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A double-blind placebo controlled experimental study of nicotine: I – Effects on incentive motivation

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Abstract

Rationale: Brain reward pathways implicated in addiction appear to be less reactive in regular drug-users; behavioural manifestations may include decreased sensitivity to natural reinforcers.

Objectives: This study aimed to replicate earlier findings of abstinence-associated incentive motivation deficits in smokers and to determine whether these can be reversed with nicotine in the form of lozenge.

Methods: 145 smokers were each tested twice, once after receiving nicotine, and once after receiving placebo lozenge in counterbalanced order. Participants completed various tests of incentive motivational functioning: a measure of subjective enjoyment, the Snaith-Hamilton Pleasure Scale (SHAPS); a simple card sorting task, the Card Arranging Reward Responsivity Objective Test (CARROT) with and without financial incentive; the modified emotional Stroop test; a cue-reactivity task; and a novel reaction time task to explore effects of signals of reward, the Incentive Motivational Enhancement of Response Speed (IMERS) Task.

Results: Compared with performance during abstinence (placebo condition), nicotine was associated with: higher self-reported pleasure expectations on the SHAPS; enhanced responsiveness to financial reward on the CARROT in smokers who smoked 15 or more cigarettes a day; and greater interference from appetitive words on the Stroop task.

Conclusions: These results are generally consistent with contemporary neurobiological theories of addiction and suggest that short-term smoking abstinence is associated with impaired reward motivation which can be reversed with nicotine.

Introduction

Contemporary neurobiological models of addiction strongly implicate brain 'reward' pathways comprising dopaminergic projections from ventral tegmental area (VTA) to nucleus accumbens (N.Acc), amygdala, anterior cingulate gyrus (CG) and prefrontal cortex (PFC; e.g. Goldstein and Volkow 2002; Robinson and Berridge 1993, 2000). These tracts are collectively referred to as the mesocorticolimbic system, and dopamine (DA) release in the N.Acc in particular has been associated with appetitive responding for a range of 'natural' rewards including food and sex and as well as for drugs of abuse (including cocaine, amphetamine, alcohol, cannabis and nicotine; Bozarth 1991; Corrigal 1992). It has been argued that drugs of abuse 'hijack' the DA system (Lubman et al. 2004) since they are capable of inducing significantly greater magnitude and longer duration increases in DA levels than are natural reinforcers. Rather than being exclusive to reward however, DA release has been implicated in responses to stimuli with other types of motivational salience including aversion and novelty (Gray 1997; Salamone 1994; Volkow et al. 2004a).

Robinson and Berridge (1993, 2000) propose that chronic drug use sensitises (increases the reactivity of) the brain reward system involved in the attribution of incentive properties to rewarding stimuli and the instigation of approach behaviour. They argue that repeated drug use leads to exaggerated orienting of attention towards drug-related cues so that they become especially salient, attractive and 'wanted'. The 'wanting' triggered by exposure to drug-related cues during the early phases of drug use evolves into the phenomenological experience of craving; ensuing behavioural consequences are likely to be compulsive drug seeking and consumption.

Although addicts may continue to experience the acute DA-enhancing effects of drugs, there is increasing evidence that tonic levels of dopamine are reduced in chronic users (see review by Volkow et al. 2004b). PET and SPECT studies have revealed lower DA D2 receptor availability in the striatum of abstinent drug-addicted individuals compared with controls (Volkow and Li 2004), paralleled by a decrease in striatal DA release (Volkow et al. 1997). Reduced DA D1 receptor binding in the N.Acc. has also been reported in the brains of human smokers compared with non-smokers (Dagher et al. 2001). Whether these abnormalities are a result of extended

drug exposure, or reflect characteristics that pre-existed, and possibly predisposed to, drug taking is still unclear. Either way, various authors, including Al-Adawi and Powell (1997), Caggiula et al. (2001) and Volkow et al. (2004b), suggest that this dampened DA activity is likely to result in decreased reactivity to natural (and secondary) reinforcers.

Imaging studies support the notion of disrupted sensitivity to non-drug rewards in addicts. For example, using fMRI, Martin Sölch et al. (2001a) found more extensive activation of dopaminergic brain circuitry in non-smokers than in smokers during a task involving monetary reward. In a second study investigating the effects of different types of reward cue, opiate addicts showed decreased limbic activation during presentation of monetary rewards compared with controls, but the opposite pattern of activation in response to drug-associated cues (Martin-Sölch et al. 2001b). Others have also shown that exposure to drug-related cues in addicts, including smokers, results in both craving and activation of brain regions innervated by the mesocorticolimbic reward circuitry (Brody et al. 2002; Childress et al. 1999; David et al. 2005; Volkow et al. 1999). Nevertheless, we have found that cue-elicited craving is not increased, and may even be decreased, in abstinent smokers (Powell et al. 2002a). Few neuroimaging studies have specifically compared abstinence and satiated smokers though one recent report found no effects of abstinence/satiety on patterns of brain activation in response to smoking cues (McClernon et al. 2005).

Thus, regular smokers may simultaneously possess a hypofunctioning tonic DA system but experience DA-enhancing effects of cigarette smoking. Their hypofunctioning DA system would thus be disguised as long as they are smoking but 'unmasked' during periods of acute abstinence - for example, at the start of a quit attempt, manifesting in blunted motivational and emotional responses to natural reinforcers. The pharmacological 'boost' achieved via smoking a cigarette, or taking nicotine replacement therapy, would reinstate 'normal' behavioural and emotional reactivity.

Consistent with this hypothesis, we have consistently found that abstinent smokers show reduced responsiveness to a financial incentive on a simple psychomotor card sorting task (the Card Arranging Reward Responsivity Objective Test [CARROT])

compared to both non-smokers and recent smokers (Al-Adawi and Powell 1997; Powell et al. 2002a; Powell et al. 2004). Powell et al. (2002a; 2004) additionally found that abstinent smokers report deriving less enjoyment from a range of ordinarily pleasurable events and activities as assessed by the Snaith-Hamilton Pleasure Scale, a self-report measure of affective responses to rewards in daily life (SHAPS; Snaith et al. 1995). Using a more ecologically valid paradigm, we have recently demonstrated that abstinent smokers experience less emotional 'uplift' after viewing positively-valenced (happy) film clips than do smokers who have recently smoked (Dawkins et al. in press). Their responses to neutral and sad clips, by contrast, were not affected.

The ability of nicotine to amplify the incentive value of other positive reinforcers has also been noted in the preclinical literature: for instance, rats will make more responses for a conditioned positive reinforcer in an environment previously paired with nicotine than in an environment previously paired with saline (Olausson et al. 2004). Thus, naturally rewarding stimuli that are motivationally salient for the general population may elicit weaker positive motivational and affective responses in drug users during periods of abstinence. This may in turn be associated with a subjective state of dysphoria or anhedonia which can effectively be alleviated by renewed drug use.

If, as argued by Salamone (1994) and Robinson and Berridge (2000), DA release in response to motivationally salient cues is associated with increased attention towards them, it follows that abstinence should be associated with decreased, and smoking with increased, allocation of attention towards stimuli of motivational salience. It is relevant to note here that whereas Robinson and Berridge's (1993; 2000) incentive sensitisation model restricts itself to the appetitive domain others highlight the critical involvement of DA in responses to stimuli with both appetitive and aversive motivational salience (Gray et al. 1997; Salamone 1994). Using an 'emotional' variant of the Stroop task in which participants had to name the ink colour of appetitive, aversive and neutral words, we previously found that non-smokers, and smokers who had just had a cigarette, were slower than abstinent smokers in colour-naming both appetitive and aversive words compared with neutral words (Powell et al. 2002b). This indicates reduced attentional 'capture' by motivational words in the latter group regardless of their valence.

The present study aimed to replicate and extend the findings of Powell et al. (2002a, 2002b). Neither of these previous studies used a blinded design and both used smokers who had either abstained or recently smoked cigarettes; thus the observed performance enhancements may have reflected demand characteristics and could not definitively be attributed to nicotine since this is one of many active ingredients in cigarettes. The present study isolated the influence of nicotine, administered in lozenge form, using a double-blind, placebo-controlled design.

The following specific hypotheses were tested:

1. *Motivational and affective responses to non-drug incentives will be dampened during abstinence and normalised by acute nicotine consumption.* If activity in the dopaminergic reward pathways is indeed compromised in chronic smokers then abstinence should be associated with reduced attentional, behavioural and subjective responsiveness to everyday incentives. Conversely, by triggering DA release in the N.Acc shell, (Gamberino and Gold 1999), nicotine ingestion should increase the reactivity of the reward system, thus enhancing these behavioural and subjective responses. These processes are measured here using three experimental tasks and one self-report measure.

2. *Increases in self reported craving in response to the sight and smell of a cigarette will be greater after participants have received nicotine relative to placebo.* We likewise hypothesise that cue-elicited craving will be reduced during abstinence and enhanced after receiving nicotine. This effect was reported by Payne et al. (1996) and observed in our earlier study (Powell et al. 2002a) consistent with priming studies, which have demonstrated inflated desire for, or use of, a drug following a small dose of the same or another drug (e.g. Spiga et al. 1998). However, others have argued that abstinence should *increase* cue-reactivity by inducing a deprivation state and thus enhancing the salience of drug-related cues (e.g. Baker et al. 1987) although we have been unable to find any empirical support for this in the literature.

Materials and methods

Design

In this repeated measures design, 145 smokers were tested on two occasions a week apart, following overnight (12 hours) abstinence from smoking on both occasions. On one occasion they received 4mg of nicotine (the dose given clinically to smokers who smoke within 30 minutes of waking, as did the majority of the present sample) via NiQuitin lozenge and on the other, a placebo lozenge. Nicotine in lozenge form was used since the manufacturer (Glaxo Smith Kline) was able to provide unmarked nicotine and placebo lozenges, comparable in appearance and taste. Order of testing was counterbalanced and participants were required to suck (and not chew) the lozenge for 30 minutes before commencement of testing to allow time for nicotine to reach the bloodstream. One hour into the testing session, a second 'top-up' lozenge, identical to the first, was given with the aim of achieving fairly stable blood nicotine levels across the 2-hour testing session. Both participant and experimenter were blind to experimental condition. This study was part of a larger overall study which aimed to explore effects of nicotine and abstinence on motivational, cognitive and personality variables. Here we report just those relating to incentive motivational functioning (see accompanying paper for measures pertaining to inhibitory control and executive functioning). Table 1 provides a schematic overview of design/order of task administration.

Table 1
here

Participants

Participants were recruited through adverts in local newspapers, radio stations, colleges, libraries and pharmacies in the South East London area and were paid for their participation. All were aged between 18 and 65, had smoked more than 10 cigarettes a day for at least one year, and reported smoking within the first hour of waking up in the morning. Exclusion criteria included pregnancy, serious heart disease or recent stroke, a current psychiatric or neurological diagnosis, regular use of prescription (or class A recreational) drugs, and salivary cotinine levels of less than 20ng/ml (which is inconsistent with active smoking; Jarvis et al. 1987).

Expired CO samples were taken prior to each experimental testing session to verify compliance with the request to remain abstinent. Participants with a reading in excess of 10ppm on either occasion were excluded from the present study since they could not be considered nicotine-free prior to the experimental manipulation.

Written informed consent was obtained before participation in the study which was approved by Goldsmiths College Ethics Committee.

Assessment Measures

<u>Baseline Assessments</u>

Salivary Cotinine. All participants provided a saliva sample a few days prior to commencement of the experimental testing sessions. Cotinine, a metabolite of nicotine, with a half-life of 48 hours, is the most sensitive marker of recent nicotine intake and saliva levels were measured using gas chromatography. Regular smokers typically show salivary cotinine levels in the region of 330ng/ml (compared to < 20ng/ml in non-smokers; Jarvis et al. 1987).

Expired carbon monoxide. Breath CO levels were taken at the beginning of each testing session. The half life of CO is approximately 4 hours, thus scores of lower than 11ppm are expected in smokers who have complied with the instruction to abstain for 12 hours (Hughes et al. 1978).

The Fagerström Test of Nicotine Dependence (FTND; Heatherton et al. 1991)
This 6-item self-report scale assesses nicotine dependence. Scores range from 0 (low dependence) to 10 (high dependence).

Dependence scale from the Smoking Motivation Questionnaire (SMQ; West and Russell 1985). Participants rate the extent to which each of 9 statements apply to them using a 4-point scale. Total score ranges between 0 (low dependence) and 27 (high dependence).

Demographic information (including age, gender, ethnicity, socioeconomic status, educational level) and further data on smoking habits (number of cigarettes smoked a day, number of years of smoking and number of quit attempts) were also collected.

The first four measures described here were as administered in our previous studies (Powell et al. 2002a; 2002b; 2004)

Anhedonia: The Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al. 1995). This 14-item self-report scale is designed to measure hedonic tone in both healthy and clinical populations. Subjects indicate the extent to which they agree or disagree with a series of statements (for example, 'I would enjoy my favourite television or radio programme') relating to their expected enjoyment of a range of normally pleasurable events or activities 'at this moment'. Items were scored 0 (strongly agree) to 3 (strongly disagree) yielding a score range from 0 to 42 with a higher score indicating greater anhedonia.

Card Arranging Reward Responsivity Objective Test (CARROT; Al-Adawi and Powell 1997). This simple card sorting task, described in detail elsewhere (see Al-Adawi and Powell 1997), measures the extent to which participants' psychomotor performance is enhanced by financial incentive. Participants are required to sort cards according to a simple rule, firstly during a baseline familiarisation trial (B) and then under conditions of reward (R) and no explicit reward (NR), presented over three experimental trials in the order NR1, R, NR2. The average card sorting rate (cards per second) in the two non-rewarded trials is computed and the rate of increase in card sorting under R versus NR is taken to index 'reward responsivity'.

Modified Stroop test of attentional bias (Powell et al. 2002b). This measures the extent to which attention is 'captured' by various classes of motivationally salient stimuli. Participants are required to colour-name the ink (red, green, yellow or blue) in which each of 88 words (11 repetitions of 8 different words from a single semantic category) is printed. We used a card version of this task (consistent with our previous study), with the 88 words appearing in 4 columns which participants are required to colour name sequentially (vertically downwards) and correct themselves if they make an error. Four classes of semantic stimuli (neutral, appetitive, aversive and smoking-related [e.g. cigarette, smoke, lighter]), matched for word frequency and length, are presented on separate cards in counterbalanced order. In our previous study we

compared both appetitive and aversive stimuli with neutral stimuli; here we additionally included smoking-related words. These may have either appetitive or aversive connotations to individual smokers, depending on how they currently feel about smoking and possible cessation, and are more likely to engage cognitive processes than are the other categories of words. In the results section we explore how each separate semantic category of word is affected by nicotine vs. abstinence. Number of errors and total naming time (no. of seconds to complete colour-naming of all 88 words) are recorded for each of the four word types.

Cue Reactivity

Smokers rated their craving for a cigarette, and also their withdrawal symptoms: (i) at baseline, before cue-exposure; (ii) following 2 minutes exposure to a neutral cue (taking Scotch tape out of a box and sniffing it); and (iii) after 2 minutes exposure to a cigarette of their preferred brand (taking the cigarette out of its box and sniffing it).

Craving was assessed via ratings of the single item, 'How strong is your desire to smoke right now' on a 7-point Likert scale ranging from 1 (not at all strong) to 7 (extremely strong).

The severity of seven symptoms commonly associated with nicotine withdrawal (depression, irritability, anxiety, drowsiness, restlessness, hunger, poor concentration) was assessed using the Mood and Physical Symptoms (MPS) Scale *(*Hughes and Hatsukami 1986). Each item was rated on a 5-point scale (0-4). The total score could range from 0 to 28 with a higher score reflecting greater severity of withdrawal symptoms/negative mood.

Incentive Motivational Enhancement of Response Speed (IMERS) Task (Pickering 2004). In addition to the above well-validated measures, we also included a novel conditioning task (IMERS) recently developed by Pickering (but as yet, not tested on smokers) to explore reward motivation in a different way. This task measures the extent to which reaction time in a simple choice reaction time paradigm is affected by a) novel neutral stimuli and b) novel conditioned rewarded stimuli. In an initial 5 minute conditioning phase, participants acquire a non-instrumental association between the presentation of a specific geometric shape (star, square, triangle or

diamond, counterbalanced across participants and condition) and winning money. To achieve this, participants sit in front of a computer screen and hold a rubber bulb which they are required to alternatively squeeze and release on command. They are told that they can win up to £3.00 but that this has nothing to do with the way they squeeze the bulb, the decision instead being randomly made by the computer. After each 'squeeze and release' of the bulb, the computer screen displays either the participant's 'lucky' symbol (a white star, square, triangle or diamond, selected quasi-randomly for each participant), in which case the experimenter places a 50 pence piece on the table beside the participant, or the 'unlucky' symbol (a pentagon) in which case they receive nothing. A 'prize bar' displayed on the right hand side of the screen logs cumulative winnings.

Following the conditioning phase, the participant is given his or her winnings (always between £2 and £3) and then completes a 2 minute practice choice reaction time task followed by a 5 minute experimental task. The target stimuli for the choice reaction time task consist of the letters H and L presented one at a time in the centre of the screen. Participants are instructed to hit the H key in response to H using the forefinger of their left hand, and the L key in response to L using the forefinger of their right hand as quickly and as accurately as possible. Just prior to each target stimulus presentation, a rapid (1 second) sequence of distractor stimuli is presented consisting of 4 circles of different colours, each occurring for 250 msec. In standard trials these follow a constant pattern of four changes in colour and position, peripheral to the target stimulus (occurring at 9, 12, 3 and 6 o'clock in blue, green, red and white respectively). The practice phase consists of 40 standard trials and runs into the experimental phase without a break. There are 130 trials in the experimental phase; on six of these, a randomly selected 'novel' associative mismatch (AM) occurs. Here, an unexpected peripheral distractor appears on the fourth step (at 6 o'clock), consisting of a white hash sign or four small circles (AM trial). On a further six trials, the individual's conditioned rewarded stimulus (white star, square, triangle or diamond) occurs in the fourth position ('signal of reward' [SR] trial). AM and SR symbols are counterbalanced across participants and testing session. Every AM and SR trial is preceded by a 'standard' trial which acts as a direct reference for AM and SR slowing or speeding effects (see Figure 1).

Figure 1 here

Reaction time (RT) differences (AM trial minus its paired standard trial or SR trial minus its paired standard trial) are computed based only on those trials which receive a correct response *and* when the control trial preceding it also receives a correct response. These scores provide indices of the change in speed attributable to AM or SR (where a positive value indicates a slowing and a negative value a speeding of response). Participants whose RT is based on 2 or fewer trials are excluded. In order to specifically measure the speeding effect of signals of reward on RT, mean RT for AM trials was subtracted from mean RT for SR trials. Negative differences represent facilitation by reward and positive differences represent slowing by reward.

In previous work with a healthy student sample (Pickering et al. 2001) the unexpected AM distractor stimulus produced a highly significant inhibitory slowing of RT compared with standard trials. On SR trials this effect was not observed. Pickering (2004) suggested that the mismatch effect was still present on SR trials but was offset by a motivating and speeding effect triggered by the signal of reward. The degree to which the speeding effect associated with SR cancelled out the slowing effect associated with AM (i.e. AM minus SR) has been shown to be predicted by extraversion ($r = 0.32$; see Pickering 2004), a trait putatively associated with functioning of the mesocorticolimbic DA system (Depue and Collins 1999).

In the present context, we predicted that, due to their dampened DA system, abstinent smokers would be less reactive to signals of reward manifesting in larger (less negative) AM minus SR difference scores compared with their responses after nicotine administration.

Statistical Analyses

Data were analysed using repeated measures analysis of variance (ANOVA) with lozenge type (LOZTYPE: nicotine vs. placebo) as the within-subjects factor and order of lozenge administration as a between subjects factor (LOZORDER: nicotine first vs. placebo first). Lozenge order is only discussed where a significant main effect or interaction involving LOZORDER is found. These analyses were also repeated a)

with just the heavier smokers ($\geq$ 15 cigarettes a day) for direct comparability with the participants in our earlier study (Powell et al. 2002a) and b) with GENDER as a between subject factor, however, in the case of b), no significant effects were found thus gender is not discussed further.

Between-groups analyses were also conducted for Time 1 data only, given that the blinding procedure was less effective at Time 2; however the patterns of results did not differ from those of the repeated measures ANOVAs and so are not discussed further.

Results

Descriptive statistics for the two groups receiving nicotine and placebo lozenges in different orders are displayed in Table 2. The two groups did not differ from each other in sex ratio ($\chi^2 = 0.31$, df = 1, ns), age ($t_{143} < 1$, ns), years in tertiary education ($t_{142} < 1.5$, ns), or any of the smoking-related variables ($t_{143} < 1.6$, ns in each case).

Both craving and withdrawal symptoms (MPS) were higher in the placebo than nicotine condition (craving: $F_{1,143} = 21.95$, $p < 0.0001$; MPS: $F_{1,143} = 6.65$, $p = 0.01$) and did not differ significantly between the two groups (craving: $F_{1,143} = 2.79$, $p = 0.10$; MPS: $F_{1,143} = 1.57$, ns; See Table 2).

Table 2
here

Participants were asked which lozenge (nicotine or placebo) they thought they had received at each testing session. 55% of participants guessed correctly at time 1, a figure at chance level ($\chi^2 = 1.67$, ns), whilst 69% guessed correctly at time 2 ($\chi^2 = 21.57$, $p < 0.001$). These figures suggest that the blinding procedure worked very well for participants at time 1 but less well at time 2.

SHAPS anhedonia

Four participants failed to complete this questionnaire. For the remaining 141 participants, the main effect of LOZTYPE was significant ($F_{1,139}$ = 6.31, p < 0.02) reflecting greater anhedonia in the placebo (mean = 9.63, SD = 5.90) than in the nicotine condition (mean = 8.67, SD = 5.82). This effect remained significant when change in withdrawal symptoms (placebo minus nicotine) was covaried out ($F_{1,138}$ = 4.40, p < 0.05).

CARROT reward responsivity

REWARD (reward vs. non-reward trials) was an additional within-subjects factor in the ANOVA.

Rate of card sorting was significantly faster in the rewarded trial (REWARD: $F_{1,143}$ = 11.24, p = 0.001) but did not differ according to lozenge type (LOZTYPE: $F_{1,143}$ < 1, ns). There was a trend towards the predicted REWARD X LOZTYPE interaction ($F_{1,143}$ = 2.16, p = 0.14) reflecting almost identical rates of card sorting under nicotine and placebo conditions in the non-rewarded trials, but faster rates in the rewarded trial in the nicotine condition (see Figure 2). This interaction however, was significant in the heavier smokers ($\geq$ 15 cigarettes a day, N = 113; $F_{1,111}$ = 4.06, p < 0.05), consistent with the findings from our previous study (Powell et al. 2002a).
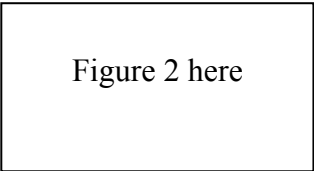
Figure 2 here

Modified Stroop

WORDTYPE (neutral, pleasure, aversive, smoking) was included in the ANOVA as an additional within-subjects variable. To test the specific theoretical questions of interest here relating to the involvement of DA in appetitive and aversive motivation separately, *a priori* contrasts were specified within ANOVA to compare words with appetitive, aversive and smoking connotations against neutral words (one-tailed). Thus it is the *a priori* contrasts rather than omnibus effects that are of specific interest here.

Errors

Individual subjects tended to make few errors on this task (overall mean: 1.07 [1.23]; range 0-7; see Figure 3). There were no main effects of either WORDTYPE ($F_{3,140} <$ 1, ns) or LOZTYPE ($F_{1,140} < 1$, ns), and the omnibus LOZTYPE X WORDTYPE interaction also fell short of significance ($F_{3,426} = 1.26$, ns). However the *a priori* contrasts revealed a significant LOZTYPE X WORDTYPE interaction specifically for pleasure vs. neutral words as predicted ($t_{142} = 1.71$, p < 0.05 for a 1-tailed test) but not for either aversive or smoking-related vs. neutral words ($t_{142} < 1$, ns in both cases). Since error data were distributed in a non-normal fashion, a non-parametric Wilcoxon signed ranks test was additionally conducted on the change scores (pleasure-word errors minus neutral-word errors) for the nicotine and placebo conditions. This revealed a significant difference for pleasure vs. neutral words (Z = -1.67, p < 0.05 for a 1-tailed test).

Figure 3 here

Naming Speed

For overall colour-naming time, there was a main effect of WORDTYPE ($F_{3,140} =$ 22.23, p < 0.0001) reflecting faster colour-naming of neutral words, no main effect of LOZTYPE ($F_{1,142} = 1.39$, ns) and no LOZTYPE X WORDTYPE interaction ($F_{3,426} <$ 1, ns). The *a priori* contrasts revealed no significant LOZTYPE X WORDTYPE interaction for any of the three salient word types (pleasure, aversive, smoking) relative to neutral words ($F_{1,142} < 1$, ns in each case).

Cue-Elicited Craving and Withdrawal

ANOVA included the additional within-subjects factor of EXPOSURE (neutral cue vs. cigarette cue).

As expected, both craving and withdrawal symptoms (MPS scores) were significantly higher in the placebo than nicotine condition (main effect of LOZTYPE: $F_{1,142} =$ 28.62 and 8.37, p < 0.005, for craving and withdrawal symptoms respectively). Craving was also higher in response to the sight and smell of a cigarette than a neutral cue (main effect of EXPOSURE: $F_{1,142} = 90.56$, p < 0.0001) although withdrawal

symptoms were not ($F_{1,142} < 1$, ns). There were no LOZTYPE X EXPOSURE interactions ($F_{1,138} < 1$, ns in both cases; see Table 3).

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Table 3
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IMERS Task

Fourteen participants did not complete this task as a result of technical problems with the computerised task; a further 11 participants were excluded from the AM analysis, and 9 from the SR analysis, because there were 2 or fewer valid trials (i.e. where both the experimental and preceding control trial are responded to correctly). These analyses were therefore based on 120 participants for AM trials and 122 for SR trials. Mean RTs for AM and SR trials, their paired standard control trials and the AM-SR differences are presented in Table 4.

For the 'AM minus paired control trials' difference score there was a significant effect of LOZTYPE ($F_{1,118} = 6.11$, $p < 0.05$), reflecting a smaller RT difference with nicotine than placebo. However there was no significant effect of LOZTYPE on the 'SR minus paired control trials' difference score ($F_{1,120} = 1.16$, ns), nor on the critical AM-SR difference score ($F_{1,116} < 1$, ns).

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Discussion

Using a double-blind, placebo-controlled design of pure nicotine administration in a large sample of smokers, this study aimed to subject to more rigorous test our previous findings that during abstinence, smokers show reduced behavioural responsiveness to, and dampened subjective enjoyment of, incentives; and that these effects are reversible by smoking. These previous studies could not unambiguously attribute the observed effects to nicotine, firstly because the non-blinded designs left open the possibility of expectancy effects, and secondly because the smoking manipulation entails exposure to multiple psychoactive substances in tobacco.

Generally speaking, the present results did corroborate these findings and confirmed that pure nicotine can reverse abstinence-related deficits which we have previously demonstrated to improve following cigarette smoking (Al-Adawi and Powell 1997; Powell et al. 2002a, 2002b).

On the SHAPS, abstinent smokers reported that they would expect to derive less enjoyment from a range of ordinary events and activities compared with their reports after receiving nicotine. Although one might expect smoking abstinence to be associated with a general malaise and anhedonia when smokers are aware of their deficit state, it was striking here that the effect was apparent despite the fact that participants were unable to judge whether they had received nicotine or not. Moreover, this effect remained significant when we controlled for subjectively rated withdrawal symptoms. Thus, the presence of nicotine delivered via lozenge does have a positive impact on hedonic tone, an effect that appears to be distinct from its effects upon the general symptoms of nicotine withdrawal.

Although the effect of nicotine on the CARROT reward responsivity measure here fell short of statistical significance within the whole sample, a significant effect was found in the heavier smokers (> 14 a day) who were directly comparable to those tested in our earlier study (Powell et al. 2002a). Specifically, during acute abstinence smokers showed virtually no reward responsivity (i.e. increase in speed of card sorting on the rewarded relative to the non-rewarded trials) but a significant effect after receiving nicotine. This confirms our predictions, at least in heavier smokers, that acute abstinence would be associated with weakened incentive motivation (putatively reflecting low levels of mesocortiocolimbic DA activity), and that this would be reversed by administration of pure nicotine. It is plausible, both theoretically and pharmacologically, that ingestion of nicotine by lozenge enhances responsiveness to incentives via its impact on mesocorticolimbic DA. Although we cannot unambiguously draw this conclusion, or indeed be certain of the impact of orally administered nicotine on the dopamine system, we note that systemic application of nicotine in animals is known to trigger DA release in the mesocorticolimbic system (Rahman et al., 2003).

There was also partial support for the hypothesis that nicotine would increase attentional bias towards stimuli with appetitive salience. Specifically, on the emotional Stroop task, participants made a relatively greater number of errors in colour-naming 'pleasure-related' words (e.g. love, adventure, euphoria) after receiving the nicotine lozenge than the placebo lozenge. This is consistent with Robinson and Berridge's conceptualisation of addictive drugs priming the reward pathways such that these appetitively salient words 'grab the attention' and accordingly impede the individual's ability to focus on other properties of the stimuli. Interestingly, however, the pattern of findings did not exactly replicate those found in our previous studies examining the effects of cigarette smoking on this task (Powell et al. 2002b). Thus the effect of nicotine did not manifest here in terms of overall *speed* of colour-naming of different word types, nor was the previously observed effect of smoking on increasing attentional bias to aversive/threat-related words (e.g. lonely, ashamed, emergency) replicated. These discrepancies might be attributable to methodological differences between the studies such as the different routes, levels, or speed of nicotine administration or to the other psychoactive components present in tobacco but not in lozenge. Further comparative studies would be needed to investigate these potential explanations.

There was no effect of nicotine on either error rate or response times to smoking-related words. Elsewhere, research using this paradigm has produced mixed results; some studies have found smokers to show attentional bias towards smoking-related cues during abstinence (e.g. Gross et al. 1993; Waters et al. 2003) whilst others have reported such biases after recent smoking (Johnsen et al. 1997); others still have reported no effect of abstinence versus recent smoking (Munafo et al. 2003; Rusted et al. 2000). In fact it is difficult to test the neurobiological model of addiction in relation to bias towards smoking-related words since both neurochemical and explicit cognitive processes, which affect attention towards such cues, are likely to be simultaneously involved, not necessarily working in the same direction. Thus, during acute abstinence a smoker is likely to be consciously preoccupied with thoughts of smoking. This will therefore lead to 'semantic priming', i.e., preferential processing of stimuli (words, pictures and so on) semantically related to smoking. This effect would tend to oppose any abstinence-related reduction in neurobiological 'appetitive priming' (i.e. impaired sensitivity to cues with any type of appetitive significance).

Conversely, in the satiated state, smokers are less likely to be thinking about their desire to smoke and so semantic priming will be less, but for the reasons previously discussed, neurobiological 'appetitive priming' will be elevated. Since the relative impact of these two sources of salience attribution/attentional bias are likely to depend on numerous factors (for example, length of abstinence, dose of nicotine, level of dependence, expectation about smoking after the experiment etc.), almost any pattern of results can be explained by recourse to this dual-route model. Accordingly, we recommend the use of non-drug-related appetitive cues to provide a 'clean' test of the incentive sensitisation model of addiction. Nevertheless, inclusion of drug-related cues is clearly of considerable clinical relevance to understanding multiply-determined 'real-world' outcomes.

Relatedly, we have argued that 'appetitive priming' via nicotine administration would increase cue reactivity in the form of craving elicited by cigarette-related cues. Some data consistent with this hypothesis have been reported (Powell et al. 2002a; Payne et al. 1996). By contrast, others (e.g. Baker et al. 1987) have argued that the incentive salience of such cues would be increased during abstinence. Interestingly however, we are unaware of any studies which have demonstrated elevated cue reactivity during acute abstinence by comparison with a satiated condition. Again, we note the possibility that two independent (and potentially opposing) biological and semantic priming mechanisms are likely to be involved.

Here, in one of the largest and best-controlled studies to date of cue-reactivity as a function of nicotine status, we found no difference between abstinent and satiated conditions in the increase in craving elicited by a smoking cue relative to that elicited by a neutral cue. This finding does not confirm the biologically based prediction of elevated cue reactivity after nicotine intake. It does suggest that if there is an effect of abstinence in promoting the incentive value of smoking cues, then it is offset by some other process. We would argue that this other process might be the biological incentive sensitisation effect. The relative influence of these two putative routes is obviously difficult to explore empirically, although one possibility might be to include, prior to the Stroop task, some measure of current cognitive content (e.g. by asking participants to rate the frequency/extent to which they are thinking about

smoking). This could then be used as a predictor in the statistical analysis of colour-naming errors/speed.

It is also possible that the single-item index of craving used here lacked sensitivity to 'real' underlying effects of nicotine. In our previous study in which we did find an effect we used a broader multi-item measure (QSU); future research might usefully compare different techniques of assessment.

In clinical terms, the fact that this study reveals no impact of nicotine lozenge in reducing cue reactivity, suggests that nicotine replacement therapy (NRT) may not protect against surges of craving that smokers attempting to quit might experience in smoking-related situations. Indeed, although NRT is effective in helping smokers to quit, nevertheless, 78-90% still relapse (Hyland et al. 2005; Swartz et al. 2005). This raises the possibility that concurrent treatment with other medications which do attenuate cue reactivity should be considered. In this regard, it is interesting that, in a recent PET study with smokers, bupropion treatment attenuated both cue-induced anterior cingulate cortex activation and craving (Brody et al. 2004).

The IMERS task was the only measure not previously used in our research with smokers. As previously found by Pickering (2004), associative mismatch (AM) trials produced a slowing of response whilst signal of reward (SR) trials went some way to offsetting this. Interestingly, the AM effect was smaller in the nicotine than placebo condition suggesting that nicotine had a speeding effect on AM trials. This is likely to be due to the stimulant properties of nicotine. However, contrary to our prediction, there was no difference between nicotine and placebo conditions in the speeding effect of signals of reward. This result appears to conflict with the observed effect of nicotine on CARROT reward responsivity. Clearly there are a number of potentially relevant procedural differences between the tasks which could account for the apparent discrepancy. For instance, the CARROT involves an instrumental response-outcome link; increasing speed of card sorting on the reward trial produces more financial gain. By contrast, there is no such response-outcome association in the IMERS task; the speed of response has no implication for the participant's personal gain. Aspects of reward pathway function putatively affected by drug priming include a) attentional processing of reward cues with concomitant motivational effects

and b) using incentive information to strategically enhance instrumental behaviours orientated to obtaining a reward. Whereas the CARROT involves both these putatively drug-dependent processes, the IMERS involves only the former. If only the latter process is important however, then only the CARROT should be affected by drug priming.

The present effect sizes were somewhat smaller than in our previous studies which compared acute abstinence with smoking. This might reflect the influence of expectancy effects/demand characteristics previously, the different routes of nicotine administration, or a combination of both. Nicotine delivered via cigarette smoking achieves high levels in the blood and rapid surges of nicotine (as a bolus) to the brain (Russell 1976); administration via lozenge or gum, by contrast, is much slower, reaches only one-third of these levels and does not produce the bolus of nicotine to the brain achieved via smoking (Keenan et al. 1995). Thus smoking may be a more potent method of reversing reward motivational impairments through its ability to deliver high concentrations of nicotine and to do it quickly. It would be interesting in future studies to explore the dose-response relationship between nicotine and task performance.

Finally, it is worth noting that although the blinding procedure worked very well at Time 1, it was less effective at Time 2 with 69% of participants correctly guessing which lozenge they had received. This is common problem with repeated measures designs and is not surprising, given that a direct comparison of the two lozenges is only possible at Time 2. Although participants were not routinely asked how they could tell, informally they often commented that they could detect a strong taste or 'burning sensation' in the throat. Since between-subjects analyses of Time 1 data only revealed the same pattern of results as the full analysis, we can conclude that subjective awareness at Time 2 cannot account for all the observed effects of nicotine.

The present findings have potentially important clinical implications. For instance, one tentative conclusion is that, although nicotine delivered in the form of a lozenge can alleviate abstinence-induced impairments of reward motivation/salience attribution, it does not diminish the craving elicited by exposure to cigarette-related cues. It is important to establish whether these deficits predict relapse, and whether

there are individual differences in the magnitude of abstinence-induced impairments (e.g. reflected in personality traits or genotype) since this would enable relevant interventions to be targeted accordingly. We are exploring both of these issues in this group of smokers as they attempt to quit.

Acknowledgments

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Table 1

ASSESSMENT	ORDER OF TESTS
Baseline	**Informed consent** **Demographic information** **Expired carbon monoxide** Tridimensional Personality Questionnaire **Fagerström Test of Nicotine Dependence** Sensation Seeking Questionnaire Hospital Anxiety and Depression Scale (HADS) Eysenck Personality Questionnaire **Smoking Motivation Questionnaire** IVE Positive Emotionality Quesionnaire **Salivary Cotinine**
	2 to 7 days later
Assessment 1 Following overnight (12 hours) abstinence Group 1: Nicotine lozenge Group 2: Placebo lozenge	**Expired carbon monoxide (must be $\leq$ 10ppm)** **Administration of lozenge** **30 minute wait** Spatial Working Memory Task Saccadic Eye Movement Task Verbal Fluency Antisaccadic Eye Movement Task **Administration of 'top-up' lozenge** **CARROT or IMERS task (counterbalanced)** Alphabet Arithmetic HADS **Snaith Hamilton Pleasure Scale (SHAPS)** **Stroop** **IMERS or CARROT (counterbalanced)** Continuous Performance Task **Cue Reactivity**
	One week later
Assessment 2 Following overnight (12 hours) abstinence Group 1: Placebo lozenge Group 2: Nicotine lozenge	**Expired carbon monoxide (must be $\leq$ 10ppm)** **Administration of lozenge** **30 minute wait** Spatial Working Memory Task Saccadic Eye Movement Task Verbal Fluency Antisaccadic Eye Movement Task **Administration of 'top-up' lozenge** **CARROT or IMERS task (counterbalanced)** Alphabet Arithmetic HADS **Snaith Hamilton Pleasure Scale (SHAPS)** **Stroop** **IMERS or CARROT (counterbalanced)** Continuous Performance Task **Cue Reactivity**

Procedures/assessment measures in **bold** represent those relevant to the present study.

Table 2

	Lozenge Order: Nicotine/Placebo N=76	Lozenge Order: Placebo/Nicotine N=69
Age		
Mean (SD)	32.43 (13.12)	31.08 (11.14)
Range	19-65	19-63
Sex ratio (M:F)	30:46	33:36
Years in further education		
Mean (SD)	4.20 (3.51)	3.43 (2.97)
Range	0-22	0-13
No. of cigarettes per day		
Mean (SD)	18.09 (5.06)	18.14 (6.68)
Range	10-35	10-40
Years of regular smoking		
Mean (SD)	15.96 (12.76)	15.08 (11.73)
Range	1-52	2-48
No. of previous quit attempts		
Mean (SD)	2.84 (3.65)	2.61 (2.74)
Range	0-20	0-10
Baseline CO		
Mean (SD)	19.24 (9.69)	17.50 (8.36)
Range	5-48	4-44
Baseline cotinine		
Mean (SD)	253.41 (128.67)	278.25 (172.03)
Range	44.60-512.60	43.60-940.30
FTND		
Mean (SD)	4.95 (1.76)	4.81 (1.94)
Range	2-9	1-9
SMQ dependence		
Mean (SD)	13.49 (4.83)	14.98 (4.59)
Range	3-24	5-27
Craving (placebo lozenge)		
Mean (SD)	3.96 (1.74)	4.03 (1.77)
Range	1-7	1-7
Craving (nicotine lozenge)		
Mean (SD)	3.50 (1.65)	3.06 (1.64)
Range	1-7	1-7
MPS (placebo lozenge)		
Mean (SD)	6.96 (4.59)	6.87 (3.83)
Range	0-18	1-18
MPS (nicotine lozenge)		
Mean (SD)	6.50 (4.29)	5.54 (4.32)
Range	0-18	0-21

FTND = Fagerstrom Test of Nicotine Dependence; SMQ=Smoking Motivation
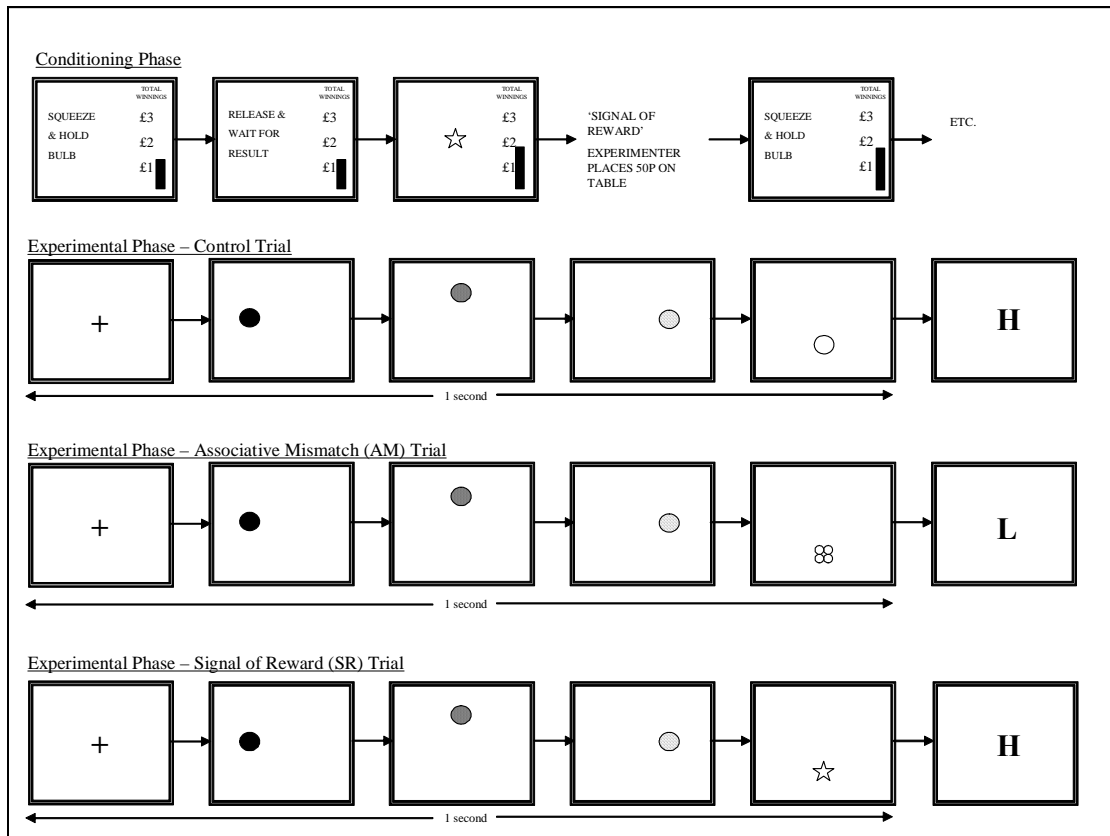Questionnaire; MPS = Mood and Physical Symptoms

Table 3

	Nicotine	**Placebo**
Craving		
Neutral cue: mean (SD)	3.15 (1.76)	3.83 (1.71)
Cigarette cue: mean (SD)	3.93 (1.81)	4.61 (1.79)
MPS		
Neutral cue: mean (SD)	4.88 (3.77)	5.80 (4.15)
Cigarette cue: mean (SD)	4.85 (3.82)	5.76 (4.04)

Table 4

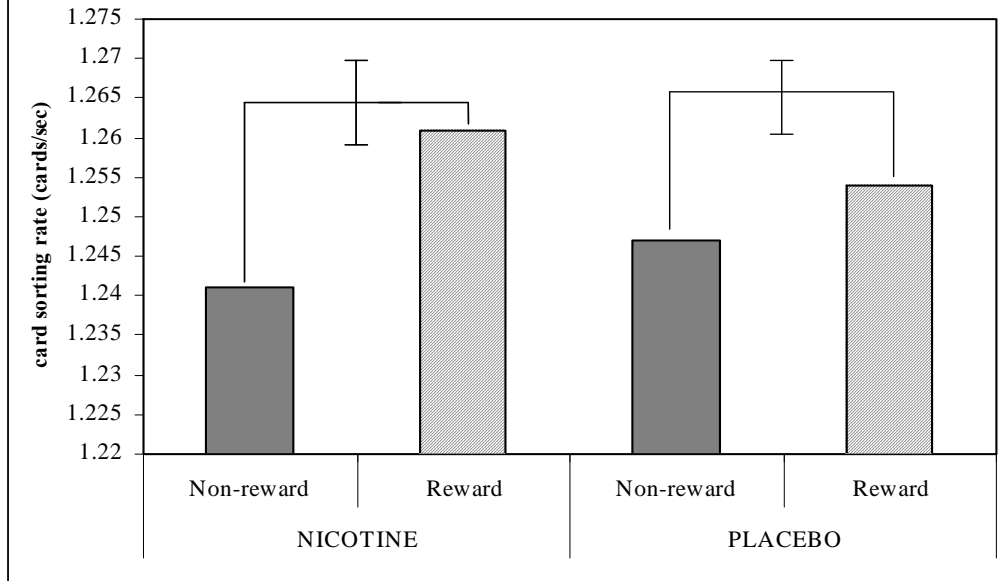|	**Nicotine**	**Placebo**
AM trials	0.519 (0.110)	0.544 (0.130)
AM paired control trials	0.452 (0.093)	0.448 (0.116)
AM – control trials	0.067 (0.078)	0.097 (0.127)
SR trials	0.481 (0.124)	0.513 (0.149)
SR paired control trials	0.447 (0.095)	0.464 (0.108)
SR – control trials	0.034 (0.088)	0.049 (0.137)
AM – SR difference	0.037 (0.112)	0.031 (0.131)

Figure 1

Conditioning Phase

	TOTAL WINNINGS			TOTAL WINNINGS			TOTAL WINNINGS	
SQUEEZE & HOLD BULB	£3 £2 £1		RELEASE & WAIT FOR RESULT	£3 £2 £1		☆	£3 £2 £1	

'SIGNAL OF REWARD' EXPERIMENTER PLACES 50P ON TABLE

	TOTAL WINNINGS
SQUEEZE & HOLD BULB	£3 £2 £1

ETC.

Experimental Phase – Control Trial

+ → ● → ● → ○ → ○ → **H**

← 1 second →

Experimental Phase – Associative Mismatch (AM) Trial

+ → ● → ● → ○ → ✿ → **L**

← 1 second →

Experimental Phase – Signal of Reward (SR) Trial

+ → ● → ● → ○ → ☆ → **H**

← 1 second →

Figure 2

card sorting rate (cards/sec)

Non-reward | Reward | Non-reward | Reward
NICOTINE | PLACEBO

Figure 3

Colour naming errors

Neutral | Pleasure | Aversive | Smoking | Neutral | Pleasure | Aversive | Smoking
NICOTINE | PLACEBO
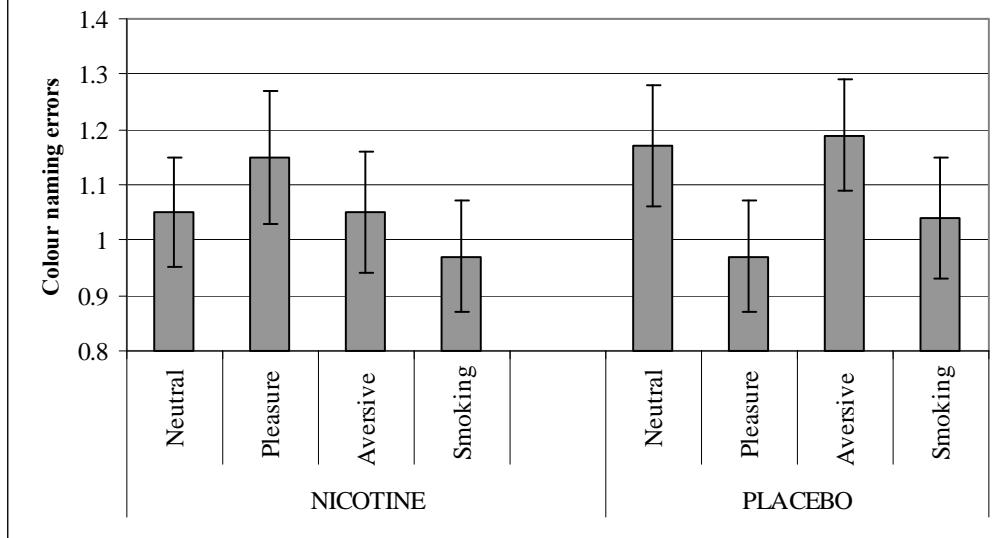
Legend for Tables and Figures

Table 1: Schematic overview of design and order of assessments

Table 2: Demographic and smoking-related information, and craving and withdrawal symptoms for the two groups tested in different orders.

Table 3: Mean (SD) reaction times for AM and SR trials and their paired standard control trials under nicotine and placebo lozenge conditions.

Table 4: Mean (SD) self-reported craving and MPS scores following exposure to neutral and cigarette cues under nicotine and placebo lozenge conditions.

Figure 1: IMERS experimental framework. 130 experimental trials comprising 112 control trials, 6 AM trials and 6 SR trials were presented in random order. AM and SR symbols were counterbalanced across participants and testing sessions. H and L represent the targets for choice reaction time responses.

Figure 2: Card sorting rate (cards per second) on the CARROT non-rewarded and rewarded trials under conditions of nicotine and placebo lozenge for all subjects. Error bars are +/- 1SE on the non-reward minus reward interaction.

Figure 3: Colour-naming errors for the four different word types on the modified Stroop task in nicotine and placebo lozenge conditions. Error bars are +/- 1SE