The behaviour is reinforced negatively because drug self-administration produces termination of withdrawal. According to negative reinforcement theories, smokers quickly acquire tolerance to the initial, appetitive motivational effects of the drug; eventually, as dependence develops, they take it merely to avoid or escape the agony of withdrawal (Siegel, 1983).

1.3.2.2 Negative Reinforcement and the Role of Learning

Previously neutral environmental stimuli associated with drug withdrawal can themselves become conditioned stimuli (CS) capable of eliciting conditioned withdrawal reactions (Wikler, 1948). Therefore, if during abstinence the addict encounters stimuli previously paired with the experience of withdrawal, then conditioned withdrawal symptoms and craving will result. This in turn may increase the likelihood of relapse. More recently, scientists proposed that the presence of cues associated with drug administration, not drug withdrawal, elicits withdrawal-like reactions (Poulos et al., 1981; Siegel, 1983). According to this interpretation, stimuli paired with drug administration (CS) elicit conditioned compensatory responses, that is, effects that are opposite to, or

compensate for, the direct or unconditioned effects of the drug. For instance, if the direct, unconditioned effect of the drug is to increase heart rate, then the conditioned compensatory response is a decrease in heart rate. Similarly, if the direct effect of the drug is to induce positive mood, then the conditioned compensatory response is an induction of negative mood. These conditioned responses may account for conditioned tolerance when the addict is taking the drug and conditioned withdrawal responses when the addict encounters a CS when abstinent. The compensatory responses themselves may manifest as withdrawal-like responses because withdrawal symptoms are often opposite to the drug effect.

1.3.2.3 Negative Reinforcement and Dependence

Under withdrawal-based models, avoidance or suppression of aversive withdrawal symptoms by drug administration increases the probability of continued and compulsive drug use. Therefore, withdrawal defines an underlying level of physical dependence (Martin & Sloan, 1977) or neuroadaptation (Edwards, 1990) that results from chronic drug administration. Over the course of continued nicotine use, smokers experience increasingly aversive states when they refrain from using the drug. Eventually, avoidance of such aversive states comes to motivate continued drug use. Physical dependence reflects drug-induced changes in neurobiology that result from the chronic receptor exposure to drug molecules (Jaffe, 1985). Therefore, according to negative reinforcement models, chronic nicotine administration is a core feature of tobacco dependence. However, the conventional view that the motivating influence of withdrawal relief is restricted to chronic and heavy smokers does not depict accurately contemporary negative reinforcement models of

dependence. The neurobiological processes that produce withdrawal (and dependence) are activated at the first exposure to nicotine (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Eissenberg, 2004).

Initial drug-use episodes, frequently characterised by low doses and irregular dosing intervals, may be insufficient to support dependence. However, they set off the neurobiological processes responsible for withdrawal (and hence dependence). Individuals who begin their tobacco use career with occasional cigarettes (e.g., smoking at weekends) may not necessarily experience withdrawal. Dependence and a concomitant abstinence-induced withdrawal syndrome become more likely as tobacco-use episodes become more frequent. Thus, initial drug-use episodes may not support behaviourally motivating withdrawal. In other words, withdrawal may not negatively reinforce subsequent drug use. At this stage, dependence may not have developed. Instead, the direct, positive actions of the drug and/or socio-cultural rewards, rather than withdrawal escape, motivate these early-use episodes. The onset of dependence occurs when escape or avoidance of withdrawal first begins to motivate drug use, and self-administration becomes driven by negative reinforcement.

The transition from behaviour motivated by other factors (e.g., positive reinforcement and socio-cultural rewards) to behaviour motivated by negative reinforcement may be a critical period in an individual's drug-use career. Drug-use episodes before this transition phase mark nondependent drug use, whereas drug-use episodes after this transition phase mark the early stages of dependent drug use. It follows that withdrawal builds incrementally over repeated exposure to nicotine (Eissenberg, 2004), that is, it is a continuous phenomenon. For example, in a US survey of 12- to 18-year-olds, the likelihood of reporting

symptoms of nicotine withdrawal increased in relation to frequency and intensity of cigarette smoking. Cessation rates, an indirect measure of withdrawal severity, in 12- to 18-year-old adolescent smokers in the US were: 46% among occasional smokers, 12% among daily smokers of 1 to 9 cigarettes, and 7% among those smoking 10 or more cigarettes per day (US Department of Health and Human Services, 1994b). The basic dependence mechanisms may be operative to some degree in all smokers, or they may be present primarily at one or more phases of the dependence trajectory. With continued tobacco use, the smoker learns that smoking reduces or prevents withdrawal-based aversive states. This learning strengthens with tobacco experience. Therefore, dependence is an emergent rather than an all-or-none phenomenon. Furthermore, learning to escape aversive conditions precedes learning to avoid these conditions (Wada, Matsuda, Jung, & Hamm, 1970). Thus, the first stages of dependence are best characterised by the gradual acquisition of tobacco-use behaviour that is motivated by escape from the withdrawal state. In later stages of dependence, however, smoking is controlled predominantly by avoidance of withdrawal (Eissenberg, 2004).

1.3.2.4 Nicotine and Negative Reinforcement

Negative reinforcement theories propose that drugs (e.g., nicotine) act as negative reinforcers; that is, their reinforcing properties are based upon relief or avoidance of aversive states. There are two broad classes of negative reinforcenment: (a) negative reinforcement based upon nondrug aversive states, such as decrements in attentional processing, discomfort associated with stress/anxiety, and depression and (b) negative reinforcement based on drug withdrawal. These will be discussed separately.

1.3.2.5 Nicotine and Nondrug Aversive States

Nicotine can act as a negative reinforcer because it prevents decrements in attentional processing and alleviates the negative affective states, or discomfort, associated with stress/anxiety and depression. The relevant evidence and possible mechanisms through which nicotine may exert its effects on attention, stress, and depression will be presented next.

1.3.2.5.1 Decrements in attention.

Self-report data suggest that most smokers attribute their smoking, in part, to its ability to help them concentrate and think more clearly (Tate & Stanton, 1990). This improvement in performance requiring attentional processing serves a reinforcing function and helps explain one aspect of smoking's attractiveness. A review of the available data suggests that nicotine enhances sustained, divided, and selective attention.

Sustained attention (vigilance) is required in order to detect and respond to changes in the environment. It is measured with the Critical Flicker Fusion Threshold, the Rapid Visual Information Processing test, and stimulated driving tasks.

The Critical Flicker Fusion (CFF) threshold is a measure of CNS functioning. An increase in threshold frequency indicates increased cortical and behavioural arousal (Smith & Misiak, 1976). Increased arousal enhances performance by narrowing attention (Wachtel, 1967). The task requires participants to discriminate flicker from fusion (single light) in an intermittent light source. The threshold (in Hertz) at which this occurs is defined as the highest number of discrete "bits" of information that the retino-cortical system can process in a unit of time. Therefore, it is an index of the functional state of

the CNS (Simonson & Enzer, 1941). Stimulant drugs raise the CFF threshold (an increase in the rate at which the light flickers before it is perceived as steady) indicating better sensory processing, whereas sedative drugs reduce thresholds. Administration of nicotine through cigarettes or nicotine gum to deprived smokers produced significant increases in CFF thresholds compared to nicotine deprivation (Sherwood, Kerr, & Hindmarch, 1992; Waller & Levander, 1980). When nicotine was administered (through gum) to sated smokers and nonsmokers, the CFF threshold was not affected (Hindmarch, Kerr, & Sherwood, 1990; Kerr, Sherwood, & Hindmarch, 1991).

In the Rapid Visual Information Processing (RIVP) test, a series of digits generated by a computer is presented on a visual display unit at the rate of 100 digits/min. Participants are instructed to press a response button as quickly as possible when they detect sequences of three consecutive odd or three consecutive even digits (i.e., one hit). Speed and accuracy of information processing provide the measure of the performance. Administration of nicotine to deprived smokers increased speed and accuracy on the RVIP task compared to saline and placebo (Foulds et al., 1996; Mancuso, Andres, Ansseau, & Tirelli, 1999; Warburton & Mancuso, 1998). Moreover, administration of nicotine increased performance after abstinence but not after nonabstinence (Hasenfratz & Bättig, 1993; Herbert, Foulds, & Fife-Schaw, 2001). Among sated smokers and nonsmokers, the evidence for an effect of nicotine on vigilance is mixed. Administration of nicotine to sated smokers and nonsmokers enhanced performance on the RIVP task (Foulds et al., 1996; Warburton & Arnall, 1994), and it improved performance in a simulated driving task (Sherwood, 1995). However, nicotine had no effect on vigilance, as measured by stimulated driving

task performance, in sated smokers and nonsmokers (Spilich, June, & Renner, 1992).

Thus, the evidence suggests that nicotine can reverse attentional deficits associated with withdrawal, but it cannot reliably enhance vigilance in satiated smokers and nonsmokers. Given that capacity limitations play a significant role in sustained attention, one explanation of these findings is that nicotine prevents reductions in processing capacity over time (Kassel, 1997).

Divided attention is the extent to which individuals can simultaneously attend to more than one sources of information. Researchers assessed the effect of nicotine gum on a dual task in which participants both tracked a target with a cursor and responded to peripheral visual stimuli via key press (Hindmarch et al., 1990; Sherwood et al., 1992). Results showed that nicotine helped reduce error tracking but had no effect on reaction to the peripheral visual stimuli.

In selective attention studies, researchers assess the degree to which individuals attend to a target stimulus while simultaneously ignoring irrelevant or distracting stimuli. A number of different measures, including the Stroop task, the Prepulse Inhibition (PPI) task, and the negative priming task, are used to assess nicotine's effects on selective attention.

The Stroop test compares the time required for participants to name the ink colour of colour words that are incongruent (e.g., the word red printed in blue) versus the ink colour of neutral stimuli, such as noncolour words or coloured squares. Typically, the incongruent task takes more time than the neutral task because the tendency to read the colour word interferes with naming its ink colour. The difference in time between the two tasks is a measure of selective attention or distractibility (Stroop, 1935). In letter-search/cancellation

tasks, the time to search for target letters in an array of letters as well as the accuracy of identifying the target letters is a measure of selective attention. Nicotine administration to deprived (for 10 to 12 hours) smokers produced faster response time on the Stroop (Hasenfratz & Bättig, 1993; Landers, Crews, Boutcher, Skinner, & Gustafsen, 1992) and better performance on letter-search tasks (Snyder & Henningfield, 1989; Parrot & Roberts, 1991). Thus, nicotine can reverse withdrawal-induced deficits in performance on tasks requiring selective attention. In studies with nonsmokers, nicotine administration had no effect on the Stroop task (Wesnes & Revell, 1984) or on letter-cancellation tasks (Heishman et al., 1993) compared to placebo. Similarly, nicotine had no effect on performance in a visual single-target search task in sated smokers and nonsmokers (Spilich et al., 1992).

The Prepulse Inhibition (PPI) effect is the phenomenon whereby a startle reflex is suppressed when preceded by a weaker stimulus. The PPI effect is a protective mechanism that serves to screen out subsequent stimuli during the brief time required for the effective analysis of the initial stimulus. Cigarette smoking in a group of healthy male smokers deprived of cigarettes overnight increased PPI compared to the smoking-deprivation condition (Kumari, Checkley, & Gray, 1996). Others (Della Casa, Hofer, Weiner, & Feldon, 1998; Kumari, Cotter, Checkley, & Gray, 1997) reported similar results. Thus, the evidence suggests that nicotine can reverse withdrawal-induced deficits in selective attention.

The negative priming effect is the finding that participants respond more slowly to target stimuli, if they ignored them on a preceding trial (Tipper, 1985). He proposed that, when participants select the target stimulus in the first trial,

interference from the distracter stimulus is reduced by suppressing the representation of the distracter. Thus, when the distracter becomes the target in the second trial, its representation is less available causing participants to respond slower to targets that were previously distracters. The suppression of an interfering stimulus, as indexed by the level of negative priming, is an adaptive process implemented to overcome interference in selective memory. As such, the efficiency with which distracting sources of information are inhibited provides a measure of selective attention (Tipper, 1985). Rodway, Dienes, and Schepman (2000) used the negative priming paradigm to test whether smoking enhanced the inhibition of distracting information. Thirty-six minimally deprived smokers (1-hour abstinence) were tested. Half smoked and half sham smoked. Smoking resulted in a significant negative priming effect in contrast to an absence of negative priming in the sham-smoking group. That is, smoking increased the suppression of distracting information compared to sham smoking. Thus, smoking reversed withdrawal-induced deficits in selective attention. However, there was no information whether this improvement was above nonabstinent levels.

In sum, nicotine can reverse attentional deficits associated with tobacco withdrawal and thus facilitate attention (a) by increasing or preventing reductions in processing capacity, (b) by enhancing attention to relevant stimuli, and (c) by decreasing susceptibility to irrelevant (distracting) stimuli. In support of these assumptions, nicotine treatment reduces attentional deficits, compared to placebo, in Alzheimer's patients (White & Levin, 1999), in schizophrenics (McEvoy & Lindgren, 1996), and in people with attention deficit/hyperactivity

disorder (Levin, Conners, Silva, Canu, & March, 2001). Thus, the evidence supports claims that smoking behaviour is reinforced negatively.

1.3.2.5.2 Stress and anxiety.

Smokers consistently attribute their smoking to its ability to reduce subjective distress, anxiety, and the associated negative affect (Brandon & Baker, 1991; Shiffman, 1993). In experimental studies, smoking and nicotine reduced stress and anxiety induced by a number of different procedures. Thus, smoking reduced anxiety induced by social interaction, where participants debated an issue on which they disagreed strongly (Gilbert & Spielberger, 1987). Smoking, compared to sham smoking, attenuated performance anxiety or failure stress in anticipation of a mental arithmetic task (Pomerleau & Pomerleau, 1984). Similarly, in minimally deprived smokers, smoking reduced subjective distress induced by a computer task (Perkins, Grobe, Fonte, & Breus, 1992). Finally, in nonsmoking students, nicotine administered by inhalator blocked increases in ratings of anxiety (File, Fluck, & Leahy, 2001).

There are some suggestions regarding the mechanisms that underlie the stress-smoking interaction. First, the smoker may interpret withdrawal symptoms as psychological stress. Thus, any effects of smoking on stress may be due to withdrawal alleviation rather than to direct effects of nicotine (Baker et al., 2004; Parrott, 1999). For example, nicotine withdrawal manifests by increases in anger, anxiety, tension, irritability, and dysphoria (Hughes & Hatsukami, 1986). Administration of nicotine reverses these adverse effects (Hatsukami, Hughes, & Pickens, 1985). Thus, smokers derive a reduction in negative affect, stress, and anxiety only through nicotine's ability to relieve withdrawal symptomatology, not through some inherent ability to transform

affective states (Parrott, 1999). Furthermore, over the course of the development of addiction, through repeated pairings of withdrawal-induced affective distress and smoking-induced alleviation of distress, smokers come to view various affective states, such as stress, as discriminative stimuli signalling that smoking will be reinforcing (Pomerleau & Pomerleau, 1984). In other words, negative affect may become a cue for smoking, even when it occurs independently of nicotine withdrawal. Nicotine has stress-reducing effects in nonsmokers too (File et al., 2001). Thus, nicotine's stress-reducing effects may also operate through some mechanism other than relief of withdrawal-induced stress.

Nicotine's effects on anxiety may be mediated through its effects on attention allocation (Kassel & Shiffman, 1997). They exposed smokers to a stressor, that is, they asked them to prepare a potentially embarrassing, self-disclosing speech. At the same time, they presented participants with a benign distracter task (viewing art slides). Smoking improved attentional focus on the distracter task. The authors suggested that, compared to smokers who did not smoke, smokers were less distracted by current internal and external stimuli that might promote anxiety. Consequently, they experienced a reduction in anxiety relative to smokers who did not smoke. This attentional-mediation effect on anxiety may be more important than any direct effect on mood because smoking in the absence of a distracter task did not reduce anxiety (Kassel & Shiffman, 1997). Thus, according to the authors, smoking is not inherently anxiolytic. Rather, it serves to divert the smoker's attention from worries that might otherwise produce or increase anxiety.

A third suggestion regarding the mechanisms that underlie the stress-smoking interaction is that physical and psychological stressors facilitate the

acquisition of drug self-administration because they increase the reinforcing efficacy of drugs of abuse (Piazza & Le Moal, 1997, 1998). In adult animals, artificial and physical stressors, such as repeated tail pinch, facilitated the acquisition of the self-administration of psychostimulants, such as cocaine and amphetamine (Piazza, Deminiere, Le Moal, & Simon, 1990). Exposure to a stressor reinstated responding for nicotine following its extinction (Buczek, Le, Wang, Stewart, & Shaham, 1999). Furthermore, exposure to stressful stimuli enhanced nicotine craving (Coffey & Lombardo, 1998). Participants who smoked after exposure to stress (social interaction) reported greater pleasure and arousal derived from smoking compared to participants not exposed to stress (Zinser, Baker, Sherman, & Cannon, 1992). One of the most likely explanations is that stress modifies, at the neurobiological level, the motivational and/or reinforcing properties of drugs of abuse (Piazza & Le Moal, 1998). One of the effects of stress is to increase glucocorticoid secretion, which is one of the principal hormonal responses to stress. That, in turn, enhances the release of DA that functions to counteract adverse effects of stressful environmental stimuli on behaviour (Piazza & Le Moal, 1997, 1998). DA serves also as a substrate for drug-induced reinforcement (Robinson & Berridge, 1993). By changing its activity, stressors could enhance the responsiveness to drugs of abuse; thus, increase drug self-administration. Why stressors increase the activity of the biological substrate of reward remains an open question. However, this could constitute a compensatory attempt to counteract the aversive effects of stress (Piazza & Le Moal, 1998).

It is possible that the different mechanisms underlying the stress-reducing effects of nicotine operate simultaneously and contribute to the reinforcing nature of smoking behaviour.

1.3.2.5.3. Depression.

An intriguing association between depression and cigarette smoking is evident in the literature (e.g., Fergusson, Goodwin, & Horwood, 2003; Lam et al., 2004; Murray & Lopez, 1997). Results provide support for a depression-to-cigarette-use pathway. In a longitudinal study of adolescents (age 12 to 15 years), depression increased the risk of smoking (Patton et al., 1996). In a prospective study of 15- to 16-year-olds, depression significantly predicted smoking onset in the subsequent 3 years (Patton et al., 1998). Similarly, in a 4-year longitudinal study of smoking adolescents, higher levels of depressive symptoms (assessed by CES-D) at baseline prospectively predicted smoking onset (Killen et al., 1997). Finally, depressive symptoms predicted later cigarette use in a longitudinal study over 8 years, during adolescence to young adulthood (Repetto, Caldwell, & Zimmerman, 2005).

One hypothesis regarding the association between depression and smoking suggests that cigarette use helps to “self-medicate” feelings of negative mood. Therefore, levels of depression casually influence subsequent levels of cigarette use (Lerman et al., 1996). The self-medication model has been supported by studies that have linked depression to self-report of smoking in an attempt to increase arousal and reduce negative affect (Kinnunen, Doherty, Militello, & Garvey, 1996; Costello, Erkanli, Federman, & Angold, 1999; Killen et al., 1997).

Consistent with the self-medication hypothesis is the suggestion that nicotine use alters neurochemical systems (e.g., neurotransmitters such as acetylcholine, DA, serotonin, and norepinephrine) that may affect, in turn, neural circuits in the brain, for example, reward mechanisms associated with mood regulation (Pontieri, Tanda, Orzi, & Di Chiara., 1996). In support of this, the brains of living smokers showed a 40% decrease in the level of monoamine oxidase B (MAO B) relative to nonsmokers and to former smokers (Fowler et al., 1996). MAO B is involved in the breakdown of DA. Thus, MAO B inhibition is associated with enhanced activity of DA, a neurotransmitter implicated in reinforcing and motivating behaviours. Depression itself may reduce the performance of behaviours that produce reinforcement. Therefore, depressed smokers will use nicotine because, through its indirect effects on DA, nicotine and smoking may increase the chances of obtaining environmental reinforcement (Hall, Munoz, Reus, & Sees, 1993).

In sum, depression may constitute a risk factor for smoking initiation, maintenance, and relapse because nicotine can serve to alleviate the negative affective state associated with depression.

Overall, the evidence suggests that some of the ways in which nicotine provides negative reinforcement include improvement in performance requiring attentional processing and alleviation of stress/anxiety and depression. However, nicotine also serves to alleviate aversive states that are associated with discontinuation of nicotine administration. Negative reinforcement based on nicotine withdrawal will be discussed next.

1.3.2.6 Nicotine and Withdrawal

The presence of a withdrawal syndrome following abrupt discontinuation of nicotine was studied extensively among adolescent and adult smokers.

Adolescent tobacco users cited withdrawal avoidance as a motivating factor for their continued tobacco use (United States Department of Health and Human Services, 1994b). Adult tobacco users also noted withdrawal as a motivating factor (United States Department of Health and Human Services, 1988). More than 50% of adolescents experienced withdrawal symptoms when they attempted to quit smoking. That compares with approximately 85% of adults who experienced withdrawal symptoms upon nicotine abstinence (Erschler, Leventhal, Fleming, & Glynn, 1989).

1.3.2.6.1 Studies with adolescents.

In a school-based study, adolescent smokers who had previously made an unsuccessful attempt to quit were identified (Rojas, Killen, Haydel, & Robinson, 1998). Participants completed withdrawal assessments based on retrospective self-reports in reference to the previous quit attempt. Assessments were based on DSM criteria, often with additional non-DSM features queried (e.g., craving). Out of 485 adolescent smokers in the 10^{th} grade, 259 reported a previous attempt to quit smoking. Most adolescents reported at least one withdrawal symptom. About a third of adolescents reported three or more symptoms. The prevalence of individual withdrawal symptoms ranged from 25% (hunger) to 49% (craving). In a similar study (McNeill, West, Jarvis, Jackson, & Bryant, 1986), female adolescent daily smokers were significantly more likely to report a withdrawal symptom (74%) than occasional smokers

(47%) were. Responses to the withdrawal symptom items were very similar to those reported by Rojas et al. (1998) with craving the most commonly endorsed symptom.

The 1-year prevalence of withdrawal symptoms in a New Zealand birth cohort sample was examined (Stanton, 1995). Withdrawal symptoms were assessed for all smokers in the sample either they had tried to quit in the past or not. This is important because withdrawal symptoms can be experienced in the absence of attempts to quit smoking (e.g., when smoking is restricted). Withdrawal symptoms in Stanton's more inclusive sample were more prevalent than were those reported in the two studies of unsuccessful quitters (Rojas et al., 1998; McNeill et al., 1986). Craving was most commonly reported (61%) followed by restlessness (46%), appetite increase or weight gain (45%), and irritability or anger (42.7%). These findings show that smokers may frequently experience withdrawal symptoms outside of a formal quit attempt.

1.3.2.6.2 Studies with adults.

Fifty male smokers (mean age 38 years) were randomly assigned to receive placebo gum during a double-blind study of the effect of nicotine gum on the signs and symptoms of tobacco withdrawal (Hughes & Hatsukami, 1986). Participants provided baseline measurements for 2 days of ad-lib smoking. After that, they were asked to abstain from smoking for the next 4 days. They were instructed to use a gum when they had a craving for a cigarette. Data on the Profile of Mood States (POMS) questionnaire were collected during baseline and during the 4 days of abstinence. Observer and participant reports of withdrawal symptoms were also collected during baseline and during the 4 days of abstinence. The symptoms that participants reported included: anxiety

(43%), irritability (40%), impatience (38%), difficulty concentrating (36%), restlessness (35%), craving (31%), sleep disturbances (31%), hunger (26%), somatic complaints (24%), fatigue (20%), gastrointestinal tract problems (16%), headaches (12%), and drowsiness (4%). Observers ignored self-reported symptoms and based their ratings on observed changes in the participants' behaviour. Observers reported most self-report withdrawal symptoms. More important, the mean scores on the POMS indicated that, during abstinence, participants were as distressed as the average psychiatric outpatient was.

Adult smokers frequently report symptoms reflective of mood and anxiety disorders, such as irritability, low mood, restlessness, and difficulty concentrating (Breslau, Kilbey, & Andreski, 1992; Madden et al., 1997). Madden et al. identified three major classes of withdrawal severity among their participants; these were labelled the "mild", "moderate", and "severe" groups. The symptoms that participants experienced following nicotine deprivation were overall very similar to those reported by Hughes and Hatsukami (1986). However, compared to smokers with mild nicotine withdrawal, individuals having either moderate or severe withdrawal had significantly elevated lifetime rates for the indicators of nicotine dependence (as measured by the Fagerström Test for Nicotine Dependence: Heatherton, Kozlowski, Frecker, & Fagerström, 1991).

The similar prevalence rates across the previous studies (both among adolescent and adult smokers) hold despite the use of different measures and the different sample characteristics in terms of gender, age, and nationality. With the exception of the study by Hughes and Hatsukami (1986), where observer reports of the participants' withdrawal symptoms were obtained, all of the other

studies are possibly limited by their reliance on self-reported withdrawal symptoms. However, objective changes that parallel self-reported withdrawal symptoms were documented in laboratory experiments (Hatsukami et al., 1985). Furthermore, results from prospective studies (Dozois, Farrow, & Miser, 1995; Smith et al., 1996) provided support for most self-reported withdrawal symptoms. Finally, the general comparability of findings across the previous studies supports the validity of the self-reported retrospective accounts of withdrawal.

Withdrawal symptoms are attributed to nicotine, rather than to behavioural aspects of tobacco use, because withdrawal symptoms can be alleviated by nicotine replacement (Jarvis, Raw, Russell, & Feyer-Abend, 1992: Smith et al., 1996) but not placebo (Russell, Stapleton, Feyerbend, Wiseman, & Gustavsson, 1993).

1.4 Indirect Reinforcing Properties of Nicotine

Although accumulated evidence indicates that nicotine is the component of tobacco smoke that leads to addiction (Stolerman & Jarvis, 1995), the means by which nicotine produces addiction remain unclear (Epping-Jordan, Watkins, Koob, & Markou., 1998). Two models of “direct” reinforcement have been put forward to explain the development and maintenance of addiction. According to the positive reinforcement model, drugs are self-administered because they induce pleasure or positive affect. On the other hand, according to the negative reinforcement model of addiction, drugs are self-administered because of the state they alleviate, for example, aversive symptoms associated with withdrawal. However, there is a third possibility of an “indirect” action of nicotine on other types of rewards. Thus, nicotine may support drug-seeking behaviour because it

taps directly into brain mechanisms that mediate other types of rewarding event. These indirect reinforcing properties of nicotine have been shown in animals and in humans.

1.4.1 Animal Studies and Intracranial Self-Stimulation

In 1954, Olds and Milner designed an experiment to determine whether the reticular formation might play a role in learning. They placed an electrode in the brains of rats to stimulate electrically the reticular formation. Because the surgical procedure needed to implant the electrodes in the brain had been developed only recently, it was not very accurate; thus, one of the electrodes ended up in the wrong place: near the opposite end of the brain, the septum. This accident was a lucky one for the investigators. To their surprise, when the rat received the brain stimulation, it sometimes sat up, looked around, and sniffed, as if reacting to a favourable stimulus. Furthermore, the animal would return to the corner of the enclosure where the electrical stimulation had been applied. In the words of Olds (1973): “By the time the third electrical stimulus had been applied the animal seemed indubitably to be ‘coming back for more’ ” (p.81). Realising that they had just seen something very important, Olds and Milner put more electrodes in rats’ brains and allowed the rats to press a lever that controlled the current to the brain. The rats quickly learned to press the lever at a rate of over seven hundred presses per hour. Subsequent studies obtained response rates of several thousand presses per hour (Olds, 1958). It turned out that the reinforcing effect of the electrical brain stimulation was very potent. When given a choice between pressing the lever and eating, drinking, or copulating, animals would choose the lever. The phenomenon led to immediate excitement and many investigators turned their attention to the study of

intracranial self-stimulation (ICSS) and the mechanisms of central reinforcement (Olds & Frobes, 1981). ICSS in laboratory animals was demonstrated in numerous brain regions, including the nucleus accumbens, amygdala, hippocampus, hypothalamus, and many more (for a review, see Olds & Frobes, 1981). These areas became known as reward centers because animals would work to obtain electrical stimulation of parts of their brain (Olds & Frobes, 1981). The effects of ICSS were demonstrated in a number of species, including monkeys and dolphins (Lilly, 1958), cats (Roberts, 1958), snails (Balaban & Maksimova, 1993), and humans (Bishop, Elder, & Heath, 1963; Mahl, Rothenberg, Delgado, & Hamlin, 1964; Sem-Jacobsen, 1976). Thus, the generality of the phenomenon is not in question.

Soon after Olds and Milner's (1954) observation that rats would repeatedly perform a response in order to deliver electrical stimulation to parts of their brain, Hess (1957) reported that feeding, drinking, and sexual behaviour could all be elicited by electrically stimulating particular brain sites. It seemed likely that these neurons were also activated when naturally occurring behaviours were observed. Further research subsequently indicated that natural and ICSS rewards are mediated via the same circuits (Mogenson, 1971, 1973). Furthermore, the same neuronal substrates that mediate the rewarding effects of ICSS and natural reinforcers also mediate the rewarding effects of drugs of abuse (Huston-Lyons, Sarkar, & Kornetsky, 1993).

1.4.1.1 Nicotine Increases Sensitivity to Reward

Interesting relationships have been identified between intracranial self-stimulation (ICSS) and the positive reinforcing effects of nicotine. Nicotine can facilitate ICSS by reducing the threshold current needed to support it. Thus,

nicotine can increase an animal's sensitivity to the rewarding impact of ICSS (Bauco & Wise, 1994; Bespalov, Lebedev, Panchenco, & Zvartau, 1999; Huston-Lyons & Kornetsky, 1992; Huston-Lyons et al., 1993; Ivanova & Greenshaw, 1997). The ability of nicotine to facilitate ICSS correlates well enough with its propensity to be self-administered. This increased sensitivity to ICSS is regarded as a model of the hedonic impact of the compound, that is, drug-induced euphoria (Bespalov et al., 1999). The fact that nicotine produces ICSS facilitation (i.e. stimulation-threshold lowering) reflects the compound's intrinsic rewarding effect; therefore, its potential addiction liability (Kornetsky, Esposito, McLean, & Jacobson, 1979). Drugs that enhance the rewarding effects of electrical brain stimulation are generally highly addictive, whereas drugs that are not addictive usually fail to enhance electrical brain stimulation. Furthermore, this effect of nicotine on ICSS provides a measure of the compound's action on important brain reward systems (see Section 1.4.1.3).

1.4.1.2 Withdrawal Decreases Sensitivity to Reward

Because nicotine, like other drugs of abuse, increases brain reward function, as indexed by decreased ICSS thresholds, abstinence from nicotine should have the opposite effect. Epping–Jordan et al. (1998) investigated whether the nicotine abstinence syndrome was characterized by decreases in brain reward function, as measured by elevations in ICSS brain reward thresholds. Rats with chronic bipolar stimulating electrodes demonstrated stable baseline ICSS reward thresholds. They were prepared with osmotic minipumps containing either nicotine or saline. The minipumps were implanted in the posterior lateral hypothalamus and delivered nine mg/kg per day nicotine hydrogen tartrate salt dissolved in saline. This dose maintains stable plasma

nicotine levels comparable to those reported by smokers consuming 30 cigarettes daily (Benowitz, 1988). Minipumps were removed under anaesthesia 7 days later. ICSS reward thresholds were determined at regular hour intervals during chronic nicotine administration and once daily after pump removal. Spontaneous nicotine withdrawal resulted in a significant decrease in brain reward function, as measured by elevations in brain reward thresholds. The decrease peaked at 6 to 8 hours and exceeded 140% of baseline values. Thresholds of saline-treated rats did not differ significantly from baseline values at any point. Mean thresholds for nicotine-treated rats returned to baseline levels by the 5th day, and thresholds for all individual nicotine-treated rats returned to baseline levels within 16 days of minipump removal.

Chronic nicotine administration induced significant elevations in ICSS reward thresholds similar to those observed during withdrawal from other addictive drugs (Kuhar & Pilotte, 1996; Wise & Mumm, 1995). Decreased function in brain reward systems during nicotine withdrawal in the rat may be a useful model of the affective aspects of nicotine withdrawal in humans. The profound perturbation within brain reward circuitries produced by chronic nicotine administration may contribute to nicotine addiction.

1.4.1.3 Sensitivity to Reward and Dopamine

DA neurons constitute a critical link in the brain's natural reward system that evolved to mediate the reinforcing effects of natural stimuli (e.g., food, water, and sex). Electrical brain stimulation and drugs of abuse activate the natural reward system in the brain by interacting with DA neurons and synapses.

1.4.1.3.1 The brain dopamine system: effects of ICSS, nicotine, and natural rewards.

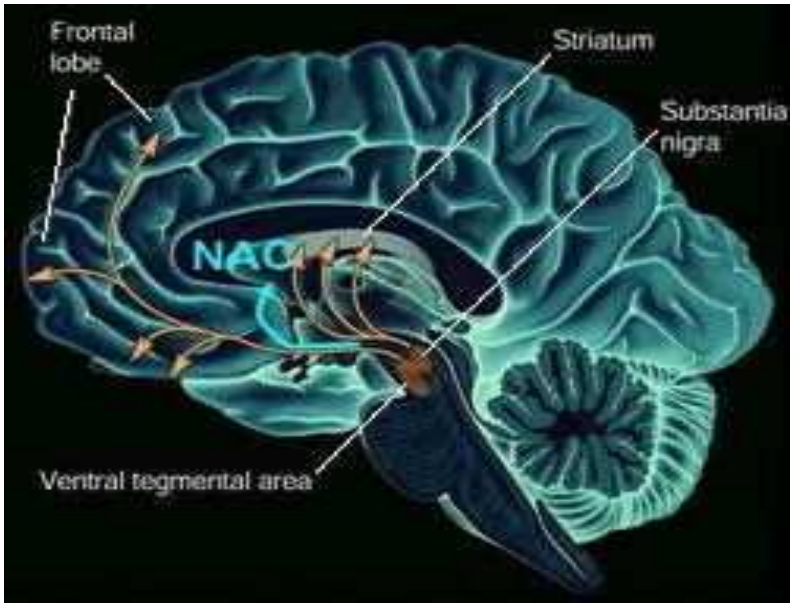

Figure 1.1. Brain dopamine pathways.
Retrieved from www.democrit.com/drugs/dopamine_pathways.jpg

Major developments in neurochemical mapping procedures have led to a detailed delineation of DA distributions in the brain. Two major dopaminergic tracts were identified: the nigrostiatal pathway, which is concerned with motor control, and the mesolimbic and mesocortical pathways (Ungerstedt, 1971), which are strongly implicated in motivational reward processes (Fuxe & Hokfelt, 1969). The cell bodies of these two systems originate in two midbrain regions: the substantia nigra (SN) and ventral tegmental area (VTA), respectively (see Figure 1.1). The DA cells of the VTA and SN form a continuous layer and project to adjacent and overlapping terminal fields. The boundaries between these "systems" are not well defined (Moal, 1995). The DA cells of the VTA innervate the ventral striatum (nucleus accumbens) but also adjacent areas, including the septum, amygdala, and hippocampus. This subset

of efferents is known as the mesolimbic DA system. The DA cells in the medial VTA that innervate the medial prefrontal cortex are known as the mesocortical DA system. There is considerable overlap between the VTA cells that project to these various targets. The two systems are often collectively referred to as the mesocorticolimbic DA system (Civelli, 1995).

Two-deoxyglucose autoradiography showed that the VTA is one of the chief regions metabolically activated during ICSS of dopaminergic pathways (Yadin, Guarini, & Gallistel, 1983). Electrodes planted directly or near the VTA elicited ICSS (Wise & Rompre, 1989). Stimulation of rewarding sites in the VTA augmented DA release in the nucleus accumbens (Fiorino, Coury, Fibiger, & Phillips, 1993). Furthermore, destruction of the mesoaccumbens projections by neurotoxic diminished the potency of VTA electrodes to elicit ICSS (Fibiger, LePiane, Jakubovic, & Phillips, 1987). DA antagonists and compounds that interfere with DA synthesis and storage (e.g., reserpine) mimic the effects of decreasing the intensity of rewarding brain stimulation (for a review, see Wise, 1996). Results from early studies did not make clear whether reduction in ICSS behaviour is due to a disruption of reward mechanisms or due to deficits in performance caused by motor impairment, or both. Many compounds exert motoric effects that might strongly influence an animal's bar-pressing ability (Gerhardt & Liebman, 1981). Furthermore, disruption to the nigrostriatal DA pathway can cause motor deficits that may render animals incapable of producing the movements required to obtain a rewarding stimulus (Dews & Morse, 1961). Consequently, researchers devised several paradigms that can dissociate motor deficits from alterations in reward intensity (e.g., Bird & Kornetsky, 1990; Esposito, Faulkner, & Kornetsky, 1979; Esposito, Perry, &

Kornetsky, 1980; Gallistel & Karras, 1984; Miliaressis, Rompre, Laviolette, Philippe, & Coulombe, 1986; Sinden & Atrens, 1982; Zarevics & Setler, 1979). Results provided further support to the theory that the mesocorticolimbic DA system is at least one of the brain pathways mediating the rewarding effects of ICSS.

Many studies demonstrated the effects of nicotine on ICSS. Thus, repeated daily injections of nicotine on the VTA of rats lowered the threshold for rewarding brain stimulation (Bauco & Wise, 1994; Bespalov et al., 1999; Huston-Lyons & Kornetsky, 1992; Huston-Lyons et al., 1993; Ivanova & Greenshaw, 1997; Kenny & Markou, 2006). This effect of nicotine was blocked by the DA receptor antagonist naloxone, haloperidol, and pimozide and the nicotine antagonist mecamylamine (Carboni, Bortone, Giua, & Di Chiara, 2000; Huston-Lyons et al., 1993; Ivanova & Greenshaw, 1997). These reward-enhancing actions of nicotine are mediated by changes in DA transmission in the shell sub-region of the nucleus accumbens (Pontieri et al., 1996). Specifically, nicotine increases DA levels in the nucleus accumbens (Benwell & Balfour, 1992). That mechanism of action is similar to that of cocaine, amphetamine, and morphine (Huston-Lyons et al., 1993; Pontieri et al., 1996) as well as to that of natural reinforcers, for example, food and water (Fibiger, Nomikos, Pfaus, & Damsma, 1992).

Thus, studies using in vivo microdialysis (measurement of neurotransmitters in the extracellular fluid of specific brain regions) showed that ingestion of food, water, and sweet solutions (i.e., primary reinforcers) was accompanied by increases in extracellular DA concentrations in the nucleus accumbens (Fibiger et al., 1992). This finding reflects the activation of the VTA

pathway. Sexual stimuli (i.e., a mate) and mating behaviour were also associated with marked increases in DA release in the nucleus accumbens (Damsma, Pfeus, Wenkestern, & Phillips, 1992).

1.4.1.3.2 Natural rewards versus artificial rewards.

Natural rewards (e.g., food) and "artificial" rewards (e.g., nicotine and ICSS) activate release of DA in the nucleus accumbens. However, certain differences between these two kinds of rewards exist that might be critical for the addictive properties of artificial rewards like drugs of abuse (Di Chiara, 2000).

First, drug rewards and ICSS can elevate nucleus accumbens DA levels three to five times more than conventional rewards that tend to elevate DA by a factor of one and a half or two (Bassareo & Di Chiara, 1999; Fiorino, Coury, & Phillips, 1997). Therefore, natural rewards may not boost DA transmission as much as artificial rewards do. In support of this, animals prefer to choose self-imposed starvation when forced to make a choice between obtaining food and water or direct electrical stimulation of their brains (Routtenberg & Lindy, 1965).

Second, as Esch and Stefano (2004) suggested, a distinction can be made by the build-up of "appetence": Natural rewards depend on a preceding build-up of appetence (e.g., hunger) to develop their reinforcing potential fully (Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001). Natural rewards (such as food) activate the DA system indirectly by stimulating peripheral sensory receptors. Following ingestion of food, appetence decreases (due to satiety). Then it needs a certain time span to return to its former levels of intensity. During this time, the same desirable experience may induce aversion (Small et al., 2001). The

results from sham-feeding experiments, where consumption is allowed to occur normally, but the food is quickly drained from the stomach and does not enter the intestine for absorption, showed that animals (and humans) continue to eat, for often more than 1 hour (Gibbs, Maddison, & Rolls, 1981). Therefore, the smell, taste, and swallowing of food (i.e., the reward) do not produce satiety. Instead, satiety is produced by food accumulating in the stomach and entering the intestine (Gibbs et al., 1981). This is not the case, however, with artificial rewards, such as drugs of abuse and ICSS. Addictive drugs and ICSS activate brain DA directly. They immediately build up high appetence levels that are not released completely, or they are released only for a short time after drug consumption (Nestler, 2001). Consequently, although the effects of natural rewards, such as food, are controlled by feedback mechanisms of satiety that modulate the value of the reward (i.e., the reward value of food), no such mechanisms control the rewarding effects of addictive drugs or ICSS. Because drugs of abuse (and ICSS) do not produce satiation as do natural rewards, drugs (and ICSS) are capable of activating DA in the nucleus accumbens in a manner that is not limited by previous drug history but only by drug availability.

Thus, the much more potent reward signal produced in the brain by drugs of abuse, as opposed to natural rewards, as well as the fact that drugs of abuse do not produce satiation may explain why drugs (e.g., nicotine) become addictive, whereas natural rewards usually do not.

DA release is associated not only with primary reinforcing stimuli but also with conditioned stimuli.

1.4.1.4 Dopamine and Conditioned Reinforcers

DA may play an important role in learning about stimuli predictive of reward. For example, DA neurons in the VTA fired in response to both primary and conditioned reinforcers (Mirenowicz & Schultz, 1996). That is, DA cells increased their firing when a monkey was given some juice (US) and after hearing a sound (CS) that was followed by the juice. In contrast, DA cells did not increase their firing when a conditioned stimulus came on (light) that was followed by an irritating puff of air (i.e., an aversive stimulus). Therefore, midbrain DA neurons may code both natural rewards and environmental cues that signal reward, but they are unlikely to code learned aversive stimuli (Mirenowicz & Schultz, 1996). In humans, anticipation of increasing monetary rewards elicited nucleus accumbens activation (i.e., DA release) but anticipation of increasing punishment did not (Knutson, Adams, Fong, & Hommer, 2001).

In monkeys, midbrain DA neurons elicited a short-latency burst of firing in response to unpredicted rewards (e.g., small quantity of fruit juice to the mouth; Schultz, Dayan, & Montague, 1997). After repeated pairings of a cue, for example, a tone (CS), with reward, the CS comes to predict reward. DA neuronal firing now occurs in response to the predictor (CS). Reward itself does not activate the neurons. However, if the reward fails to occur, then dopaminergic activity is depressed at exactly the time of the expected reward; hence, reporting an error in the prediction of reward. Midbrain DA activity codes for expectations about external stimuli or reward, and it codes for errors between predictors and actual reward timing and magnitude (Schultz, Tremblay, & Hollerman, 1998). Moreover, DA release occurs more robustly in the nucleus accumbens during reward anticipation than during reward consumption (Berridge & Robinson, 1998; Ikemoto & Panksepp, 1999).

The DA system, which is critical for reward function, becomes increasingly responsive to reward predictors and seemingly unresponsive to the reward "itself" (Mirenowicz & Schultz, 1996; Schultz et al., 1997, 1998). This raises the question whether DA is important for the prediction, rather than the "receipt", of reward. Although Wise (2002) acknowledged the fuzziness of the distinction between receipt and prediction of reward, he argued that what might tend to be designated as the receipt of reward might more accurately be designated as a more proximal predictor of reward. He suggested that in the human situation (e.g., the excitement of winning the lottery), reward is experienced upon announcement of the winning number rather than at the receipt of the food that the money eventually buys. Thus, although money is a reward, it is a conditioned reward, not a primary one. Money is a reward because it is associated with things to come (e.g., food, bigger house, better car). It follows that stimuli that predict reward (CS) should activate the DA system as much as, if not more than, unconditioned rewards do (Wise, 2002).

Conditioned reinforcers (for food) increased the release of DA in the nucleus accumbens, whereas DA-depleting lesions of the nucleus accumbens attenuated the effect of conditioned (learned) incentives on behaviour (Robbins, Cador, Taylor, & Everitt, 1989). Taylor and Robbins (1984) examined the enhancement of conditioned reinforcement following microinfusions of d-amphetamine into the nucleus accumbens of rats. They found that d-amphetamine produced a significant dose-dependent increase in responding on the CR lever (presentation of light previously paired with food). There was no significant increase in responding on the NCR lever (no programmed consequences). Therefore, the enhancement of responding for a CS (i.e., light)

with intra-accumbens d-amphetamine was behaviourally specific. The lack of concomitant increases in responding on the NCR lever demonstrated that the control over behaviour exerted by d-amphetamine was maintained only by a motivationally significant stimulus. The enhanced control over behaviour by a CR with d-amphetamine demonstrated that stimulant drugs could exaggerate the effects of stimuli that predict reinforcers. Therefore, one mechanism by which drugs may come to control behaviour is by potentiating the effects of stimuli that are predictive of other reinforcers (Taylor & Robbins, 1984).

In support of this suggested mechanism, nicotine cannot only act as a primary reinforcer, but it can also potentiate the reinforcing properties of other reinforcing stimuli through nonassociative mechanisms (e.g., Chaudhri, 2005; Chaudhri et al., 2006; Donny et al., 2003).

1.4.1.5 The Reinforcement-Enhancing Effect of Nicotine

Nicotine can directly enhance behaviour maintained by salient nonnicotine stimuli and does not require a contingent relationship between drug administration and responding (Donny et al., 2003; Chaudhri, 2005; Chaudhri et al., 2006). For example, rats were allowed to acquire lever pressing for nicotine paired with a visual stimulus (which has been shown to have primary reinforcing properties; Caggiula et al., 2002), saline paired with the visual stimulus, nicotine alone, and saline alone. Rats that self-administered (contingent) nicotine paired with the visual stimulus also controlled the delivery of nicotine infusions to a separate group of animals (noncontingent nicotine) that responded for the visual stimulus alone. Contingent and noncontingent nicotine increased response rates maintained by the visual stimulus compared with the other conditions. Therefore, nicotine can enhance the reinforcing value of, and

therefore behaviour maintained by, an already reinforcing nonpharmacological stimulus through nonassociative mechanisms (Donny et al., 2003). Associating nicotine with the visual stimulus produced a synergistic and not just an additive enhancement of self-administration. That is, response rates generated by the combination of visual stimulus and nicotine were more than twice the sum of response rates produced by the visual stimulus alone or nicotine alone. Furthermore, unlike nicotine, noncontingent delivery of food pellets did not enhance responding for the visual stimulus compared to lever pressing for the visual stimulus alone. Therefore, the increase in response rates was a direct, pharmacological action of nicotine and not a property of all reinforcers (Donny et al., 2003).

In addition to unconditioned reinforcing stimuli, nicotine can also enhance behaviour maintained by conditioned reinforcers. For instance, a brief tone-light stimulus was paired or not with sucrose pallets. After training, two separate levers were introduced. Responding on one lever was reinforced by the stimulus in the absence of sucrose. Animals with sucrose-paired training responded considerably more on the stimulus-reinforced lever compared to the nonreinforced lever or to rats in the sucrose-unpaired condition. Therefore, the paired stimulus became a conditioned reinforcer, whereas the unpaired stimulus had only weak reinforcing strength. Subsequently, animals were divided into three groups and were tested daily on a progressive-ratio reinforcement schedule. Lever pressing was reinforced by the stimulus with contingent nicotine, noncontingent nicotine, and noncontingent saline. Rats with sucrose-unpaired training demonstrated moderate responding for the stimulus (with saline) compared to rats with sucrose-paired training that responded at a

significantly greater level for the stimulus (with saline). Therefore, prior pairing of the stimulus with sucrose made it a comparatively stronger positive reinforcer. More important, contingent nicotine elevated responding for the stimulus equally in the sucrose-unpaired and sucrose-paired groups. Noncontingent nicotine more effectively increased responding for the sucrose-paired as opposed to the sucrose-unpaired stimulus (Chaudhri, 2005). Thus, if the nonpharmacological stimulus possesses some reinforcing strength prior to nicotine exposure, then the reinforcement-enhancing effect of nicotine (assessed using noncontingent nicotine) is pronounced (Chaudhri et al., 2005). The evidence that noncontingent nicotine can enhance responding for unconditioned as well as conditioned reinforcing stimuli provides further support for the reinforcement-enhancing actions of nicotine

Furthermore, in animal studies, nicotine increased motivation to obtain food (Popke, Mayorga, Fogle, & Paule, 2000) and potentiated alcohol and cocaine self-administration (Clark, Lindgren, Brooks, Watson, & Little, 2001). Likewise, in humans, smoking often occurs in conjunction with other reinforced behaviour (e.g. drinking alcohol; Bien & Burge, 1990). Although these effects are often interpreted as being pharmacologically specific (e.g., nicotine-alcohol interactions), an alternative interpretation is that nicotine acts more broadly, potentiating the effects of reinforcing stimuli. Consistent with that, neurophysiological evidence suggests that nicotine has a more general effect: The net GABAergic and glutamatergic influence on brain DA systems may shift towards a more excitable state following nicotine exposure (Mansvelder, Keath, & McGehee, 2002).

In sum, results from studies on animals provide strong support for the reinforcement-enhancing actions of nicotine. The major neurochemical mechanism underlying these effects is enhanced release of DA in the nucleus accumbens (Benwell & Balfour, 1992; Pontieri et al., 1996). The results from human studies support the animal data.

1.4.2 Human Studies and Reward Responsivity

1.4.2.1 Nicotine Enhances Release of Dopamine

Researchers reported increased DA activity in human smokers relative to nonsmokers (Salokangas et al., 2000; Stein et al., 1998). In addition, there is indirect evidence that smoking triggers DA release. Thus, the amount of nicotine found in the blood of smokers was similar to that required to release DA in experimental animals (Rowell, Carr, & Garner, 1987). Furthermore, in an attempt to compensate for the reduced reinforcing efficacy of nicotine, habitual smokers increased their rate of nicotine consumption when administered the DA blocker haloperidol (Caskey, Jarvik, & Wirshing, 1999; Dawe, Gerada, Russell, & Gray, 1995). On the other hand, administration of the D2 DA agonist, bromocriptine, was associated with a decreased smoking rate (Caskey et al., 1999). Further evidence linking nicotine with DA activity comes from pharmacological and neuroimaging studies. Women who smoked had lower prolactin concentrations than nonsmokers (Baron, 1986). Because the usual action of DA is to inhibit prolactin secretion, this finding is consistent with nicotine-induced DA release. Furthermore, there was a 40% decrease in MAO-B levels (involved in the metabolism of DA) in the brains of smokers compared to nonsmokers (Fowler et al., 1996). In a functional Magnetic Resonance Imaging (fMRI) study, injections of nicotine administered to smokers were associated

with increases in neuronal activity in a distributed system of brain regions congruent with DA circuitry, including the nucleus accumbens (Stein et al., 1998). In a later study, Positron Emission Tomography (PET) techniques were used to study DA activity in smoking and nonsmoking human participants in vivo. DA activity was significantly higher in smokers compared to nonsmokers (Salokangas et al., 2000). Finally, PET was used to determine the binding potential (an indirect measure of DA release) in the ventral striatum regions (including nucleus accumbens) of nicotine dependent participants (10 smoked a cigarette and 10 did not). The group that smoked had greater reductions in receptor binding potential (indicative of increased DA release) in the ventral striatum compared to the group that did not smoke. The magnitude of the binding potential was comparable to that found in studies that used similar methods to examine the effects of other addictive drugs (Brody et al., 2004).

Thus, nicotine increases DA levels in the nucleus accumbens of human smokers. This effect of nicotine is mediated through activation of acetylcholine receptors (Paterson & Nordberg, 2000). Nicotine is an agonist at the nicotine acetylcholine receptors (nAChRs) located in the VTA, and nicotine induces DA release partly by binding directly to nAChRs located in the mesolimbic DA system, especially within the VTA (Nisell, Nomikos, & Svensson, 1994). Thus, although direct infusions of nicotine in the VTA produced a long lasting increase in DA release in the nucleus accumbens (Nisell et al., 1994), infusion of a nAChR antagonist (dihydro-β-erythroidine) directly into the VTA produced a significant decrease in nicotine self-administration behaviour (Corrigal, Cohen, & Adamson, 1994). Similarly, administration of the nAChR antagonist mecamylamine blocked nicotine self-administration in the rat, indicating that

activation of nAChRs is involved in the reinforcing actions of nicotine (Watkins, Epping-Jordan, Koob, & Markou, 1999).

In short, nicotine has an indirect excitatory effect upon DA neurons in the VTA; this increased activity in the mesocorticolimbic DA system mediates the reinforcing effects of nicotine (Gamberino & Gold, 1999).

1.4.2.2 Dopamine, Nicotine Withdrawal, and Chronic Nicotine Administration

Results from animal and human studies showed that nicotine withdrawal is associated with a depression of mesolimbic DA. Rats addicted to nicotine showed reduced levels of DA in the striatum and a decreased number of D2 DA receptors in the nucleus accumbens 24 hours after nicotine withdrawal relative to baseline, that is, when they were receiving nicotine (Fung, Schmid, Anderson, & Lau, 1996). This was paralleled by a reduction in locomotor activity. The nicotine receptor-antagonist mecamylamine was used to induce withdrawal in chronic nicotine-treated rats. Following mecamylamine microinjections DA levels in the nucleus accumbens and amygdale decreased (Hildebrand, Nomikos, Hertel, Schilström, & Svensson, 1998; Panagis, Hildebrand, Svensson, & Nomikos, 2000). In abstinent smokers of several hours, the cerebrospinal levels of the DA metabolite homovanillic acid were 50% less than were those found in nonsmokers (Geracioti et al., 1999). It is noteworthy that the smoking-cessation aid buproprion (Zyban) acts, at least in part, by inhibiting neuronal uptake of DA; thereby, enhancing DA transmission (Terry & Katz, 1997).

Reviewing an international symposium on this topic, Altmann et al. (1996) concluded that “withdrawal from various drugs of abuse is associated with a reduction in DA transmission in the ventral striatum (nucleus

accumbens), an effect that is opposite to the common property of drugs of abuse to stimulate DA transmission" (p. 316).

The hypodopaminergic state observed during withdrawal from nicotine and other drugs of abuse is due, in part, to adaptations occurring at the cellular level in DA neurons in the nucleus accumbens (Self & Nestler, 1995). In animals, chronic continuous administration of nicotine can cause an overall decrease in DA release compared to the effect of acute administration (Grenhoff, Jannson, Svensson, & Fuxe, 1991; Lapin, Maker, Sershen, & Lajtha, 1989; Reilly, Lapin, Maker, & Lajtha, 1987). Amphetamine and cocaine have the same effects (Ginovart, Farde, Halldin, & Swahn, 1999; Graziella De Montis, Co, Dworkin, & Smith, 1998). Furthermore, recent human studies provide support for the argument that chronic nicotine administration may cause an overall decrease in DA release and a concomitant disturbance in reward responsivity. In one study, PET was used to measure DA receptor density in 11 smokers and 18 nonsmokers. There was a reduction in DA receptor density in the ventral striatum (especially the nucleus accumbens) of smokers relative to nonsmokers (Dagher et al., 2001). Therefore, the mesolimbic DA system may be chronically underactive in smokers either as an antecedent or because of addiction to cigarettes. Such a hypodopaminergic state may play an important role in sustaining nicotine self-administration behaviour. Similar results were reported in cocaine abusers (Volkow, Fowler, & Wang, 2002). PET was used to investigate the differences between smokers and nonsmokers in the activation of brain regions involved in the processing of reward information. The brains of smokers reacted in a different way to reward compared with the brains of nonsmokers. There were two conditions involving nonmonetary reward or

monetary reward with a baseline condition in which nonsense feedback was presented. Regional cerebral blood flow (rCBF) was measured while participants performed a pre-learned pattern recognition task. Monetary reward, but not nonmonetary reward, activated typical dopaminergic regions, such as the striatum, in nonsmokers but not in smokers. Smokers did not exhibit increased rCBF in the striatum in either the monetary or nonmonetary reward conditions (Martin-Sölch et al., 2001). These results were replicated in a later study (Martin-Soelch, Missimer, Leenders, & Schultz, 2003). The different patterns of activation suggested that brain dopaminergic regions might be underactive in smokers probably because of tobacco smoking (Martin-Sölch et al., 2001). The results of these studies (Dagher et al., 2001; Martin-Soelch et al., 2003; Martin-Sölch et al., 2001) led the authors to conclude that the reinforcing effects of drugs during self-administration create an environment that, if perpetuated, triggers the neuronal adaptations that result in addiction. Therefore, addiction results from the repeated perturbation of brain reward circuitries—marked increases in DA during drug administration followed by marked DA decreases during drug withdrawal. This results in disruption of DA function and a concomitant disruption in ability to respond to rewards. If the development of addiction is accompanied by a disruption in the ability to experience reward, then highly dependent smokers might be less able to experience reward compared with less dependent smokers. However, as yet, there are no studies comparing responsivity to reward in highly dependent and less dependent smokers. One objective of the current thesis was to make this comparison in order to further examine the argument that increasing levels of dependency are

associated with increasing disturbances in DA function and reduction in the ability to experience reward.

DA function is implicated in the experience of reward and in the capacity to experience the positive emotional states associated with rewards. If nicotine withdrawal and dependence disturb DA function and reward responsivity, then they might also disturb positive emotional states. In the remaining part of this chapter, the link between DA, reward, and positive emotional states is examined (see Section 1.4.2.3). The evidence that nicotine withdrawal and dependence disturb reward responsivity and affect (see Section 1.4.2.4 and Section 1.4.2.5) provides a rationale for the research, which makes up the body of this thesis.

1.4.2.3 Dopamine, Reward, and Pleasure

Before discussing the relationship between DA, reward, and pleasure/positive emotional states, some clarification of terminology may be needed. The terms *reinforcement* and *reward* are often used interchangeably. However, "reward is more often used to represent the stimulus, whereas reinforcement is used to refer to the process of strengthening specific responses of the organism" (Stellar & Stellar, 1985, p. 30). Furthermore, the term reward denotes a positive, pleasant effect, whereas reinforcement can be both positive and negative. In distinguishing between reward and reinforcement, Bozarth (1991) stated:

> Reward serves to elicit approach behaviour and processes that the subject "seeks" to activate. Reward functions to direct the animal's behaviour toward whatever stimulus or response is most strongly associated with reward expectancy; reinforcement refers to the process where these

expectancies are developed, frequently through simple contiguity (p. 306). Thus, reward usually governs normal behaviour through pleasurable experiences (Bozarth, 1994). Pleasure is defined as "The condition or sensation induced by the experience or anticipation of what is felt to be good or desirable, a feeling of happy satisfaction or enjoyment, delight, sensual or sexual gratification; opposed to pain" (Soanes & Stevenson, 2005). However, Snaith (1993) pointed out that, "Pleasure, like happiness, is impossible to define because every person will have their own concept of experience" (p. 958). In addition, Feibelman (1964) wrote:

> Pleasure is generally recognised as a quality and qualities are impossible to describe; they are intelligible only to those who have experienced them. All we can hope to achieve is to tag the quality and describe the nature of its associations. (p. 257)

Thus, pleasure is a subjective phenomenon or quality that has been associated with rewarding activities. Pleasure is a competence or function of the reward circuitries. Pleasure and reward systems share common mechanisms and morphological structures; thus, pleasure and reward circuitry are biologically interconnected (Esch & Stefano, 2004). However, other investigators do not regard the subjective state of pleasure as the basis of reinforcement (e.g., Robinson & Berridge, 1993; Tiffany & Carter, 1998).

Many investigators argue that the DA system, which arises from cell groups located in the VTA of the midbrain and has projections throughout the cortex, is a key player in positive emotional states and reward responsivity. Mesolimbic DA projections from the VTA of the brain to reward-related regions, such as the ventral striatum, the amygdale, and the orbitofrontal cortex,

support a system critical to pleasant mood and reward-related behaviour (Spanagel & Weiss, 1999). In humans, the pleasurable or euphoric effects of certain addictive drugs (e.g., heroin, cocaine, and nicotine) are renowned. These drugs produce their rewarding effects by increasing DA levels. Thus, investigators examined the relationship between subjective emotional experience and DA release induced by administration of psychostimulant drugs (Drevets et al., 2001; Stein et al., 1998; Volkow et al., 1999).

PET was used to correlate the change in endogenous DA concentrations following intravenous dextroamphetamine (AMPH) administration (0.3 mg/kg) with the associated affective response in healthy human participants. The magnitude of the DA release produced by administration of AMPH correlated positively with the affective (euphoric) responses to AMPH (Drevets et al., 2001). PET was also used to measure changes in brain DA after different doses of intravenous methylphenidate (MP), a cocaine-like psychostimulant, in 14 healthy participants. Furthermore, the relationship between self-reported drug effects and MP-induced changes in brain DA was assessed. The intensity of the high induced by MP significantly correlated with the levels of released DA. Thus, participants who had the greatest increases were those who perceived the most intense high. Furthermore, participants for whom MP did not increase DA did not perceive a high (Volkow et al., 1999).

In an fMRI study, intravenous nicotine in 16 active cigarette smokers induced a dose-dependent increase in neuronal activity in a distributed system of brain regions congruent with DA circuitry (including the nucleus accumbens, amygdala, and frontal lobes). In addition, nicotine administration induced a dose-dependent increase in self-reported feelings of high, rush, and drug liking

(Stein et al., 1998). Moreover, PET was used to assess the binding potential, and thus release of DA, in the ventral striatum in 10 smokers. Participants were tested twice on separate days. In one condition, participants smoked their usual brand of cigarettes while in the scanner; in the other condition, they remained nicotine abstinent. On each day, participants monitored the hedonic properties of their experience, that is, elation and euphoria. Smoking produced a reduction in receptor binding potential in the ventral striatum (which is proportional to the increase in DA release), and it produced euphoria and elation. Among participants experiencing an increase in elation/euphoria in response to smoking, there was a significant (21.3%) decrease in binding potential. Thus, pleasurable drug experiences were associated with increased DA transmission in the striatum (Barrett et al., 2004).

Similar results were reported with alcohol too. That is, nucleus accumbens dopaminergic function correlated with ratings of intoxication and high (Yoder et al., 2005). These results represent clear demonstrations that drug-induced high, a mood descriptor that reflects reinforcing/rewarding effects of drugs in humans, is associated with increases in brain DA and that there is a quantitative relationship between levels of DA release and the intensity of the high.

The dopaminergic system is associated with the incentive aspect of rewards; that is, it underlies the affective change produced by rewards typically experienced as an increase in pleasure or positive affect (Di Chiara & North, 1992). In addition, enhanced DA release in the nucleus accumbens underlies responsiveness to incentive or “reward responsivity” (Salamone, 1994). In other words, DA release underlies both the capacity to experience pleasure associated

with rewards and the ability to respond to rewards with the requisite behavioural output.

1.4.2.4 Anhedonia

Rewards as well as the positive affect that they induce are mediated by increased release of DA (e.g., Barrett et al., 2004). Disruption of the DA system, on the other hand, is associated with an inability to derive pleasure from situations and stimuli that usually induce pleasure; that is described as a syndrome of anhedonia (Tcheremissine & Krupitsky, 2004).

Anhedonia, the reduced ability to experience pleasure/reward, derives from the Greek words *an,* meaning without and *hedone,* meaning pleasure. Anhedonia is defined as lack of interest and pleasure (Tcheremissine & Krupitsky, 2004) and as the inability to derive pleasure from normally pleasurable stimuli (Koob & Weiss, 1992). The affective component of anhedonia is characterised by symptoms of anxiety, irritability, tension, sadness, nervousness, loss of interest in many aspects of everyday life, lack of motivation, and disturbance of sleep (Tcheremissine & Krupitsky, 2004). Thus, anhedonia involves a general dampening in approach motivation, including increased negative affect, reduced positive affect, and reduced responsivity to rewarding stimuli (Bressan & Crippa, 2005). Anhedonia is a major symptom of the withdrawal syndrome observed in abstinent smokers (Carton, Jouvet, & Widlocher, 1994; Carton, Le Houezec, Lagrue, & Jouvent, 2000; Powell, Dawkins, & Davis, 2002; Powell, Pickering, Dawkins, West, & Powell, 2004; Richardson, Powell, & Curran, 2003). In addition, anhedonia is a cardinal feature of depression (Markou, Kosten, & Koob, 1998).

In the animal model of anhedonia, researchers employed the intracranial self-stimulation (ICSS; Olds & Milner, 1954) procedure to measure brain reward thresholds (see Section 1.4.1). Results showed that decreased function of reward systems or anhedonia is a common element of withdrawal from chronic administration of several classes of abused drugs, including nicotine (e.g., Epping-Jordan et al., 1998). Because anhedonia, or decreased reward responsivity, is also a main feature of depression (Henriques & Davinson, 2000), investigators suggested that nicotine withdrawal precipitates symptomatology similar to depression (Markou et al., 1998; Markou & Kenny, 2002). Depressed smokers may use nicotine in an attempt to self-medicate the underlying lack of positive affect present in depression (Markou et al., 1998). Crucially, withdrawal enhances the incentive value of the drug and suppresses the incentive value of nondrug stimuli (Harrison, Liem, & Markou, 2001). Thus, withdrawal, like clinical depression, produces diminished interest and pleasure in response to a variety of rewarding stimuli probably because withdrawal elevates thresholds for incentive processing (Harrison et al., 2001). Self-administration of the drug will not only ameliorate aversive withdrawal symptoms; it will also restore the incentive value of nonpharmacological incentives (Baker et al., 2004). As Baker et al. (2004) put it, “Drug self-administration fills the world with potential reinforcers” (p. 44).

The anhedonia associated with nicotine withdrawal is related to reduced DA release in the mesocorticolimbic system (Salamone, 1994). Following a period of constant exposure to nicotine, DA neurons in the nucleus accumbens may become dependent upon nicotine to maintain normal levels of activity. Reductions in plasma nicotine concentration after a period of chronic exposure

may result in decreased DA function; thus, decreased sensitivity of reward circuits to stimulation by natural rewards. As Everitt (1992) stated, “DA makes the world a brighter place” (as cited in Robinson & Berridge, 1993, p. 262). Decreased DA function and the concomitant decrease in reward sensitivity during withdrawal might be synonymous to an anhedonic state (i.e., depressed mood and lack of motivation) that smokers might seek to avoid by continuing to smoke. In fact, anhedonia is an important factor involved in the transition from recreational drug use to excessive drug taking (Ahmed & Koob, 1998) and in relapse (Koob & Le Moal, 2005; Volkow, Fowler, Wang, & Goldstein, 2002). In support of these claims, anhedonic smokers (i.e., those with chronically low positive affect) reported a greater increase in craving during nicotine withdrawal than less anhedonic smokers did (Cook, Spring, McChargue, & Hedeker, 2004). Furthermore, anhedonia was associated with decreased abstinence; therefore, it was implicated indirectly in smoking cessation failure (Al’Absi, Hatsukami, Davis, & Wittmers, 2004). On the other hand, high levels of positive affect at baseline predicted greater likelihood of abstinence (Doran et al., 2006).

Anhedonia, as a major symptom of nicotine withdrawal, is also a symptom of nicotine dependence. Chronic smokers are at risk for the development of depressive symptoms (or anhedonia) as a result of the neuroadaptations brought about by chronic nicotine use (Balfour & Ridley, 2000). Koob and Le Moal (1997, 2001, 2005), in a modification on Solomon and Corbit’s (1974, 1977) opponent-process theory, suggested that dependence may involve a change in hedonic set point that includes decreased function of brain reward systems and recruitment of anti-reward systems that drive aversive emotional states (Koob & Le Moal, 2005). Acutely, nicotine produces a reward-

facilitating effect and a mood-elevating effect through its actions on brain DA and other neurotransmitter systems. These effects would be followed by opposing reactions that would tend to slowly return the system to the initial level of hedonic responsivity (Koob, 1996). However, with continued increased drug administration the opponent process would fail to return the system to its homeostatic level before drug taking would begin again, thereby gradually decreasing brain reward function and increasing subjective negative affect (Koob & Le Moal, 2005). As a result, increased nicotine intake would be required to reach the desired level of stimulation. The neuroadaptations proposed to occur with chronic nicotine use would manifest during abstinence as decreased reward function and increased negative affective consequences; thus, contributing to the maintenance of nicotine dependence (Ahmed & Koob, 1998; Koob & Le Moal, 1997, 2001, 2005). Over time, a new level of low reward responsivity and high negative affect would represent an allostatic state (Koob & Le Moal, 1997, 2001); that is, a chronic deviation of the reward system from its normal (homeostatic) operating level. This suggests that drug administration would not return the system to its initial homeostatic level. Therefore, it is possible that smokers would be constantly in some form of withdrawal; in other words, they would be constantly in a state of decreased brain reward function and increased negative mood. These disturbances would become larger with increased nicotine consumption and dependence. In fact, a dose-response relationship was found: Affective distress was associated more with heavy smoking and nicotine dependence and less so with intermittent or nondependent smoking (Breslau, Kilbey, & Andreski, 1994).

In sum, nicotine withdrawal and nicotine dependence disrupt the function of the DA system. This disruption can manifest itself as reduced ability to experience pleasure/reward (anhedonia) and as increased affective distress (i.e., increased negative affect and/or decreased positive affect). However, affect and reward may have rather complex relationships and in some cases appear to behave independently (e.g., Hobbs, Remington, & Glautier, 2005). Therefore, to study nicotine withdrawal (and dependence) in a more comprehensive way, the effects of withdrawal and dependence on reward sensitivity and affect were examined simultaneously (see chapter 8).

1.4.2.5 Tests of the Model

The observations presented in this section suggest the hypothesis that, in otherwise healthy individuals, smoking might be associated with alterations in motivation as indexed by reward responsivity and/or measures of goal-directed behaviour. For instance, acutely, nicotine might enhance reward responsivity; used chronically, there may be neural adaptations that could manifest during withdrawal as impairments of motivation. These impairments, seen during abstinence, could be either temporary deficits resulting from reversible neuroadapations or permanent deficits resulting from irreversible neural changes. Alternatively, disturbances of motivation may predate and be redressed by smoking and thus constitute a risk factor for nicotine dependence.

In a naturalistic study, Al-Adawi and Powell (1997) explored whether nicotine abstinence and consumption by chronic smokers was associated with alterations in reward responsivity. They used the Card Arranging Reward Responsivity Objective Test (CARROT; Powell, Al-Adawi, Morgan, & Greenwood, 1996), a psychomotor test that measures responsiveness to small financial incentive.

They predicted that chronic smokers would show increased reward responsivity immediately after smoking relative to during abstinence. They assessed a sample of smokers during a period of voluntary acute abstinence observed for religious reasons (Ramadan) and then immediately after they had smoked a cigarette at the end of this abstinence period. Smokers showed significantly lower reward responsivity on the CARROT when they were tested after 6 hours of abstinence (Group DAYQUIT) and after at least 10 days of abstinence (RAMQUIT) than when they were tested after smoking. In addition, smokers showed significantly lower reward responsivity than a comparable group of nonsmokers. Baseline psychomotor speed did not differ between conditions or groups.

The authors suggested that, when nicotine-deprived, endogenous DA function in smokers is downregulated. This might render them less able to respond to incentives in the normal way and result in suboptimal performance on tests subserved by central DA activity. The acute effect of smoking may be to stimulate DA activity to higher levels; therefore, improve performance on these tasks. These findings potentially have the important clinical implication that when smokers initially quit, they may experience diminished responsiveness to other environmental sources of pleasure or reward. The consequent psychological state of being poorly motivated to engage in other enjoyable activities could elevate the likelihood of relapse.

Although in the Al-Adawi and Powell study (1997) the DAYQUIT and RAMQUIT participants did not differ in reward responsivity when they were satiated, the RAMQUIT group rated themselves as significantly less dependent. They reported that they gained less stimulation from smoking than did the DAYQUIT group. This may suggest that smokers have low levels of

dopaminergic function even prior to becoming dependent. However, this has yet to be established by an investigation into the differences in reward responsivity between low and high dependence participants.

In a later study, Powell et al. (2002) replicated and extended the findings of Al-Adawi and Powell (1997) of reduced CARROT reward responsivity in abstaining smokers. Twenty-six smokers in satiation and withdrawal and 26 nonsmokers were tested on the CARROT (Powell et al., 1996). Smokers showed lower reward responsivity when abstinent than when they had just smoked. To complement the experimental behavioural measure of reward responsivity (i.e., the CARROT) the authors used a subjective measure, the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995). The SHAPS was used to quantify respondents' expectations of enjoying a range of naturalistic reinforcers (e.g. social events, a favourite meal). Smokers showed low responsiveness to normally pleasurable stimuli when abstinent and high responsiveness to pleasurable stimuli after smoking. Abstaining smokers, but not recent smokers, showed reduced expectancies relative to nonsmokers. However, investigators have not examined yet the relative progression of alterations in these different neural systems with the development of dependence. Such information would be useful in understanding the mechanisms by which nicotine produces dependence.

1.4.3 Implications, Aims, and Hypotheses

The findings of Powell et al. (2002) replicated and extended the earlier findings (Al-Adawi & Powell, 1997) of reduced reward responsiveness (as measured by the CARROT) in abstaining smokers. However, the observed effects of smoking on the CARROT may reflect a more general impact on

arousal and thus on attentional processes. This could indirectly lead to improvement in card-sorting performance over the series of the CARROT trials merely through practice (i.e., in the absence of any changes in reinforcement contingencies). In his early work, Thorndike (1911) distinguished between effect (reinforcement) and exercise (practice), regarding both factors as important but independent. The methodologies of the studies that used the CARROT (e.g., Al-Adawi & Powell, 1997; Powell et al., 2002), described in detail elsewhere (see Section 2.1.3.1), do not allow us to distinguish between practice effects and the effects of nicotine withdrawal on reward.

In the CARROT, participants have to sort cards under one of two conditions: with and without reward. In the reward condition, a small amount of money is earned for every card sorted. This typically increases sorting speed. Al-Adawi and Powell (1997) found that withdrawal decreased reward responsivity. This finding was later replicated (Powell et al., 2002).

In published studies, the CARROT measure of reward responsivity was based on the difference in performance between rewarded and nonrewarded trials when a rewarded trial was placed between two nonrewarded trials in a series of three trials (Al-Adawi & Powell, 1997; Powell et al., 2002). Although these experiments included a practice trial before the three-trial series, it is nevertheless possible that performance was still improving across these trials as a result of continued practice. Moreover, practice may have had different effects under conditions of withdrawal and satiation (e.g., see Chapter 7 and Section 9.1.2). Thus, an apparent effect of withdrawal on performance across the trial series that make up the CARROT could be the result in differences in the amount of improvement between adjacent trials in the three-trial sequence. For

example, suppose that—as a result of practice alone—card-sorting rate reached an asymptote more slowly under withdrawal than under satiation. This could produce an apparent effect of withdrawal on reward responsivity when it was measured using as a difference score as described above.

To remove this potential confound, the research reported in the present thesis used an adaptation of the CARROT that included a counterbalancing procedure. This meant that rewarded and nonrewarded trials occurred equally often in each position of a two-trial sequence (Study 1) and a four-trial sequence (Study 2 and Study 3). This modification allowed us to investigate whether withdrawal might have an indirect effect on CARROT performance independent of reward.

Furthermore, the studies by Powell and colleagues (i.e., Al-Adawi & Powell, 1997; Powell et al., 2002) did not illuminate either the aetiology or the time course of the observed deficits during smoking abstinence. It is possible that, in habitual smokers, nicotine reverses deficits, which are the result of neuroadapations that have taken place over the period of chronic smoking (e.g., Fowler et al., 1996). Alternatively, these deficits may be the result of neuroadapations that antedated the initiation of smoking and potentially acted as vulnerability factors for nicotine use (Volkow, Fowler, Wang, & Goldstein, 2002; Volkow et al., 1999). These issues have yet to be examined.

It is possible that the reward responsivity deficit seen in abstinent smokers during withdrawal preceded the onset of regular smoking; that is, it represents a constitutional dopaminergic deficit. This might have increased the risk for regular smoking in the first place. In this case, nicotine may have possible clinical uses. Nicotinic agents with reduced toxicity and few side

effects could be developed to treat motivational deficits. Such nicotinic agents could prevent people from taking up smoking as a means of self-medication because, in most cases, taking up smoking eventually leads to loss of the voluntary ability to control its use. On the other hand, the reward deficit seen in abstinent smokers may reflect a dopaminergic neuroadaptation "unmasked" during nicotine withdrawal. If so, then it would be crucial to establish the point in time when this neuroadaptation begins developing and ultimately "usurps" normal behaviour and motivational processes. If the onset of dependence occurs when avoidance or relief of withdrawal motivates drug-taking behaviour, then drug use before this point in time might be targeted by dependence-prevention interventions, whereas drug use after this point might require pharmacological treatment.

Therefore, the next step in this line of research would be to extend the findings of Powell and colleagues (e.g., Al-Adawi & Powell, 1997; Powell et al., 2002) by (a) using a modified version of the CARROT where the presentation of the rewarded and nonrewarded trials is counterbalanced in order to control for possible practice effects and (b) by investigating the differences in reward responsivity between high and low dependence participants in an attempt to establish the point when recreational tobacco use becomes compulsive. Based on the findings of Epping-Jordan et al. (1998) and Powell and colleagues it was hypothesised that:

a. There would be a main effect of smoking status on reward responsivity (measured behaviourally). Satiated smokers would have higher reward responsivity scores compared to abstinent smokers.

b. There would be an interaction effect. If highly dependent smokers experienced more severe withdrawal compared to low dependence smokers, then there would be a greater difference in reward responsivity (measured behaviourally) in satiation and withdrawal for the highly dependent participants.

Furthermore, given the complex relationship between reward sensitivity and affect and the fact that both are compromised during nicotine withdrawal (Hughes & Hatsukami, 1986; Powell et al., 2002) and dependence (Koob & Le Moal, 2005), the effects of nicotine withdrawal and dependence on reward responsivity and affect were examined simultaneously (see chapter 8). To my knowledge, this has not been done before. It was hypothesised that:

c. There would be a main effect of smoking status on reward sensitivity (measured subjectively), positive affect, and negative affect. Satiated smokers would have higher reward responsivity scores, higher positive affect scores, and lower negative affect scores compared to abstinent smokers.

d. There would be an interaction effect. If highly dependent smokers experienced more severe withdrawal compared to low dependence smokers, then there would be a greater difference in reward sensitivity (measured subjectively), positive affect, and negative affect in satiation and withdrawal for the highly dependent participants.

CHAPTER 2

GENERAL METHODOLOGY: MEASURES, PARTICIPANTS, PROCEDURE

In this research, I aimed to extend the findings of reduced reward responsivity in abstaining smokers by using a counterbalanced CARROT design and by investigating the differences in reward responsivity between low and high dependence participants. I also aimed to examine the effects of smoking status and dependence on affect.

This chapter presents a discussion of the general methodology used and indicates how this methodology relates to the aims of the research. The description of each measure is followed by a discussion of the measure's psychometric properties and use in the field. The final sections of the chapter include information on participants, the general procedure and designs used, and data cleaning, assumptions checking, and transformation procedures.

2.1 Measures

2.1.1 Smoking Status: Expired Carbon Monoxide (ECO)

2.1.1.1 Description of the Measure

Carbon monoxide (CO) is a derivative of incomplete tobacco combustion. It is absorbed and disseminated throughout the lungs upon inhalation of tobacco smoke and is found in exhaled breath. ECO indicates the amount of CO carried in red blood cells. Therefore, measurement of ECO levels biochemically verifies smoking status, that is, whether smokers have recently smoked or have abstained. Therefore, ECO is an indirect measure of nicotine levels.

Researchers measure ECO levels using a breath CO monitor. The monitor is standardized and calibrated against a control gas as recommended by the manufacturer. Participants are asked to inhale deeply, hold their breath for 15 seconds, and then to exhale slowly into a mouthpiece connected to the smokerlyzer aiming to empty their lungs. Once a sufficient sample is obtained, the smokerlyzer shows a “parts per million” (ppm) ECO reading.

The half-life of CO is about 2 to 5 hours (Powell et al., 2002). Thus, there is a marked difference between the ECO levels of smokers who just smoked compared to smokers who remained abstinent for more than 6 hours. ECO levels are measured at the beginning of each test session. Typically, the difference in ECO levels between satiation and after overnight abstinence is significant (Powell et al., 2002; Powell et al., 2004; Richardson et al., 2003; Smolka, Budde, Karow, & Schmidt, 2004; Zinser et al., 1992).

Investigators consider ECO values equal to or greater than 10 ppm to be an indicator of recent smoking (Attebring, Herlitz, Berndt, Karlsson, & Hjalmarson, 2001) and commonly accept them as cut-off points in the literature (Hogle & Curtin, 2006; Powell et al., 2004; Ruth & Neaton, 1991; Smith et al., 2003). However, some investigators used cut-off points of 15 ppm (Hutchinson, LaChance, Niaura, Bryan, & Smolen, 2002; Richardson et al., 2003). Some others even accepted mean ECO levels during abstinence of 20.7 ppm (Tidey, Rohsenow, Kaplan, & Swift, 2005). If individuals live in an environment that is not smoke free (e.g., spent the night in a room where they had been smoking), then their ECO levels during overnight abstinence may not fall below 10 ppm. Therefore, in this research, a cut-off point of 15 ppm was used (except in Study 1 where a cut-off point of 10ppm was used).

2.1.2 Dependence: The Fagerström Test for Nicotine Dependence (FTND)

2.1.2.1 Description of the Measure and Psychometric Properties

The FTND (Heatherton et al, 1991) is a shorter and improved version of the Fagerström Tolerance Questionnaire (FTQ; Fagerström, 1978), a self-report method of dependency to nicotine. Scores on the FTND range from 0 (*low dependence*) to 10 (*high dependence*). The items and scoring of the FTND are in Appendix B. The FTND consists of six of the original eight FTQ items. "Nicotine yield" and "inhale" items were excluded from the FTND as they lacked validity (Heatherton et al., 1991; Kozlowski, Heatherton, & Ferrence, 1989). Furthermore, the scoring for two of the retained items was revised. Item 1, "time to first cigarette", consisted of two categories in the FTQ (≤ 30 versus > 30 minutes) but four categories in the FTND (≤ 10, 11-20, 21-30, ≥ 31 minutes) because more categories/finer distinctions contributed to the item's sensitivity (Heatherton, Kozlowski, Frecker, Rickert, & Robinson, 1989). Similarly, Item 4, "number of cigarettes per day", had three categories on the FTQ (1-15, 16-25, ≥ 26) but four categories on the FTND (≤ 10, 11-20, 21-30, ≥ 31). These modifications provided higher face and predictive validity for the FTND compared to the FTQ; thus, improving the scale's overall quality (Heatherton et al., 1991; Kozlowski, Potter, Orleans, Pope, & Heatherton, 1994; Payne, Smith, McCracken, McSherry, & Antony, 1994; Pomerleau, Majchrezak, & Pomerleau, 1989; Pomerleau, Pomerleau, Majchrezak, Kloska, & Malakuti, 1990).

Although many investigators have used the FTND as a continuous measure, others have used FTND cut-off points. Fagerström et al. (1996) suggested that a FTND score of 6 or higher might identify smokers with high nicotine dependence. Others have used the FTND scores to assign their

participants to several dependence groups (e.g. very low, low, moderate, high, and very high dependence; Horn, Fernandes, Dino, Massey, & Kalsekar, 2003). However, owing to difficulties in obtaining large samples of highly dependent smokers, FTND cut-off points that investigators have used to designate high dependence versus low dependence are often at the median or average of the sample actually studied (e.g., Al'Absi et al., 2004; Al-Adawi & Powell, 1997). Powell et al. (2002) used the FTND to measure level of dependency in their sample. In the present research, I aimed to replicate and extend the findings of Powell et al. with a modified procedure. Therefore, I used the same dependency measure, to allow for direct comparisons. In addition, following other investigators (e.g. Al'Absi et al., 2004; Al-Adawi & Powell, 1997; Powell et al., 2002), in order to compare different levels of dependence in my sample, I defined smokers with FTND scores of ≤ 3 as low dependence and the remainder as high dependence (see Section 2.2). The FTND cut-off score of 3 was based on the median score of the sample recruited in Study 1. Thus, dependence was considered as a two-level factor in the Analyses of Variance that were used for the main analyses throughout the thesis.

The FTND is significantly associated with several independent self-report and biochemical indicators of nicotine dependence in the expected direction. Thus, the FTND was significantly related to the number of years smoked (Burling & Burling, 2003; Haddock, Lando, Klesges, Talcott, & Renaud, 1999; John et al., 2003; Pomerleau, Carton, Lutzke, Fressland, & Pomerleau, 1994), to age of smoking onset (Burling & Burling, 2003), and to number of smoking-related physical symptoms (i.e., coughing, shortness of breath, chest pain, being easily tired out, headaches, and problems with sense of

smell and taste; Burling & Burling, 2003). It was also related to cigarette brand. That is, smokers of regular brand cigarettes had higher nicotine dependence scores compared to those who preferred light, ultra-light, or had no usual brand (Haddock et al., 1999). Furthermore, the FTND was related to the Smoking Withdrawal Questionnaire (SWQ; Shiffman & Jarvik, 1976) on the craving/addiction subscale (Buckley et al., 2005) and to biochemical markers of nicotine, such as expired breath carbon monoxide (Buckley et al., 2005; Burling & Burling, 2003; Yang, McEvoy, Wilson, Levin, & Rose, 2003) and cotinine levels (Burling & Burling, 2003). The FTND was also associated with achieving short-time smoking cessation (i.e., biochemically verified continuous abstinence for at least 4 weeks postquit; Burling & Burling, 2003). It was found to be predictive of self-reported 48-hours quit attempts (Bobo, Lando, Walker, & McIlvain, 1996), of smoking cessation at 1-year follow-up assessments (Haddock et al., 1999), and of long-term (i.e., 2 years) smoking abstinence (Breslau & Johnson, 2000).

Internal consistency (i.e., the coefficient of test scores or, put more simply, the consistency of results across items within a single test) of the FTND was reported to be reasonable for a six-item measure (a = .56 - .68; Heatherton et al., 1991; Payne et al., 1994; Pomerleau et al., 1994). High FTND test-retest correlations were reported in a number of studies: .85 in a French sample (Etter, Duc, & Permeger, 1999), .88 in an American sample (Pomerleau et al, 1994), .78 in a study of schizophrenic smokers (Yang et al., 2003), and .82 in a study of Post Traumatic Stress Disorder smokers (Buckley et al., 2005). The FTND was used to estimate the accuracy of retrospective reports of dependence (Hudmon, Pomerleau, Brigham, Javitz, & Swan, 2005; Vink, Willemsen, Beem, &

Boomsma, 2005). Test-retest reliability was .66 for male ex-smokers and .71 for female ex-smokers in an average interval of 1.8 years between the two measurements (Vink et al., 2005). In an interval of 5 to 12 years, reliability was .72 (Hudmon et al., 2005). Therefore, retrospectively assessed FTND scores yielded acceptable levels of accuracy and reliability (Hudmon et al., 2005; Vink et al., 2005).

Some researchers reported a one-factor structure of the FTND (Etter et al., 1999; Wellman et al., 2006). However, in the majority of published studies, researchers reported two factors regardless of the population studied, correlation technique used, or rotated solution considered (Buckley et al., 2005; Burling & Burling, 2003; Haddock et al., 1999; Radzius et al., 2003; Uysal et al., 2004). The first factor assesses the degree of urgency to restore nicotine levels to a given threshold after nighttime abstinence. The second factor reflects the persistence with which nicotine levels are maintained at about that threshold during waking hours (Radzius et al., 2003). Therefore, the FTND may assess distinguishable self-reported pharmacological dimensions of nicotine addiction; thus, it may provide indirect assessment of a smoker's daily nicotine intake (Colby et al., 2000; Radzius et al., 2003).

There is a lack of concordance between the FTND and DSM instruments. Thus, these instruments may assess different aspects of the nicotine addiction phenomenon (Breslau, et al., 1994; Breslau & Johnson, 2000; Moolchan et al., 2002). Nicotine addiction consists of pharmacological and nonpharmacological variables (Russell, Peto, & Patel, 1974). It is likely that the FTND assesses nicotine addiction's pharmacological dimensions (Colby et al., 2000; Radzius et al., 2003). Thus, the FTND may provide a stronger measure of

physical dependence, whereas the DSM may tap other domains, for example, awareness of dependence, behaviours resulting from that awareness, and psychiatric symptomatology (Moolchan et al., 2002). Therefore, DSM measures of dependency may be more suitable for use in clinical settings, whereas the FTND may be more suitable for use in smoking research.

2.1.2.2 Studies using the FTND

The FTND is one of the most widely accepted measures of nicotine dependence (Fagerström et al., 1996). It has been used in research (Al'Absi, et al., 2004; Al-Adawi & Powell, 1997; Cinciripini et al., 2006; Hutcinson et al., 2002; Powell et al., 2002) and in clinical settings with depressed smokers (John, Meyer, Rumpf, & Hapke, 2004; Lerman et al., 1996), schizophrenic smokers (Yang et al., 2003), Post Traumatic Stress Disorder smokers (Buckley et al., 2005), and brain-injured smokers (Richardson et al., 2003). Furthermore, the FTND was used in studies of smokers who abuse drugs or alcohol (Bobo et al., 1996; Burling & Burling, 2003; Clarke, Stein, McGarry, & Cogieni, 2001; Perine & Schare, 1999).

2.1.3 Reward Responsivity

In the current research, I measured reward responsivity using a behavioural measure, the Card Arranging Reward Responsivity Objective Test (CARROT; Powell et al., 1996). To complement this, I also used a subjective measure, the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995). The SHAPS measures responsivity to environmetal pleasure/reward.

2.1.3.1 Behavioural Measure: The Card Arranging Reward Responsivity Objective Test (CARROT)

2.1.3.1.1 Description of the measure and psychometric properties.

The CARROT (Powell et al., 1996) is a simple psychomotor test that measures responsiveness to small financial incentive; thus, it measures a motivational parameter. Participants are given a stack of cards each of which has five digits printed on it; one, and only one, is either a "1", "2", or "3" (see Appendix D). They are required to sort the cards as quickly as possible between three correspondingly numbered piles (see Figure 2.1).

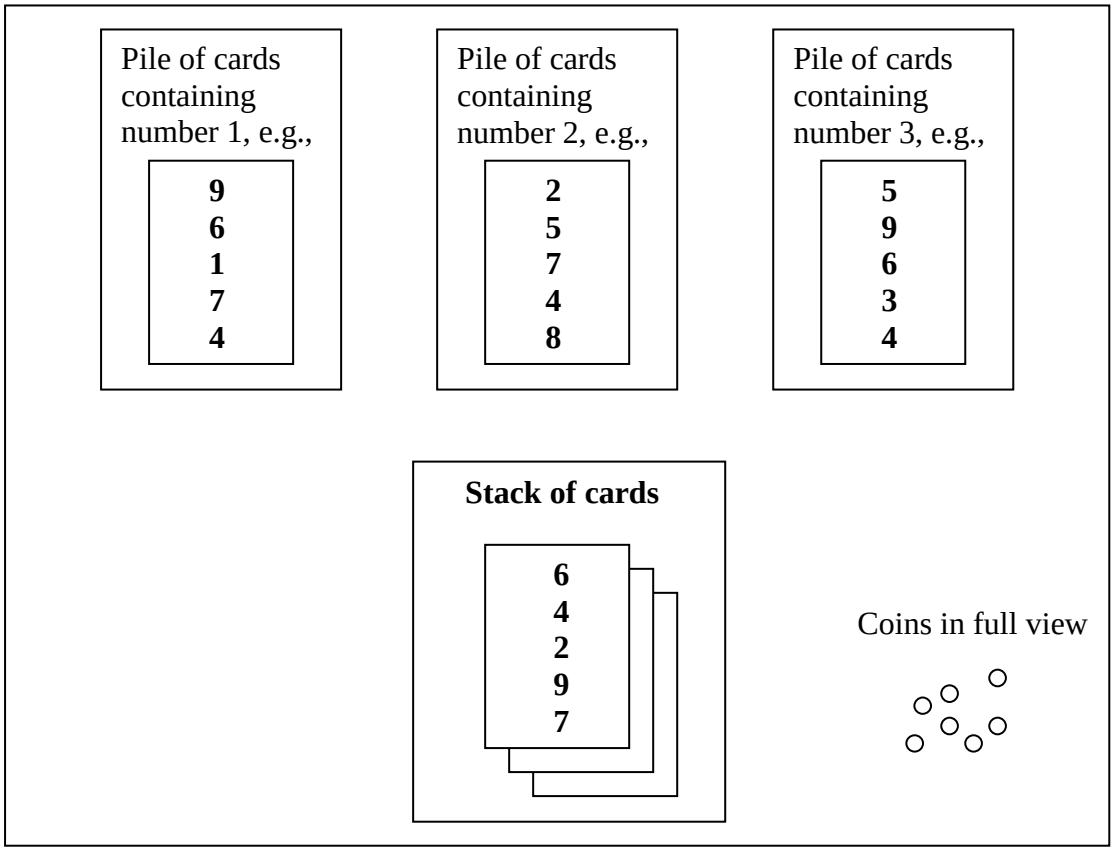

Figure 2.1. Illustration of the CARROT task.

The original or full version of this task involves four trials (Trial 1 [T1] = Baseline, Trial 2 [T2] = Nonrewarded trial, Trial 3 [T3] = Rewarded trial, Trial 4 [T4] = Nonrewarded trial) performed with just a brief rest period between each. After a short practice trial where participants familiarise themselves with the cards, the first trial (Baseline) is used to establish baseline speed for sorting exactly 60 cards. The CARROT was first used with brain-injured patients who are slow to initiate or respond (Powell et al., 1996). Thus, the purpose of the baseline trial (T1) was to "allow subsequent trial times to be adjusted to control for any sensory, motor, or cognitive deficits, which reduce baseline speed" (p. 418). However, it is not clear whether the baseline trial (T1) would be necessary when examining responsiveness to small financial incentive in a sample of healthy participants. Nevertheless, the individually determined time to sort 60 cards in T1 is used as the fixed time limit for the following three trials within each of which the number of cards is inexhaustible and the total number sorted is recorded. Participants are instructed to sort as quickly and as accurately as possible in all trials, but the Rewarded trial (R) differs from the Nonrewared trials (N) in that participants are informed that in R they will be rewarded with 10 pence for every five cards sorted. Coins are placed on the table in full view following every fifth correct card. The average number of cards sorted in R indexes rewarded speed, whereas the number of cards sorted in the N indexes nonrewarded speed. Number of cards sorted in R can be compared either with the average of the two scores for the N trials, that is, R - (N + N) /2, or with just the preceding N trial, that is, R - N, to estimate "reward responsivity" (REWRESP), that is, acceleration in sorting rate under reward.

In order to extend the findings of reduced reward responsivity in withdrawal, as measured by the CARROT (e.g., Al-Adawi & Powell, 1997; Powell et al., 2002), the CARROT was used with a modified procedure (the reasons for this modification are discussed in Section 1.4.3). Thus, instead of presenting three CARROT trials (i.e., NRN), either one rewarded and one nonrewarded or two rewarded and two nonrewarded trials were presented in counterbalanced order; reward responsivity was calculated as R - N.

In pilot work with healthy nonsmokers, there was a highly significant enhancement in sorting rate in the rewarded condition (Pickering et al., 1997). Neurological patients (nonsmokers) with severely impaired motivation in daily life showed a virtual lack of response to financial incentive (Al-Adawi, Powell, & Greenwood, 1998). Furthermore, reward responsivity was enhanced in 18 brain-injured smokers after a cigarette had been smoked compared to when abstinent (Richardson et al., 2003); thus, generalising previous findings from noninjured participants (Al-Adawi & Powell, 1997; Powell et al., 2002). Furthermore, in a study of 11 brain-injured patients with motivational impairments, CARROT performance and participation in therapeutic activities (an ecological measure of motivation) normalised after treatment with the DA agonist bromocriptine (Powell et al., 1996). Finally, heavy drinkers displayed a significant increase in responsivity to reward, as measured by the CARROT, after exposure to alcohol (Kambouropoulos & Staiger, 2001).

2.1.3.1.2 Studies using the CARROT.

Investigators first used the CARROT to assess brain-injured patients' motivation before and after treatment with a DA agonist (Powell et al., 1996).

Since then, researchers have used this behavioural measure to assess impairments in motivation during nicotine abstinence.

The CARROT was used to explore whether nicotine abstinence and consumption by chronic smokers was associated with alterations in reward responsivity in a within-participants design (Al-Adawi & Powell, 1997). Although the CARROT consisted of four trials (T1 = baseline, T2 = nonrewarded, T3 = rewarded, and T4 = nonrewarded), the authors decided to omit T4 when calculating REWRESP. Thus, they calculated REWRESP as T3 - T2. They justified this by referring to unpublished data where REWRESP computed using the mean of both T2 and T4 correlated almost perfectly with the computation using just T2. They predicted that chronic smokers would show increased reward responsivity immediately after smoking compared to during abstinence. Twenty-four Muslim smokers were elected to abstain from smoking either for the whole month of Ramadan (RAMQUIT: n = 11; mean age = 26.7 years, SD = 5.8; mean FTND score = 3.2, SD = 1.8) or during daylight hours (DAYQUIT: n = 13; mean age = 25.2 years, SD = 5.0; mean FTND score = 7.9, SD = 1.8). Nonsmokers participated too (NOSMOKE: n = 12; mean age = 27.3 years, SD = 6.7). All groups were assessed on two occasions 6 hours apart (Test 1 and Test 2). DAYQUIT participants had abstained for 6 hours at Test 1 and smoked a single cigarette prior to Test 2. RAMQUIT participants had abstained for at least 10 days prior to Test 1 and remained abstinent at Test 2. NOSMOKE and RAMQUIT participants ate a small snack prior to Test 2 to control for non-specific consummatory effects. The three groups performed at similar levels in the nonrewarded condition. There was little change by any group across the two test occasions. However, the NOSMOKE group was substantially faster in the

rewarded than the nonrewarded trial on both occasions, whereas the DAYQUIT group showed little effect of reward at Test 1 but a pronounced effect at Test 2. The RAMQUIT group showed little effect of reward on both occasions. Thus, smokers abstinent from nicotine for either a few hours (DAYQUIT) or over 1 week (RAMQUIT) were not impaired in the baseline speed of their motor responses on a simple card-sorting task (CARROT). However, by comparison with nonsmokers, smokers showed significantly less acceleration in response to financial incentive (reward responsivity). Subsequent consumption of a single cigarette by DAYQUIT participants was effective in elevating reward responsivity to the normal range. By contrast, there was negligible change in reward responsivity after the same delay and after consumption of a few biscuits by either the RAMQUIT or NOSMOKE participants (Al-Adawi & Powell, 1997).

In a later study, Powell et al. (2002) replicated and extended the findings of Al-Adawi and Powell (1997) of reduced reward responsivity in abstaining smokers. Twenty-six smokers were tested twice, 1 week apart, once after they had abstained from smoking overnight and up to the time of the test session—at least 10 hours in total—and once just after participants had smoked a cigarette. Half of the participants were randomly assigned to the order abstinence/cigarette (Group AB/CIG: mean age = 26.2 years, *SD* = 7.4; mean FTND score = 3.9, *SD* = 2.6) and half to the order cigarette/abstinence (Group CIG/AB: mean age = 21.8 years, *SD* = 2.3; mean FTND score = 3.5, *SD* = 1.7). Twenty-six never-smokers (mean age = 24.5 years, *SD* = 7.2) were also tested twice to provide normative data against which to compare the absolute levels of performance of the smoking groups on each occasion separately. REWRESP was calculated as

T3 - (T2 + T4) /2, that is, REWRESP = R - (N + N) /2. Smokers showed lower reward responsivity when abstinent than when they had just smoked. Recent smokers did not differ significantly from nonsmokers in reward responsivity. However, abstaining smokers showed significantly lower reward responsivity than nonsmokers. Thus, on a simple card-sorting task (the CARROT), smokers who smoked showed responsivity to financial incentive that was equivalent to that of nonsmokers. By contrast, abstinence was associated with significantly lower responsivity. In the absence of financial incentive, all groups (abstinent smokers, recent smokers, and nonsmokers) sorted at similar rates. This suggested that impaired reward responsivity during abstinence could not reflect a generalised reduction in psychomotor speed or the operation of a ceiling effect. When the authors controlled for subjectively rated withdrawal symptoms, the reward responsivity effect remained significant. Thus, according to Powell et al., the reward responsivity effects were not secondary to the general malaise associated with acute abstinence.

The findings of reduced reward responsivity during nicotine abstinence (Al-Adawi & Powell, 1997; Powell et al., 2002) were replicated in later studies (e.g., Powell et al., 2004; Smolka et al., 2004) where REWRESP was calculated by subtracting the mean of both nonrewarded trials from the number of cards sorted in the rewarded trial.

In the first study (Powell et al., 2004), the CARROT was used to assess 82 smokers (mean age = 31.0 years, *SD* = 11.9; mean daily cigarette consumption = 19.0, *SD* = 6.3) in two separate testing occasions. They assessed smokers abstinent overnight after administering to them nicotine (4mg) or placebo lozenges that looked and tasted similar to the active ones (order

counterbalanced) in a double-blind placebo-controlled between-participants design. Researchers gave participants a lozenge (either active or placebo) to start sucking approximately 25 minutes before the commencement of testing and 1 hour after administration of the first lozenge. They gave participants another identical one to suck in order to achieve more or less stable levels of blood nicotine throughout the testing procedures. Nicotine administration was associated with a near-significant increase in response to financial incentive. Sorting rates in the nonrewarded trials were similar for the nicotine and placebo conditions. Thus, nicotine administration reversed impairments of incentive motivation (as indexed by the CARROT). Furthermore, the study used a placebo-controlled design. Nicotine was administered in lozenge form. Thus, the previously observed effectiveness of cigarettes in reversing these impairments was due to their nicotine content rather than to other ingredients or expectancy effects.

In the second study, the CARROT was used to assess 37 smokers (mean age = 24.9 years, *SD* = 3.2; mean FTND score = 5.7, *SD* = 1.2) whilst smoking (i.e., Test 1) and after abstaining overnight for 12 hours (i.e., Test 2; Smolka et al., 2004). A control group of 18 nonsmokers (mean age = 27.1 years, *SD* = 4.3) was also examined twice. At Test 1, performance in the CARROT was similar in smokers and nonsmokers. However, at Test 2, abstinent smokers showed an impaired response to financial incentive in the CARROT in comparison with nonsmokers and in comparison with their own performance when they were satiated (Test 1). The reduced capacity to improve performance in a simple psychomotor task when reward was present indicated impaired incentive motivation due to withdrawal from nicotine. This was a consequence of the

disturbance in the central DA system induced by nicotine withdrawal. Decreased DA secretion would prevent a normal response to the financial incentive and would cause an impaired outcome in the CARROT (Al-Adawi & Powell, 1997; Powell et al, 2002).

2.1.3.2 Subjective Measure: The Snaith-Hamilton Pleasure Scale (SHAPS)

2.1.3.2.1 Description of the measure and psychometric properties.

The SHAPS (Snaith et al., 1995) is a self-assessment scale designed to assess anhedonia or the absence of hedonic tone (i.e., the degree to which a person is not able to experience pleasure/reward or the anticipation of a pleasurable/rewarding experience). It has been used in healthy (e.g., Powell et al., 2002, 2004) and psychiatric populations (e.g., Isella et al., 2003; Tremblay, Naranjo, Cardenas, Herrmann, & Busto, 2002). The scale consists of 14 items (see Appendix C) covering four domains of hedonic experience: interests/pastimes, social interaction, sensory experience, and food/drink. Participants are instructed to indicate the degree to which each item causes them pleasure on a four-point scale: definitely agree, agree, disagree, strongly disagree. Either of the “disagree” responses scores 1 point, and either of the “agree” responses scores 0 points. Thus, the score range is 0 to 14. A cut-off score of 2 provides the best discrimination between “normal” and “abnormal” level of hedonic tone. A score of 2 or less indicates normal hedonic tone, whereas a score of above 2 indicates abnormal hedonic tone and hence more anhedonic symptoms (Snaith et al., 1995). The scale was constructed in a way that cultural, social class, nationality, gender, and age biases were kept to a minimum (Snaith et al., 1995). The items of the scale relate to experiences likely to be encountered by most people (Snaith et al., 1995).

Snaith et al. (1995) reported that the SHAPS has good face validity (i.e., it looks like it is going to measure what it is supposed to measure). That rests upon the wording of its items. Furthermore, the SHAPS has good content validity (i.e., it represents all facets of hedonic tone, or lack of) because it is based on a coverage of domains of pleasure (i.e., interest/pastimes, social interaction, sensory experience, and food/drink). The convergent validity of the SHAPS (i.e., its relation to what it should theoretically be related to) is supported by its correlations with the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) Hedonic Tone Item (Gilbert, Allan, Brough, Malley, & Miles, 2002) and the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Franken, Rassin, & Muris, in press). Its divergent validity (i.e., its relation to what it should not be theoretically related to) is shown by negative correlations between the SHAPS and the Behavioural Activation Scale (BAS; Carver & White, 1994; Gray, 1987) Reward Responsiveness subscale (Franken et al, in press), the Positive and Negative Affect Schedule Scales (PANAS Scales; Watson, Clark, & Tellegen, 1988) Positive Affect Subscale (Gilbert et al., 2002; Franken et al., in press), and the Satisfaction With Life Scale (SWLS; Diener, Emmons, Larsen, & Griffin, 1985). Furthermore, there was a lack of association between the SHAPS and the MADRS Anxiety Items (Snaith et al., 1995). Because anhedonia is defined as the absence of pleasurable feelings and not the mere presence of aversive emotions, such as anxiety, the lack of association between the SHAPS and the MADRS Anxiety Items contributes to the validity of the SHAPS as a pure measure of anhedonia (Franken et al., in press). The internal consistency of the SHAPS (i.e., consistency of results across items in a single test) was .91 in a

nonpatient sample (Franken et al., in press), .95 in a major depression group (Franken et al., in press), and .91 in a substance-dependent group (Janiri et al., 2005). Thus, the SHAPS has good internal consistency in both healthy and psychiatric samples. Lastly, the SHAPS has good test-retest reliability. Fifty participants (undergraduate psychology students) completed the SHAPS with an interval of 3 weeks. The mean SHAPS scores on the first (22.4, *SD* = 4.8) and second (22.4, *SD* = 4.8) occasions were not different (Snaith et al., 1995).

Overall, the SHAPS is a reliable and valid measure of hedonic tone and its absence, anhedonia. It was employed successfully to study the neurophysiological correlates of anhedonia in a healthy population (Franken, Van Strien, & Nijs, 2006), which confirms further its validity as an instrument for measuring anhedonia.

2.1.3.2.2 Studies using the SHAPS.

Anhedonia or reduced reward responsivity is a major symptom of the withdrawal syndrome observed in abstinent smokers (Carton et al, 1994, 2000; Powell et al, 2002; 2004; Richardson et al., 2003). Thus, the SHAPS was used to quantify smokers' expectations of enjoying a range of pleasurable stimuli (Powell et al., 2002, 2004). Smokers completed the SHAPS during abstinence and in satiation. Nonsmokers also completed the SHAPS. Smokers showed low responsiveness to pleasurable stimuli when abstinent and high responsiveness to pleasurable stimuli after smoking. Thus, abstaining smokers rated themselves as expecting significantly lower hedonia (pleasure) than did those who had just smoked. Abstaining smokers, but not recent smokers, showed reduced expectancies relative to nonsmokers. Therefore, abstaining smokers showed reduced ability to enjoy a range of normally pleasurable events, as indexed by

the SHAPS, which correlated with abstaining smokers' reward responsivity, as indexed by the CARROT (Powell et al., 2002). In a later study, participants completed the SHAPS after receiving nicotine or placebo lozenges. Anhedonia was significantly greater in the placebo condition than in the nicotine condition, as indexed by the SHAPS and the CARROT (Powell et al., 2004). Thus, abstinent smokers showed impairments in their experience of environmental pleasure that were reversed by nicotine.

The period since detoxification inversely correlated with anhedonia, as measured by the SHAPS, in a study of detoxified opiate, alcohol, and multiple substance-dependent participants (Janiri et al., 2005). Finally, the SHAPS was used extensively to assess the anhedonia associated with depression (Tremblay et al., 2002; Tremblay et al., 2005), schizophrenia (Nathans-Barel, Feldman, Berger, Modai, & Silver, 2005; Silver & Shlomo, 2002; Stevens et al., 2002), and Parkinson's disease (Lemke, 2002; Lemke, Brecht, Koester, Kraus, & Reichmann, 2005; Lemke, Brecht, Koester, & Reichmann, 2006; Pluck & Brown, 2002).

2.1.4 Mood: The Positive and Negative Affect Schedule (PANAS) Scales

Because emotional experience is an internal, subjective event, researchers have widely used self-report to measure what a person is feeling. Theorists described emotional experience or mood or affective structure in several different ways (see Figure 2.2). Although they used different words in the construction of their affective models, what is common between the different descriptive structures/models of affect (Figure 2.2) is that they include two dimensions: pleasure and activation. Pleasure – displeasure or valence is a dimension of experience that refers to hedonic tone. Activation is a dimension

that refers to a sense of mobilization or energy. The two dimensions have proven influential in shaping the field's thinking about emotion and how it is best conceptualised and measured (e.g., Feldman Barrett & Russell, 1999; Watson & Tellegen, 1985). Pleasantness and activation have appeared in studies of self-report feelings, in the semantics of affect-related words across many cultures, and in ratings of facial expression of emotion (for reviews, see Russell, 1980, 1991). Furthermore, pleasantness and activation are dimensions of consciousness that have neurophysiological correlates (Heilman, 1997).

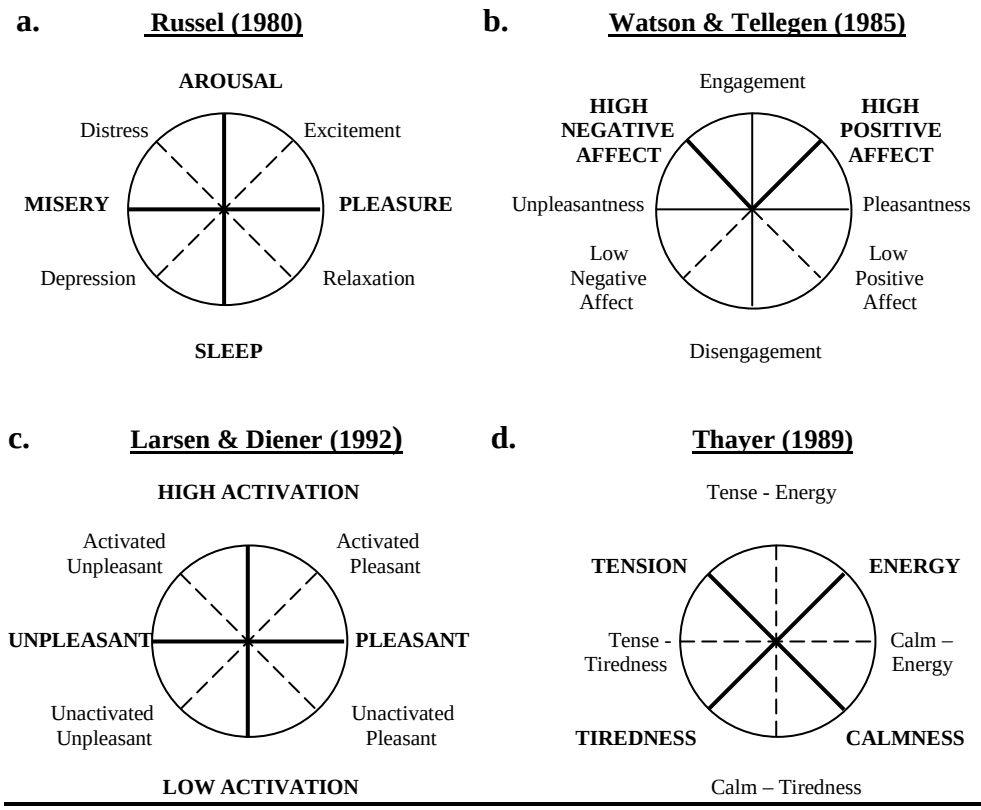

Figure 2.2. Four descriptive models of affect within a two-dimensional space. Reprinted from Feldman Barrett and Russell (1999). The structure of current affect: controversies and emerging consensus, *Current Directions in Psychological Science, 8,* p.11. The focal dimensions are shown in capital letters.

In a series of studies, Feldman Barrett and colleagues (Feldman Barrett & Russell, 1998; Yik, Russell, & Feldman Barrett, 1999) integrated the four different structures of affect (Figure 2.2). When random and nonrandom measurement errors (e.g., acquiescence, extreme response style) were taken into account and when the adjective checklists used consisted of semantic opposites, the two principal dimensions of affect (pleasantness – activation) were bipolar and almost fully independent of one another (Green, Goldman, & Salovey, 1993; Green & Salovey, 1999; Yik et al., 1999). Feldman Barrett and colleagues also demonstrated that other affective descriptors (e.g., thrilled, calm, distressed, depressed) can be defined as combinations of valence and activation (see Figure 2.3). In other words, both pleasant and unpleasant affect words vary in the level of activation versus deactivation they denote. In addition, words denoting activation and deactivation vary in valence. Furthermore, the entire space can be thought of as degrees of pleasantness or unpleasantness and as degrees of activation or deactivation. However, although there are between 500 and 2,000 terms in English that have to do with emotion, their position within the affective space (Figure 2.3) has not been clearly established (Russell & Feldman Barrett, 1999). Nevertheless, each word in the affective space has a bipolar opposite 180^{o} away that is opposite on both components. Pairs of orthogonal (independent) dimensions also exist: For any dimension placed at an angle, another dimension exists, which is 90^{o} and therefore independent (see Figure 2.2.b). As Figure 2.2.b shows, the dimensions that Watson and Tellegen (1985) picked in the affective space to define Positive Affect (PA) and Negative Affect (NA) are about 90^{o} apart in the structure of affect; therefore, they are

independent, uncorrelated dimensions (e.g., Egloff, 1998; Tellegen, Watson, & Clark, 1999; Watson & Tellegen, 1985).

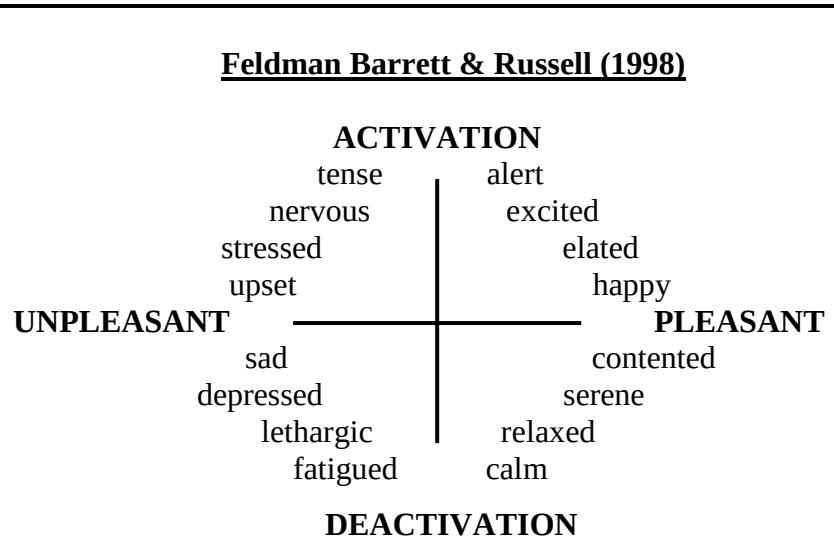

Figure 2.3. A schematic for the two-dimensional semantic structure of affect. Reprinted from Feldman Barrett and Russell (1999). The structure of current affect: controversies and emerging consensus, *Current Directions in Psychological Science, 8*, p.11.

As such, PA, according to Watson and Tellegen (1985), is not the set of all positive affect states (the right half of Figure 2.3) but a specific subset that includes states that are both pleasant and activated. NA is not the set of all negative affect states (the left half of Figure 2.3) but a specific subset that includes states that are both unpleasant and activated. Therefore, PA is not the bipolar opposite of NA or of negative affect in general. NA is not the bipolar opposite of PA or of positive affect in general. PA and NA do have bipolar opposites: Opposite PA is a cluster of unpleasant, low activation items (e.g., tired, bored), and opposite NA is a cluster of pleasant low activation items (e.g., relaxed, serene). Thus, Watson and colleagues used the phrases Positive Affect and Negative Affect in a highly specific way (Watson & Tellegen, 1985).

2.1.4.1 Description of the Measure and Psychometric Properties

Based on the affect model by Watson and Tellegen (1985), Watson, Clark, and Tellegen (1988) developed the Positive and Negative Affect Schedule (PANAS) Scales (see Appendix G), a self-report measure of affect, that is, the tendency to experience positive and negative affects. According to Watson et al., PA is a dimension that reflects one's level of pleasurable engagement with the environment and represents the extend to which a person feels a zest for life. PA is most clearly defined by such expressions of energy and pleasurable engagement as active, delighted, interested, enthusiastic, and proud, with low PA characterised by sadness and lethargy. NA is a general factor of subjective distress and subsumes a broad range of negative mood states, including upset, anger, guilt, fear, disgust, and worry, with low NA being a state of calmness and serenity (Watson & Tellegen, 1985; Watson, Clark, & Tellegen, 1988).

The PANAS Scales consist of two 10-item mood scales: one measuring positive affect (PA) and the other measuring negative affect (NA). PA is assessed with the following adjectives: interested, excited, strong, enthusiastic, proud, alert, inspired, determined, attentive, and active. NA is assessed with the adjectives: distressed, upset, guilty, scared, hostile, irritable, ashamed, nervous, jittery, and afraid. Participants are asked to indicate the extend to which they experience these particular mood states during a specified time frame. Seven different time frames can be used depending on the nature of the investigation: at the present moment (e.g., to what extend you feel this way *in the present moment*), today, past few days, past week, past few weeks, past year, and in general, that is, on average. For the purposes of this thesis, participants were

asked to indicate to what extend they feel this way right now, that is, at the present moment. Answers range from 1 (*very slightly or not at all*) to 5 (*extremely*). Thus, the scores for each PANAS subscale (i.e., PA subscale and NA subscale) range from 10 to 50 and are sums of scores from the items included in each subscale. The PANAS items are randomly distributed throughout the questionnaire

The PANAS Scales have good internal consistency with alpha coefficients in a student sample ranging from .86 to .90 for PA and .84 to .87 for NA across the seven time instructions (Watson, Clark, & Tellegen, 1988). In an adult sample, alpha reliabilities were .86 for PA and .87 for NA (Watson, Clark, & Tellegen 1988). In a more recent study in a representative sample of UK adults (N = 1,003), researchers reported coefficients of .89 for PA and .85 for NA (Crawford & Henry, 2004). In a psychiatric inpatient sample, coefficients were .85 for PA and .91 for NA with the general instructions (Watson, Clark, & Tellegen, 1988). Similar coefficient values were obtained in clinical and nonclinical populations (Jolly, Dyck, Kramer, & Wherry, 1994; Roesch, 1998). The measure shows good discriminate validity (Chen, Dai, Spector, & Jex, 1997; Mehrabian, 1998; Watson, Clark, & Tellegen, 1988). The correlation between the PA and NA scales is low ranging from -.09 to -.23. Thus, the two scales share approximately 1% to 5% of their variance (Watson, Clark, & Tellegen, 1988). To compare the factorial validity of the PANAS Scales with those of other investigators, Watson, Clark, and Tellegen correlated the PANAS with other PA/NA measures, for example, the PA/NA scales developed by Diener and Emmons (1984), Hedges, Jandorf, and Stone (1985), and McAdams and Constantian (1983). Coefficients ranged from .76 to .92 suggesting good

convergent validity. The PANAS Scales correlated with measures of distress and psychopathology, such as the Hopkins Symptom Checklist (HSCL; Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974), which measures general distress and dysfunction, and the Beck Depression Inventory (BDI; Beck et al., 1961), a self-report measure of depressive symptomatology. For the HSCL, correlations with NA ranged from .65 to .74, and correlations with PA ranged from -.19 to -.29 across different time frames. For the BDI, correlations with NA ranged from .56 to .58, and correlations with PA ranged from -.35 to -.36 across different time frames. These findings confirmed the external validity of the PANAS Scales. Thus, the PANAS could be used to complement more traditional measures of depression with the advantage of providing measures for two affective components (Watson, Clark, & Tellegen, 1988). Test-retest reliability of the PANAS Scales is acceptable. Two-month retests of the PANAS Scales in samples of 502 and 399 undergraduates produced coefficients of .70 and .64, respectively, for NA and .71 and .59, respectively, for PA (Watson & Clark, 1994). Among elderly rehabilitation patients, coefficients for PA and NA were .79 and .93, respectively, in a 3-month retest period (Ostir, Smith, Smith, & Ottenbacher, 2005). Watson and Walker (1996) initially assessed participants as undergraduates and re-tested those participants 6 to7 years later. Initial scores on the PANAS Scales correlated significantly with the PANAS scores obtained several years later. Thus, the PANAS Scales were substantially stable even across extended time spans (Watson & Walker, 1996).

Furthermore, researchers identified positive affect and negative affect, as measured by the PANAS, across different sets of descriptors and response formats and in both within- and between-participants analyses (Watson &

Tellegen, 1985; Watson, 1988; Watson & Clark, 1997). The structure emerged even in data sets compromised by methodological problems, such as acquiescence bias and response formats (Watson & Tellegen, 1985; Watson, 1988). In later studies, researchers replicated the structure (Baker, Cesa, Gatz, & Mellins, 1992; Crawford & Henry, 2004). However, research on the measurement and factorial validity of the PANAS across cultures is lacking (Crawford & Henry, 2004).

Positive and negative affect (measured by a number of different scales) have distinctive correlational patterns with other variables. Thus, only positive affect is related to diverse measures of social activity (Watson, Clark, & Tellegen, 1988), exercise, and reports of pleasant events (Watson, Clark, & Carey, 1988). Negative affect alone is correlated with health complaints, especially those of physical health (e.g., indigestion, sore throat, joint pain; Watson & Pennebaker, 1989), perceived stress (Watson, Clark, & Carey, 1988), poor coping (Kanner, Coyne, Schaefer, & Lazarus, 1981), and unpleasant events (Clark & Watson, 1991). High levels of negative affect—but not positive affect—are associated with anxiety, whereas low levels of positive affect are more important in depression (Clark & Watson, 1991; Watson, Clark, & Carey, 1988; Watson & Tellegen, 1985). Positive affect is linked to the body's circadian cycle (Clark, Watson, & Leeka, 1989) and to seasonal variations, whereas negative affect shows no circadian pattern (Clark & Watson, 1991). The experience of positive affective states has been linked to the activation of the Behavioural Activation System (BAS; Gray, 1987; Fowles, 1993), which regulates response to rewarding stimuli, whereas negative affective states have been linked to the activation of the Behavioural Inhibition System (BIS; Gray,

1987), which regulates response to signals of punishment. Finally, positive and negative affect have different biological bases (Davidson, 1992). Thus, resting levels of left prefrontal activation reflect the subjective experience of positive affect, whereas resting levels of right frontal activation reflect the subjective experience of negative affect (Tomarken & Keener, 1998). The bipolarity seen in the affective space is not observed at the neurophysiological level (Cacioppo, Gardner, & Bernston, 1997). However, even if the neural processes of affect are independent of one another, bipolarity is likely to emerge in forming conscious affective feelings (Feldman Barrett & Russell, 1998; Yik et al., 1999).

2.1.4.2 Studies using the PANAS Scales

The PANAS Scales were used to investigate the effects of buproprion (a monocyclic antidepressant) on affect during smoking abstinence (Dale et al., 2002). Sixty-eight adult (age ≥ 18 years) smokeless tobacco (ST) users who were motivated to stop using ST were enrolled in a randomised, double-blind, placebo-controlled pilot study of buproprion sustained release or placebo for 12 weeks. At baseline, half of the participants were assigned to receive buproprion (150 mg) by mouth in a specific dosing schedule. The other half were assigned to receive an identical-appearing placebo tablet on the same dosing schedule. Participants set a quit date 1 week after starting the medication. They returned for assessments weekly during the first 8 weeks, biweekly for the last 4 weeks of the medication phase, and at weeks 15 and 24 during the post-medication phase. The mean baseline PA scores (M = 30.9, SD = 7.2, for buproprion; M = 30.5, SD = 7.1, for placebo) and NA scores (M = 15.0, SD = 4.8, for buproprion; M = 15.3, SD = 6.1, for placebo) were similar between treatment groups. At the end of the first week following the target quit date, both groups had, compared to

baseline, a decrease in PA score (*M* = -2.1, *SD* = 5.8, *p* = .06, for buproprion; *M* = -3.0, *SD* = 5.7, *p* = .01, for placebo) and an increase in NA score (*M* = 2.8, *SD* = 6.2, *p* = .02, for buproprion; *M* = 3.6, *SD* = 7.9, *p* = .02, for placebo). PA and NA scores were not significantly different from baseline for either treatment group at any other period. At no time there was any evidence suggesting that the change from baseline in PA or NA differed significantly between treatment groups. The authors did not provide an explanation for the observed effects on PA and NA after the first week of abstinence. It may be that after the first week of abstinence PA and NA scores started returning to baseline. Nevertheless, 1 week's abstinence produced significant decreases in PA and increases in NA despite the use of buproprion (Dale et al., 2002).

In a later study, the PANAS was used to examined fluoxetine's (SSRI inhibitor) effects on changes in PA and NA following quitting smoking (Cook, Spring, McChargue, Borrelli, et al., 2004). Researchers randomised adult smokers (*N* = 175; mean age = 42.6, *SD* = 12.9; mean FTQ score = 6.8, *SD* = 1.8) without clinically significant depression on a double-blind basis to receive fluoxetine hydrochloride (30 or 60 mg daily) or placebo for 10 weeks. Participants quit smoking 14 days after the beginning of the medication phase so that a therapeutic drug level could be achieved prior to quitting. The researchers postulated that fluoxetine would beneficially influence post-cessation changes in PA and NA. Relative to placebo, those (*n* = 58) on 60 mg fluoxetine experienced an increase in PA that grew across time resulting in assessments of PA that exceeded prequit levels. There were no significant differences between 30 mg (*n* = 75) and placebo (*n* = 60). Relative to placebo, those on 60 mg fluoxetine experienced a decrease in NA. However, across time, this advantage

appeared to diminish. There were no significant differences between 30 mg fluoxetine and placebo. Those in the placebo condition experienced decreases in PA levels and increases in NA levels compared to prequit, which persisted for more than 3 weeks. The fact that fluoxetine exerted a more sustained influence on PA than on NA suggests that these two parameters of affective responses are partially independent (Cook, Spring, McChargue, Borrelli, et al., 2004).

Finally, the PANAS was used to examine the relationship between cigarette consumption and affect (Becona, Vasquez, Fuentes, & Lorenzo, 1999). Of the 1,615 participants selected randomly from the population, 63.7% were nonsmokers (i.e., not smoking within the previous 30 days) and 36.3% were smokers. The groups were divided by cigarette consumption as 0 (nonsmoking) and 1-15, 16-30, and 31 or more cigarettes/day. Analysis of variance of cigarette consumption indicated that there were no significant differences in PA. However, there were significant differences in NA between groups 1 to15 versus 31 or more cigarettes/day. The group smoking 31 or more cigarettes/day reported significantly higher NA compared to the group smoking 1 to 15 cigarettes/day. The results indicated a relationship between cigarette consumption and NA in smokers with a consumption of 31 or more cigarettes daily (Becona et al., 1999).

In addition, because the PANAS has good psychometric properties, it was used extensively in different lines of smoking research (e.g., Cinciripini et al., 2006; Kenford et al., 2002; McChargue, Cohen, & Cook, 2004; Niaura, Shadel, Goldstein, Hutchinson, & Abrams, 2001; Patterson et al., 2003; Smith et al., 2003; Wetter et al., 1994).

2.2 Participants

I used posted adverts (see Appendix A) and on-line adverts displayed in the Department of Psychology electronic experimental booking system to recruit participants from the University of Southampton campus for research into "the experience of reward in nicotine dependence". Participants included both students and staff members. Prior to Study 1, I asked participants to fill in the FTND (Heatherton et al., 1991) to screen them in terms of their level of dependency. I classified participants as high or low dependence according to a median split on their FTND score. If their FTND score was greater than the median (3 >), then I classified them as high dependence. If their FTND score was equal or smaller than the median (≤ 3), then I classified them as low dependence. I used this classification in all subsequent studies in this research.

Prior to each experimental session (studies 1, 2, 4, and 5), I randomly assigned participants to two conditions: withdrawal and satiation. In the withdrawal condition, I asked participants to abstain from smoking overnight or for at least 8 hours during the day before testing. In the satiation condition, I asked them to smoke as usual before coming to the laboratory. In addition, in the satiation condition I asked participants to smoke a cigarette immediately before coming to the laboratory in order to ensure that the difference between the withdrawal and satiation conditions was maximised.

As mentioned at the end of chapter 1, in this research, I aimed to replicate and extend the finding of Powell et al. (2002) of reduced reward responsivity in withdrawal using a modified CARROT procedure. Therefore, I conducted power analysis to determine the number of participants needed to identify the large effect size reported by Powell et al. The effect size for the

comparison of withdrawn and satiated participants on reward responsivity in Powell et al. was .58. According to Cohen (1992), at an alpha level of .05, I need 393 participants in each group to detect a small effect size (d = .20), 64 participants to detect a medium effect size (d = .50), and 26 to detect a large effect size (d = .80).

2.3 Procedure

Sessions were carried out on weekdays between 9.00 and 17.00 hours in one of the Psychology Department laboratories.

When participants initially arrived at the laboratory, I gave them an information sheet and consent form to sign (see Appendix E), if they agreed to participate. I made them aware, both verbally and on the consent form, of their right to terminate the test at any stage.

I verified participants' smoking status by analysing their expired carbon monoxide (ECO) levels with a CO monitor (Bedford EC50 Micro III Smokerlyzer, Bedford Scientific Instruments Ltd, Kent, UK). Satiation was verified by ECO levels > 15 ppm, whereas overnight abstinence was verified by ECO levels ≤ 15 ppm. When participants' ECO levels were above 15 ppm in the abstinence condition, I asked them to come back for testing on another day. I rescheduled 3 participants. ECO levels of one of those participants were well above 15 ppm the second time he came for testing. Therefore, this participant was not allowed to complete the study.

After verifying participants' smoking status, I asked them to complete the CARROT (Powell et al., 1996). The procedure of the CARROT varied across studies. The CARROT procedure used in each study is described in detail in the "Measures and Apparatus" section of each study. After participants

completed the CARROT, I asked them to fill in the SHAPS (Snaith et al., 1995) and lastly, I asked them to fill in the PANAS (Watson, Clark, & Tellegen, 1988).

The procedure lasted on average 30 minutes across studies.

After collecting the data, I made available to each participant a debriefing statement (see Appendix F). I gave all participants the amount of money they gained in the CARROT, which was on average £5.00 per participant across studies. Furthermore, participants earned £3.50 for their participation. Psychology students earned credits (2 per 30 minutes) that counted towards their coursework grade.

2.4 Design

I measured reward responsivity behaviourally using the CARROT task in Study 1, Study 2, Study 3, and Study 4. In Study 1, Study 2, and Study 3, I carried out the conditions of the reward responsivity test within-participants. In Study 4, I manipulated the conditions both within- and between-participants. In Study 5, I measured reward responsivity using a questionnaire measure of responsivity to environmental pleasure/reward (the SHAPS) under different between-participant conditions.

In Study 1, Study 2, Study 4, and Study 5, I manipulated smoking status (withdrawal/satiation) between-participants, whereas in Study 3 smoking status was manipulated within-participants.

The dependent variable in Study 1, Study 2, and Study 3 was sorting rate (i.e., number of cards sorted divided by the time it took to sort them) under reward and no reward. In Study 4, the dependent variable was reward responsivity (REWRESP) calculated as mean sorting rate under reward minus

mean sorting rate under no reward. In Study 5, the dependent variable was mean SHAPS score as well as mean positive and mean negative affect scores (as measured by the PANAS).

2.5 Data Cleaning, Assumptions Checking, and Transformations

I used histograms, boxplots, and descriptive statistics to screen the data. I detected incorrectly entered values and corrected them. I checked the data for outliers. I identified (and removed) one case with extreme scores (i.e., absolute *z*-scores > 3.3; e.g., Field, 2005) on the PANAS measure. The rest of the data (i.e., absolute z-scores for every case) fell within the limits for a normal distribution (e.g., Field, 2005).

Further checks were conducted to establish whether the data met the parametric assumptions (i.e., normal distribution, homogeneity of variance, interval data, and independence; Field, 2005). The negative affect (PANAS-NA) and the SHAPS variables were not normally distributed. Therefore, they were transformed (square root transformation) before being entered into the analysis (chapter 8).

CHAPTER 3

STUDY 1:

REWRAD RESPONSIVITY (BEHAVIOURAL MEASURE) IN SATIATION AND WITHDRAWAL AMONG LOW AND HIGH DEPENDENCE SMOKERS

I aimed to extend previous findings of reduced CARROT reward responsivity during withdrawal (e.g., Al-Adawi & Powell, 1997; Powell et al., 2002) by including a counterbalancing CARROT procedure and dependence as a factor. Powell and colleagues calculated reward responsivity as the difference in performance between a rewarded trial and two nonrewarded trials when the former was placed second in a series of three trials (Al-Adawi & Powell, 1997; Powell et al., 2002). Because nicotine has been shown to improve task performance (e.g., Sherwood, 1993), it is possible that performance across the trial series that make up the CARROT (i.e., practice effects) was improving more under satiation than under withdrawal. This might show up as an apparent effect of withdrawal on reward responsivity when reward responsivity was calculated as a difference score. Therefore, I counterbalanced the presentation of the rewarded and nonrewarded trials in a two-trial sequence to control for effects of practice. It was necessary to validate this new procedure before examining the effects of withdrawal and dependence on reward responsivity.

3.1 Method

3.1.1 Participants

Thirty-two people participated (11 males and 21 females). Their mean age was 26.7 years (minimum = 18 years, maximum = 45 years; *SD* = 6.39). There were 19 low dependence smokers with a mean dependence score of 1.47

(minimum = 0, maximum = 3; *SD* = 1.17) and 13 high dependence smokers with a mean dependence score of 5.38 (minimum = 4, maximum = 8; *SD* = 1.50).

3.1.2 Measures and Apparatus

The Expired Carbon Monoxide (ECO) Monitor

I biochemically verified the participants' smoking status by analysing carbon monoxide (CO) levels in an end-expiratory air after asking participants to hold their breath for 15 seconds. CO levels were analysed using a breath CO monitor (Bedford EC50 Micro III Smokerlyzer, Bedford Scientific Instruments Ltd, Kent, UK).

The Fagerström Test for Nicotine Dependence (FTND)

The measure was used as described in chapter 2 (see Section 2.1.2).

The Card Arranging Reward Responsivity Objective Test (CARROT)

The measure was used as described in chapter 2 (see Section 2.1.3.1); however, in the present study one rewarded (R) and one nonrewarded (N) trial was presented in counterbalanced order. Reward responsivity was calculated as R - N.

The Snaith-Hamilton Pleasure Scale (SHAPS)

The measure was used as described in chapter 2 (see Section 2.1.3.2).

The Positive and Negative Affect Schedule (PANAS) Scales

The measure was used as described in chapter 2 (see Section 2.1.4).

3.1.3 Procedure

The following procedures were carried out with some exceptions (see Section 1.2.5).

I randomly assigned participants to two conditions: withdrawal, where I asked them to abstain from smoking overnight before testing, and satiation,

where I asked them to smoke as usual before coming to the laboratory. Following that, I randomly assigned participants from each smoking status (satiation/withdrawal) group into two conditions: in the first condition, participants completed the rewarded trial (R) of the CARROT first, whereas in the second condition they completed the nonrewarded trial (N) of the CARROT first. Then, I classified participants as high or low dependence on the basis of a median split on their FTND scores.

I verified participants' smoking status by analysing their expired carbon monoxide (ECO) levels. Satiation was verified by ECO levels > 10 ppm (parts per million), whereas overnight abstinence was verified by ECO levels ≤ 10 ppm.

After biochemically verifying participants' smoking status, I asked them to complete the CARROT. After completing the CARROT, I asked participants to fill in the SHAPS and the PANAS.

The procedure lasted approximately 20 minutes.

After collecting the data, I gave all participants the amount of money they gained in the CARROT, estimated to be a maximum of £1.50 per participant. In addition, most participants earned £3.50 in return for their participation. Psychology students, however, earned one course credit in return for participation.

3.1.4 Design and Analysis

I used 2 × 2 × 2 (Reward × Smoking Status × Dependence) factorial mixed design. The between-participants factors were dependence with two levels (high dependence or low dependence) and smoking status with two levels (satiation or withdrawal/abstinence). The within-participants factor was reward

with two levels (nonrewarded trial [N] and rewarded trial [R]). The key dependent variable was sorting rate (i.e., number of cards sorted in R or N divided by the time taken to sort them).

3.1.5 Some Exceptions to the Aforementioned Procedures

I tested most participants in one of the Psychology Department laboratories; however, I tested 3 participants in the morning hours at their home. Although I allocated 2 of those participants to the withdrawal condition, they expressed doubts about managing to abstain from smoking until they came to the laboratory. In order to ensure that they did remain abstinent for the testing, I visited them at their home were I carried out the procedure in exactly the same way as in the laboratory.

Of the total 32 participants, I tested 10 in slightly different conditions to the remaining 22. The different conditions are described below.

Initially, I decided to screen participants in order to check their level of dependence and only test those smokers whose scores were less than 3 (*low dependence*) or more than 7 (*high dependence*) in the FTND. Thus, first, I allocated participants to a high or low dependence group. Then, I randomly counterbalanced them to the satiation and withdrawal conditions. I tested the first 10 people under these conditions. However, it soon became evident that it was hard to find smokers with an FTND score above 7. Therefore, I decided to test every smoker without screening him/her. Thus, I randomly assigned the remaining 22 participants to the satiation and withdrawal conditions first, subject to constraint of equal numbers. Then, I allocated participants retrospectively to a high or low dependence group according to a median split. This resulted in a final sample with 19 participants in low dependence (10 in

withdrawal and 9 in satiation) and 13 participants in high dependence (5 in withdrawal and 8 in satiation).

Initially, I also decided that participants would receive only the money they earned in the CARROT (estimated to be a maximum of £1.50 per participant) and no extra money for their participation. However, due to the very low rates of participation, I decided to pay participants £3.50 for their participation in addition to the money they earned in the CARROT. The first 10 participants received only the money they earned in the CARROT, whereas the remaining 22 received an extra £3.50 for their participation.

Furthermore, for 2 participants the assignment to the satiation and withdrawal conditions was not random. Although I asked those 2 participants to abstain from smoking before coming for testing, they failed to do so. They refused to try to abstain. As I did not want to miss their data, I tested those smokers under satiation.

3.2 Results

The withdrawal manipulation was successful. An independent samples *t* test showed that the ECO level of participants in satiation (*M* = 22.66; minimum = 12, maximum = 54; *SD* = 7.58; *n* = 17) was significantly higher than the ECO level of participants in withdrawal (*M* = 5.70; minimum = 2, maximum = 10; *SD* = 2.47; *n* = 15), *t* (18.69) = 5.22, $p \leq .001$ (Because Levene's Test for Equality of Variances was significant, equal variances were not assumed).

I used 2 × 2 × 2 (Reward × Smoking Status × Dependence) repeated measures Analysis of Variance (ANOVA). The between-participants factors were dependence (low dependence/high dependence) and smoking status (withdrawal/satiation). The within-participants factor was reward (nonrewarded trial/rewarded trial). The dependent variable was sorting rate.

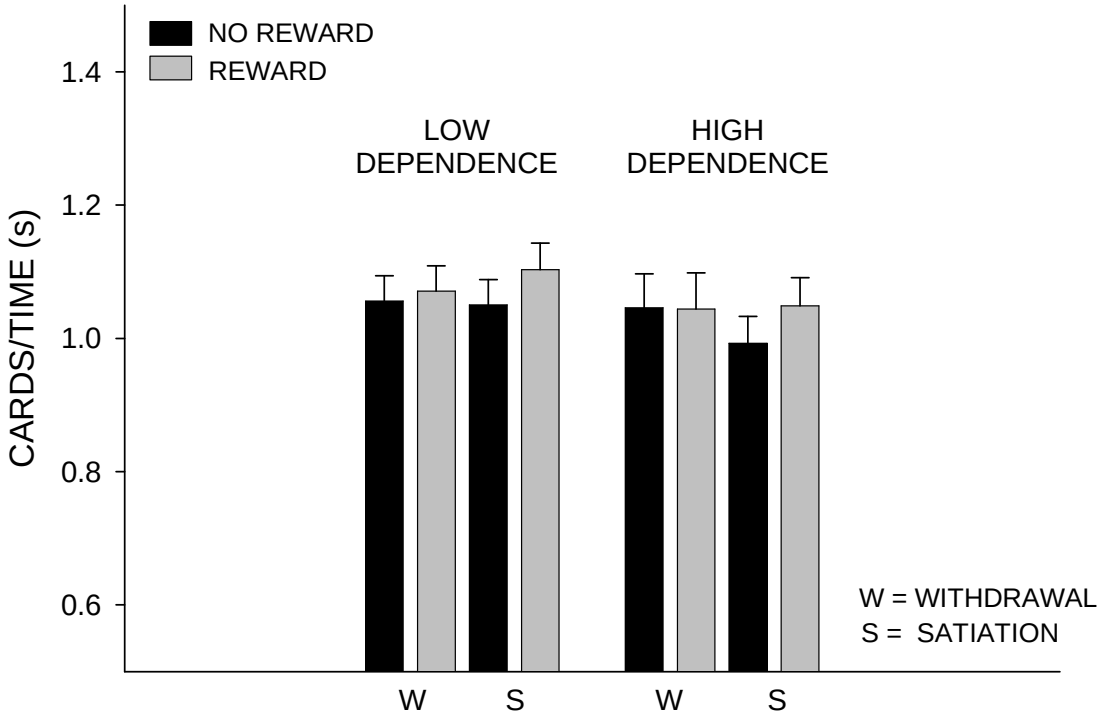

Figure 3.1. Mean CARROT sorting rate (+*SE*) in reward and no reward for low dependence (W: *n* = 10; S: *n* = 9) and high dependence (W: *n* = 5; S: *n* = 8) participants.

Figure 3.1 shows the mean CARROT sorting rate in each of the experimental conditions for low and high dependence participants. As Figure 3.1 shows, both high and low dependence participants increased their CARROT sorting rate in the rewarded trial but only in the satiation condition. In the withdrawal condition, low dependence participants slightly increased their CARROT sorting rate in the rewarded trial, whereas high dependence participants slightly decreased their CARROT sorting rate in the rewarded trial.

The statistical analysis (Table 3.1) confirmed these impressions. The results of the three-way ANOVA (Table 3.1) showed that, with an alpha level of .05, there was a significant main effect of reward and a marginally significant

Reward × Smoking Status interaction. There were no other significant main effects or interactions.

Table 3.1

Analysis of Variance for CARROT Sorting Rate

Source	*df*	*F*	*p*
	Between subjects		
Smoking Status (S)	1	< 1	.89
Dependence (D)	1	< 1	.36
S × D	1	< 1	.65
Error	28	(.03)	
	Within subjects		
Reward (R)	1	5.17	.03
R × S	1	3.21	.08
R × D	1	< 1	.80
R × S × D	1	< 1	.71
Error (R)	28	(.00)	

Note. Values enclosed in parentheses represent mean square errors.

Figure 3.2. Mean CARROT sorting rate (+*SE*) in reward and no reward in withdrawal (*n* = 15) and satiation (*n* = 17).

Figure 3.2 shows the mean CARROT sorting rates in each of the experimental conditions for all participants and illustrates the marginally significant Reward × Smoking Status interaction. There was an effect of reward under satiation but not under withdrawal (see Figure 3.2). Thus, participants increased their sorting rate in the rewarded trial when they were satiated but not when they were withdrawn. Comparisons of the sorting rates under satiation and under withdrawal showed that there was a significant difference between the sorting rates of the nonrewarded and rewarded trials under satiation, $t(16) = 3.39$, $p < .01$, but this effect did not approach significance under withdrawal, $t(14) = .47$, *ns*.

3.3 Discussion

In the present study, I adopted a counterbalanced CARROT design to investigate the hypothesis that abstinent smokers show decreased reward responsivity compared to satiated smokers (e.g., Al-Adawi & Powell, 1997; Powell et al., 2002). I also investigated the differences in reward responsivity between high and low dependence participants.

There was a significant main effect of reward, which confirmed the validity of the counterbalanced CARROT procedure.

Moreover, there was a marginally significant Reward × Smoking Status interaction: Both high and low dependence participants significantly increased their mean CARROT sorting rates in the rewarded trial under satiation but not under withdrawal. The difference between the sorting rates of the rewarded and nonrewarded trials was significant under satiation; however, the effect did not approach significance under withdrawal. This is consistent with findings by Al-Adawi and Powell (1997) and Powell et al. (2002) who found that abstinent smokers showed significantly less acceleration in response to financial incentive compared with satiated smokers and nonsmokers. Subsequent consumption of a cigarette was effective in elevating reward responsivity to the normal range. It is also consistent with findings by Epping-Jordan et al. (1998) who showed that spontaneous nicotine withdrawal in rats resulted in a significant decrease in brain reward function, as measured by elevations in brain reward thresholds, which persisted for days.

Empirical evidence indicates that the mesocorticolimbic DA system mediates, at least in part, the reinforcing properties of psychoactive drugs,

including nicotine. Most psychoactive drugs increase dopaminergic transmission within this system, especially in the nucleus accumbens (Koob & LeMoal, 1997). Thus, the findings suggest that abstaining smokers may have impaired dopaminergic function or, in other words, abstaining smokers show weakened incentive motivation that may reflect low levels of activity in mesocorticolimbic pathways. Therefore, smoking might be associated with alterations in motivation as indexed by reward responsivity. Support for this comes from findings that showed that brain reward pathways are less activated in nicotine addicts compared to healthy controls (e.g., Martin-Soelch et al., 2001).

It was expected that, because highly dependent smokers experience more severe withdrawal compared to low dependence smokers, the difference in reward responsivity in satiation and withdrawal would be greater for highly dependent smokers. However, I found no evidence to support this view. The results indicated that the effects of withdrawal on reward responsivity were the same for the high and low dependence participants. This suggests that withdrawal effects are present even in low dependence smokers. Alternatively, the high dependence sample was not dependent enough.

In sum, I used a counterbalanced CARROT procedure and found a Reward × Smoking Status interaction. Thus, participants increased their mean CARROT sorting rate when they were satiated but not when they were withdrawn. However, the effect was marginally significant. This result provides weak support to previous findings (Al-Adawi & Powell, 1997; Powell et al., 2002). To overcome potential limitations of the present study, the aim of the next study was to use a bigger sample and a better, counterbalanced again, CARROT procedure. I needed 26 participants per group to achieve a power of

.80 at the .05 level of significance (Cohen, 1992). Because I only had 32 participants in total, I increased the number of participants to 80, 40 in each smoking status group. Moreover, I improved the CARROT procedure. Thus, instead of giving participants 20 cards to sort as practice, I increased the number of cards to 60. In addition, I added more rewarded and nonrewarded trials to the CARROT. I made these modifications to the procedure of the CARROT to reduce measurement error.

CHAPTER 4

STUDY 2

REWARD RESPONSIVITY (BEHAVIOURAL MEASURE) IN SATIATION AND WITHDRAWAL AMONG LOW AND HIGH DEPENDENCE SMOKERS REVISITED

4.1.1 Method

4.1.1.1 Participants

Eighty participants (40 males and 40 females) with a mean age of 24.06 years (minimum = 18 years, maximum = 45 years; *SD* = 5.32) took part. There were 40 low dependence smokers with a mean FTND score of 1.2 (minimum = 0, maximum = 3; *SD* = 1.16) and 40 high dependence smokers with a mean FTND score of 5.25 (minimum = 4, maximum = 8; *SD* = 1.48).

4.1.1.2 Measures and Apparatus

Differences from Study 1 are noted.

The Card Arranging Reward Responsivity Objective Test (CARROT)

The CARROT consisted of five trials instead of three (Study 1), and the practice trial involved sorting 60 cards instead of 20 (Study 1). I made these alterations in order to reduce measurement error. I used the first trial (baseline) to establish baseline speed for sorting exactly 60 cards. Then, I used this individually determined time as the fixed time limit for the following four trials that consisted of two rewarded and two nonrewarded trials in counterbalanced order. Thus, there were four orders to the task. The presentation of the rewarded (R) and nonrewarded (N) trials was as follows for each order: Order 1: RNNR, Order 2: NRRN, Order 3: RNRN, and Order 4: NRNR.

4.1.1.3 Procedure

I randomly assigned participants from each dependence group (low/high) to the two smoking status conditions: withdrawal and satiation. Following that, I randomly counterbalanced withdrawn and satiated participants into the four CARROT-order conditions described in Section 4.1.1.2.

I verified overnight abstinence by ECO levels ≤ 15 ppm. Next, I asked participants to complete the CARROT. After that, I asked them to fill in the SHAPS and the PANAS.

The procedure lasted approximately 20 minutes.

After collection of the data, I made available a debriefing statement to each participant. I gave all participants the amount of money they gained in the CARROT, estimated to be a maximum of £3.00 per participant. In addition, participants earned £2.50 in return for their participation. Psychology students earned one course credit in return for participation.

4.1.1.4 Design and Analysis

I used 2 × 2 × 2 (Reward × Smoking Status × Dependence) factorial mixed design. The between-participants factors were dependence (low/high) and smoking status (satiation/withdrawal). The within-participants factor was reward (nonrewarded trials/rewarded trials). The key dependent variable was sorting rate. The presentation order of the nonrewarded and rewarded trials was counterbalanced across participants.

4.1.2 Results

The withdrawal manipulation was successful. An independent samples *t* test showed that the ECO level of participants in satiation (M = 16.22; minimum = 1, maximum = 51; SD = 10.75; n = 40) was significantly higher than the ECO level of participants in withdrawal (M = 6.07; minimum = 1, maximum = 15; SD = 4.59; n = 40), $t(52.91) = 5.51$, $p < 0.001$ (Because Levene's Test for Equality of Variances was significant, equal variances were not assumed).

I employed 2 × 2 × 2 (Reward × Smoking Status × Dependence) repeated measures Analysis of Variance (ANOVA). The between-participants factors were dependence (low/high) and smoking status (withdrawal/satiation). The within-participants factor was reward (nonrewarded trials/rewarded trials). The dependent variable was sorting rate.

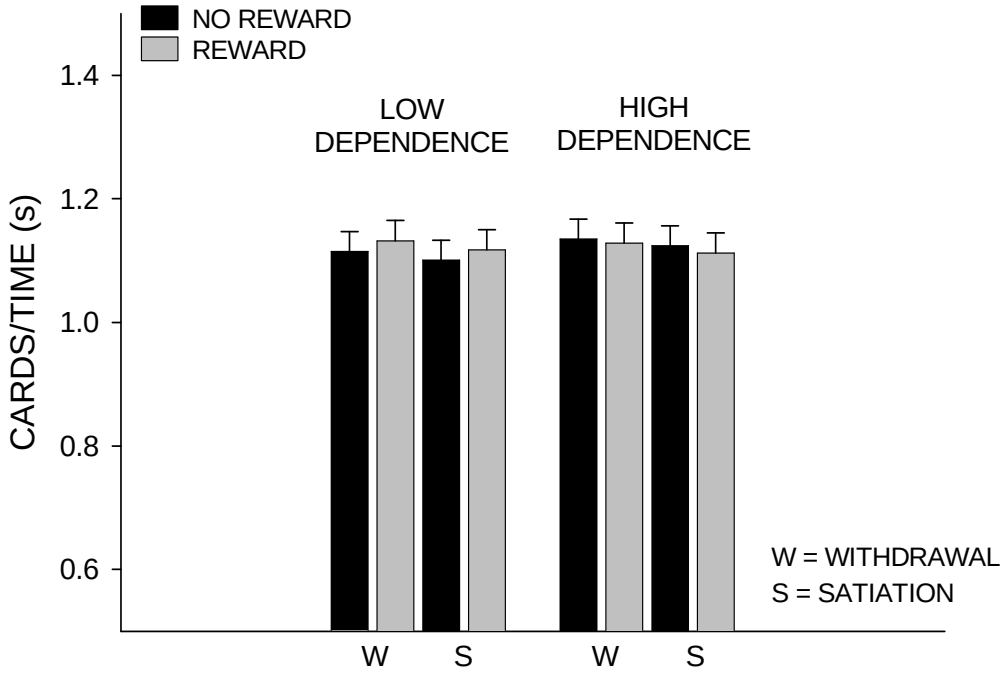

Figure 4.1. Mean CARROT sorting rate (+*SE*) in reward and no reward for low dependence (W: *n* = 20; S: *n* = 20) and high dependence (W: *n* = 20; S: *n* = 20) participants.

Figure 4.1 shows the mean CARROT sorting rates in each of the experimental conditions for low and high dependence participants. Low dependence participants increased their sorting rate in the rewarded condition, whereas high dependence participants increased their sorting rate in the nonrewarded condition (see Figure 4.1).

The statistical analysis (Table 4.2) confirmed these impressions. The results of the three-way ANOVA (Table 4.2) showed that, with an alpha level of .05, there was a significant Reward × Dependence interaction but no other main effects or interactions.

Table 4.1

Analysis of Variance for CARROT Sorting Rate

Source	*df*	*F*	*p*
	Between subjects		
Smoking Status (S)	1	< 1	.66
Dependence (D)	1	< 1	.78
S × D	1	< 1	.99
Error	76	(.04)	
	Within subjects		
Reward (R)	1	<1	.58
R × S	1	<1	.83
R × D	1	3.99	.05
R × S × D	1	< 1	.88
Error (R)	76	(.00)	

Note. Values enclosed in parentheses represent mean square errors.

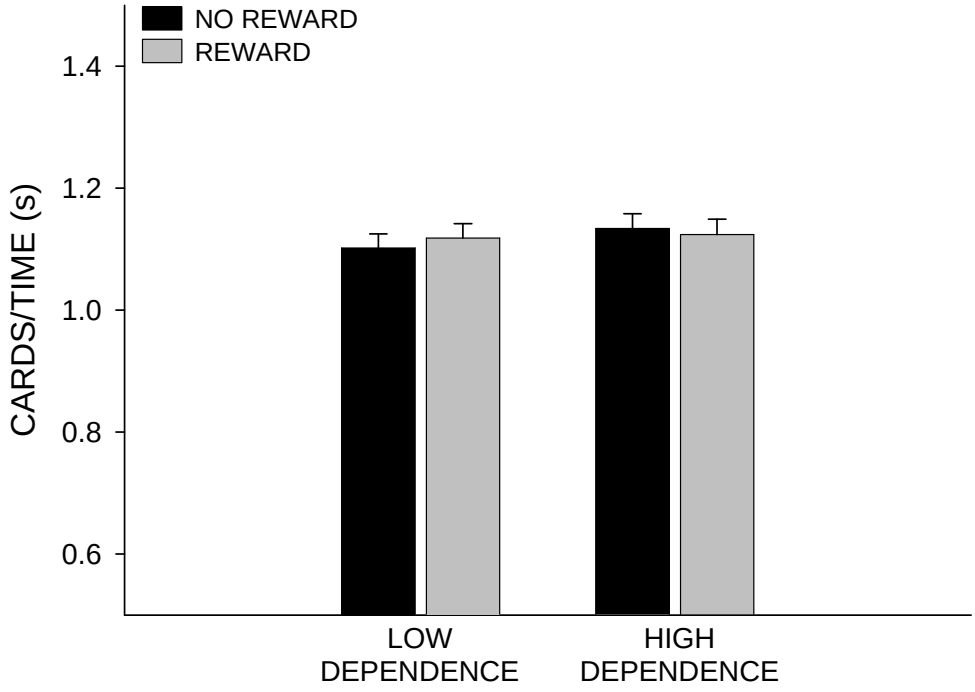

Figure 4.2. Mean CARROT sorting rate (+*SE*) in reward and no reward for low dependence (*n* = 40) and high dependence (*n* = 40) participants.

Figure 4.2 shows the mean CARROT sorting rates in the rewarded and nonrewarded trials for low and high dependence participants and illustrates the significant Reward × Dependence interaction. Low dependence participants increased their rate of sorting in the rewarded trial, whereas high dependence participants increased their sorting rate in the nonrewarded trial (see Figure 4.2). Comparisons between the sorting rates in the rewarded and nonrewarded trials for low and high dependence participants showed that there was a significant difference between the rewarded and nonrewarded trials for the low dependence participants, $t(39) = 2.00$, $p = .05$; however, this effect did not approach significance for the high dependence participants, $t(39) = .96$, *ns*.

4.1.3 Discussion

There was a just significant Reward × Dependence interaction: Low dependence smokers increased their sorting rate in the rewarded condition compared with high dependence smokers. The difference between the rewarded and nonrewarded trials was significant for low dependence participants. Highly dependent smokers slightly increased their sorting rate in the nonrewarded trials; however, the difference in sorting rate between the rewarded and nonrewarded trials was not significant. This may suggest that highly dependent smokers are not sensitive enough to the introduction of the reward. Compared with low dependence smokers, highly dependent smokers may not be motivated to "work harder" (i.e., sort the cards faster) in order to gain more money. This impairment in reward responsivity may reflect alterations in motivation associated with chronic nicotine administration. Although alterations in motivation, as indexed by reward responsivity, would be expected to manifest during withdrawal, this was not the case. Highly dependent participants failed to respond to monetary reward either they were withdrawn or satiated.

In this study, I did not replicate the main effect of reward that was found in Study 1. Furthermore, there was no evidence to support the first hypothesis; reward responsivity scores were not higher in satiation compared to withdrawal. This is not consisted with earlier findings (Study 1). Because the sample size was adequate to detect medium to large effects at alpha = .05 with power > .80 (e.g., Cohen, 1992) and the withdrawal manipulation was successful, failure to replicate the effect of reward found in Study 1 might be due to limitations in the way the behavioural measure (CARROT) was administered. For example, according to CARROT instructions, participants were required to sort the cards

as quickly and as accurately as possible into three piles. The sorting was based on whether the numeral 1, 2, or 3 appeared on the card. It soon became evident that there was great variability in the way the cards were sorted. Some participants would throw the cards onto each pile, minimising the movement of their card-sorting hand; others would carefully place the cards on top of each pile, maximising precision at the expense of speed. This inter-participant variability was unsystematic and contributed to random error. In addition, although I asked participants to sort the cards as quickly and as accurately as possible, most of the participants compromised accuracy for speed. That is, they were more concerned with sorting the cards fast rather than sorting them accurately. This, in turn, might have produced ceiling effects in sorting rate that could have masked any effect of reward.

Thus, the aim of the next two studies (Pilot 1 and Pilot 2) was to address these "key" problems in the look for an effect of reward. In the two pilot studies, I examined whether a number of changes to the procedure of the task would increase the task's reliability. Thus, in Pilot 1, I reduced the variability in the way the cards were sorted by introducing cardboard boxes into which they had to be placed with reasonable accuracy. Moreover, I introduced a monetary penalty for mistakes in order to increase the time taken to sort the cards. These changes appeared to produce a slight improvement in the measure's reliability. In Pilot 2, I made a further change to the procedure of the CARROT: I increased the time taken to complete each rewarded and nonrewarded trial in an attempt to increase the effort participants put in the rewarded trials. This produced the desired improvement in the measure's reliability. The two pilot studies will be presented next.

4.2 Pilot 1: Improving the Reliability of the Behavioural Measure

4.2.1 Method

4.2.1.1 Participants

Twenty-four people (6 males and 18 females) took part. Their mean age was 25.7 years (minimum = 19 years, maximum = 31 years; *SD* = 3.07).

4.2.1.2 Measures and Apparatus

The Card Arranging Reward Responsivity Objective Test (CARROT)

The measure was used as described in Study 2; however, in the present study, participants had to sort 30 cards as practice. To reduce the variability in the way cards were sorted, I asked participants to place the cards in cardboard boxes that they could not move. The boxes were approximately 2.5 cm wider and longer than the cards and approximately 5 cm high. The position of the boxes was identical for all participants. I instructed participants to place the cards in the boxes carefully, making sure that they did not miss the boxes. Thus, the task became more difficult because it required more precise movements. Moreover, I asked that the cards be sorted both as quickly and as accurately as possible; I stressed that accuracy should not be compromised for speed. I informed them that for every mistake they made (including cards missing the box) they would lose 10 pence from the money gained in the rewarded trials. I introduced this monetary penalty to reduce error by increasing participants' attention at correct card sorting. Additionally, the procedure reduced the possibility of ceiling effects.

4.2.1.3 Procedure

The procedure was as described in Study 2; however, in the present study, dependence and smoking status were not examined. The procedure lasted

approximately 10 minutes. After collection of the data, I gave participants the amount of money they gained in the CARROT, estimated to be a maximum of £3.00 per participant. Psychology students earned one course credit in return for their participation.

4.2.1.4 Design and Analysis

Reward was manipulated within-participants. A paired samples *t* test was employed. The variables were mean CARROT sorting rate in the rewarded trials and mean CARROT sorting rate in the nonrewarded trials.

4.2.2 Results

A paired samples *t* test was used to compare mean CARROT sorting rate in the rewarded trials (M = .82, SD = .10) and nonrewarded trials (M = .81, SD = .10). The results of the *t* test showed that, with an alpha level of .05, the difference in mean CARROT sorting rate between the rewarded and nonrewarded trials was only marginally significant, $t(23) = 1.92$, $p = .07$.

4.2.3 Discussion

There was a main effect of reward; however, it was marginally significant. Thus, although changes in the procedure of the CARROT did improve the measure's reliability, this improvement was moderate. Since a reliable reward effect was essential to further this investigation, further changes to the procedure of the task were made. The task, as administered in Study 1 and Study 2, was relatively short and easy. Participants were sorting the cards as fast as they could in every trial irrespective of the existence of reward. In fact, a lot of them mentioned that in each successive trial they were trying to "break their own record", that is, sort more cards than they did in the previous trial. If I extended the time required to complete the task by increasing the time taken to complete each rewarded and nonrewarded trial, then participants might decide to sort faster in the rewarded trials only. Thus, if the time taken to complete each trial was increased, then participants might decide to put more effort in sorting the cards when their effort would be rewarded, rather than try to sort as many cards as they could in every successive trial.

Thus, the aim of the next pilot study (Pilot 2) was to examine whether attempting to affect the amount of effort put in the rewarded trials, by increasing the time taken to complete each rewarded and nonrewarded trial, would increase the measure's reliability.

4.2 Pilot 2: Improving the Reliability of the Behavioural Measure

4.3.1 Method

4.3.1.1 Participants

Twenty-eight people (5 males and 23 females) with a mean age of 21.4 years (minimum = 18 years, maximum = 34 years; *SD* = 3.81) took part.

4.3.1.2 Measures and Apparatus

The Card Arranging Reward Responsivity Objective Test (CARROT)

The measure was used as described in Pilot 1; however, in the present study, there was no baseline trial; each rewarded and nonrewarded trial lasted 5 minutes. This time was the same for all participants. Sorting rate was calculated as the number of cards sorted divided by the 5 minutes it took to sort them.

4.3.1.3 Procedure

The procedure was as described in Pilot 1; however, in the present study, it lasted 40 minutes. After collection of the data, I gave participants the amount of money they gained in the CARROT, estimated to be a maximum of £6.00 per participant. Psychology students earned one course credit in return for their participation.

4.3.1.4 Design and Analysis

The design and analysis were as described in Pilot 1.

4.3.2 Results

A paired samples *t* test was used to compare mean CARROT sorting rate in the rewarded trials (M = .78, SD = .08) and nonrewarded trials (M = .76, SD = .07). The results of the *t* test showed that, with an alpha level of .05, the difference in mean CARROT sorting rate between the rewarded and nonrewarded trials was significant, $t(27) = 2.20$, p = .04.

4.3.3 Discussion

There was a significant main effect of reward in Pilot 2: Sorting rate was significantly higher in the rewarded trials compared to the nonrewarded trials. Thus, the reliability of the behavioural measure (CARROT) increased after a number of changes were made to its procedure.

The changes were made in order (a) to reduce the variability in the way participants sort the cards, (b) to increase the time taken to sort cards and overcome possible ceiling effects, and (c) to influence the amount of effort that participants put in completing the rewarded and nonrewarded trials.

I wanted to reduce the variability in the way the cards were sorted; therefore, participants were asked to place the cards in cardboard boxes. As this made the task more difficult, sorting times might be reduced. In order to reduce sorting times further and overcome possible ceiling effects, participants were required to pay more attention at correct card sorting: They were informed that for every mistake they made (including cards missing the box) they would lose 10 pence from the money they earned in the rewarded trials. Lastly, in order to influence the amount of effort that participants put in completing the rewarded and nonrewarded trials, I increased the difficulty of the task by increasing the time taken to complete each rewarded and nonrewarded trial. The time taken to complete each trial was increased to 5 minutes (300 seconds) as opposed to 68.5 seconds that was the average time it took participants to sort the cards in each trial in the previous studies. After increasing the time to complete each trial to 5 minutes, instead of sorting the cards as fast as they could irrespective of the existence of reward, participants appeared to put more effort in sorting the cards when their effort was rewarded. In sum, the aforementioned changes to the

procedure were successful at improving the measure's reliability; therefore, ensuring that the CARROT could be used to detect any differences in the effect of withdrawal on reward responsivity between different levels of dependence.

Thus, the aim of the next study was to use this new improved CARROT procedure to investigate the differences in reward responsivity between high and low dependence smokers in satiation and after overnight abstinence.

CHAPTER 5

STUDY 3:

REWARD RESPONSIVITY (BEHAVIOURAL MEASURE) IN SATIATION AND WITHDRAWAL AMONG LOW AND HIGH DEPENDENCE SMOKERS – REVISITED AGAIN

5.1 Method

5.1.1 Participants

Thirty-two smokers (5 males and 27 females) with a mean age of 24.41 years (minimum = 18 years, maximum = 41 years; *SD* = 6.53) took part. There were 16 low dependence smokers with a mean FTND score of 1.50 (minimum = 0, maximum = 3; *SD* = 1.21) and 16 high dependence smokers with a mean FTND score of 5.50 (minimum = 4, maximum = 7; *SD* = 1.09).

5.1.2 Measures and Apparatus

Differences from Study 1 are noted.

The Card Arranging Reward Responsivity Objective Test (CARROT)

The measure was used as described in Pilot 2; however, in the present study, the practice trial lasted 2 minutes. I extended the time taken to complete the practice trial in an attempt to influence further the effort put in the rewarded and nonrewarded trials.

5.1.3 Procedure

The procedure was as described in Study 2; however, in the present study, smoking status was examined within-participants. Participants were asked to come to the laboratory twice: once after they had abstained from smoking overnight (withdrawal condition) and once after they had smoked as usual (satiation condition). I did this to control for possible differences between the

withdrawal and satiation groups that could mask any effects of reward. Half of the participants took part in the satiation condition first, whereas the other half took part in the withdrawal condition first. The withdrawal and satiation conditions were counterbalanced to control for possible carry-over effects. The procedure lasted approximately 40 minutes.

After collection of the data, I gave participants the amount of money they earned in the CARROT, estimated to be a maximum of £6.00 per participant. Psychology students earned three course credits in return for their participation.

5.1.4 Design and Analysis

The design and analysis were as described in Study 2 except smoking status was manipulated within-participants.

5.2 Results

Once again, the withdrawal manipulation was successful. A paired samples *t* test confirmed that the ECO level of participants in satiation (M = 19.28; minimum = 1, maximum = 52; SD = 12.70) was significantly higher than the ECO level of participants in withdrawal (M = 4.81; minimum = 0, maximum = 15; SD = 4.01), $t(31) = 8.33$, $p \leq 0.001$.

I employed 2 × 2 × 2 (Reward × Smoking Status × Dependence) repeated measures Analysis of Variance (ANOVA). The between-participants factor was dependence (low/high). The within-participants factors were smoking status (withdrawal/satiation) and reward (nonrewarded trials/rewarded trials). The dependent variable was sorting rate.

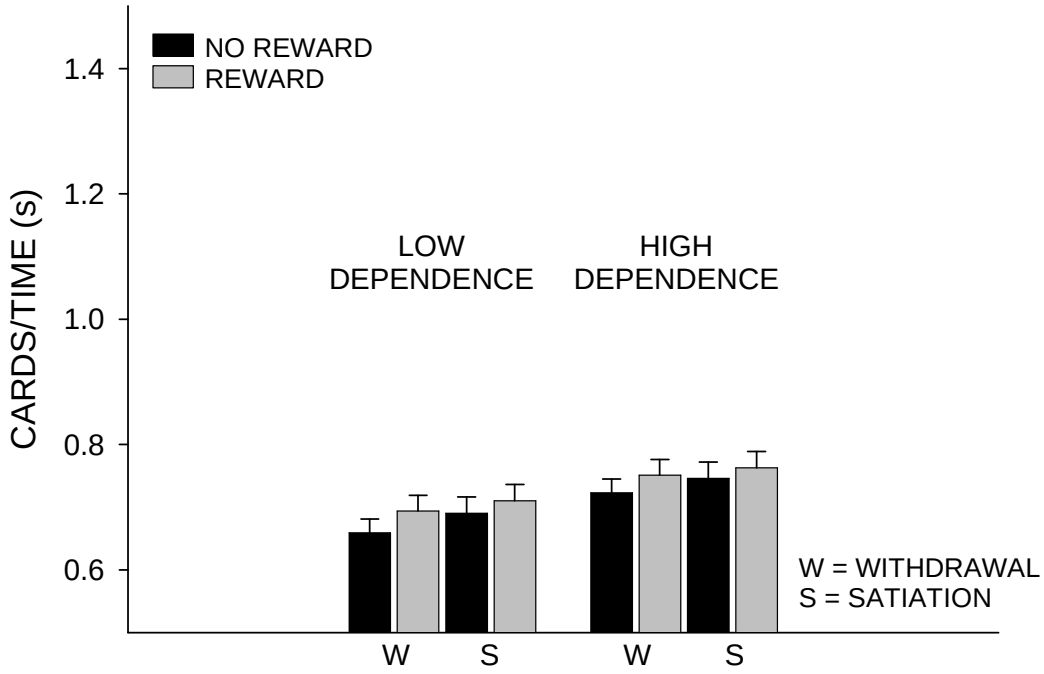

Figure 5.1. Mean CARROT sorting rate (+*SE*) in reward and no reward for low dependence (W/S: *n* = 16) and high dependence (W/S: *n* = 16) participants.

Figure 5.1 shows the mean CARROT sorting rate in each of the experimental conditions for low and high dependence participants. As Figure 5.1 shows, both low and high dependence participants increased their sorting rate under reward in withdrawal and satiation. Furthermore, for both low and high dependence participants, sorting rate in the nonrewarded and rewarded trials was higher in satiation compared to withdrawal (see Figure 5.1). Moreover, both low and high dependence participants increased their sorting rate from the nonrewarded to the rewarded trials more under withdrawal than under satiation. Therefore, there was no indication that the effect of reward was larger under satiation. Finally, it looks like high dependence smokers had

higher sorting rates in all experimental conditions compared with low dependence smokers.

The statistical analysis (Table 5.1) confirmed these impressions. The results of the three-way ANOVA showed that, with an alpha level of .05, there was a significant main effect of reward, a significant main effect of smoking status, and a marginally significant Reward × Smoking Status interaction. The main effect of dependence fell short of statistical significance.

Table 5.1

Analysis of Variance for CARROT Sorting Rate

Source	*df*	*F*	*p*
	Between subjects		
Dependence (D)	1	3.12	.09
Error	30	(.03)	
	Within subjects		
Reward (R)	1	16.83	.00
R × D	1	< 1	.69
Error (R)	30	(.00)	
Smoking Status (S)	1	4.10	.05
S × D	1	< 1	.78
Error (S)	30	(.00)	
R × S	1	3.58	.07
R × S × D	1	< 1	.77
Error (R X S)	30	(<.00)	

Note. Values enclosed in parentheses represent mean square errors.

There was a significant main effect of reward (Table 5.1). Thus, CARROT sorting rate was significantly higher in the rewarded trials (M = .73, SD = .10) compared to the nonrewarded trials (M = .70, SD = .09). Moreover, there was a significant main effect of smoking status (Table 5.1). Thus, CARROT sorting rate was significantly higher in satiation (M = .73, SD = .10) compared to withdrawal (M = .71, SD = .09).

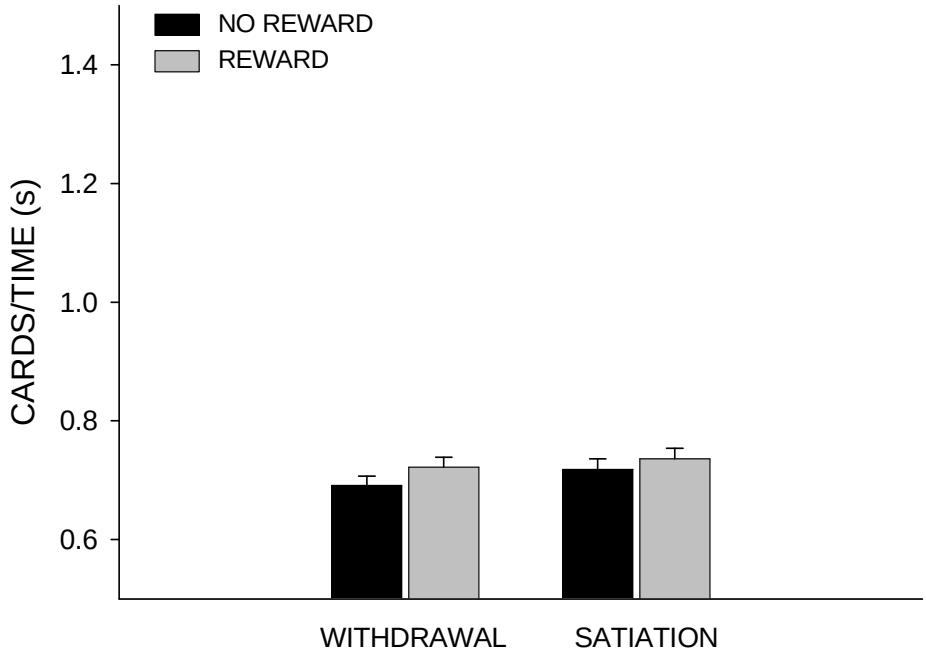

Figure 5.2. Mean CARROT sorting rate (+*SE*) in reward and no reward in withdrawal (*n* = 32) and satiation (*n* = 32).

Figure 5.2 shows the mean CARROT sorting rate in each of the experimental conditions and illustrates the marginally significant Reward × Smoking Status interaction (Table 5.1). As Figure 5.2 shows, there was a main effect of reward: Mean CARROT sorting rate was higher in the rewarded trials in withdrawal and satiation compared with the mean CARROT sorting rate in the nonrewarded trials in withdrawal and satiation. Moreover, there was a main effect of smoking status (see Figure 5.2). Thus, satiated smokers had higher mean CARROT sorting rates in the rewarded and nonrewarded trials compared with withdrawn smokers. Figure 5.2 also shows that the effect of reward was more pronounced under withdrawal than under satiation. That is, participants increased their sorting rate in the rewarded trials when they were withdrawn

more than they did when they were satiated. Comparisons showed that the difference between the sorting rates of the nonrewarded and rewarded trials was significant under withdrawal, $t(31) = 4.68$, $p = .00$, and it was also significant under satiation, $t(31) = 2.56$, $p = .02$. However, the difference between the sorting rates of the nonrewarded and rewarded trials was bigger under withdrawal. This is in direct contrast to the findings of Study 1.

5.3 Discussion

There was a strong main effect of reward: Sorting rates were significantly higher under reward than under no reward. Therefore, the modifications that were made to the procedure of the CARROT improved the measure's reliability. However, there was no evidence to support the first hypothesis. Reward responsivity scores were not higher in satiation compared to withdrawal. Although this could be due to the fact that strong reward effects might be less vulnerable to the impact of withdrawal, a marginally significant Reward × Smoking Status interaction was found. However, it was opposite to the predicted direction: Reward responsivity scores were higher in withdrawal compared to satiation. This was in contrast to the findings of Study 1. There was no evidence to support the second hypothesis. The difference in reward responsivity between satiation and withdrawal was not greater with higher levels of dependence. This result did not replicate the findings of Study 2. However, there was a main effect of smoking status, with satiated smokers showing higher sorting rates compared to smokers in withdrawal.

I did not replicate the Reward × Smoking Status interaction reported in the literature (e.g., Powell et al., 2002) and found in Study 1. It is unlikely that failure to replicate the interaction was due to limitations in the way I administered the behavioural measure for two reasons. First, the changes that were made to the procedure of the CARROT increased the measure's reliability; thus, a strong main effect of reward was found in the present study. Second, the withdrawal manipulation was successful. In an attempt to find out why I failed to replicate the Reward × Smoking Status interaction reported in the literature, the methodology I used in the studies of the present thesis was examined and

compared to the methodology used in the studies where the interaction was reported (e.g., Powell et al., 2002). This will be discussed in the next section.

CHAPTER 6

INTERIM DISCUSSION AND ADDITIONAL ANALYSES

In the studies of the present thesis, the presentation of the rewarded and nonrewarded trials was counterbalanced. REWRESP was calculated as mean sorting rate in R minus mean sorting rate in N, that is, REWRESP = R – N. I did not replicate the Reward × Smoking Status interaction reported in the literature (Powell et al., 2002). Powell et al. used a NRN design where REWRESP was calculated as R – (N + N) /2 and reported a Reward × Smoking Status interaction: The difference between nonreward and reward was pronounced under satiation but not under withdrawal. Powell et al. did not use a control condition in which no reward was used throughout. Therefore, their results might reflect the different global effects of satiation and withdrawal on performance over the three trials of the CARROT task (i.e., practice effects) rather than the different effects of satiation and withdrawal on CARROT reward responsivity (i.e., reward effects). Because withdrawal can produce attentional deficits, and nicotine can improve attentional performance (Koelega, 1992), performance might have improved more across the series of the three trials when participants were tested under satiation than when tested under withdrawal.

Recall that Powell et al. calculated reward responsivity as a difference score in performance between the average of the first and third trial and the second (i.e., T2 – [T1 + T3] /2). This measure could confound the practice and reward effects of smoking status. For example, if practice in satiation led to a rapid asymptote in sorting performance, whereas practice in withdrawal led to only gradual improvement between trials, then the measure would show an

apparent reward responsivity effect even if none existed. However, practice effects can be controlled by counterbalancing such that rewarded and nonrewarded trials occur equally often in each position of a two- or four-trial series. Reward responsivity would then be calculated as the average performance in the rewarded trials minus the average performance in the nonrewarded trials. This revised design allowed a determination of whether impaired performance in the CARROT during nicotine withdrawal should be properly characterised as an effect of withdrawal on reward responsivity.

I looked at practice effects in the data of Study 3 in order to examine whether improvement in performance over a series of trials (i.e., practice effects) was different under satiation and under withdrawal. I carried out 2 × 2 (Trial × Smoking Status) repeated measures Analysis of Variance (ANOVA) using CARROT sorting rate as the dependent variable. The within-participants factors were smoking status (withdrawal/satiation) and trial (trials 1-4). Table 6.1 shows the results of the two-way ANOVA. It can be seen that, with an alpha level of .05, there was a significant main effect of trial and a marginally significant main effect of smoking status.

Table 6.1

Analysis of Variance for CARROT-Trial Sorting Rate

Source	*df*	*F*	*p*
	Between subjects		
Error	31	(.07)	
	Within subjects		
Trial (T)	3	10.80	.00
Error (T)	93	(.00)	
Smoking Status (S)	1	3.69	.06
Error (S)	31	(.01)	
T × S	3	1.17	.32
Error (T × S)	93	(.00)	

Note. Values enclosed in parentheses represent mean square errors.

There was a significant main effect of trial (Table 6.1). Table 6.2 shows the mean CARROT sorting rate (+ *SD*) in each of the four trials. Participants' increased their sorting rate with each successive trial.

Table 6.2

CARROT Sorting Rate in Each of the Four Trials (N = 32)

CARROT sorting rate	Trial 1	Trial 2	Trial 3	Trial 4
Mean	.69	.71	.72	.74
Standard Deviation	.10	.09	.10	.10

Moreover, there was a marginally significant main effect of smoking status (Table 6.1). Thus, CARROT sorting rate was significantly higher in satiation (M = .73, SD = .10) compared to withdrawal (M = .71, SD = .09).

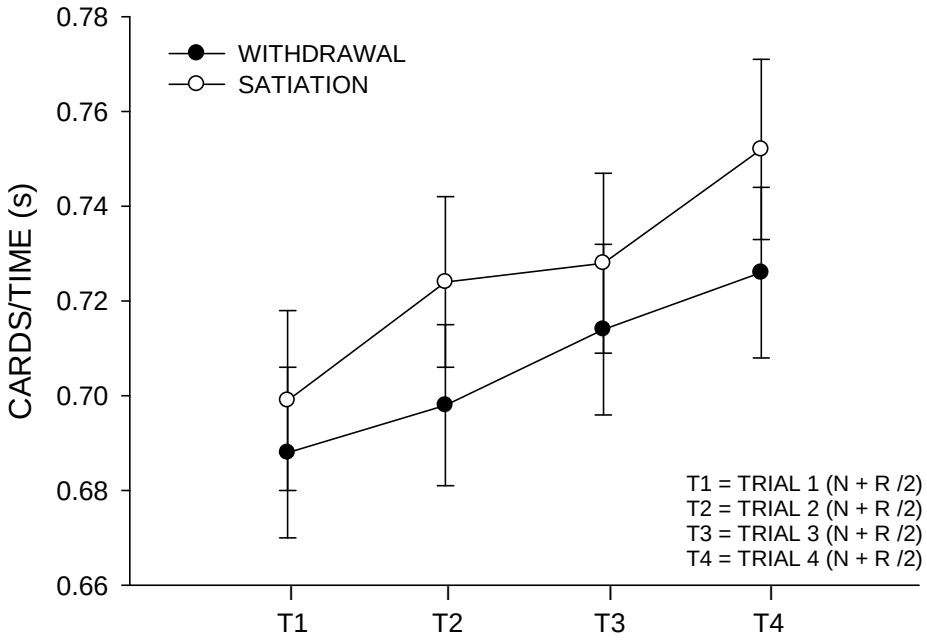

Figure 6.1. Sorting rate during the four trials of the CARROT task in withdrawal (W) and satiation (S). Points represent the mean CARROT sorting rate, that is, the average sorting rate under reward (R) and no reward (N) in each of the four trials in W and S; vertical lines depict standard errors of the means.

Figure 6.1 shows the mean CARROT sorting rate in each of the four trials in withdrawal and satiation. It illustrates the significant main effect of trial (Tables 6.1 and 6.2) and the marginally significant main effect of smoking status (Table 6.1). As Figure 6.1 shows, participants in both withdrawal and satiation increased their sorting rate with successive trials. Thus, there was a practice effect: Participants' performance improved across the series of the four trials. That is, participants got faster at card sorting over the series of the four trials. Furthermore, satiated smokers had higher sorting rates across all trials compared to withdrawn smokers (see Figure 6.1). Although the Trial × Smoking Status interaction was not significant (Table 6.1), comparisons between the sorting rates in each trial showed that the difference in sorting rates between withdrawal and satiation was significant in Trial 2, $t(31) = 2.71$, $p = .01$. This suggests that satiated smokers increased their sorting rate from Trial 1 to Trial 2 more than withdrawn smokers did. Thus, satiated smokers reached their maximum sorting rate faster than withdrawn smokers did. This, in turn, provides some indication that practice effects differ in withdrawal and satiation: Practice effects appear to be stronger under satiation than under withdrawal. In other words, participants' performance improved over the series of the trials when they were satiated but not when they were withdrawn.

The pattern in Figure 6.1, where the design is fully counterbalanced, suggests that practice effects that are different under withdrawal and satiation may have an impact on REWRESP when REWRESP is calculated as T2 - (T1 + T3) /2 (where T1 = Nonrewarded trial, T2 = Rewarded trial and T3 = Nonrewarded trial). Figure 6.2 is a hypothetical graph of mean sorting rates

under withdrawal and satiation in a NRN design, which is the one used by Powell et al. (2002).

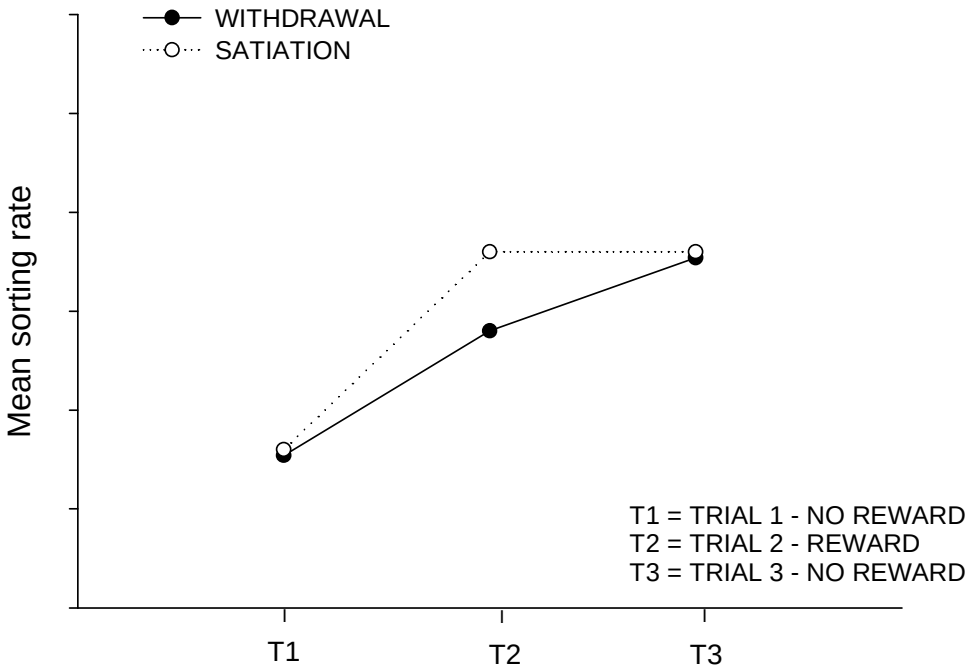

Figure 6.2. Hypothetical graph of CARROT sorting rate in withdrawal (W) and satiation (S) in T1 (Trial 1), T2 (Trial 2), and T3 (Trial 3). Points represent the mean CARROT sorting rate in each of the three trials in W and S.

Looking at Figure 6.2, it was hypothesised that if practice effects for satiated smokers are stronger compared to practice effects for withdrawn smokers, then satiated smokers would increase their sorting rate from Trial 1 to Trial 2 more than withdrawn smokers would. Satiated smokers would reach their maximum sorting rate in the rewarded Trial 2. After that, their sorting rate would either remain the same or decrease in Trial 3. However, if practice effects were weaker under withdrawal compared to satiation, then withdrawn smokers would increase their sorting rate from Trial 1 to Trial 2 less than satiated smokers would. Withdrawn smokers would not reach their maximum

sorting rate in Trial 2. Their sorting rate would still increase from Trial 2 to Trial 3; they would either reach their maximum sorting rate in Trial 3 or not. If practice effects asymptote later under withdrawal than under satiation, then this could produce an impression of a withdrawal effect on REWRESP under a T2 – (T1 + T3) /2 design (Figure 6.2).

In order to investigate this hypothesis, I requested the data that were not available in the published article by Powell et al. (2002). The data were kindly provided for re-analysis. Powell et al. (2002) used a NRN design but no control group. They calculated REWRESP as T2 - (T1 + T3) /2. Under a T2 - (T1 + T3) /2 design, they found a significant Reward × Smoking Status interaction: Satiated smokers increased their sorting rate in the rewarded trial (T2) significantly more than withdrawn smokers did. Thus, satiated smokers were able to respond to reward, whereas withdrawn smokers were not. However, when I examined practice effects (i.e., improvement in performance) for satiated and withdrawn smokers across the three trials in Powell et al.'s data, I found that practice effects differed for satiated and withdrawn smokers.

Table 6.3 shows the results of the 2 × 2 (Trial × Smoking Status) ANOVA. The within-participants factors were smoking status (withdrawal/satiation) and trial (trials 1-3). The dependent variable was CARROT sorting rate. It can be seen (Table 6.3) that, with an alpha level of .05, there was a significant main effect of trial and a significant Smoking Status × Trial interaction.

Table 6.3

Analysis of Variance for CARROT-Trial Sorting Rate (Powell et al., 2002 data)

Source	*df*	*F*	*p*
	Between subjects		
Error	25	(.15)	
	Within subjects		
Trial (T)	2	22.55	.00
Error (T)	50	(.00)	
Smoking Status (S)	1	< 1	.68
Error (S)	25	(.03)	
T × S	2	5.12	.01
Error (T × S)	50	(.00)	

Note. Values enclosed in parentheses represent mean square errors.

There was a significant main effect of trial (Table 6.3). Table 6.4 shows the mean CARROT sorting rate (+ *SD*) in each of the three trials. Participants increased their sorting rate with each successive trial.

Table 6.4

CARROT Sorting Rate in Each of the Three Trials (Powell et al., 2002 data)

CARROT sorting rate	Trial 1	Trial 2	Trial 3
Mean	1.25	1.30	1.32
Standard Deviation	.17	.18	.17

Note. $N = 26$

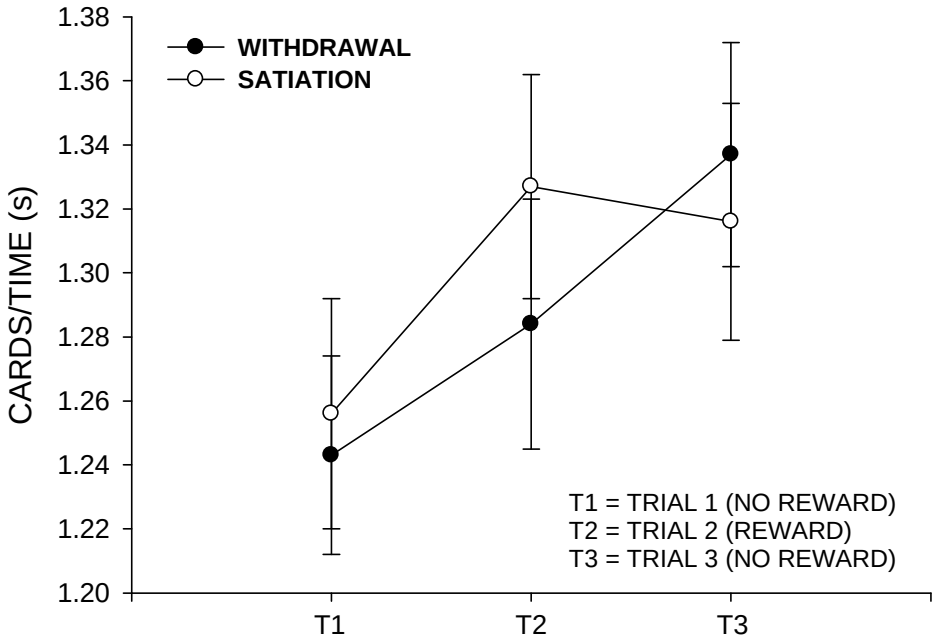

Figure 6.3. CARROT sorting rate in withdrawal (W) and satiation (S) in T1 (Trial 1), T2 (Trial 2), and T3 (Trial 3)--Powell et al., 2002 data. Points represent mean CARROT sorting rate in each of the three trials in W and S; vertical lines represent standard errors of the means.

Figure 6.3 shows the mean CARROT sorting rate in withdrawal and satiation in each of the three trials and illustrates the significant Smoking Status × Trial interaction (Table 6.3). As Figure 6.3 shows, practice effects differed in withdrawal and satiation. That is, improvement in performance (or increase in

sorting rate with successive trials) differed between withdrawal and satiation. In Trial 1 and Trial 2, sorting rate was higher under satiation, whereas in Trial 3, sorting rate was higher under withdrawal (see Figure 6.3). Comparisons of the sorting rates between withdrawal and satiation for each trial showed that the difference in sorting rate between withdrawal and satiation was not significant in any of the three trials. Furthermore, as can be seen (Figure 6.3), withdrawn smokers increased their sorting rate from Trial 1 to Trial 2 and from Trial 2 to Trial 3. Satiated smokers increased their sorting rate from Trial 1 to Trial 2, but their sorting rate decreased from Trial 2 to Trial 3. Comparisons of the sorting rates between the three trials under withdrawal and under satiation showed that for withdrawn smokers the difference between Trial 1 and Trial 2 was not significant, $t(25) = 2.21$, $p = .04^{*}$, but the difference between Trial 2 and Trial 3 was significant, $t(25) = 4.01$, $p = .00$. For satiated smokers, the difference between Trial 1 and Trial 2 was significant, $t(25) = 5.89$, $p = .00$, but the difference in sorting rate between Trial 2 and Trial 3 was not, $t(25) = .75$, *ns*. Baseline CARROT sorting rate is not shown in Figure 6.3. However, satiated smokers had slightly lower mean CARROT sorting rate at baseline (1.20) compared with withdrawn smokers (1.21). Satiated smokers increased their CARROT sorting rate with each successive trial and reached their maximum sorting rate at Trial 2, after which their sorting rate decreased. Withdrawn smokers increased their sorting rates with successive trials less than satiated smokers did; they reached their asymptote at Trial 3 or Trial 4 (if the latter was included). Therefore, withdrawn smokers reached their maximum sorting rate later than satiated smokers did.

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* significance: $\underline{p} \leq .01$

Thus, the withdrawal effect on REWRESP under a T2 – (T1 + T3) /2 design appears to be, at least in part, due to the fact that practice effects asymptote later under withdrawal than under satiation. That is, sated smokers improve their performance in the CARROT task and reach their asymptotic level (i.e., maximum sorting rate) faster than withdrawn smokers do. However, it is also possible that the increase in sorting rate in the rewarded trial (Trial 2) reflects a combination of reward-induced plus practice-based speeding.

This was investigated in the next study. I used group NRN (where the second of the three trials was rewarded) and looked at the effect of reward under a T2 – (T1 + T3) /2 within-participants design to facilitate comparisons with Powell et al. (2002). The dependent variable was calculated as T2 – (T1 + T3) /2 for group NRN. In order to examine whether withdrawal might interact with practice effects, I used group NNN (where all three trials were nonrewarded) as control. The dependent variable was calculated as T2 – (T1 + T3) /2 for groups NRN and NNN. Finally, I examined the effect of reward in a between-participants design (groups NNN and RRR) to avoid practice artefacts. Reward respoonsivity was calculated as the average of the three rewarded trials (group RRR) minus the average of the three nonrewarded trials (group NNN).

CHAPTER 7

STUDY 4:

REWARD RESPONSIVITY (BEHAVIOURAL MEASURE) IN SATIATION AND WITHDRAWAL AMONG LOW AND HIGH DEPENDENCE SMOKERS – AN EXAMINATION OF REWARD AND PRACTICE EFFECTS

7.1 Method

7.1.1 Participants

Sixty-six people (29 males and 37 females) took part. Their mean age was 22.65 (minimum = 18 years, maximum = 40 years; *SD* = 4.78). Low dependence smokers (*n* = 36) had a mean FTND score of 1.08 (minimum = 0, maximum = 3; *SD* = .94), whereas high dependence smokers (*n* = 30) had a mean FTND score of 4.97 (minimum = 4, maximum = 9; *SD* = 1.27).

7.1.2 Measures and Apparatus

Differences from Study 1 are noted.

The Card Arranging Reward Responsivity Objective Test (CARROT)

The practice trial involved sorting cards for 2 minutes. Each of the three nonrewarded and rewarded trials lasted 5 minutes. There were three CARROT groups. In Group 1, participants completed three rewarded trials (R) of the CARROT (i.e., RRR). In Group 2, they completed three nonrewarded (N) trials of the CARROT (i.e., NNN). In Group 3, they completed three trials of the CARROT: The first was a nonrewarded trial, the second was a rewarded trial, and the third was a nonrewarded trial (i.e., NRN). The three different CARROT groups were used to examine reward responsivity (REWRESP) as a within- and a between-participants factor.

7.1.3 Procedure

The procedure was as described in Study 2. However, in the present study participants were randomly counterbalanced into the three CARROT groups described in Section 7.1.2.

After completing the CARROT, participants filled in the SHAPS and the PANAS.

The procedure lasted approximately 40 minutes.

After collection of the data, I gave participants the amount of money they earned in the CARROT, estimated to be a maximum of £7 per participant. Psychology students earned two course credits in return for their participation.

7.1.4 Design and Analyses

Three analyses were carried out. The design employed in each was as follows:

(a) A 2 × 2 (Smoking Status × Dependence) mixed factorial design. The between-participants factors were dependence (low/high) and smoking status (withdrawal/satiation). The dependent variable was the T2 – (T1 + T3) /2 measure of reward responsivity. Rewarded and nonrewarded trials were manipulated within-participants (i.e., group NRN).

(b) A 2 × 2 × 2 (Group × Smoking Status × Dependence) mixed factorial design. The between-participants factors were smoking status (withdrawal/satiation), dependence (low/high), and group (group NNN = all three trials nonrewarded/group NRN = first trial nonrewarded, second trial rewarded, third trial nonrewarded). The dependent variable was the T2 – (T1 + T3) /2 measure of reward responsivity. Rewarded and nonrewarded trials were manipulated within-participants.

(c) A 2 × 2 × 2 × 2 (Trial × Group × Smoking Status × Dependence) mixed factorial design. The within-participants factor was trial (trials 1 – 3). The between-participants factors were smoking status (withdrawal/satiation), dependence (low/high), and group (group NNN = all three trials nonrewarded/group RRR = all trials rewarded). The dependent variable was calculated as the average of the three rewarded trials (group RRR) minus the average of the three nonrewarded trials (group NNN).

7.2 Results

The withdrawal manipulation was successful. An independent samples *t* test showed that the ECO level of participants in satiation (*M* = 18.33, *SD* = 10.58, minimum = 3, maximum = 45; *n* = 33) was significantly higher than the ECO level of participants in withdrawal (*M* = 5.73, *SD* = 3.62, minimum = 1, maximum = 14; *n* = 33), *t* (39.37) = 6.47, $p \leq 0.001$ (Because Levene's Test for Equality of Variances was significant, equal variances were not assumed).

7.2.1 Group NRN

In order to look at the effect of reward under a T2 – (T1 + T3) /2 within-participants analysis to facilitate comparisons with Powell et al. (2002), I used the T2 – (T1 + T3) /2 measure of reward responsivity as the dependent variable. I carried out 2 × 2 (Smoking Status × Dependence) univariate ANOVA for group NRN. The between-participants factors were smoking status (withdrawal/satiation) and dependence (low/high). Table 7.2 shows the results of the two-way ANOVA. It can be seen that, with an alpha level of .05, there was a marginally significant main effect of smoking status but no other significant main effects or interactions.

Table 7.1

Analysis of Variance for CARROT Reward Responsivity (Group NRN)

Source	*df*	*F*	*p*
	Between subjects		
Smoking Status (S)	1	3.86	.06
Dependence (D)	1	<1	.96
S × D	1	<1	.36
Error	18	(<.00)	

Note. Values enclosed in parentheses represent mean square errors.

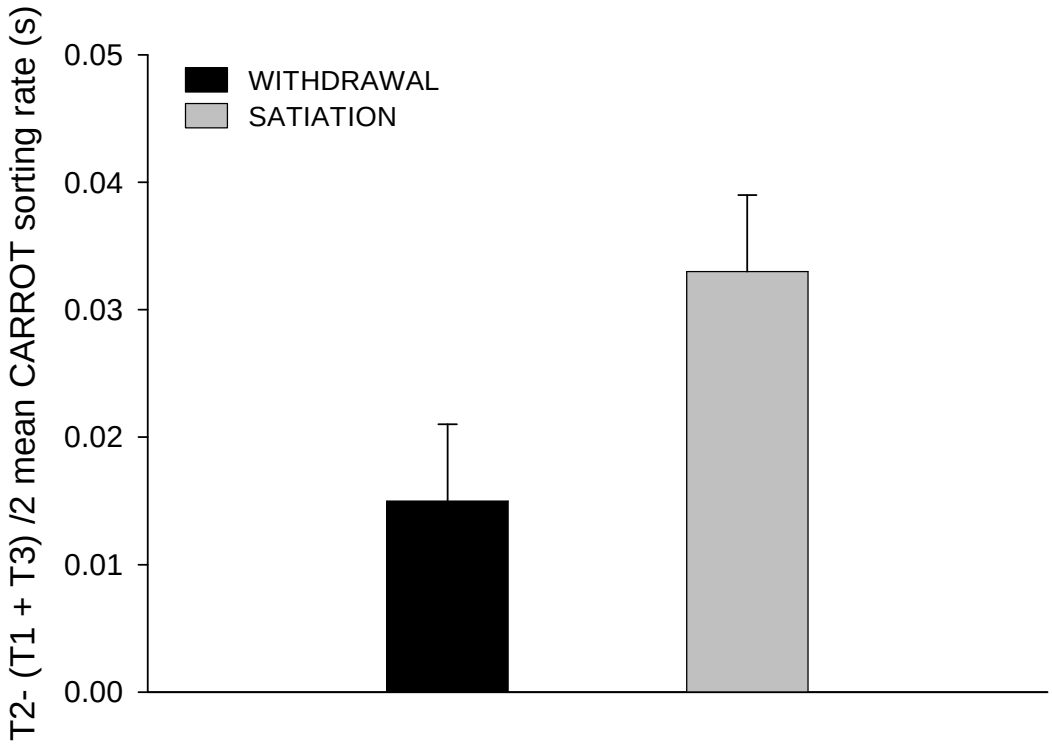

Figure 7.1. T2 - (T1 + T3) /2 mean CARROT sorting rate (+*SE*) in withdrawal (*n* = 33) and satiation (*n* = 33) in group NRN.

Figure 7.1 shows the T2 – (T1 + T3) /2 mean sorting rate in withdrawal and satiation in NRN and illustrates the marginally significant main effect of smoking status (Table 7.1). As Figure 7.1 shows, participants in withdrawal showed lower reward responsivity than participants who were satiated, consistent with Powell's publications.

Thus, in a within-participants NRN design where reward responsivity was calculated as T2 – (T1 + T3) /2 there appeared to be a withdrawal effect on reward responsivity, such that the difference between reward and no reward was smaller under withdrawal than under satiation.

7.2.2 Groups NNN-NRN

Given that withdrawal might interact with the practice effects that were observed in Study 3 and given the re-analysis of Powell's (2002) data, I assessed the effect of withdrawal on reward responsivity using group NNN as control. I calculated the dependent variable as T2 – (T1 + T3) /2 for both groups. I carried out 2 × 2 × 2 (Group × Smoking Status × Dependence) univariate ANOVA. The between-participants factors were group (NRN/NNN), smoking status (withdrawal/satiation), and dependence (low/high). Table 7.2 shows the results of the three-way ANOVA. It can be seen that, with an alpha level of .05, there was a significant main effect of group and a marginally significant main effect of smoking status but no other significant main effects or interactions.

Table 7.2

Analysis of Variance for CARROT Reward Responsivity (Groups NNN-NRN)

Source	*df*	*F*	*p*
	Between subjects		
Group (G)	1	12.03	.00
Smoking Status (S)	1	3.93	.05
Dependence (D)	1	< 1	.55
G X S	1	< 1	.73
G X D	1	< 1	.59
S X D	1	1.10	.30
G X S X D	1	< 1	.95
Error	36	(.00)	

Note. Values enclosed in parentheses represent mean square errors.

Thus, the effect of smoking status on reward responsivity did not differ in the NNN and NRN groups (i.e., the Group × Smoking Status interaction was not significant).

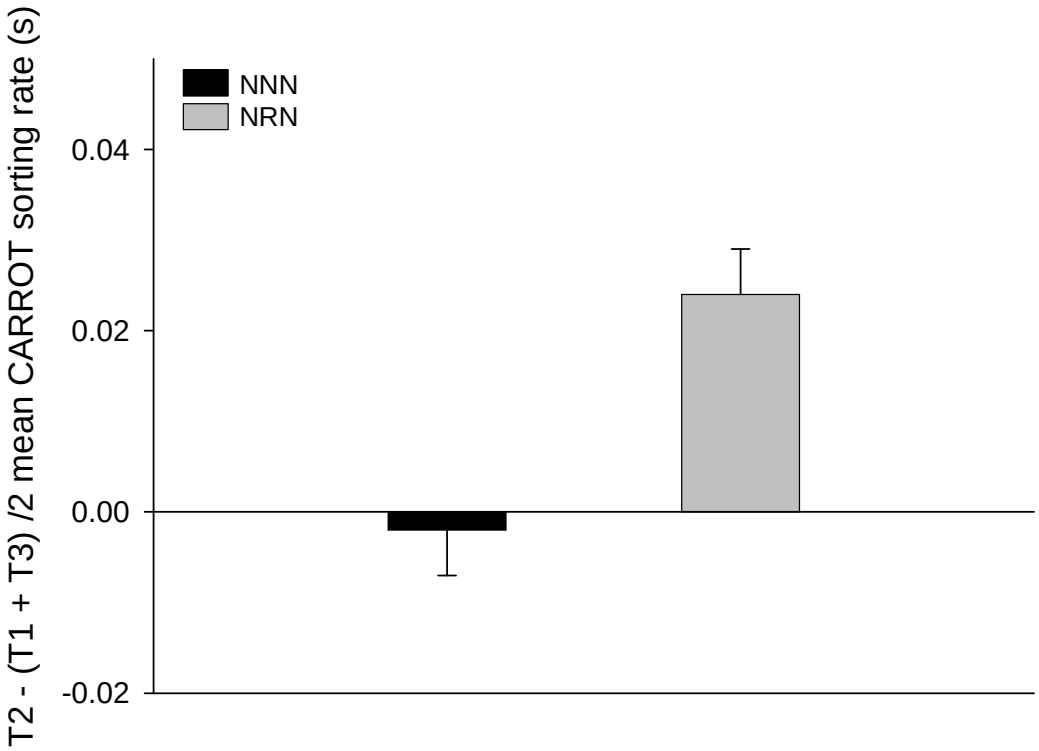

Figure 7.2. T2 - (T1 + T3) /2 mean CARROT sorting rate (+*SE*) in groups NNN (*n* = 22) and NRN (*n* = 22).

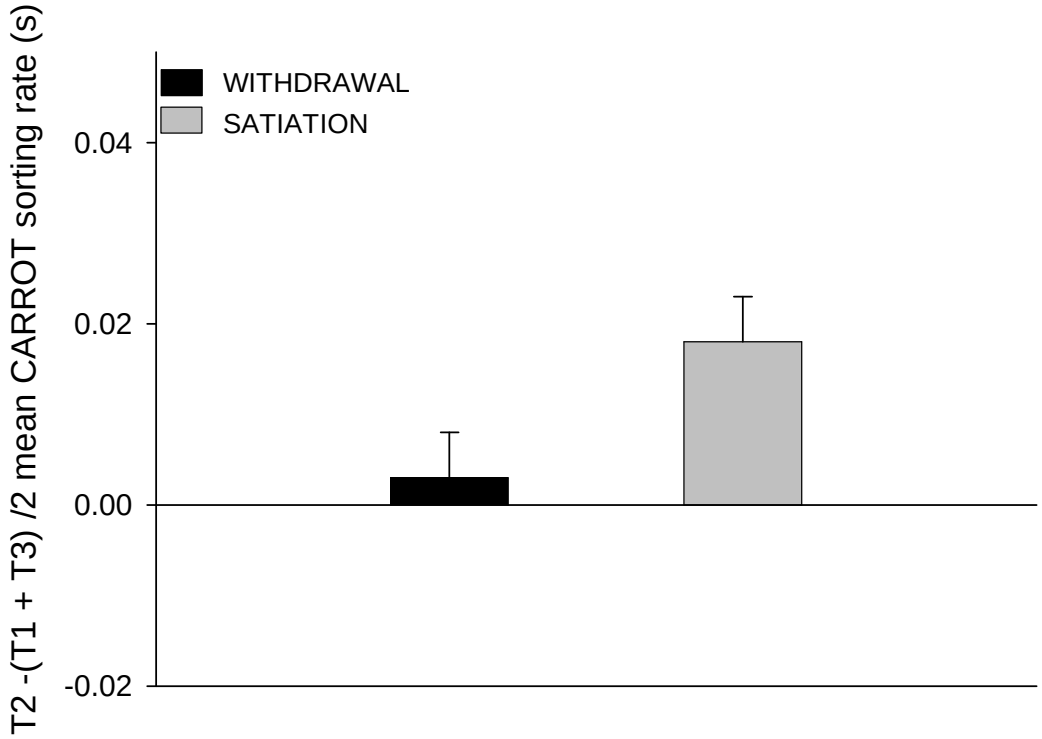

Figure 7.3. T2 - (T1 + T3) /2 mean CARROT sorting rate (+*SE*) in withdrawal (*n* = 22) and satiation (*n* = 22) in groups NNN and NRN combined.

Figure 7.2 illustrates the main effect of group (Table 7.2): Reward responsivity was higher in NRN compared to NNN. Figure 7.3 illustrates the main effect of smoking status (Table 7.2): Reward responsivity was higher in satiation compared to withdrawal. These results indicate that reward did indeed have an effect, resulting in bigger T2 – (T1 + T3) /2 value in group NRN, and that the T2 – (T1 + T3) / 2 measure was lower in withdrawal. However, these two effects were independent, that is, there was no Group × Smoking Status interaction.

In order to determine whether the smoking status effect could be interpreted as an effect of practice, I used polynomial contrasts to examine the trends in sorting rate across the three trials.

I carried out 2 × 2 × 2 (Trial × Group × Smoking Status) repeated measures ANOVA. The within-participants factor was trial (trials 1-3). The between- participants factors were group (NNN/NRN) and smoking status (withdrawal/satiation). The tests for the trends of interest are given in Table 7.4. As can be seen (Table 7.3), there was a significant quadratic contrast for the Trial × Smoking Status interaction and a significant quadratic contrast for the Trial × Group interaction.

Table 7.3

Analysis of Variance for Linear and Quadratic Trends (Groups NNN-NRN)

Source	*df*	*F*	*p*
Trial × Smoking Status			
Linear	1	1.45	.23
Quadratic	1	5.68	.02
Trial × Group			
Linear	1	3.70	.06
Quadratic	1	12.20	.00

Thus, in the case of the smoking status effect, the effect was primarily due to participants reaching their asymptotic sorting rate significantly more quickly when they were sated. However, this effect was independent of that produced by introducing a reward in Trial 2.

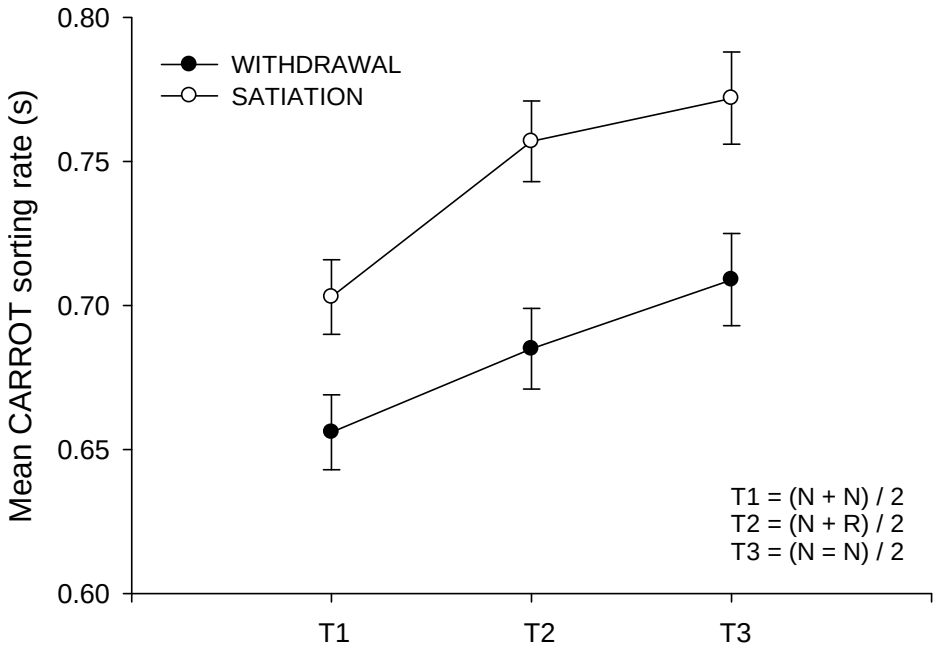

Figure 7.4. CARROT sorting rate across the three trials in withdrawal (W) and satiation (S) in groups NNN and NRN combined. Points represent mean CARROT sorting rate in each of the three trials in W and S; vertical lines represent standard errors of the means.

Figure 7.4 shows the mean CARROT sorting rate in withdrawal and satiation and illustrates the significant quadratic contrast (Table 7.3), that is, the levelling-off of performance across trials. As can be seen (Figure 7.4), further increase in sorting rate after T2 was less marked in satiation compared to withdrawal. This suggests that satiation pushed sorting rates to a faster adaptation compared to withdrawal and produced a bigger difference between T2 (reward) and (T1+ T3) /2 (no reward) compared to withdrawal. However, this effect was identical for groups NNN and NRN.

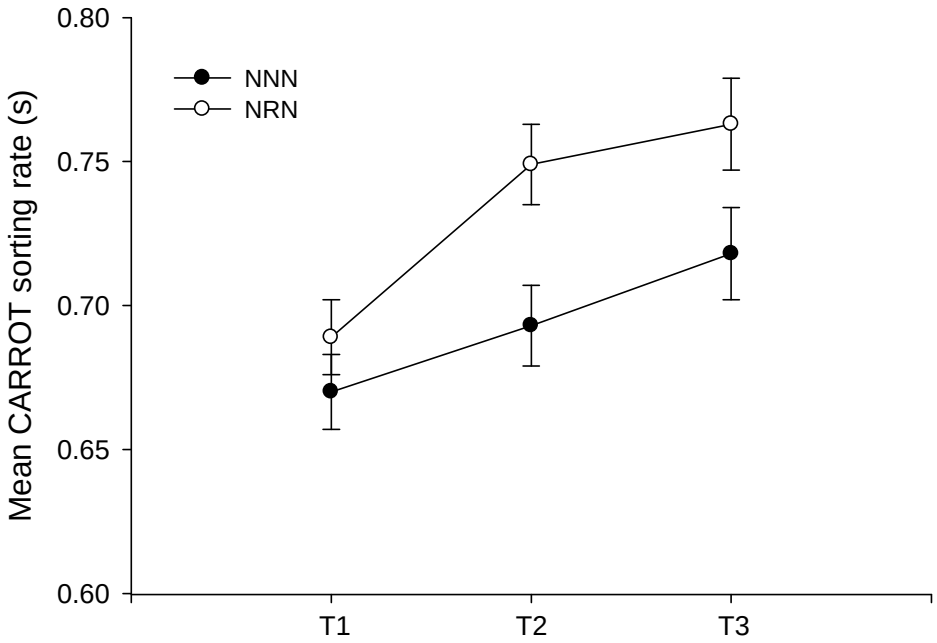

Figure 7.5. CARROT sorting rate across the three trials in groups NNN and NRN. Points represent mean CARROT sorting rate in each of the three trials in groups NNN and NRN; vertical lines represent standard errors of the means.

Figure 7.5 shows the mean CARROT sorting rate across the three trials for groups NNN and NRN and illustrates the marginally significant linear contrast (i.e., the upward trend in performance across trials) and the significant quadratic contrast (Table 7.3). As can be seen, sorting rate increased across the three trials for both groups; however, the increase in sorting rate after T2 was less pronounced for group NRN. Thus, the effect of reward in T2 in NRN produced a bigger increase in sorting rate from T1 to T2 for NRN compared to NNN. However, removal of the reward in T3 prevented a significant increase in sorting rate from the rewarded T2 to the nonrewarded T3. The difference between T2 and T3 was significant for NNN where reward was constantly absent. Therefore, the presence of reward in T2 in NRN pushed sorting rates to a faster adaptation (i.e., to the asymptotic or maximum sorting rate) and produced

a bigger difference between T2 (reward) and (T1+ T3) /2 (no reward) for group NRN compared to NNN. This effect was independent of smoking status.

Looking at the patterns in Figure 7.4 and Figure 7.5, it can be seen that sorting rate across the three trials under satiation was similar to sorting rate across the three trials under reward (i.e., group NRN). Similarly, sorting rate under withdrawal was similar to sorting rate under no reward (i.e., group NNN). The presence of reward in Trial 2 pushed sorting rates to a faster adaptation irrespective of smoking status. Similarly, satiation pushed sorting rates to a faster adaptation irrespective of the presence of reward. On the other hand, a fast adaptation was prevented by withdrawal irrespective of the presence of reward In addition, a fast adaptation was prevented when no reward was introduced irrespective of smoking status. Thus, satiation and reward produced a similar pattern of sorting rate across the three trials. That is, participants reached their asymptote faster when they were satiated or when a reward was introduced in Trial 2. Withdrawal and the absence of reward also produced a similar pattern of sorting rate across the three trials: Participants did not reach their asymptote as fast when they were withdrawn or when there was no reward introduced in Trial 2.

In other words, practice effects were stronger in satiation compared to withdrawal and stronger under reward compared to no reward. Thus, the T2 – (T1 + T3) /2 value was increased in satiation; however, that increase was independent of group. The T2 – (T1 + T3) /2 value was also increased by reward; however, that increase was independent of smoking status.

For both groups (NNN and NRN), adaptation was faster under satiation than under withdrawal. When group NRN only was examined under a T2 –

(T1+ T3) /2 design, there was an effect of withdrawal on reward responsivity, consistent with the results reported by Powell et al (2002). However, when a control condition was included, the effect of withdrawal was similar either reward was present or absent. Thus, withdrawal did not affect reward responsivity. Rather, withdrawal interacted with practice effects and produced an impression of a withdrawal effect on reward responsivity under a NRN design.

7.2.3 Groups NNN-RRR

In order to investigate the effect of reward in a between-participants design without practice artefacts, I calculated reward responsivity as the average of the three rewarded trials (group RRR) minus the average of the three nonrewarded trials (group NNN). I carried out 2 × 2 × 2 × 2 (Trial × Group × Smoking Status × Dependence) repeated measures ANOVA for groups RRR and NNN. The within-participants factor was trial (trials 1-3). The between-participants factors were group (RRR/NNN), smoking status (withdrawal/satiation), and dependence (low/high). Table 7.4 shows the results of the four-way ANOVA. It can be seen that, with an alpha level of .05, there was a significant main effect of trial and a significant main effect of smoking status but no other significant main effects or interactions.

Table 7.4

Analysis of Variance for CARROT Reward Responsivity (Groups NNN-RRR)

Source	*df*	*F*	*p*
	Between subjects		
Group (G)	1	< 1	.60
Smoking Status (S)	1	7.50	.01
Dependence (D)	1	< 1	.83
G × S	1	< 1	.71
G × D	1	1.09	.30
S × D	1	< 1	.95
G × S × D	1	< 1	.96
Error	36	(.03)	
	Within subjects		
Trial (T)	2	42.49	.00
T × G	2	< 1	.49
T × S	2	1.58	.21
T × D	2	< 1	.86
T × G × S	2	1.47	.24
T × G × D	2	1.21	.30
T × S × D	2	1.54	.22
T × G × S × D	2	1.09	.34
Error (T)	72	(.00)	

Note. Values enclosed in parentheses represent mean square errors.

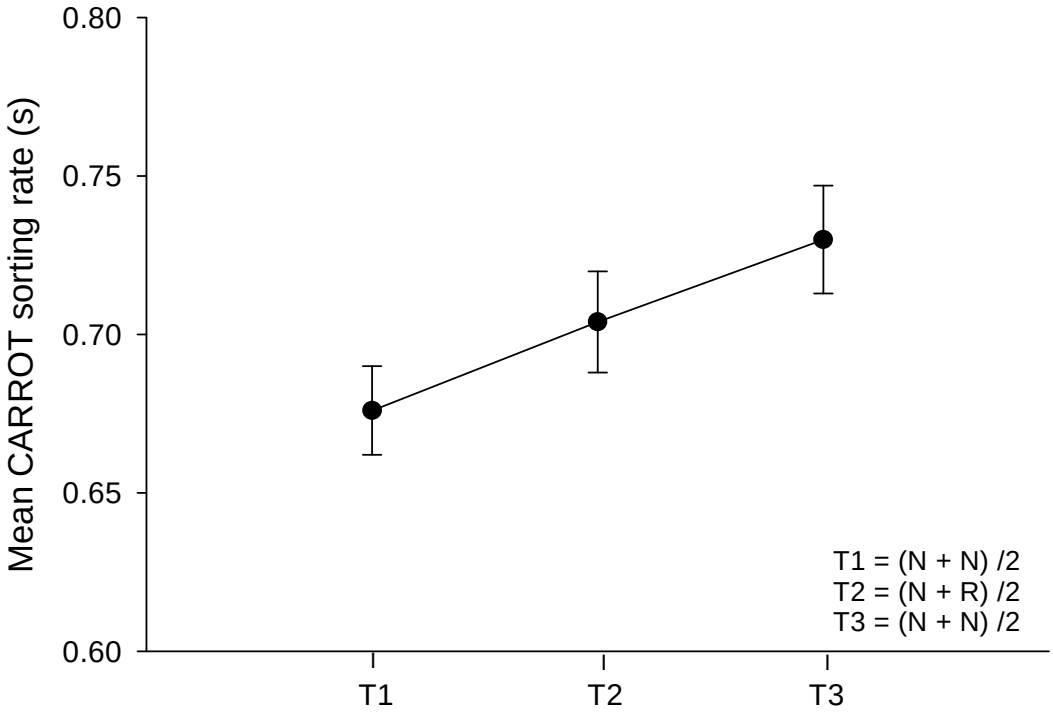

Figure 7.6. CARROT sorting rate across the three trials for groups NNN and RRR combined. Points represent mean CARROT sorting rate in each of the three trials; vertical lines represent standard errors of the means.

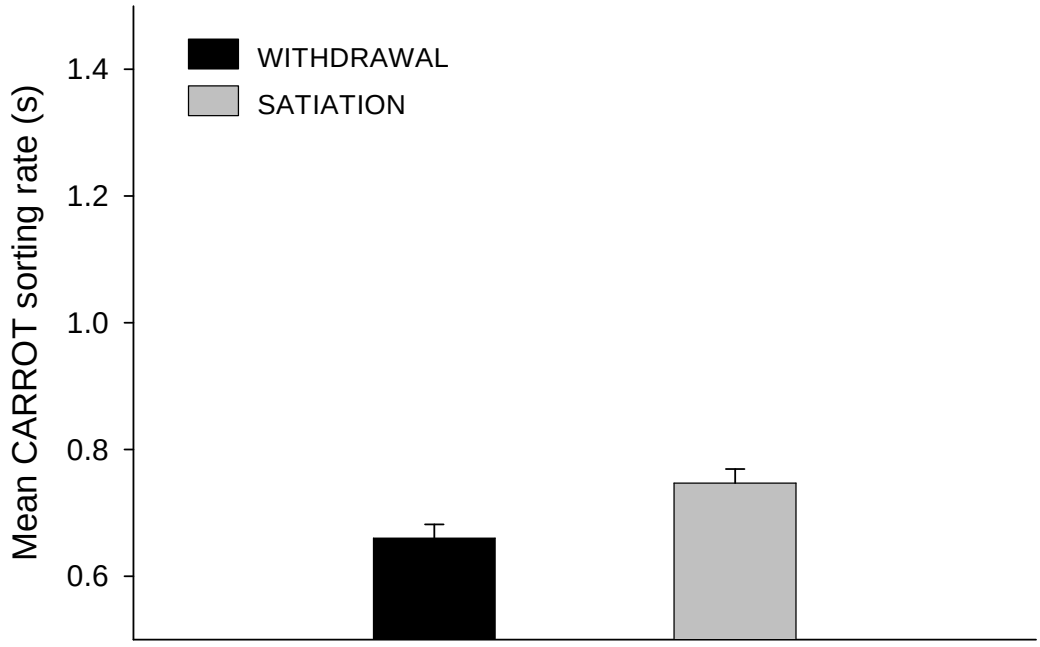

Figure 7.7: Mean CARROT sorting rate (+*SE*) in withdrawal (*n* = 22) and satiation (*n* = 22) in groups NNN and RRR combined.

Figure 7.6 illustrates the main effect of trial (Table 7.4): Mean CARROT sorting rate increased with successive trials. Thus, mean CARROT sorting rate increased from Trial 1 to Trial 2, $t(43) = 4.71$, $p = .00$, and from Trial 2 to Trial 3, $t(43) = 6.60$, $p = .00$. Figure 7.7 illustrates the main effect of smoking status (Table 7.4): Satiated smokers had higher mean sorting rate compared to withdrawn smokers.

Although a main effect of group was expected in the between-participants design where reward responsivity was calculated as (average sorting rate in RRR) – (average sorting rate in NNN), there was not one. That is, participants who completed rewarded trials did not have significantly higher sorting rates compared with participants who completed nonrewarded trials. The main effect of reward was significant only when reward and no reward were manipulated within-participants. This suggests that it was the contrast between reward and no reward that produced the reward effect.

7.3 Discussion

There was an effect of withdrawal on reward responsivity in the within-participants NRN design where reward responsivity was calculated as T2 – (T1 + T3) /2. Thus, the difference between reward and no reward was smaller under withdrawal than under satiation. However, when the effect of withdrawal on reward responsivity—calculated as T2 – (T1 + T3) /2—was assessed using group NNN as control, the main effect of withdrawal on reward responsivity disappeared. There was a main effect of smoking status and a main effect of group. Therefore, satiated smokers had higher reward responsivity scores compared to withdrawn smokers. Moreover, reward responsivity scores were higher in group NRN compared to group NNN. However, these two effects were independent of one another. In other words, the effect of smoking status was similar either reward was present (i.e., group NRN) or absent (i.e., group NNN); the effect of group (or reward) was the same either participants were sated or withdrawn. Thus, practice effects were stronger in satiation compared to withdrawal and stronger under reward compared to no reward. However, the effects of practice and reward did not interact. That is, the T2 – (T1 + T3) /2 value was greater in satiation compared to withdrawal; however, this effect was independent of the presence of reward in Trial 2. In addition, the T2 – (T1 + T3) /2 value was greater in group NRN compared to group NNN; however, this effect was independent of smoking status. Therefore, in the case of the smoking status effect, this was due to participants reaching their maximum sorting rate faster when they were satiated compared to when they were withdrawn; however, this effect was independent of that produced when reward was introduced in Trial 2. The fact that the effect of withdrawal on reward

responsivity was found only when group NRN was examined under a T2 – (T1 + T3) /2 design, but this effect was similar either reward was present or absent when group NNN was included as control, suggests that withdrawal does not impact reward responsivity. Withdrawal interacts with practice effects to produce an impression of a withdrawal effect on reward responsivity under a NRN design.

When the effect of reward was examined in a between-participants design (i.e., groups NNN and RRR) to avoid practice artefacts, reward responsivity was calculated as the average of the three rewarded trials (group RRR) minus the average of the three nonrewarded trials (group NNN). There was a main effect of trial: Mean CARROT sorting rate increased with successive trials. Furthermore, there was a main effect of smoking status: Satiated smokers had higher mean sorting rate compared to withdrawn smokers. However, the effect of group (i.e., reward) was not significant. That is, participants who completed rewarded trials did not have significantly higher sorting rates compared with participants who completed nonrewarded trials. This stands in contrast to earlier results (Study 1, Pilot 2, and Study 3) where a reliable effect of reward was found. It seems likely that this discrepancy is due to the different sensitivities of the within- and between-participants designs. The main effect of reward was significant only when nonreward and reward were manipulated within-participants. Perhaps it was the contrast between nonreward and reward that produced the reward effect in the within-participants design. When that contrast was removed in the between-participants design (NNN – RRR), the effect of reward did not approach statistical significance.

In sum, the results of the present study did not confirm the hypothesis that reward responsivity is reduced in withdrawal. Furthermore, there was no evidence that the difference in reward responsivity scores between satiation and withdrawal was bigger with higher levels of dependency. Thus, there was no evidence in support of the indirect reinforcing properties of nicotine in humans. However, it may be that these effects do exist but are hard to measure with the procedures available due to nicotine's effects on psychomotor performance and attention.

CHAPTER 8

STUDY 5:

SUBJECTIVE MEASURES: REWARD RESPONSIVITY, POSITIVE AND NEGATIVE AFFECT

Reward sensitivity and affect are compromised during nicotine withdrawal (e.g., Epping-Jordan et al., 1998; Hughes & Hatsukami, 1986; Powell et al., 2002) and in nicotine dependence (Breslau et al., 1994; Koob & Le Moal, 2005). Given the complex relationships between reward responsivity and affect (e.g., Esch & Stefano, 2004, Robinson & Berridge, 1993), I decided to look at the effects of smoking status and dependence on reward sensitivity and affect simultaneously. This would provide a more efficient examination.

8.1 Method

In Study 1, Study 2, Study 3, and Study 4, participants filled in the Fagerström Test for Nicotine Dependence (FTND), the Snaith-Hamilton Pleasure Scale (SHAPS), and the Positive and Negative Affect Schedule (PANAS). This chapter examines the effects of smoking status and dependence on these measures.

8.1.1 Participants

Data from 209 smokers was examined. There were 115 males. The average age of the sample was 24 years (minimum = 18 years, maximum = 45 years; *SD* = 5.55). Low dependence smokers (*n* = 111) had a mean FTND score of 1.28 (minimum = 0, maximum = 3; *SD* = 1.10), whereas high dependence smokers (*n* = 98) had a mean FTND score of 5.19 (minimum = 4, maximum = 9; *SD* = 1.34).

8.1.2 Measures and Apparatus

The Expired Carbon Monoxide (ECO) Monitor, the Fagerström Test for Nicotine Dependence (FTND), the Snaith-Hamilton Pleasure Scale (SHAPS), and the Positive and Negative Affect Schedule (PANAS) were used as described in Study 1.

8.1.3 Procedure

Participants attended the laboratory as described in Study 1, Study 2, Study 3, and Study 4 and filled in the SHAPS and the PANAS questionnaires.

8.1.4 Design and Analyses

A 2 × 2 between-participants factorial design was used. The two independent variables were smoking status (withdrawal/satiation) and dependence (low/high). Because there were six dependent variables (the four SHAPS subscales [i.e., Sensory Experience, Food/Drink, Social Interaction, and Interests/Pastimes], the PANAS-Positive Affect [PA], and the PANAS-Negative Affect [NA]), Multivariate Analysis of Variance (MANOVA) was used, as outlined by Field (2005). Significant effects from the overall MANOVA were followed up with univariate ANOVAs to determine the contribution of individual variables.

8.2 Results.

The withdrawal manipulation was successful. An independent samples *t* test showed that the ECO level of participants in satiation (*M* = 17.61; minimum = 1, maximum = 52; *SD* = 10.69; *n* = 106) was significantly higher than the ECO level of participants in withdrawal (*M* = 5.79; minimum = 0, maximum = 15; *SD* = 3.99; *n* = 103), $t(207) = 10.52$, $p \leq .001$ (Because Levene's Test for Equality of Variances was significant, equal variances were not assumed).

With an alpha level of .05, the 2 × 2 MANOVA yielded significant main effects of smoking status, $F(6, 200) = 2.13$, $p = .05$, and dependence, $F(6, 200) = 2.86$, $p = .01$. The Smoking Status × Dependence interaction was not significant, $F(6, 200) = 1.09$, *ns*. In order to determine which variables were responsible for the significant MANOVA tests, those were followed up by univariate ANOVAs on all of the dependent variables. A Bonferroni correction was applied to the subsequent ANOVAs. Significance level after Bonferroni correction was .01.

Table 8.1 shows the results of the ANOVAs. As can be seen, with an alpha level of .01, there was a significant main effect of smoking status on PANAS-PA, a significant main effect of dependence on SHAPS-Social Interaction, and a significant main effect of dependence on SHAPS-Interests/Pastimes. Although significant with an alpha value of .05, the effect of dependence on PANAS-NA did not reach significance using Bonferroni corrected alpha.

Table 8.1

Multivariate Analysis of Variance for Responsivity to Environmental Pleasure/Reward (i.e., SHAPS Subscales: Food/Drink, Sensory Experience, Social Interaction, Interests/Pastimes), Positive Affect (PANAS-PA), and Negative Affect (PANAS-NA)

Source	*DV*	*df*	*F*	*p*
	Between subjects effects			
Smoking Status	Food/Drink	1	<1	.90
	Sensory Experience	1	<1	.91
	Social Interaction	1	1.79	.18
	Interests/Pastimes	1	<1	.53
	PANAS-PA	1	11.29	.00
	PANAS-NA	1	<1	.66
Dependence	Food/Drink	1	1.73	.19
	Sensory Experience	1	<1	.83
	Social Interaction	1	7.51	.00
	Interests / Pastimes	1	7.04	.00
	PANAS-PA	1	<1	.63
	PANAS-NA	1	4.87	.03
Error	Food/Drink	205	(.06)	
	Sensory Experience	205	(.08)	
	Social Interaction	205	(.04)	
	Interests/Pastimes	205	(.09)	
	PANAS-PA	205	(.39)	
	PANAS-NA	205	(.22)	

Note. Values enclosed in parentheses represent mean square errors.

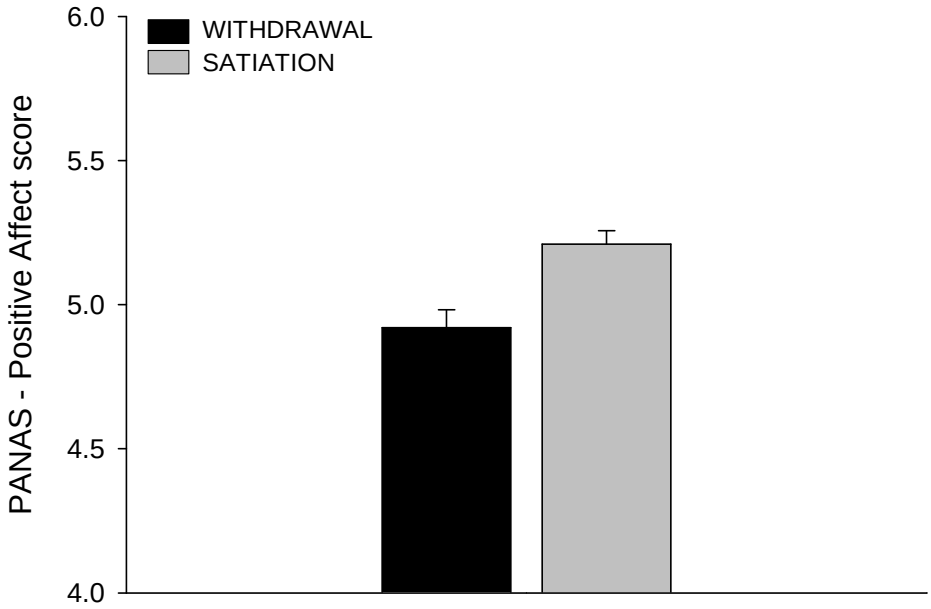

Figure 8.1. Mean positive affect score (+*SE*) in withdrawal (*n* = 103) and satiation (*n* = 106).

Figure 8.1 shows the mean PANAS-Positive Affect score in withdrawal and satiation and illustrates the significant main effect of smoking status (see Table 8.1). As can be seen (Figure 8.1), participants reported significantly higher levels of positive affect when they were under satiation compared to when they were under withdrawal.

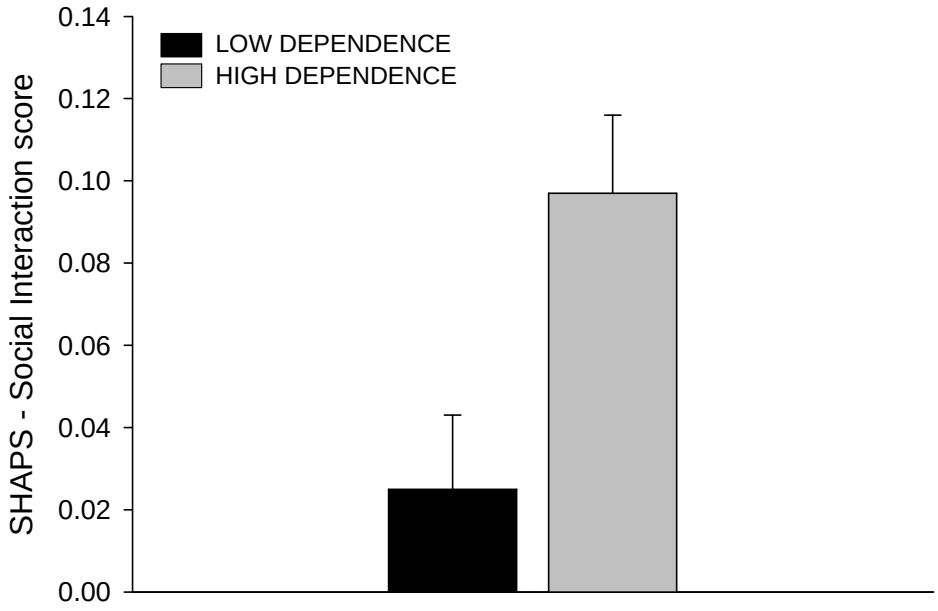

Figure 8.2. Mean SHAPS-Social Interaction subscale score (+*SE*) in low dependence (*n* = 111) and high dependence (*n* = 98).

Figure 8.2 shows the mean SHAPS-Social Interaction subscale score in low and high dependence and illustrates the significant main effect of dependence (see Table 8.1). As can be seen (Figure 8.2), high dependence participants had significantly higher SHAPS-Social Interaction subscale score compared with low dependence participants. That is, high dependence participants reported significantly higher anhedonia or lower ability to experience pleasure/reward associated with their social interactions compared to low dependence participants.

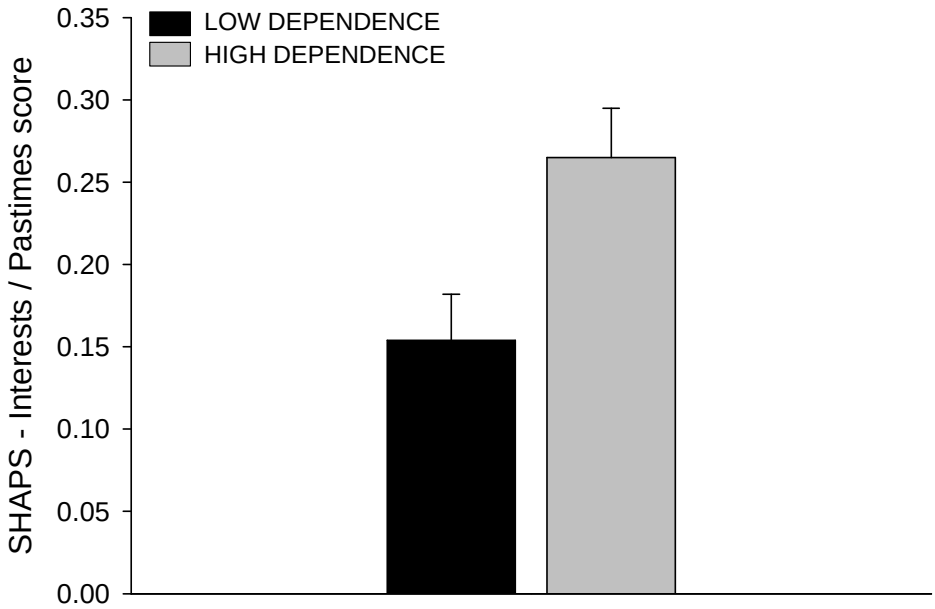

Figure 8.3. Mean SHAPS-Interests/Pastimes subscale score (+*SE*) in low dependence (*n* = 111) and high dependence (*n* = 98).

Figure 8.3 shows the mean SHAPS-Interests/Pastimes subscale score in low and high dependence and illustrates the significant main effect of dependence (see Table 8.1). As can be seen (Figure 8.3), high dependence participants had significantly higher SHAPS-Interests/Pastimes subscale score compared with low dependence participants. That is, high dependence participants reported significantly higher anhedonia or lower ability to experience pleasure/reward associated with their interests and pastimes compared to low dependence participants.

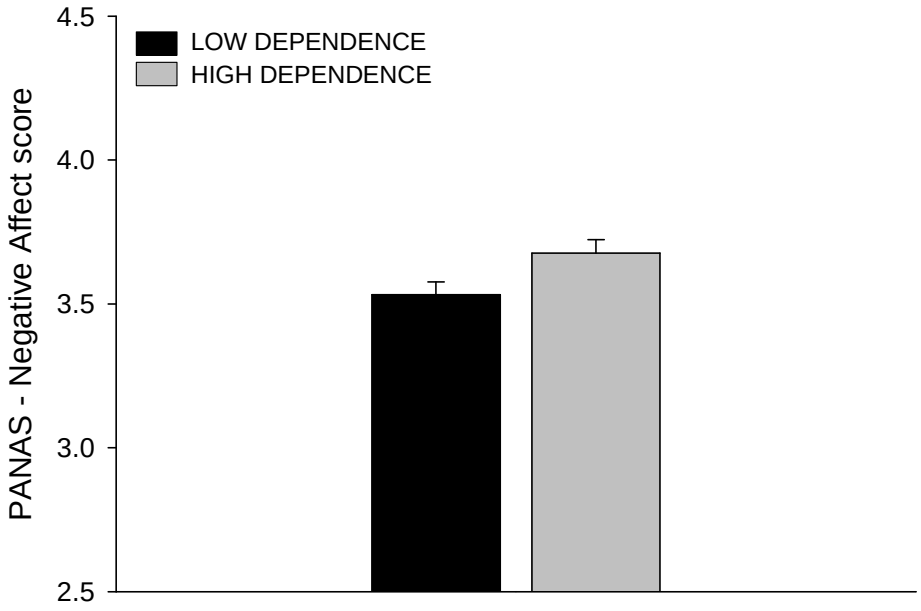

Figure 8.4. Mean negative affect score (+*SE*) in low dependence (*n* = 111) and high dependence (*n* = 98).

Figure 8.4 shows the mean PANAS-Negative Affect score in low and high dependence and illustrates the main effect of dependence, which, although significant at the .05 level (see Table 8.1), did not reach significance using Bonferroni corrected alpha. As can be seen (Figure 8.4), high dependence participants reported higher levels of negative affect compared to low dependence participants.

In sum, satiated smokers reported higher levels of positive affect compared to withdrawn smokers. Moreover, high dependence smokers reported higher levels of negative affect compared to low dependence smokers. In addition, high dependence smokers were less able to respond to pleasure/reward associated with their interests/pastimes and social interactions compared to low dependence smokers.

8.3 Discussion

There was a significant main effect of smoking status on the positive affect measure: Satiated smokers reported significantly higher levels of positive affect compared to withdrawn smokers. This means that one of the reasons smokers self-administer nicotine is to obtain an increase in positive affect; however, this effect did not vary with level of dependency. That is, there was no Smoking Status × Dependence interaction. Both low and high dependence participants reported experiencing similar levels of positive affect in withdrawal. This might be because withdrawal disturbs affect similarly in low and high dependence smokers. Alternatively, the low and high dependence samples of the present study were not different enough to detect a greater effect of withdrawal on positive affect in high dependence participants.

Moreover, there was a main effect of dependence on the negative affect measure: High dependence smokers reported higher levels of negative affect compared to low dependence smokers. Although the effect of dependence was significant at the .05 level, it did not reach statistical significance using Bonferroni corrected alpha. Furthermore, the main effect of dependence on the negative affect measure was not moderated by smoking status. This might be because the negative affect measure (i.e., PANAS-NA subscale) was not sensitive to smoking status. Alternatively, it might be that the affective distress that smokers experience during abstinence is due to decreases in positive affect rather than to increases in negative affect.

The overall SHAPS measure of reward sensitivity was not sensitive to smoking status. That is, there was no indication that withdrawn smokers show reduced ability to experience environmental pleasure/reward compared to

satiated smokers. Furthermore, the effect of smoking status was the same for low and high dependence participants. Powell et al. (2002, 2004) reported reduced ability to experience environmental pleasure/reward in withdrawal in their sample of smokers. This is not consistent with the results of this research (potential reasons for this discrepancy are discussed in Section 9.1.1.2).

There was a significant main effect of dependence on two out of the four SHAPS subscales: the Interests/Pastimes subscale and the Social Interaction subscale. Thus, highly dependent participants reported significantly less ability to experience pleasure/reward associated with their interests/pastimes and social interactions compared to low dependence participants. This may suggest that impairments in responsivity to environmental pleasure/reward develop with chronic nicotine administration. Deficits in environmental pleasure/reward were not observed among the low dependence participants. This could be because deficits in sensitivity to environmental pleasure/reward are too small to observe among the low dependence smokers. Alternatively, such deficits have not started developing yet.

Although it was expected that the difference in ability to experience environmental pleasure/reward between withdrawal and satiation would be bigger in highly dependent smokers, this was not the case. This might be because the present dependence sample had medium to low levels of dependency. If disturbances in reward sensitivity develop with chronic nicotine administration, then a more dependent sample than the one of the present research would be more appropriate.

In sum, although smokers self-administered nicotine in order to increase their levels of positive affect, with the development of dependence higher levels

of negative affect were reported. Moreover, highly dependent smokers were less able to experience pleasure/reward associated with their social interactions and interests/pastimes compared to low dependence smokers. This provides some support for nicotine's indirect reinforcing properties.

CHAPTER 9

GENERAL DISCUSSION

9.1 Key Results and Implications

9.1.1 Reward Responsivity

9.1.1.1. Behavioural Measure: CARROT

One of the reasons smoking is maintained is because nicotine has reward-enhancing actions. That is, nicotine can increase responsivity to reward (e.g., Chaudhri et al., 2006). Consistent with this, results from animal studies have shown that nicotine can lower the threshold for rewarding brain stimulation (Bauco & Wise, 1994; Bespalov et al., 1999; Huston-Lyons & Kornetsky, 1992; Huston-Lyons et al., 1993; Ivanova & Greenshaw, 1997; Olds & Miner, 1954), whereas abstinence from nicotine produces elevations in rewarding brain stimulation (Epping-Jordan et al., 1998). Furthermore, nicotine can enhance responding for a reinforcing nonnicotine stimulus (Chaudhri, 2005; Chaudhri et al., 2006; Donny et al., 2003; Popke et al., 2000). More specifically, nicotine can enhance behaviour maintained by unconditioned (Donny et al., 2003) and conditioned reinforcers (Chaudhri, 2005). However, these studies (i.e., Chaudhri, 2005; Donny et al., 2003) did not assess the effect of withdrawal on the behaviour maintained by other reinforcers.

In humans, the effect of smoking status on the reward-enhancing properties of nicotine was assessed in four studies (Al-Adawi & Powell, 1997; Powell et al., 2002, 2004; Smolka et al., 2004). Investigators in all four studies used the CARROT (Powell et al., 1996) to measure reward responsivity. The results they reported were consistent: Abstinent smokers showed reduced reward responsivity compared to satiated smokers. Researchers concluded that, in

humans, nicotine administration increases sensitivity to reward, whereas nicotine withdrawal decreases sensitivity to reward. However, the results of the present research suggest that human studies on the effects of nicotine on reward responsivity, measured behaviourally using the CARROT task (e.g., Al-Adawi and Powell, 1997; Powell et al., 2002, 2004; Smolka et al., 2004), are limited due to the methodology they employed. Thus, what has been reported as an effect of withdrawal on reward responsivity is actually an impression of a withdrawal effect. It is produced because practice effects (i.e., improvements in performance over time or over successive CARROT trials) are stronger in satiation compared to withdrawal. That is, card-sorting performance across a series of three CARROT trials improves faster under satiation compared to under withdrawal. This was not evident in the published studies (e.g., Al-Adawi & Powell, 1997; Powell et al., 2002, 2004; Smolka et al., 2004) because a control condition was not employed. In this research, when I used a control group (i.e., all trials non-rewarded) to examine whether practice effects might interact with reward effects, I found that the effects of reward and practice (i.e., smoking status) were independent of one another. Furthermore, when I examined reward responsivity between-participants to avoid practice artefacts, the effect of reward did not approach statistical significance.

In addition, although highly dependent smokers should experience more severe withdrawal compared to low dependence smokers, withdrawal effects on reward responsivity were the same for low and high dependence participants. This suggests that withdrawal effects are present even in low dependence smokers. Alternatively, the high dependence sample was not dependent enough; most FTND scores were at the low (1-3) and middle range (3-6).

Overall, there was no evidence to support the hypothesis that reward responsivity (measured behaviourally) is compromised during nicotine withdrawal. The results showed that withdrawal affected task performance independent of reward responsivity. Thus, the results of this research do not provide support to the view that nicotine has indirect reinforcing properties in humans (as measured by the CARROT task).

9.1.1.2 Subjective Measure: SHAPS

In the present research, I used the SHAPS to complement the behavioural measure of reward responsivity (CARROT). Investigators reported that withdrawn smokers show reduced ability to experience environmental pleasure/reward (i.e., elevated scores on the SHAPS) compared with satiated smokers (e.g., Powell et al., 2002, 2004). Thus, in this research, the aim was to replicate the finding of reduced ability to experience environmental pleasure/reward under withdrawal and to investigate the differences in ability to experience environmental pleasure/reward in withdrawal and satiation between low and high dependence participants.

The overall SHAPS measure of reward responsivity was not sensitive to smoking status. That is not consistent with the findings of Powell et al. (2002, 2004) who reported that withdrawn smokers show reduced ability to experience environmental pleasure/reward (i.e., elevated scores on the SHAPS). This is unlikely to be due to a difference in the level of dependence (and hence withdrawal severity) in the present sample because the mean FTND score of the present sample is comparable to that of Powell et al.'s (2002). The discrepancy between the findings reported by Powell et al. (2002) and the results of the present research might be due to potential differences in the characteristics of

the sample that were not accounted for. For example, pre-existing depressive symptoms in the sample of Powell et al. might have been exacerbated during nicotine withdrawal; thus, they contributed to reduced responsivity to environmental pleasure/reward. There is no information regarding the FTND score of participants in the study by Powell et al. (2004). Therefore, comparisons cannot be made. Clearly, the effect of smoking status on SHAPS reward sensitivity reported by Powell et al. (2002, 2004) requires replication.

There was a significant main effect of dependence on two out of the four SHAPS subscales: the Interests/Pastimes subscale and the Social Interaction subscale. Thus, highly dependent participants reported significantly less ability to experience pleasure/reward associated with their interests/pastimes and social interactions compared to low dependence participants. It might be that deficits in sensitivity to environmental pleasure/reward are too small to observe among the low dependence smokers. Alternatively, such deficits have not started developing yet. The fact that, unlike low dependence smokers, highly dependent smokers were not able to respond to pleasure/reward (associated with their interests/pastimes and social interactions) provides support to the argument that impairments in responsivity to environmental pleasure/reward develop with chronic nicotine administration. An interesting finding is that dependence had an effect only on the two SHAPS subscales that tap on the construct of motivation (i.e., the Interests/Pastimes and Social Interaction subscales). Dependence had no effect on the other two SHAPS subscales that measure sensory gratification (i.e., the Food/Drink and Sensory Experience subscales). Again, this provides support to the argument that normal motivational processes are compromised in nicotine addiction.

The effect of dependence on the Interests/Pastimes and Social Interaction subscales was not moderated by smoking status. That is, the difference in the two SHAPS subscales scores between withdrawal and satiation was not greater with higher levels of dependence. This could be because the high dependence sample of the present research was not dependent enough (i.e., mean FTND score greater than 7). If disturbances in reward responsivity (as measured by the SHAPS subscales) develop with chronic nicotine administration, then a more dependent sample would be more appropriate to examine the differences in environmental pleasure/reward in satiation and withdrawal between low and high dependence participants.

In sum, although there was no evidence that responsivity to reward (as measured by the SHAPS) was compromised in withdrawal or that the difference in reward responsivity between satiation and withdrawal was higher with higher levels of dependency, the main effects of dependence on the Interests/Pastimes and Social Interaction subscales provide some support for nicotine's indirect reinforcing properties.

9.1.2 Satiation and overall CARROT Sorting Rates

Satiated smokers increased their sorting rate speed from trial to trial more than withdrawn smokers did. In addition, satiated smokers had significantly higher overall CARROT sorting rates compared to withdrawn smokers. Given the nature of the CARROT task, nicotine's effects on arousal, and thus on psychomotor performance and attention, might explain the effect of smoking status on CARROT sorting rates.

The arousing effects of smoking include heightened cardiovascular activity and electroencephalography (EEG) indices of heightened arousal

(Knott, Bosman, Mahoney, Ilivitsky, & Quirt, 1999). Arousal increases when nicotine is given to deprived smokers, whereas nicotine deprivation generally leads to decreased arousal (Parrott, 1998). Because of its effects on arousal, smoking, in comparison with continued abstinence, tends to increase task performance; thus, sated smokers generally show better task performance than deprived smokers do (Heishman, Taylor, & Henningfield, 1994; Parrott & Roberts, 1991; Sherwood, 1993). Through its effects on arousal, nicotine may improve performance by improving psychomotor speed (Houlihan, Pritchard, & Robinson, 1996) and/or by improving ability for a more efficient allocation of attentional resources (Knott, Kerr, Hooper, & Lusk-Mikkelsen, 1995).

Psychomotor performance can be assessed by measuring the finger-tapping rate of participants. That is, participants tap a key on a computer keyboard with a finger of their preferred or nonpreferred hand. The number of key taps in a particular amount of time (or the time taken to make a certain number of key taps) is taken as a measure of psychomotor performance. Administration of nicotine (in the form of cigarettes or nasal spray) increased finger-tapping rate compared with no smoking, sham smoking, or placebo nasal spray in smokers who were deprived of nicotine from 1 to 12 hours (Perkins et al., 1990; Roth & Battig, 1991). In a study of 118 fire-fighter recruits, successful job performance was assessed by looking at the length of time (in minutes) required to complete five different job-related tasks. Tasks were performed sequentially in the same order without pausing while wearing full protective gear and demand-breathing apparatus. Smokers (n = 43) and nonsmokers (n = 75) did not differ significantly in performance on tasks that required mostly upper arm strength in a relatively stationary stance (e.g., raising a ladder).

However, nonsmokers took significantly less time than smokers did to carry a standpipe hose load up four flights of stairs. Moreover, nonsmokers required less time than smokers did to complete the simulated rescue of a dummy from the fifth floor of a building. Participants did these tasks sequentially. The smokers took about 27% longer than did the nonsmokers to perform all tasks. Because smokers were not allowed to smoke during the tasks, it is possible that they were in some form of withdrawal that slowed their performance (Fowler, 1989). These results illustrate the stimulant actions of nicotine on psychomotor performance. Because the CARROT requires speed in card sorting, nicotine-induced increases in psychomotor activation could be interpreted as enhanced performance in the CARROT.

CARROT performance also requires sustained attention (vigilance) to detect and respond to changes in the numbers that appear on the cards and selective attention in order to attend to the target number on the card while simultaneously ignoring the irrelevant or distracting numbers. Accurate card sorting meant quick card sorting. Participants were required to correct mistakes in card sorting (when they realised they made them) by placing the cards in the correct boxes. Thus, insufficient attention to the numbers on the cards during card sorting and subsequent inaccuracy decreased card-sorting speed.

Nicotine has been shown to reliably reverse attentional deficits associated with withdrawal (e.g., Mancuso et al., 1999; Sherwood et al., 1992). For example, nicotine administration reversed deprivation-induced deficits in vigilance, and subsequent doses maintained normal functioning (Hasenfratz & Bättig, 1993; Foulds et al., 1996; Mancuso et al., 1999; Sherwood et al., 1992; Waller & Levander, 1980; Warburton & Mancuso, 1998). A study examining

the effects of nicotine on overnight performance showed that nicotine prevented the natural fatigue-related decreases in vigilance and thus in attentional performance (Parkin, Fairweather, Shamsi, Stanley, & Hindmarch, 1998). Similarly, nicotine administration to deprived smokers reversed withdrawal-induced deficits in performance in measures of selective attention, such as the Stroop task (e.g., Hasenfratz & Bättig, 1993; Landers et al., 1992) and letter search tasks (e.g., Parrot & Roberts, 1991; Snyder & Henningfield, 1989). Finally, in smokers who were abstinent for 1 hour, smoking increased the suppression of distracting information, thus enhanced attentional performance, compared to sham smoking (Rodway et al., 2000).

Overall, the evidence suggests that nicotine can increase arousal and reverse psychomotor and attentional deficits associated with withdrawal. In addition, nicotine can prevent fatigue-related decreases in psychomotor and attentional performance. Consistent with this, satiated smokers had significantly higher overall CARROT sorting rates compared to withdrawn smokers and increased their sorting rate speed from trial to trial more than withdrawn smokers did.

These findings might be due to three reasons or combinations of those.

First, this result might be consistent with negative reinforcement theories of addiction (e.g., Siegel, 1983; Wikler, 1948). According to these theories, drugs are self-administered because of the state they alleviate, in this case psychomotor and attentional deficits associated with withdrawal. Nicotine may be initially self-administered for its positively reinforcing properties, that is, for an absolute enhancement in psychomotor performance (e.g., Tucha & Lange, 2004; West & Jarvis, 1986). However, the fact that withdrawn smokers had

significantly lower sorting rates compared to satiated smokers may suggest that psychomotor and attentional performance were compromised during withdrawal. Thus, it may be that, with the development of dependence, smokers self-administer nicotine primarily in order to reverse deficits in performance associated with nicotine withdrawal.

Second, it may be that the present sample of smokers had inherent deficits in psychomotor and attentional performance, which increased the risk of taking up smoking in the first place. In this case, self-administration of nicotine would also be negatively reinforcing because it would serve to reverse inherent deficits. Because there is no information regarding participants' psychomotor and attentional performance before they initiated smoking, it is difficult to determine whether nicotine was self-administered in order to reverse inherent deficits or withdrawal-induced deficits in performance.

Finally, it may be that increases in performance observed among satiated smokers were absolute; that is, smokers' psychomotor performance increased with every cigarette smoked. In that case, nicotine self-administration would be positively reinforcing. However, unless researchers tested satiated smokers' psychomotor performance every time smokers had an additional cigarette and found that psychomotor performance increased, it is hard to draw conclusions about whether nicotine administration is positively reinforcing.

In sum, the fact that satiated smokers had higher CARROT sorting rates compared to withdrawn smokers may be either due to nicotine's positive or negative reinforcing properties, or both.

9.1.3 Smoking Status and Positive Affect

Satiated smokers reported significantly higher levels of positive affect compared to withdrawn smokers. This means that one consequence of smoking is an elevation in affect; thus, smokers might well self-administer nicotine in order to obtain this effect. This finding is in agreement with the results of studies that showed that low levels of positive affect maintain smoking behaviour by increasing nicotine craving during withdrawal (e.g., Cook, Spring, McChargue, Borrelli, et al., 2004); thus, decreasing the likelihood of nicotine abstinence (e.g., Al'Absi et al., 2004). The effect of smoking status on positive affect did not vary with level of dependency. In other words, the affective distress that smokers experienced during nicotine withdrawal was not greater for the highly dependent participants of the present sample. This suggests that, at least in the present dependence sample, withdrawal disturbed affect similarly whether participants were highly dependent or not. It might be that decreases in positive affect are an aspect of nicotine withdrawal that sets in early in a smoker's career and does not progress further with time (i.e., with increasing levels of nicotine use). Alternatively, it might be that the low and high dependence samples of the present study were not different enough to detect a greater effect of withdrawal on positive affect in the high dependence sample. The mean FTND score of the high dependence participants in this study was 5.22. The mean FTND score of the low dependence participants was 1.28. Scores on the FTND range from 0 (*low dependence*) to 10 (*high dependence*). If a high dependence sample had a mean FTND score higher than 7, then it might be possible to detect a greater difference in levels of positive affect between withdrawal and satiation for the highly dependent sample. However, this has yet to be examined.

The finding that smokers self-administer nicotine to increase feelings of pleasure might be consistent with the positive reinforcement theory of addiction (e.g., Stewart et al., 1984, Wise & Bozarth, 1987). According to this theory, drugs are self-administered because of the state they induce, that is, pleasure or positive affect. Nicotine, like other psychostimulant drugs, increases DA release in the nucleus accumbens. This mediates the rewarding properties of the drug, which reinforce its self-administration (Wise & Bozarth, 1987). Furthermore, increased stimulation of DA receptors is associated with increased incentive learning or the attribution of increased incentive salience to the cues associated with acquisition and delivery of the drug (e.g., Balfour, Wright, Benwell, & Birrell, 2000). In addition, the mood-elevating effects of drugs are due to their reward-enhancing effects (Ahmed & Koob, 2005). Thus, according to positive reinforcement theories of addiction, drugs are self-administered for their primary reinforcing effects (i.e., increases in pleasure or positive affect).

The finding that satiated smokers reported significantly higher positive affect compared to withdrawn smokers does not provide support to the notion of addiction as proposed by Robinson and Berridge (1993). They argue against a pleasure-seeking interpretation of drug self-administration. They believe that it is not the pleasure or liking associated with drug taking that motivates continued drug use but sensitisation-induced excessive wanting that is independent of liking. Although this distinction was not tested in this thesis, the finding of higher positive affect among satiated smokers suggests that nicotine self-administration occurs, at least in part, because nicotine is liked, that is, it produces pleasure or positive affect.

Because administration of nicotine relieves symptoms of withdrawal (e.g., dysphoria and depressed mood), it is possible that smokers self-administer nicotine to increase feelings of pleasure (i.e., positive affect) that are compromised during drug withdrawal. This would be consistent with negative reinforcement theories of addiction (e.g., Siegel, 1983; Wikler, 1948). According to these theories, drugs are self-administered not because of the state they induce (i.e., pleasure/positive affect) but because of the state they alleviate, that is, depressed mood associated with withdrawal and/or other non-drug aversive states (e.g., pre-existing depression).

Other theories have explained drug administration as an interplay between both positive and negative reinforcement. For example, Solomon and Corbit (1974, 1977), in their opponent process theory, claimed that drugs initiate an a-process that is experienced as drug pleasure. Activation of the a-process results in initiation of a b-process that opposes the a-process. This serves to counteract the effect of the drug and return the body to homeostasis. The sum result of those two opposing processes is the subjective hedonic state experienced by the individual. These hedonic states are either positively reinforcing A-states (pleasurable) or negatively reinforcing B-states (aversive), according to the strength of the a- and b- processes. Solomon and Corbit also posited that repeated drug use strengthens the b-process and, as a result, tolerance to the pleasurable effects of the drug develops. Thus, with repeated drug use, higher drug doses are required to gain the same pleasurable drug experience as was initially experienced. With repeated drug use, the b-process becomes so strong that it results in withdrawal symptoms when the drug is

discontinued. Thus, drug use is maintained both to achieve a pleasurable A-state and to avoid an unpleasant B-state.

In sum, it is difficult to determine whether the higher positive affect reported by satiated smokers (as compared to withdrawn smokers) is positively- or negatively-reinforced behaviour. A comparison of levels of positive affect between satiated smokers, withdrawn smokers, and nonsmokers might shed further light on this question. For example, if nonsmokers reported lower positive affect compared to satiated smokers, then it might be argued that smoking behaviour is positively reinforced. If, on the other hand, nonsmokers reported higher or similar levels of positive affect as satiated smokers did, it might be argued that smoking behaviour is negatively reinforced. However, the fact that smokers and nonsmokers differ on a variety of genetic, personality, and environmental factors (Gilbert, 1995) suggests that nicotine may differentially affect these groups. This might limit interpretations of results when comparing smokers with nonsmokers. Ideally, researchers would have to measure the positive affect levels of smokers before and after they took up smoking in order to draw some conclusions as to whether their smoking behaviour is positively or negatively reinforced.

9.1.4 Dependence, Responsivity to Environmental Pleasure/Reward, and Negative Affect

High dependence participants reported reduced ability to experience pleasure/reward derived from their interests/pastimes and social interactions. The fact that high dependence smokers differed significantly from low dependence smokers on aspects of motivation and not on aspects of sensory gratification (i.e., food/drink and sensory experience) provides support to the

argument that normal motivational processes are compromised with increasing levels of dependency.

In addition, high dependence participants reported higher levels of negative affect. This result is consistent with findings from previous research (e.g., Becona et al., 1999; Breslau et al., 1994). In the study by Becona et al., dependence was measured by daily cigarette consumption. Affect was measured using the PANAS. The sample of smokers in Becona et al.'s study was divided into four groups according to their daily cigarette consumption: 0 (nonsmoking), 1 to 15, 16 to 30, and 31 or more cigarettes/day. There were significant differences in negative affect between groups 1 to 15 versus 31 or more cigarettes/day. The group smoking 31 or more cigarettes/day reported significantly higher levels of negative affect compared to the group that smoked 1 to 15 cigarettes/day. Although in the present study a different dependence measure was used (i.e., FTND score), the results of the present study are similar to those by Becona et al. These findings provide support to the argument that higher levels of dependency are associated with higher levels of negative affect. Furthermore, the main effect of dependence on negative affect is consistent with the results of a study by Breslau et al. (1994). They found that affective distress was associated more with heavy smoking and nicotine dependence and less so with intermittent or nondependent smoking. The main effect of dependence on negative affect was not moderated by smoking status. This might suggest that the negative affect measure (i.e., PANAS-NA subscale) was not sensitive to smoking status. It might be that the affective distress that smokers experience during abstinence is due to decreases in positive affect rather than to increases in negative affect.

The main effects of dependence on the SHAPS subscales and on the negative affect measure fit in well with Koob and Le Moal's (1997, 2001, 2005) model of addiction. According to this model, negative reinforcement mechanisms operate in the maintenance of nicotine addiction. Koob and Le Moal (2005), in a modification on Solomon and Corbit's (1974, 1977) opponent-process theory, suggested that dependence might involve a change in hedonic set point that includes decreased reward sensitivity and increased aversive emotional states. The acute reward-enhancing and mood-elevating effects of nicotine would be followed by opposing reactions that would tend to return the system to its initial level of hedonic capacity (i.e., homeostasis). However, with continued increased drug self-administration the opponent process would fail to return the system to homeostasis before drug taking began again. This chronic deviation of the reward system from its homeostatic level would manifest as decreased reward sensitivity and increased negative affect; that is, an allostatic state. Because the allostatic state described by Koob and Le Moal would be a result of chronic increased drug self-administration, the disturbances in reward sensitivity and mood would become larger with increasing levels of nicotine dependency. Consistent with this, highly dependent smokers reported significantly higher levels of negative affect and reduced ability to experience environmental pleasure/reward compared to low dependence smokers.

In sum, the main effect of dependence on responsivity to some aspects of environmental pleasure/reward provides only weak support for the indirect reinforcing properties of nicotine. The main effect of dependence on negative

affect and on responsivity to environmental pleasure/reward is consistent with a negative reinforcement model of addiction (e.g., Koob & Le Moal, 2005).

9.2 Limitations and Further Research

9.2.1 Behavioural Measure: CARROT

What has been reported as an effect of withdrawal on reward responsivity in humans (measured behaviourally using the CARROT task; e.g., Al-Adawi & Powell, 1997; Powell et al., 2002, 2004; Smolka et al., 2004) is an impression of a withdrawal effect. It is produced because improvement in card-sorting performance over a series of three CARROT trials (i.e., practice effects) is faster in satiation compared to withdrawal. That does not necessarily mean that an effect of withdrawal on reward responsivity does not exist in humans. It may exist, as the animal data suggest, but the psychomotor effects of nicotine may mask it. In animal studies of ICSS, the effects of nicotine on performance were dissociated from its effects on reward (e.g., Gallistel & Karras, 1984; Miliaressis et al., 1986; Zarevics & Setler, 1979). Therefore, procedures that discriminate between drug-induced performance effects and drug-induced reward effects need to be employed in human studies of reward sensitivity.

One way towards dissociating nicotine's effects on psychomotor performance from its effects on CARROT reward responsivity might be to give participants extended practice trials. This might shift learning from an action-outcome (A-O) form to a stimulus-response (S-R) or "habit" one. In the S-R form of learning (i.e., habit), attentional processes are not engaged. Therefore, nicotine's effects on attentional performance might not interfere with nicotine's effects on reward responsivity.

In recent years, the view that learning can take two fundamentally different forms has become increasingly popular (Yin & Knowlton, 2006). The S-R habit learning (Hull, 1943) is one in which the occurrence of a stimulus automatically elicits a response without any anticipation of the consequences. That is, behaviour is not guided by outcome expectancy; it is controlled by antecedent stimuli (Everitt & Robbins, 2005). According to the S-R theory of learning, the occurrence of the stimulus will activate a response in an automatic way, that is, without requiring attention. Furthermore, the outcome is not part of the S-R association but merely strengthens or weakens it (Robbins & Everitt, 1999; Yin & Knowlton, 2006). The other form of learning is the A-O one whereby knowledge is stored in the form of an expectation that can be recalled as needed to plan behaviour. For example, both animals and humans can encode the casual relationships between their actions and the outcome. Moreover, both animals and humans can control their actions according to their anticipation of, and desire for, the outcome. Thus, A-O learning is controlled by the consequences or outcomes of actions (Dickinson, 1985; Yin & Knowlton, 2006).

Extensive research showed that the amount of training or practice (in particular the number of rewarded responses) is a crucial factor in determining the shift from A-O to S-R control over behaviour; that is, habit formation (Yin & Knowlton, 2006). Therefore, overtraining or extended practice tends to promote habit formation (Adams, 1982; Colwill & Rescorla, 1988; Dickinson, Balleine, Watt, Gonzalez, & Boakes, 1995). In other words, extended practice can transform an action into a simple habit that is relatively autonomous of the value of its original goal (Dickinson, 1985; Everitt & Robbins, 2005). As

Dickinson observed, during extended practice, the animal no longer experiences a correlation between variations in performance and variations in the associated consequences. This is because, with extended practice, the animal tends to respond in a consistently high rate; thus, experiences little change in the rate of reward. As a result, responding becomes habitual. Similarly, and for example, interval schedules (where a response is rewarded after a certain time interval has elapsed) tend to promote habit formation because the correlation between response rates and reward rates is low (Dickinson, 1985; Yin & Knowlton, 2006). On the other hand, ratio schedules (where a response results in a certain probability of reward with more responses yielding more rewards) produce goal-directed actions controlled by the A-O contingency. This is because ratio schedules set up a strong correlation between response rates and reward rates (Dickinson, 1985; Yin & Knowlton, 2006). In sum, as Dickinson argued, a well-documented account of habit formation is that:

> Instrumental behaviour, which starts out as an action controlled by knowledge about its relation to the goal, with repeated practice becomes a response, autonomous of the current value of the goal and simply triggered by the stimuli in whose presence it has been repeatedly performed. (p. 72)

One simple example of the above in human behaviour is the learning of motor skills, such as driving. At first, learners have to pay close attention to what they are doing. However, with practice, the movements become automatic or habitual. That is, the learner can drive without thinking about it and can even carry on a conversation at the same time. Similar automation or habit formation occurs in perceptual learning. For example, initially in letter-identification tasks, participants responded slowly and found it difficult to concentrate on more than

one targets presented simultaneously. With practice, however, participants' performance improved substantially. Eventually, they could carry out the task automatically or habitually without any decrements in their performance when multiple targets were presented (Schneider & Shiffrin, 1977). The authors concluded that with extended practice strong associations are formed between the perception of a letter and the response to it. When these associations become sufficiently strong, the process occurs automatically or habitually at great speed and without conscious attention.

The above observations suggest that giving participants extended practice trials on the CARROT task might make their card-sorting behaviour habitual. That is, with extended practice trials participants might reach a point where they sort the cards to their corresponding piles automatically or habitually. The aim would be to give enough practice trials so that both satiated and withdrawn participants reach their asymptotic sorting rate. If card sorting became habitual and attentional processing was no longer required to sort the cards, then it might be possible to examine whether the introduction of reward during the CARROT task would increase participants' sorting rates from asymptote. If introduction of the reward increased sorting rates above the asymptote, then it might be argued that there was an effect of reward that was not confounded by practice effects. It would be expected that sorting rate under reward would increase more for satiated smokers than it would for withdrawn smokers. However, researchers still have to examine this.

Another possible way to bring out the effects of nicotine on reward responsivity might be to increase the reward, that is, the amount of money given to participants. The CARROT measures reward responsivity by measuring

responsiveness to financial incentive. Because money is a conditioned reinforcer, according to results from animal studies, nicotine (as opposed to abstinence) should enhance responding for that conditioned reinforcer. Furthermore, the impact of the reinforcement-enhancing effects of nicotine should lessen with stimuli of decreasing reinforcing strengths (e.g., Chaudhri, 2005). In other words, operant responding should decrease as the reinforcing value of the operant that supports responding decreases. As Herrnstein (1970) put it in his theory of response strength, which became known as the matching law, the absolute rate of any response is proportional to its associated reinforcement. Thus, if participants received a larger amount of money, then they would increase their card-sorting rate more. In the present research, participants received 10 pence for every five cards sorted accurately. Failure to find an effect of reward in the between-participants design and failure to reproduce the Reward x Smoking Status interaction reported in the literature might be because the amount of money participants received in the rewarded trials was not large enough. As such, it did not produce significant increases in sorting rate under reward or a significant difference in reward responsivity between satiated and withdrawn smokers. Thus, in future research using the CARROT, the value of the monetary reward could be increased. This monetary increase might make the effect of reward apparent. Furthermore, it might make the measure more sensitive to the impact of withdrawal on reward sensitivity.

Moreover, alternative measures of motivation, such as the progressive ratio (PR) procedure, might be used. The PR procedure involves responding on a button in order to obtain a reinforcer (e.g., cigarettes or money) under a progressively increasing work requirement (i.e., if five responses are required

for the first reinforcer, then the response requirement doubles for every subsequent reinforcer). The point at which the participant stops working to obtain an increasingly infrequent reinforcer is termed “the breaking point” (Hodos, 1961) and provides a measure of motivational strength. Hodos argued that this procedure could measure reward strength guessing that better rewards would lead to higher breaking points. It was also argued that the PR procedure is sensitive to changes in dopaminergic tone (Carr, Vaca, & De Krahne, 2004). As such, the PR may be a good measure for assessing nicotine’s effects on reward motivation. If reward responsivity is compromised during withdrawal, then it might be expected that withdrawn smokers’ breaking point would be much lower that that of satiated smokers. Because withdrawn smokers might not perceive the reward as “good enough” or “rewarding”, they might stop responding for it sooner that satiated smokers would.

Thus, if an effect of withdrawal on reward responsivity does exist in humans, then the use of alternative procedures and measures might be necessary in order to detect it. Once the effect is detected, then researchers could examine whether or not the reward responsivity disturbance seen in abstinent smokers reflects a symptom of withdrawal. It could equally represent a deficit that preceded onset of regular smoking.

Smokers who have low reward sensitivity prior to taking up smoking might initiate smoking in an attempt to normalise their inherited deficit in reward sensitivity. For example, there is genetic evidence that low levels of dopaminergic function (and hence reward responsivity) prior to becoming highly nicotine dependent is a vulnerability factor (Noble, 1997; Noble, Jeor, & Ritchie, 1994). Prospective studies are needed in order to clarify whether the

observed deficits during smoking abstinence developed during chronic smoking or preceded the onset of smoking.

If the deficits during withdrawal are due to chronic smoking, then it could be assumed that chronic nicotine consumption potentially leads to neural adaptations that manifest during withdrawal as impairments of motivation. To test the hypothesis that disturbances in motivation (as indexed by reward responsivity) develop with time, it would be necessary to examine differences in reward responsivity between withdrawal and satiation in both low and high dependence participants. Such an investigation would require samples of smokers with high levels of dependency. Alternatively, disturbances in reward function may be established early in smokers' career and do not progress further with time. This would suggest that, to detect any differences in the effect of withdrawal on reward responsivity between different levels of dependence (and possibly the point at which the underlying dopaminergic disturbance becomes manifest), the most appropriate comparison would be between smokers who have only recently taken up smoking and long-term low dependence smokers.

Establishing an effect of withdrawal on reward responsivity (measured behaviourally) and examining the time course of that effect are crucial steps in research into the indirect reinforcing properties of nicotine in humans.

9.2.2 Subjective Measure: SHAPS

There was no indication that responsivity to environmental pleasure/reward was reduced in withdrawal. This is not consistent with previous findings where, compared with satiated smokers, withdrawn smokers showed reduced ability to experience environmental pleasure/reward (e.g., Powell et al.,

2002, 2004). This inconsistency might be due to potential differences in the characteristics of the sample that were not controlled for (see Section 9.1.1.2).

In addition, it might be that failure to find an effect of withdrawal on the SHAPS measure was due to the measure's response format. The original SHAPS was designed primarily as a diagnostic tool to discriminate normal from abnormal hedonic tone and uses a categorical scoring scheme for each item. There are 14 items in the SHAPS. A cut-off point of 2 is used to provide the discrimination between normal and abnormal level of hedonic tone. A score of 2 or less indicates normal hedonic tone, whereas a score of above 2 indicates abnormal hedonic tone. This categorical scoring scheme makes the measure insensitive to variations in the general population. For example, data from Snaith et al. (1995) indicated that out of a sample of 82 people from the general population, 68 (82%) scored maximum. Therefore, in future studies using the SHAPS, researchers could modify the response format to a Likert-scale type in order to improve the measure's sensitivity. MacLeod and Conway (2005), for example, modified the response format of the SHAPS to a 7-point Likert scale, where 1 = not very enjoyable and 7 = extremely enjoyable. The authors reported good internal reliability ($\alpha = .86$) and good test-retest reliability over a 2- to 4-week period ($r = .85$). Therefore, in future research assessing the effects of smoking status and dependence on responsivity to rewards (as measured by the SHAPS), use of a Likert-scale response format for the SHAPS items would improve the measure's sensitivity.

Additionally, measures of reward motivation, such as the Behavioural Activation Scale (BAS; Carver & White, 1994), could be used in conjunction with behavioural and other subjective measures of reward responsivity (e.g., the

SHAPS). The BAS measures sensitivity to signals of reward (or reward responsivity) and pursuit of appetitive goals. Investigators suggested that anhedonic symptoms are especially likely to be associated with a deficiency in incentive responsiveness or low BAS strength (Beevers & Meyer, 2002; Harmon-Jones & Allen, 1997). Thus, the BAS could be used to assess a potential deficiency in reward responsivity and reward motivation during nicotine abstinence and nicotine dependence.

9.2.3 Affect Measure: PANAS Scales

There was a main effect of smoking status on the positive affect measure (i.e., PANAS-PA subscale); however, this effect did not vary with level of dependency. Furthermore, there was a main effect of dependence on the negative affect measure (i.e., PANAS-NA subscale); however, this effect was not moderated by smoking status. The lack of a significant Smoking Status × Dependence interaction on the PANAS measure of affect might be due to the sensitivity of the measure (for alternative reasons see Section 9.1.4).

The PANAS-PA subscale is not equivalent to positive affect in general but includes only items that are pleasant and high in activation. Similarly, the PANAS-NA subscale is not equivalent to negative affect in general but includes only items that are unpleasant and high in activation. In other words, the PA and NA scales of the PANAS do not cover all affective experience but only a part of it. In fact, Watson and Tellegen (1985) suggested that low activation states (e.g., depressed and serene) should not be considered as affective states, even if they are valenced. Clearly, such a view of affect is restrictive. Thus, any possible conclusions about the effects of smoking status and dependence on the PANAS measure of affect may be limited.

Measures of affect with greater sensitivity could be used in future research on the effects of smoking status and dependence on affect. For example, the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2005) was developed to provide a set of standardised, internationally accessible stimuli (i.e., colour photographs) for the experimental investigation of emotion. The IAPS assesses three dimensions of affective experience: valence (pleasure-displeasure), activation or arousal (high activation-low activation), and dominance or control (high dominance/in control-low dominance/dominated), that is, feelings of being in control, important, influential, and dominant when viewing a particular picture. Using affect measures with finer distinctions of affective experience would provide more detailed information about the effects of nicotine withdrawal and dependence on affect.

9.2.4 Additional Limitations and Suggestions for Future Research

Although the main effect of dependence on negative affect did not reach statistical significance after Bonferroni correction, the effect was significant at the .05 level. Moreover, there was a significant main effect of dependence on two of the SHAPS subscales: the Interests/Pastimes subscale and the Social Interaction subscale. Given these results and the relationships that exist between reward sensitivity and affect, researchers could investigate a potential mediation function of reward sensitivity or affect. For example, it might be that dependence influences responsivity to rewards through its effects on negative affect. Alternatively, dependence might increase negative affect through its effects on reward responsivity. Such an investigation might require a more dependent sample than the one of the present research and more reliable and

sensitive measures of reward sensitivity (e.g., the SHAPS with an improved response format).

Furthermore, in future research, more reliable and sensitive measures of reward sensitivity and affect could be used to examine the relationship between reward sensitivity and affect. Reward sensitivity might be measured using the CARROT task with an improved procedure, the progressive ratio procedure, the BAS, and/or the SHAPS with an improved response format. Affect could be measured using the IAPS. The purpose of such an investigation would be to identify the affective impact of the indirectly reinforcing properties of nicotine.

In addition, the effects of smoking status and dependence on reward responsivity (measured behaviourally) and affect could be examined simultaneously (as in chapter 8). In the present research, such an investigation was not possible because the methodology of the CARROT measure was different in every study. Therefore, the different data sets could not be treated as one in order to increase the sample size and hence the power to detect significant effects.

9.3 Concluding Remarks

There was an effect of withdrawal on improvement in performance on the CARROT task over a series of trials and an overall effect of withdrawal on CARROT performance. The effect of withdrawal on performance was independent of that produced by introducing a performance-contingent reward. Therefore, I did not replicate results from human data. Furthermore, there was no evidence that the difference in reward responsivity scores between satiation and withdrawal was bigger in higher levels of dependency. However, there was a main effect of dependence on some aspects of environmental pleasure/reward.

Moreover, I found reduced positive affect in withdrawal and increased negative affect in high dependence. These results provide weak support for nicotine's indirect reinforcing properties in humans (measured subjectively). The results suggest that nicotine's direct reinforcing properties may be more important in the development of dependence. It is concluded that, in order to observe nicotine's effects on reward sensitivity in humans, investigators need to empirically separate nicotine's effects on reward responsivity from its effects on arousal and attention.

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Appendix A

Recruitment Poster

SMOKERS WANTED

For a Psychology experiment looking at:

The experience of reward in nicotine dependence

You can come for testing either after having abstained from smoking overnight or after having smoked as usual. You will be asked to complete a task that consists of three trials and involves sorting cards into piles. In one of the trials you will be given the opportunity to gain some money (10 pence for every five cards sorted).

You will also be asked to fill in three short questionnaires.

The session will last 20 minutes.

Payment: £3.5 plus the money earned in the card task

(or 2 credits for Psychology students)

Please email me at **nk100@soton.ac.uk,** if you have any queries, or if you would like to take part.

You can also log on to **http://www.psychobook.psy.soton.ac.uk** and book a slot for the experiment 'reward and nicotine dependence'.

Thank you for your time

Natasha Kalamboka

Appendix B

Items and scoring for Fagerström Test for Nicotine Dependence (FTND)

Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette?	Within 5 minutes	3
	6-30 minutes	2
	31-60 minutes	1
	After 60 minutes	0
2. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in cinema, etc.)?	Yes	1
	No	0
3. Which cigarette would you hate most to give up?	The first one in the morning	1
	All others	0
4. How many cigarettes/day do you smoke?	10 or less	0
	11-20	1
	21-30	2
	31or more	3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

Appendix C

Items and Scoring for the Snaith – Hamilton Pleasure Scale (SHAPS) and SHAPS Subscales

This questionnaire is designed to measure your ability to experience pleasure at the present moment, that is, right now. It is important to read each statement *carefully*. Tick *one* of the boxes □ to indicate how much you agree or disagree with each statement

Agree / Strongly agree = 0

Disagree / Strongly disagree = 1

1. I would enjoy my favourite television programme:

Strongly agree □

Agree □

Disagree □

Strongly disagree □

2. I would enjoy being with my family or close friends:

Strongly agree □

Agree □

Disagree □

Strongly disagree □

3. I would find pleasure in my hobbies or past times:

Strongly agree □

Agree □

Disagree □

Strongly disagree □

4. I would be able to enjoy my favourite meal:

Strongly agree □

Agree □

Disagree □

Strongly disagree □

5. I would enjoy a warm bath or refreshing shower:

Strongly agree □

Agree □

Disagree □

Strongly disagree □

6. I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread:

Strongly agree □

Agree □

Disagree □

Strongly disagree □

7. I would enjoy seeing other people's smiling faces:

Strongly agree □

Agree □

Disagree □

Strongly disagree □

8. I would enjoy looking smart when I have made an effort with my appearance:

Strongly agree □

Agree □

Disagree □

Strongly disagree □

9. I would enjoy reading a book, magazine or newspaper:

Strongly agree □

Agree □

Disagree □

Strongly disagree □

10. I would enjoy a cup of tea or coffee or my favourite drink:

Strongly agree □

Agree □

Disagree □

Strongly disagree □

11. I would find pleasure in small things, e.g. bright sunny day, a telephone call from a friend:

Strongly agree □

Agree □

Disagree □

Strongly disagree □

12. I would be able to enjoy a beautiful landscape or view:

Strongly agree □

Agree □

Disagree □

Strongly disagree □

13. I would get pleasure from helping others:

Strongly agree □

Agree □

Disagree □

Strongly disagree □

14. I would feel pleasure when I receive praise from other people:

Strongly agree □

Agree □

Disagree □

Strongly disagree □

Snaith-Hamilton Pleasure Scale Subscales

1. Sensory Experience Items:

5. I would enjoy a warm bath or refreshing shower.
6. I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread.
7. I would enjoy seeing other people's smiling faces.
8. I would enjoy looking smart when I have made an effort with my appearance.
11. I would find pleasure in small things, e.g. bright sunny day, a telephone call from a friend.
12. I would be able to enjoy a beautiful landscape or view.

2. Food/Drink Items:

4. I would be able to enjoy my favourite meal.
10. I would enjoy a cup of tea or coffee or my favourite drink.

3. Social Interaction Items:

2. I would enjoy being with my family or close friends.
13. I would get pleasure from helping others.
14. I would feel pleasure when I receive praise from other people.

4. Interests /Pastimes Items:

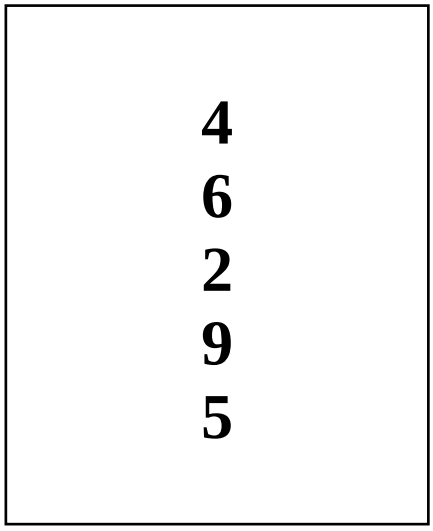
1. I would enjoy my favourite television programme.

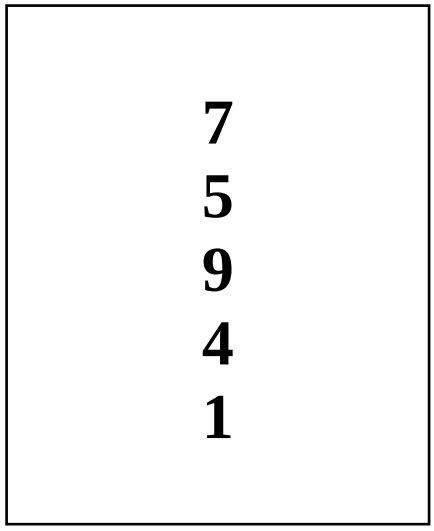
3. I would find pleasure in my hobbies or past times.

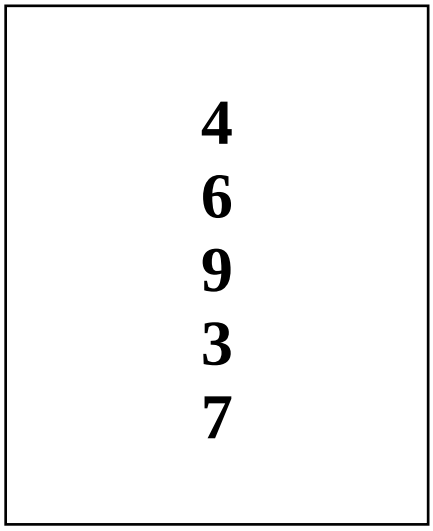
9. I would enjoy reading a book, magazine or newspaper.

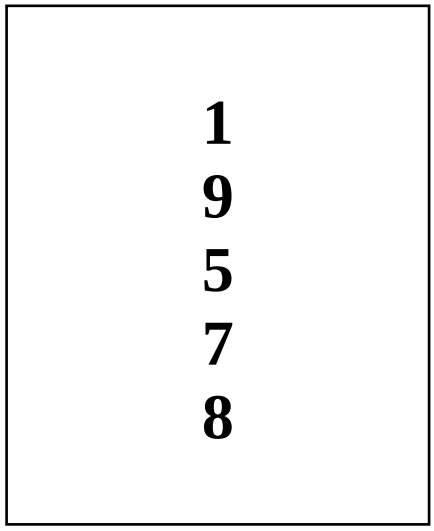
Appendix D

Examples of CARROT Cards









Appendix E

Information Sheet and Consent Form

The experience of reward in nicotine dependence

Consent Form for Research Participants

Information sheet

I am Natasha Kalamboka, an MPhil/PhD student in Psychology. I am requesting your participation in a study looking at the experience of reward in nicotine dependence. This will involve you coming to the lab either after you have been asked to abstain from smoking overnight or after having smoked as usual. Once in the lab, you will be asked to take part in a simple task which consists of three trials. For each trial you will be asked to sort some cards as quickly as possible between three piles. In one of these trials you will be given the opportunity to gain some money by sorting as many cards as possible (10 pence for every five cards sorted). Finally, you will be asked to fill in short questionnaires. The session will last 30 minutes maximum.

Personal information will not be released to or viewed by anyone other than researchers involved in this project. Results of this study will not include your name or any other identifying characteristics. Your participation is voluntary and you may withdraw your participation at any time. If you are a student in the Psychology Department and you choose not to participate there will be no consequences to your grade or to your treatment as a student in the department. If you have any questions please ask them now, or contact me, Natasha Kalamboka, at nk100@soton.ac.uk.

Name: Natasha Kalamboka Date:

Statement of Consent

I _____have read the above informed consent.

[*participants name]*

I understand that I may withdraw my consent and discontinue participation at any time without penalty or loss of benefit to myself. I understand that the data collected as part of this research project will be treated confidentially, and that published results of this research project will maintain my confidentiality. In signing this consent letter, I am not waiving my legal claims, rights or remedies. A copy of this consent letter will be offered to me.

(Circle Yes or No)

I give consent to participate in the above study Yes No

Signature Date

Name *[participants name]*

I understand that if I have questions about my rights as a participant in this research, or if I feel that I have been placed at risk, I can contact the Chair of the Ethics Committee, Department of Psychology, University of Southampton, Southampton, SO17 1BJ.

Phone: (023) 8059 3995.

Appendix F

Debriefing Statement

The experience of reward in nicotine dependence.

Debriefing Statement

Theoretical background

The aim of this research was to investigate the experience of reward in nicotine dependence. It was expected that level of dependence as well as abstinence would affect your experience of reward.

Previous animal and human research has shown that nicotine withdrawal affects sensitivity to reward. More specifically, smokers in withdrawal show diminished interest or pleasure in rewarding stimuli. There is considerable evidence suggesting that dopaminergic activity in the nucleus accumbens is disrupted in nicotine dependence; during withdrawal dopamine transmission is downregulated and this results in impaired motivation and negative mood. Your data will help our understanding of some of the mechanisms that are responsible for the development of nicotine dependence.

The following references provide more information about this topic:

Al-Adawi, S. & Powell, J. (1997). The influence of smoking on reward responsiveness and cognitive functions: a natural experiment. *Addiction, 92* (12), 1773-1782.

Epping-Jordan, M., P., Watkins, S., S., Koob, M., A. & Markou, A. (1998). Dramatic decreases in brain reward function during nicotine withdrawal. *Nature, 393,* 76-79.

Hughes, J., R. & Hatsukami, D. (1986). Signs and symptoms of tobacco withdrawal. *Archives of General Psychiatry, 43,* 289-294.

Salamone, J., D. (1994). The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. *Behavioural Brain Research, 61,* 117-123.

Methodology

The main dependent variable was sorting rate, that is, the increase in sorting speed on the introduction of the incentive in the card-sorting task. The main independent variables were level of dependence (high/low), smoking status (withdrawal/satiation) and test order.

Once again results of this study will not include your name or any other identifying characteristics. The research did not use deception. You may have a copy of this summary if you wish.

If you have any further questions please contact me Natasha Kalamboka at nk100@soton.ac.uk

Thank you for your participation in this research.

Name: Natasha Kalamboka Date:

If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee, Department of Psychology, University of Southampton, Southampton, SO17 1BJ.Phone: (023) 8059 3995.

Appendix G

Items and scoring for the Positive and Negative Affect Schedule (PANAS)

Scales

This Scale consists of a number of words that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to the word. Indicate to what extend you feel this way at the present moment, that is, right now. Use the following scale to record your answers.

1	2	3	4	5
very slightly or not at all	a little	moderately	quite a bit	extremely

_____ interested	_____ irritable
_____ distressed	_____ alert
_____ excited	_____ ashamed
_____ upset	_____ inspired
_____ strong	_____ nervous
_____ guilty	_____ determined
_____ scared	_____ attentive
_____ hostile	_____ jittery
_____ enthusiastic	_____ active
_____ proud	_____ afraid

Thank you for your time and participation.