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Cognitive and psychological correlates of smoking abstinence, and predictors of successful cessation

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Abstract

The neural circuitry implicated in addictive drug use, which appears to be down-regulated in early abstinence, corresponds closely with brain reward pathways. A literature review suggests that responses to incentive stimuli and the ability to inhibit reflexive responses, both of which have been associated with normal functioning in these pathways, might be weakened during acute abstinence from chronic drug use. In an ongoing study, 82 smokers, abstinent overnight before two separate testing occasions, have been assessed after administration of nicotine and placebo lozenges (order of sessions counterbalanced). Nicotine administration is associated with a significant reduction in anhedonia, a near-significant increase in response to financial incentive, enhanced ability to inhibit reflexive eye movements, and increased attentional bias to words with appetitive significance. Fifty-nine participants then initiated a quit attempt and 19 reported relapsing within 7 days. Comparing their performance in the two prequit lozenge assessment sessions, relapsers showed a stronger effect of nicotine on enhancing their ability to inhibit reflexive eye movements and a near-significant trend towards greater nicotine-induced increases in attentional bias toward appetitive words.

Keywords: Smoking; Abstinence; Incentive motivation; Response inhibition

1. Introduction

An intricate system of biological engineering connects the momentary action of ingesting a drug with the ensuing complex of cognitive, affective, and behavioural reactions. The essence of addiction lies in the behavioural reaction, shown by some individuals, of continuously repeating the original act of drug ingestion despite many apparently maladaptive physical and psychosocial consequences. These behavioural reactions, however, are likely to be in large part mediated by the impact of the drug both on various parameters of the physical functioning of the brain and on associated subjective experiences. These effects are liable to vary as a function of extent and frequency of drug exposure. For instance, a particular drug administered acutely may have a transient and subjectively positive effect on the functioning of brain structures and pathways involved in anxiety. Chronic use, however, may be associated with the evolution of longer term alterations to brain structure or function, which mean that administration of the drug now produces a rather different constellation of physical effects that manifest in a different set of subjective experiences.

The complexity of potential drug effects is further exacerbated by preexisting differences between individuals in parameters of their brain function and personality, either constitutional or acquired, and by situational factors (e.g., current exposure to stressors) that themselves directly affect brain activity and mood as well as providing a psychological context for the physiological and subjective impact of drugs. Despite, or perhaps because of, this complexity, the coupling of increasingly sophisticated technologies for mapping brain–behaviour relationships with well-articulated neuropsychological theories of cognitive and affective information processing has led to the emergence over the past two decades of some compelling neuroscientific models of addiction. However, although empirical validation of key tenets of these models is gradually accumulating, there is as yet a lack of data concerning the extent of their clinical utility in allowing ‘‘at-risk’’ individuals to be identified or effective treatments to be derived and then targeted appropriately.

The purpose of the present paper is first to consider some of the neuropsychological and clinical implications of evidence implicating the mesocorticolimbic ‘‘reward’’ pathways in the use of addictive drugs, specifically in the use of nicotine. We also present some preliminary data from an ongoing study of smoking cessation designed to test theoretically derived hypotheses concerning the effect of acute nicotine administration and abstinence on cognitive and affective functions in chronic smokers, and also to explore whether individual differences in the magnitude of these effects predicts success/failure in maintaining abstinence over a 3 month period.

1.1. Addiction and brain reward pathways

There is now substantial preclinical and clinical evidence that repeated use of centrally acting ‘‘recreational’’ substances (including nicotine, alcohol, cannabis, psychomotor stimulants, and opiates) is associated with abnormal functioning in brain pathways that underlie both reward motivation and the ‘‘executive’’ cognitive processes involved in strategy formation and inhibitory response control.

The neural circuitry implicated in the above functions—the mesocorticolimbic brain system—comprises dopaminergic projections from the ventral tegmental area (VTA) to structures including the nucleus accumbens (NAcc), amygdala, anterior cingulate, and prefrontal cortex (PFC). Activation of these structures has been found to be associated with appetitive behaviours directed at obtaining a wide range of reinforcers including brain electrostimulation, food, and sex (e.g., Wise, 1998), and collectively they are consequently referred to as the ‘‘reward system.’’ A substantial empirical literature shows that dopamine release is triggered both by consumption of a drug and, through classical conditioning, by exposure to stimuli, which have formerly been predictive of drug consumption. Conditioning studies have confirmed that formerly neutral stimuli repeatedly paired with either food (e.g., Schultz, Apicella, & Ljungberg, 1993) or drugs (e.g., Di Ciano, Blaha, & Phillips, 1995) can indeed come to elicit conditioned release of DA in the NAcc. In their ‘‘incentive sensitisation’’ model of addiction, Robinson and Berridge (1993, 2000) have argued that repeated drug use sensitises (enhances the reactivity of) this system so that stimuli with motivational significance (particularly drug related) elicit stronger reactions; subjectively, they ‘‘grab the attention’’ and acquire greater incentive salience. This leads to heightened appetitive urges or ‘‘cravings’’ that in turn contribute, along with other more explicit cognitive processes, to the maintenance of a compulsive pattern of drug seeking and ingestion (Berridge & Robinson, 2003). Other researchers have similarly postulated that increases in dopamine activity are associated with heightened sensitivity and/or behavioural responsiveness to stimuli with motivational significance, including those with aversive as well as appetitive connotations (e.g., Salamone, 1994).

Consistent with this model, there is evidence for ‘‘cross-priming,’’ in which users of one addictive substance show elevated craving for or consumption of that drug if they have previously been administered a dose of another dopamine agonist (see review by Self, 1998). For example, Reid, Mickalian, Delucchi, Hall, and Berger (1998) found in a double-blind, placebo-controlled study that the increases in craving reported by abstaining cocaine addicts during exposure to cocaine-related cues were strongly enhanced by an acute dose of nicotine administered via a transdermal patch. Additional support accrues from numerous neuroimaging studies showing drug craving to be accompanied by activation of brain areas traversed by mesocorticolimbic dopaminergic pathways (e.g., Childress et al., 1999; Grant et al., 1996; Sell et al., 1999; Volkow, Wang, et al., 1999).

1.2. Abnormalities of brain dopamine pathways during abstinence

Chronic use of addictive drugs has been associated with abnormalities in dopaminergic pathways. For example, Kuhar and Pilotte (1996) reported long-lasting decreases in DA transporter levels in the NAcc in animals after cocaine withdrawal; similarly, in humans Volkow, Fowler, and Wang (1999) concluded from a series of PET studies that addictive cocaine users have abnormally low levels of dopamine D2 receptors and that this in turn is associated with decreased metabolism in the cingulate gyrus and orbitofrontal cortex. Confirming this abnormality, Little, Patel, Clark, and Butts (1996) found depleted dopamine levels at postmortem in the frontal cortex of cocaine users by comparison with those of matched noncocaine users. Altmann et al. (1996) concluded from an extensive literature review that ‘‘withdrawal from various drugs of abuse is associated with a reduction in dopamine transmission in the ventral striatum, an effect that is opposite to the common property of drugs of abuse to stimulate dopamine transmission. . .’’ (p. 316).

1.3. Brain reward pathways and cognitive functioning

In addition to providing some explanation of subjective and behavioural phenomena in drug addiction, such as the urges or cravings that substance users experience when exposed to drug-related cues and the difficulty in maintaining abstinence after a single lapse, this neurobiological model has implications for cognitive functioning. The mesocortical projections activated by dopamine release in the VTA terminate widely throughout the PFC: Differing regions within the PFC are critical for a variety of high-level ''executive'' functions essential to the inhibition of automatic reflexive responses and the generation, execution, and monitoring of effective problem solving or strategically controlled behaviours (e.g., Norman & Shallice, 1983), though, as Aron, Robbins, and Poldrack (2004) note, there have been conflicting findings in relation to neuroanatomical correspondences between specific executive functions and subregions of PFC.

Jentsch and Taylor (1999) have reviewed a substantial body of preclinical and clinical studies suggesting that chronic use of addictive substances is associated with impairments of impulse control (or response inhibition), an aspect of behaviour that elsewhere has been linked with activity in the orbitofrontal cortex (e.g., Arana et al., 2003). Jentsch and Taylor make a strong case that such impairments may play a critical role in vulnerability to relapse, in that they will reduce the addict's ability to resist the strong habitual drug-using responses elicited by drug-related cues. Consistent with this, substance users have been found to show impairments of automatic response inhibition (e.g., Kaufman, Ross, Stein, & Garavan 2003), as well as elevated impulsiveness and risk taking on behavioural tasks (e.g., Lejuez et al., 2002). Relatedly, Bechara et al. (2001) found substance users' decision making to be abnormally strongly influenced by short-term over long-term outcomes (a pattern also shown by patients with prefrontal brain lesions and associated with trait impulsiveness; Hinson, Jameson, & Whitney, 2003). Of particular interest here, Spinella (2002) reported that in smokers, the degree of impairment on such tasks correlated positively with the amount they reported smoking.

Goldstein and Volkow (2002) have explicitly linked the motivational and cognitive disruptions theoretically likely to arise from the effects of addictive drugs on reward pathways within a framework that they term Impaired Response Inhibition and Salience Attribution (I-RISA), and they cite extensive neuroimaging data supporting the associations between addiction, abnormalities of brain structure and function, and disturbances of cognitive and behavioural responding.

1.4. Smoking and brain reward pathways

When administered acutely, nicotine directly stimulates dopamine release within the mesocorticolimbic circuitry: It attaches to acetylcholine receptors on neurons in the VTA that project to the NAcc and, by so doing, increases release of dopamine in the shell of NAcc (Gamberino & Gold, 1999). Confirming the correlation between activation of these pathways and the subjective effects of smoking in an fMRI study, Stein et al. (1998) found that injections of nicotine in smokers induced parallel increases in reports of various drug-positive sensations and activity in the NAcc, amygdala, limbic thalamus, anterior cingulate, and dorsolateral, orbital, and medial frontal regions of the frontal lobes.

Complementing these acute effects, long-term nicotine use—like chronic use of other addictive drugs—appears to be associated with neuroadaptations in dopaminergic pathways. For example, Fung et al, (1996) report that rats addicted to and then withdrawn from nicotine for 24 h showed reduced levels of DA in the striatum and NAcc and decreased numbers of DA receptors in the NAcc. By contrast, DA levels in the striatum were increased 5 days after nicotine administration, returning to baseline levels after 14 days (Fung & Lau, 1988). Whereas long-term administration has been found not to lead to any alteration in the degree to which nicotine ingestion triggers the release of DA in the NAcc (Gamberino & Gold, 1999), Epping-Jordan, Watkins, Koob, and Markou (1998) found that across 4 days of nicotine withdrawal rats showed significantly increased thresholds for intracranial stimulation; thus, there do appear to be changes in functional characteristics of the brain reward circuitry during abstinence. Paralleling these preclinical findings, in humans positron emission tomography (PET) has shown the brains of current smokers, but not ex-smokers, to be characterised by abnormally low levels of monoamine oxidase B, an enzyme that metabolises DA (Fowler et al., 1998). In smokers who had abstained for several hours, Geracioti, Scott, West et al., (1999) found CSF levels of the DA metabolite homovanillic acid to be half that of a group of nonsmokers, whereas in a PET

study by Dagher et al. (2001), smokers showed reduced dopamine D1 receptor binding in the ventral striatum compared with nonsmokers.

It remains unclear from cross-sectional studies such as these whether the observed abnormalities antedated or were a consequence of chronic smoking: Although the normality of some aspects of functioning in ex-smokers might suggest that the impairments seen in current smokers are reversible sequelae of nicotine use, it is also possible that successful quitters are atypical of the broader population of smokers. Prospective longitudinal studies tracking smokers over weeks or months of abstinence are needed to determine whether abnormalities do in fact recover over time, and to differentiate between transient withdrawal effects and longer term down-regulation.

Taken together, these data suggest that although regular smokers continue to experience dopamine-boosting effects of nicotine, their endogenous dopamine systems are likely to be suppressed or down-regulated in some manner that will be revealed during a period of acute abstinence. Indeed, Wise and Munn (1995) have suggested that acute dopamine depletion during withdrawal might underlie the characteristic subjective reports of anhedonia and dysphoria. A recent study by Gilbert et al. (1999) found that by comparison with current smokers, abstaining smokers showed abnormalities of right–left EEG asymmetry that persisted without substantial change across 31 days of abstinence and that correlated with trait depression. Elsewhere, EEG asymmetry has been considered a physiological marker of approach motivation and has been shown to increase during exposure to smoking-related cues (Zinser, Fiore, Davidson, & Baker, 1999). Although these findings do not directly demonstrate dopaminergic alterations, they do suggest that abstinence may be associated with prolonged physiological abnormalities.

1.5. Nicotine: effects of acute abstinence and smoking

If dopaminergic brain reward mechanisms in chronic smokers are indeed dysfunctional during acute abstinence, then from the foregoing neuropsychological analysis it follows that acutely abstinent smokers should show disturbances in their responses to incentives and in their ability to inhibit prepotent or reflexive responses. Although little research has directly examined these cognitive and behavioural processes as a function of nicotine use and abstinence, Bickel, Odum, and Madden (1999) and Mitchell (1999) both reported that current smokers were more likely than nonsmokers or ex-smokers to respond preferentially for smaller, immediate monetary rewards over delayed but larger rewards. This pattern of responding, often characterised as ‘‘impulsive,’’ may be construed as reflecting a heightened salience of the immediately available reward and/or difficulty in inhibiting an automatic tendency to respond for immediate reward.

Our group has now conducted a number of studies with smokers to investigate responses to motivationally salient (but non-drug-related) cues and inhibitory response control under conditions of acute abstinence and immediately after smoking. To measure individual variation in response to incentive, we used the Card Arranging Reward Responsivity Objective Test (CARROT; Powell, Al-Adawi, Morgan, & Greenwood, 1996). Here, the participant is presented with a stack of cards, each having five digits printed on it; one (and only one) of the digits is either a 1, 2, or 3, and the cards have to be sorted into three piles corresponding to these digits. Four trials are given (T1, T2, T3, and T4). In T1, the participant is told to sort a stack of 60 cards as quickly as possible. The time taken to do so is recorded, and is used as the individually determined time given for subsequent trials. T1 thus serves both to familiarise the participant with the task and, of particular relevance in the case of neurological or psychiatric groups, to ensure that subsequent trial times are adjusted to control for any sensory, motor, or cognitive deficits. In T2 and T4, the participant is required simply to sort the cards as quickly as possible. The mean rate of card sorting in these two trials represents ‘‘nonrewarded’’ rate (NRRATE). T3 differs only in that the participant is told that for every five cards sorted, he will receive a reward of 10 pence. During the trial, coins are placed on the table in full view after every fifth card. Rate of card sorting in this trial represents ‘‘rewarded’’ rate (REWRATE). ‘‘Reward responsivity’’ (REWRESP) is then computed as (REWRATE − NRRATE). Pilot work in healthy volunteers showed a highly significant enhancement in sorting rate in the rewarded condition ($P < .001$; Pickering, Corr, Powell et al., 1997), whereas neurological patients with severely impaired motivation in daily life showed a virtual lack of response to financial incentive (Al-Adawi, Powell, & Greenwood, 1998). In a case series of 11 such patients, both CARROT performance and an ecological measure of motivation (participation in therapeutic activities) normalised after treatment with a dopamine agonist, bromocriptine (Powell et al., 1996).

In relation to nicotine, a naturalistic study by Al-Adawi and Powell (1997) involved assessing a sample of smokers firstly 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 a few hours abstinence than when they were retested after smoking, and also showed significantly lower reward responsivity than a comparable group of nonsmokers. Baseline psychomotor speed did not differ between conditions or groups.

We replicated and extended the above findings in an experimental study with 26 smokers (Powell, Dawkins, & Davies, 2002) where testing order (abstinent vs. after smoking) was counterbalanced. A comparison group of nonsmokers was assessed at the same time points. In addition to the CARROT, response inhibition was assessed using an oculomotor task that required participants to inhibit reflexive eye movements (‘‘prosaccades’’) towards a peripheral stimulus and instead to make ‘‘antisaccades’’ (movements in the opposite direction from the stimulus). This task has previously been linked with activation of both PFC and anterior cingulate (e.g., Everling & Fischer, 1998; Gooding, Iacono, & Grove, 1997) and, functionally, with executive cognitive processes (e.g., Findlay & Walker, 1999).

The results of this study were striking. Firstly, reward responsivity was significantly lower in the abstinent than the just-smoked condition, regardless of order of testing; performance in the just-smoked condition did not differ from that of nonsmokers. This effect remained significant, to almost the same degree, when the influence of subjective withdrawal symptoms was covaried out. By contrast, psychomotor speed in the baseline trial of the CARROT did not differ as a function of abstinence. Secondly, the error rate for antisaccades, but not reflexive saccades, was likewise significantly higher during abstinence than just after smoking and than in nonsmokers. Again, severity of withdrawal symptoms did not explain this pattern. Impairment on the antisaccadic task during abstinence (computed by subtracting abstinence score from postsmoking score) was strongly correlated with number of cigarettes smoked per day ($r=.53$, $P < .01$), suggesting that more severely addicted individuals experience greater smoking-induced enhancements of their ability to inhibit reflexive responses than do lighter smokers.

We also included a measure of response to ecological incentives in daily life: the Snaith– Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995). This asked participants to rate their enjoyment of various normal enjoyable activities over the last few days. Here a significant negative effect of abstinence was again observed, by comparison both with the smoking condition and with nonsmokers.

A third study (Powell, Tait, & Lessiter, 2002) tested a different prediction derived from the incentive motivational model concerning attentional bias. Salamone (1994) and Robinson and Berridge (2000), among others, have argued that dopamine release during exposure to cues with motivational significance is associated with an increased tendency to notice or attend to them. If there is indeed such a causal link, we hypothesised that individuals with high functional dopamine activity—including smokers who have just had a cigarette—should find it harder to ignore motivationally relevant information than individuals with relatively low functional dopamine activity; this latter group should include acutely abstinent smokers. We assessed this by using a modified Stroop task in which participants were instructed to name the ink colours in which an array of different words were printed. In one version of the task the words were affectively neutral (e.g., ‘‘pavement,’’ ‘‘emulsion,’’ ‘‘cadet’’); in another version they were appetitively toned but unconnected with nicotine or other drug use (e.g., ‘‘affection,’’ ‘‘caress,’’ ‘‘passion’’); and in a third they were aversive or threat related (e.g., ‘‘coffin,’’ ‘‘blunder’’, ‘‘ambulance’’). The different word categories were matched for word frequency and word length. Twenty-one smokers were assessed on all three versions, once after several hours abstinence and once immediately after smoking; orders of condition and word category were counterbalanced. Ten nonsmokers, equivalent to the smoking group in sex ratio, age, and educational level, were assessed once only. The dependent variable of primary interest was the time it took to colour name the words of each type. As predicted, both appetitive and aversive words slowed colour naming in recent smokers and nonsmokers, whereas abstinent smokers showed no greater effect of these word types than of neutral words. This did not reflect any overall psychomotor slowing. These data appear to demonstrate that attentional orienting is affected in a very specific way by nicotine consumption and/or abstinence. The results are consistent with a dopaminergic model of incentive motivation, but are crucially different from the results of other assessment tools we have used in

showing nicotine-related effects at an earlier stage in the processes linking perception of environmental stimuli with behavioural responses.

One significant limitation of all of the above studies is that nicotine was administered via cigarette smoking. Although nicotine is believed to be the primary psychoactive ingredient in tobacco, it is by no means the only one and it is therefore possible that the observed effects are not directly attributable to nicotine. Perhaps more problematically, it was not possible to find a suitable placebo control: Smokers are well able to detect the difference between no/low nicotine and high nicotine cigarettes. Consequently the studies used nonblinded designs and left open the possibility that beliefs and expectancies on the part of either the participants or the researchers might have influenced task performances. A study currently in progress has therefore elected to administer nicotine in lozenge form, with an indistinguishable placebo provided by the pharmaceutical manufacturer. This has enabled us to achieve double blindness and to deliver nicotine in a pure form.

In addition to attempting a replication of the previously observed findings using the more rigorous methodology, the study aimed to address two additional questions of theoretical and clinical significance.

1.5.1. Do impairments observed during acute abstinence predict relapse?

There are at least two reasons for hypothesising that this might be the case. Firstly, if incentive motivation is lowered, the abstaining smoker's resultant state of anhedonia or inertia means that the smoker may fail to engage in or achieve the same degree of enjoyment as before from normally pleasurable activities. Thus, not only has the smoker lost the pleasure normally afforded directly by smoking, but exposure to, or enjoyment of, alternative sources of pleasure may be reduced. The ''quick fix'' provided through exogenous stimulation of reward pathways by smoking may therefore be more salient. Secondly, and in parallel, the more that response inhibition is impaired during abstinence, the greater should be the difficulty in resisting reflex response to smoke a cigarette when one is available or when the response is cued by a particular context.

1.5.2. Do impairments observed during acute abstinence show recovery over protracted abstinence?

The abnormalities seen during acute abstinence could either (i) be temporary deficits resulting from reversible neuroadaptations; (ii) be permanent deficits resulting from irreversible neural changes; or (iii) have antedated the onset of smoking. If (i) is the case, then functioning should gradually normalise over a period of abstinence.

Few if any studies to date have tracked any aspects of cognitive functioning across weeks or months of abstinence, and the evidence in relation to physiological functioning is complex. For example, most mood and physical withdrawal symptoms self-reported by abstaining smokers ameliorate over a period of up to 4 weeks; increases in appetite are the exception to this profile of recovery (e.g., West, Hajek, & Belcher, 1987). However, the changes induced by nicotine dependence go beyond those that are manifest as withdrawal symptoms. This is clearly illustrated by a recent study (Carboni, Bortone, Ciua, & Di Chiara, 2000) in which rats were experimentally addicted to nicotine. Nicotine dependence was shown to be associated with alterations in dopaminergic function in the NAcc, but whereas administration of the opiate antagonist naloxone triggered physical withdrawal symptoms it had no effect on central DA transmission. The authors concluded that ''the physical signs of nicotine dependence [may be] dissociated from the motivational state of withdrawal (anhedonia) and from the mechanism of motivational dependence'' (p.101).

2. Methods

2.1. Design

The present data come from an ongoing prospective longitudinal investigation addressing the above questions. We are aiming to recruit a total of 200 smokers who are willing to make an attempt to quit, and of these 75% will be randomly allocated to a quit group and the remaining 25% to a nonquit (''smoke'') group.

Before randomisation between quit and ‘‘smoke’’ groups, all participants are evaluated on a range of cognitive and behavioural tasks using a mixed within- and between-subjects design. They are assessed on two separate mornings, after overnight abstinence on both occasions, under two experimental conditions that are administered in counterbalanced order. On both sessions they are given a lozenge to start sucking approximately 25 min before the commencement of testing; in one session this contains 4 mg nicotine, and in the other it is a placebo constructed by the pharmaceutical company (Glaxo Smith Kline) to look and taste similar. This lozenge dissolves over the course of the next 45 min or so, and an hour after administration of the first lozenge, participants are given another identical one to suck. This procedure is designed to achieve more or less stable levels of blood nicotine throughout the testing procedures. Both the participant and the assessor are blind to experimental condition.

Participants are notified of their group allocation after completion of the second session, and ‘‘quit’’ participants commence their abstinence attempt immediately. They are not permitted to use nicotine replacement therapy of any form. Follow-up assessments are conducted with participants in both groups 7, 30, and 90 days after randomisation, the randomised design controlling for the effects of repeated assessment.

Based on typical clinical relapse rates, it is anticipated that approximately 75 of the quit group will remain abstinent at 7 days, 45 at 30 days, and 20–30 at 90 days. Relapse is defined operationally as self-reported smoking in any amount, or use of any nicotine product, or a salivary cotinine concentration of greater than 20 ng/ml. Relapsers are asked to participate in the next scheduled assessment after their relapse, where they are assessed for a final time on the experimental measures and are interviewed concerning the nature and extent of the relapse; thereafter they do not take part in subsequent assessments.

Because the recruitment, assessment and data entry are all ongoing, the present preliminary report is restricted to a comparison of the effects of nicotine and placebo lozenges on four measures of incentive motivation and response inhibition, and to correlations between these variables and duration of abstinence up until the first (7 day) assessment. We have not yet entered sufficient data to address the question of possible recovery in functioning over increasing duration of abstinence, nor do we report here the full range of measures used in the full study, where additional cognitive, behavioural, personality, and genetic variables are assessed.

2.2. Participants

Participants are recruited through advertisement in local newspapers and notices displayed in community facilities such as colleges, GP surgeries, and libraries. All participants are aged 18–65 years, have smoked a minimum of 10 cigarettes a day for 6 months, and must be willing to make an attempt to quit. Exclusion criteria include current treatment for depression or any other psychiatric condition, use of any other prescribed or recreational drugs on a regular basis, and pregnancy.

2.3. Procedure

Participants in the quit group are given an information booklet, access to a telephone ‘‘helpline’’ and brief individualised advice and support at the end of each assessment session designed to maximise abstinence rates and retention to the study. They are required to refrain from using any nicotine-replacement therapy (NRT) or other psychotropic medication (e.g., bupropion) during the quit attempt. Salivary cotinine levels are measured at each assessment to characterise participants’ level of nicotine intake and to verify self-reported abstinence.

All participants in both groups are paid £20 for attending each of the six assessments they attend, but, to minimise attrition, do not receive their accumulated ‘‘earnings’’ (other than any travel costs) until they have attended their final assessment.

2.4. Baseline assessments

In addition to basic demographic information (age, gender, ethnicity, socioeconomic status, and educational level), various indices of extent of smoking and dependence are gathered including the following:

- The Fagerström Test for Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker,& Fagerström 1991): on this six item self-report scale scores range from 0 (low dependence) to 10 (high dependence).

- Expired carbon monoxide, to index recent smoking, is recorded via a breath CO monitor. Nonsmokers and smokers who have abstained overnight typically have levels < 11 ppm.

2.5. Cognitive and motivational assessments

2.5.1. Incentive motivation

2.5.1.1. Card Arranging Reward Responsivity Objective Test. This yields an index of the extent to which participants enhance performance on a simple psychomotor task when offered a financial incentive. Briefly, participants are given a stack of cards to sort into three piles based simply on the presence of one of three numbers on the card. After a familiarisation trial their rates of sorting in three subsequent trials are recorded: In the first and third of these, participants are requested to sort as quickly as they can, but are not given any financial incentive, whereas in the second trial they are offered an incentive of 10 pence for every five cards they sort within an individually determined time limit (the number of seconds they took to sort 60 cards during the familiarisation trial). The variable of principal interest is ‘‘reward responsivity’’—the increment in rate of sorting seen in the rewarded trial compared with the average of the two nonrewarded trials.

2.5.1.2. Modified Stroop test of attentional bias. Participants are required to name the colours of the ink in which an array of 88 words (eight repetitions of each of 11 different words, in random order) are printed on a handheld sheet. There are four trials, each presenting words of a different semantic type (neutral, appetitive, threat, smoking related), matched for word frequency and length, given in counterbalanced order across participants so that each word type occurs equally often in each sequential position. Number of errors and total naming time are recorded for each word type.

2.5.1.3. Anhedonia. The SHAPS (Snaith et al., 1995) is a 14 item self-report scale designed to assess state-dependent hedonic tone in both the general population and psychiatric patients. Subjects are asked whether each of 14 normally pleasurable events or activities would give them pleasure; here, each item is scored 1 (strongly agree) to 3 (strongly disagree). Thus, the score range is from 0 to 42, with a higher score indicating greater anhedonia.

2.5.2. Response inhibition/impulsiveness

2.5.2.1. Eye movement task. Participants are instructed either to move their gaze towards a visually presented peripheral stimulus (the ‘‘prosaccadic’’ reflexive response) or to inhibit this response and look instead in the opposite direction (‘‘antisaccadic’’ response).

The procedure used that employed by Fukushima, Fukushima, Miyasaka, and Yamashita (1994) and Clementz, McDowell, and Zissok (1994). Participants are tested in a quiet, darkened room where they are seated in front of a 35-cm computer monitor and fitted with eye-tracking headgear. A chin rest, positioned 25 cm from the screen, minimises head movements. The equipment is calibrated for each participant before each of the two tasks by asking them to look at a white dot subtending a visual angle of < 0.25 against a dark background at three positions (central fixation, + 24j and −24j) for 5 s each. Horizontal eye movements are measured for the right eye only by using an infrared reflection technique (IRIS IR 6500 by Skalar Medical) with a sampling rate of 120 Hz. Incoming eye-movement recordings are digitised using a Brain Boxes 12-bit analogue to digital conversion card.

In the experimental task, a central fixation target is presented for a period varying randomly between 2 and 4 s. Two hundred milliseconds after extinction of the fixation point, one of six peripheral targets is

illuminated for 500 ms. The central fixation point is then reilluminated. Peripheral targets vary in both direction (left or right of the central fixation point) and amplitude (i.e., 8j, 12j, or 24j) and are presented in a randomised order. Sixty peripheral stimuli are presented, 10 in each of the six possible positions.

This procedure is conducted firstly with prosaccades, when participants are instructed to look at the peripheral target as quickly and accurately as possible, and then, after a 5-min break, with antisaccades, when they are told instead to look in the opposite direction as quickly as possible and at approximately equal distance from the fixation point. Within each condition, responses are classified as incorrect if the initial movement is in the wrong direction regardless of whether or not it is subsequently corrected. The dependent variables analysed here are the number of correct responses (across all stimulus locations; maximum score = 60) and mean response latency for correct responses (ms).

3. Results

At this stage in the study,[1] we have entered data on 109 participants who have attended both baseline lozenge (nicotine and placebo) sessions; of these, 73 allocated to the quit group have data for duration of abstinence up to 7 days. Therefore, in the analyses described below, whereas comparisons of cognitive test performance between nicotine and placebo conditions are based on the full sample of 109 participants, the predictive relationship of these measures to abstinence duration across the first week is limited to the smaller sample.

3.1. Participant characteristics

The participants comprise 50 men and 59 women, with a mean age of 31.0 years (S.D. = 11.9, range 19–63). Average duration of smoking is 15.2 years (S.D. = 12.2, range 1–50), and mean daily cigarette consumption is 19.0 (S.D. = 6.3, range 10–40).

3.2. Effects of nicotine versus placebo lozenges

Twenty-seven participants gave breath CO readings in excess of 10 ppm on one or both of the two lozenge testing occasions, suggesting that they had not complied with the experimental instruction to abstain overnight beforehand or, for very heavy smokers, that there was still residual nicotine in their system. These participants were therefore excluded from further comparisons, leaving 82 in the analyses of experimental measures. Data were analysed using repeated measures analyses of variance with the within-subjects factor of lozenge type (LOZTYPE: placebo vs. nicotine) and with order of lozenge sessions as a between-subjects factor (LOZORDER: placebo first vs. nicotine first). Because LOZORDER in no case interacted significantly with LOZTYPE, it is not mentioned further.

3.2.1. CARROT reward responsivity

ANOVA included the additional within-subjects factor of REWARD (rewarded vs. mean of the two nonrewarded trials).

Sorting rate was significantly faster in the rewarded trial [0main effect of REWARD: $F(1,80) = 8.5$, $P < .005$]. Although there was no main effect of LOZTYPE [$F(1,80) < 1.0$, ns], there was a trend towards the predicted REWARD x LOZTYPE interaction [$F(1,80) = 3.5$, $P < .07$] with similar sorting rates in the nonrewarded trials for nicotine and placebo conditions but a greater acceleration in response to reward in the nicotine condition (see Fig. 1).

[1] As the study is ongoing, not all data collected have yet been entered.

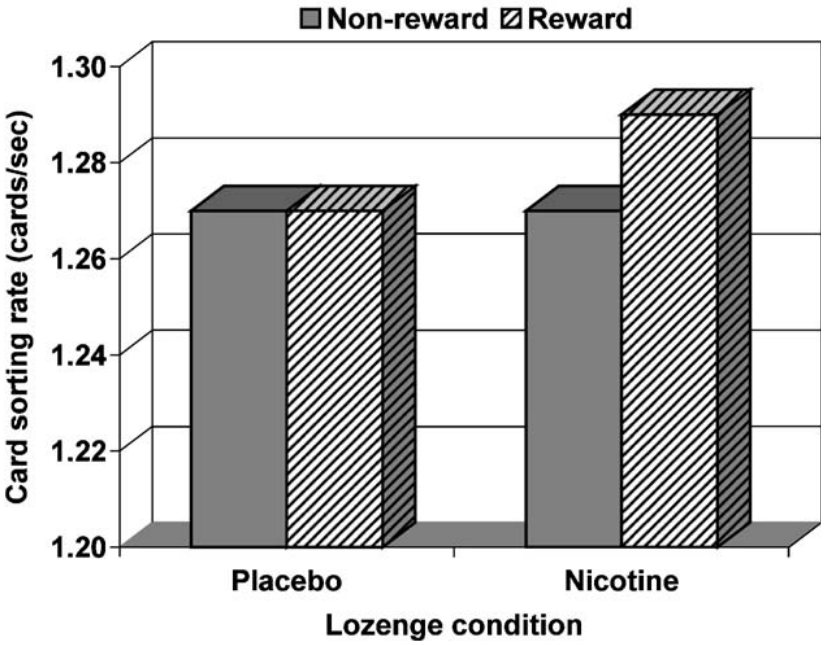

Fig. 1. Card-sorting rates (cards per second) on the CARROT in nicotine and placebo lozenge conditions.

3.2.2. Modified Stroop

ANOVA included the additional within-subjects factor of WORDTYPE (neutral, pleasure, aversive, smoking). To compare the effect of nicotine on interference from each of the three salient word types (pleasure, aversive, and smoking), we specified a priori contrasts of each of these three word types individually against the neutral words.

There was no main effect of LOZTYPE for either colour-naming times or errors [$F(1,79) = 1.6$ and < 1, both ns]. For colour-naming times, although the omnibus LOZTYPE x WORDTYPE interaction also fell short of significance [$F(3,77) = 1.4$, ns], the a priori contrasts revealed that relative to the speed of colour naming neutral words, there was a trend for nicotine to be associated with heightened interference from pleasure words [$F(1,79) = 3.5$, $P=.07$] but not from either aversive or smoking-related words [$F(1.38) < 1$, ns, in both cases)].

For errors, however, the omnibus LOZTYPE x WORDTYPE interaction was significant [$F(1,79) = 3.0$, $P < .05$], and this reflected greater interference from pleasure relative to neutral words in the nicotine than in the placebo condition [$F(1,79) = 9.2$, $P < .005$; see Fig. 2]. There was no effect of nicotine on interference from either aversive or smoking-related words [$F(1,79) = 1.0$ and 1.6, ns, in both cases]. Given that the error data were not normally distributed, with over half the participants making only one or no errors for any given word type, the effect of nicotine on neutral words (i.e., errors under placebo minus errors under nicotine) was additionally compared with its effect on pleasure words using the nonparametric Wilcoxon's signed rank test. This confirmed the difference as significant ($Z = -2.8$, $P < .01$).

3.2.3. SHAPS scores

Data were missing for four participants. For the remaining 78 participants, anhedonia was significantly greater in the placebo condition ($M= 9.4$, S.D. = 5.6) than in the nicotine condition [$M= 7.9$, S.D. = 5.6; $F(1,76) = 11.3$, $P < .001$].

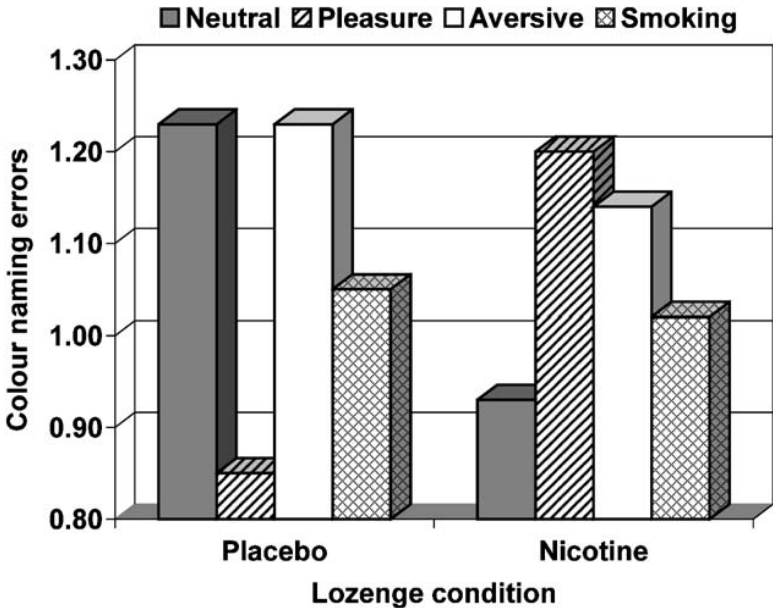

Fig. 2. Colour-naming errors for different word types on the modified Stroop, in nicotine and placebo lozenge conditions.

3.2.4. Saccadic and antisaccadic eye movements

ANOVA included the additional within-subjects factor of SACCTYPE (prosaccades vs antisaccades). Some data were missing for 14 participants owing to technical difficulties during one or both testing sessions; thus the analysis is based on 68 participants.

For accuracy, there were main effects of LOZTYPE [$F(1,66) = 10.3$, $P < .002$] and SACCTYPE [$F(1,66) = 206.0$, $P < .001$], with more errors being made for antisaccades than prosaccades and more errors overall under placebo than nicotine. The LOZTYPE x SACCTYPE interaction was highly significant [$F(1,66) = 10.7$, $P < .002$]: Participants scored at close to ceiling on the prosaccadic task regardless of lozenge condition but made markedly more errors on the antisaccadic task in the placebo than in the nicotine condition. These data are shown graphically in Fig. 3.

Reaction times (for accurate responses) were no faster under nicotine than placebo [$F(1,66) = 1.9$, ns], although, generally, reactions were much slower on antisaccadic than prosaccadic trials [$F(1,66) = 435.0$, $P < .0001$]. There was no LOZTYPE x SACCTYPE interaction [$F(1,66) < 1$, ns].

3.3. Prediction of duration of abstinence at 7-day follow-up

Of the 59 participants who were subsequently allocated to the quit group and assessed after 7 days, 40 (66%) reported still being abstinent. As yet full salivary cotinine data are not available to verify these self-reports.

For the four experimental measures reported above, the effect of nicotine was computed for each individual participant. In most cases this was achieved by subtracting their score in the placebo condition from their score in the nicotine condition, but where a high score indicated poor functioning

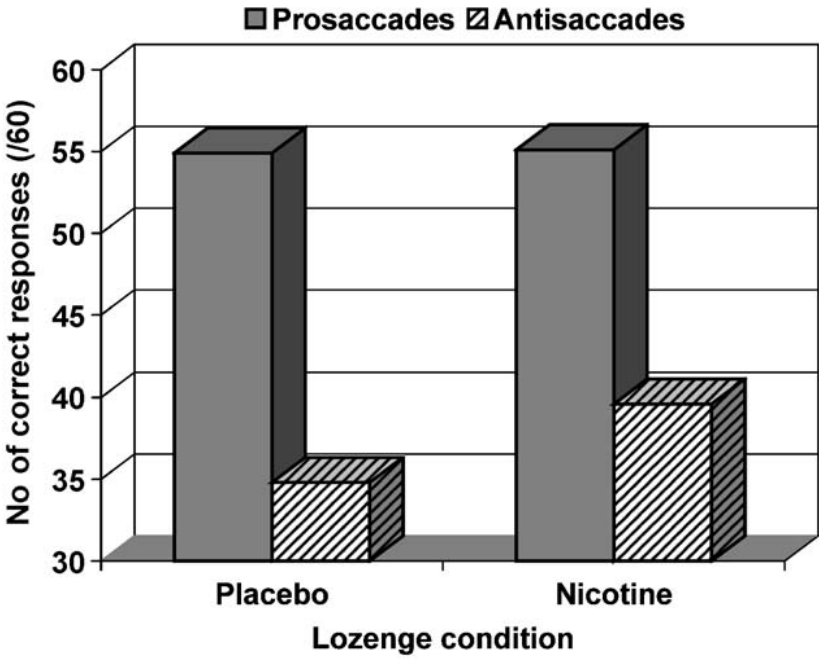

Fig. 3. Accuracy (number of correct out of 60) on the prosaccadic and antisaccadic trials of the oculomotor task, in nicotine and placebo lozenge conditions.

(e.g., reaction times, SHAPS anhedonia), nicotine scores were subtracted from placebo scores. Thus, in each case a high positive score indicates a beneficial effect of nicotine. The hypothesis that participants who had experienced greater benefits of nicotine (or detriments of abstinence) would be at greater risk of early relapse was tested by comparing relapsers versus nonrelapsers via a series of independent samples t tests.

The two groups did not differ in the extent to which nicotine ameliorated anhedonia (relapsers, M=1.4±3.6; nonrelapsers, M=1.9±4.7; $t < 1$, ns) or increased CARROT reward responsivity (relapsers, M= 0.03±0.07; nonrelapsers, M= 0.02±0.12; $t < 1$, ns).

On the Stroop task, the comparisons of interest related to the interference effect from pleasure words (i.e., the difference between pleasure and neutral words). In relation firstly to error rates, the previously observed effect of nicotine in increasing interference from pleasure related words on colour-naming accuracy did not differ between the relapsers and nonrelapsers (M= 0.1±1.8, and M= 0.83±2.2, respectively; $t = 1.2$, ns). However, for colournaming times (where overall nicotine was found to selectively increase response times to pleasure words relative to neutral words) there was a trend for the relapsers to show a more pronounced effect of nicotine in increasing attentional bias towards pleasure words than the nonrelapsers (M= 3.3±6.3 and M=_0.8±8.2, respectively; $t = 1.9$, P=.06).

Finally, for the oculomotor response inhibition task, the indices of key interest were the differences in error rates and response latencies between the prosaccadic and antisaccadic conditions. In each case, response inhibition impairment was computed by subtracting the prosaccadic score from the antisaccadic score so that a high positive score indicated greater difficulty in the antisaccadic condition. The effect of nicotine in improving response inhibition was therefore calculated by subtracting the nicotine score from the placebo score. Participants who went on subsequently to relapse showed markedly greater benefit from nicotine in improving their response inhibition (M= 10.7±14.9) than did those who were still abstinent a week later (nonrelapsers: M= 1.1±10.7; $t = 2.6$, $P < .01$). However, there was no difference between the two groups in the extent to which nicotine decreased the relative response latency for accurate antisaccadic responses (relapsers, M= 0.02 ± 0.09; nonrelapsers, -.01± 0.05; $t < 1$, ns).

4. Discussion

These preliminary analyses on about half of our projected final sample of 200 smokers are largely consistent with our previous findings that acutely abstinent smokers show impairments of incentive motivation and response inhibition that can be reversed by smoking. The fact that the present study used a placebo-controlled design in which nicotine was administered in lozenge form strongly suggests that the previously observed effectiveness of cigarettes in reversing these impairments is attributable to their nicotine content rather than to other ingredients or expectancy effects.

There were, however, one or two minor discrepancies from previous findings. Firstly, the effect of nicotine on reward responsivity on the CARROT fell just short of significance, despite the sample being larger than in our previous work using cigarettes. It remains to be seen whether the effect will achieve significance when recruitment is complete; however, the weaker effect may reflect variations in pharmacokinetics associated with different mechanisms of delivery: thus, smoking achieves a more rapid surge in blood nicotine levels than does the slow, steady release produced by sucking a lozenge. The second discrepancy is in relation to the Stroop test of attentional bias, where the present sample showed increased sensitivity to appetitive stimuli (as reported previously) but not to stimuli with aversive connotations; in our earlier study (Powell, Tait et al., 2002), nonsmokers and smokers who had just had a cigarette showed equivalent biases towards both classes of motivationally salient cue. However, corresponding with the present findings, in a more recent unpublished study using the same task with social drinkers (McFie and Powell, in preparation) a priming dose of alcohol was found to increase bias specifically towards the appetitive and not the aversive words.

Although we currently have follow-up data 1 week after commencement of a quit attempt on only about 60 participants, and as yet do not have available a complete set of objective physiological indicators of abstinence to verify subjective reports, there are nevertheless already some interesting indications that deficits on some tasks during acute abstinence may indeed contribute to early relapse. In particular, relapse within 1 week of cessation was significantly predicted by the extent to which nicotine ameliorated abstinence-related impairments of both response inhibition and attentional bias towards words with incentive salience on the Stroop task. At this stage we have not embarked on regression analyses to explore the extent to which different predictors contribute independently to outcome, although this will clearly be a matter of priority when data are available on the full, considerably larger, sample.

As noted previously, there are a number of additional issues that the present study has been designed to address and that we have as yet not begun to explore. These include, importantly, the question of whether deficits that are manifest after only a few hours abstinence show recovery with increasing duration of abstinence. It may be that some measures are more susceptible to practice effects than others, thereby limiting their predictive utility and also their sensitivity to recovery over time; the CARROT, for instance, may be one such test since inspection of the current data set suggests that the difference between participants tested under nicotine and placebo conditions—although still evident—was much less pronounced on the second lozenge session than in the first.

Another interesting issue concerns possible interrelationships between susceptibility to relapse, the experimental measures used here, and personality and genetic factors that have been theoretically or empirically linked with functioning of brain reward or dopamine pathways: It may be, for instance, that some individuals with constitutionally hypofunctioning reward systems may be particularly drawn to the use of addictive substances because they are particularly effective for them in modulating psychological experience (see, e.g., Blum et al., 2000). In this case, we might expect nicotine administration to be associated with stronger effects in personality or genetically defined subgroups. Data pertaining to some such variables have been collected within this study and will allow exploration of individual differences in drug effects.

To conclude, contemporary neurobiological theories of addiction and their associated investigative techniques are already delivering much more than a detailed description of the physiological processes associated with drug use: They have amplified our understanding of clinically observed features of addiction such as craving, motivational distortions, and poor impulse control, and will undoubtedly continue to do so. They complement cognitive and psychological accounts of these phenomena, and have the potential to contribute to the refinement and individual targeting of psychosocial and pharmacological intervention strategies.

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