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A double-blind placebo controlled experimental study of nicotine: II – Effects on response inhibition and executive functioning

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Abstract

Rationale: Smokers may show abnormal functioning in prefrontal cortex during acute abstinence, reflecting deficient activity in mesocorticolimbic circuitry. Cognitive correlates of this putatively include impaired response inhibition and other aspects of executive functioning.

Objectives: To investigate whether inhibitory control and other executive functions in smokers are impaired during acute abstinence relative to post-nicotine.

Methods: 145 smokers were tested twice following overnight abstinence, once after nicotine and once after placebo lozenges (order counterbalanced, double-blind), on: an antisaccade task; a Continuous Performance Task (CPT); a delayed response Spatial Working Memory (SWM) task; and a verbal fluency test.

Results: Compared with placebo, nicotine was associated with better inhibitory control on the antisaccade task and fewer impulsive responses to filler stimuli (motor errors) on the CPT; at the first assessment only, nicotine also reduced impulsive responses to 'catch' stimuli on the CPT. However, it did not affect CPT response bias (an index of impulsive vs. cautious decision-making), spatial working memory, or verbal fluency.

Conclusions: Smoking abstinence appears to be associated with difficulty in inhibiting prepotent motor responses, and nicotine to attenuate this difficulty. However, more 'cognitive' forms of inhibitory control (e.g. decision-making) and the other aspects of executive function tested here appear to be unaffected.

Keywords:
Nicotine, abstinence, response inhibition, executive functioning, working memory, dopamine, lozenge

Introduction

The ability of drugs to increase brain dopamine (DA) concentrations in the mesocorticolimbic (MCL) brain circuitry is considered critical for their rewarding effects (e.g., Di Chiara and Imperato 1988; Wise 1996). Addiction may be associated with abnormal activity in these pathways: although addicts continue to experience acute upsurges in DA levels in response to drug ingestion (Di Ciano et al. 1995), there is increasing evidence from PET and SPET studies that by comparison with non drug users, abstinent addicts have fewer DA D2 receptors and show decreased DA release in the striatum (Dagher et al. 2001; Volkow et al. 1997, 2004).

Within the MCL system, dopaminergic neurons from the ventral tegmental area project diffusely throughout pre-frontal cortex (PFC). In chronic drug users, reduced numbers of DA D2 receptors in the striatum appear to be paralleled by reduced DA activity in these cortical regions (Volkow et al. 1993; 2001). Relatedly, there is neuroimaging evidence that drug abusers show abnormalities in the structure and function of PFC, particularly orbitofrontal cortex (OFC), anterior cingulate gyrus (ACG; London et al. 2000; Volkow et al., 1993) and dorsolateral prefrontal cortex (DLPFC; Robinson et al. 2001). The varied high-level 'executive' cognitive functions ascribed to specific sub-regions of the PFC show considerable overlap (see, e.g., Aron et al., 2004), but include: processing the affective value of stimuli and making appropriate decisions, functions commonly attributed to OFC function; the inhibition of automatic reflexive responses, which has been associated with ACG function; and monitoring of strategically guided behaviour and working memory, which have been shown to involve DLPFC; for more detailed reviews, see Elliott et al. (2000), Kiehl et al. (2000), Krawczyk (2002) and Royall et al. (2002).

If PFC function, in some or all subregions, is indeed disturbed in chronic smokers, as it appears to be in users of other substances, then it follows that during early abstinence they should show deficits in some or all of the cognitive functions mediated by activity in these regions. Conversely, the pharmacological 'boost' achieved via smoking a cigarette - or taking nicotine replacement therapy - should at least transiently enhance or normalise such functions.

Informed by the neuroimaging findings, recent theories of addiction have focused on perturbations of cognitive processes mediated by the PFC, particularly response inhibition. Jentsch and Taylor (1999) were among the first to propose that PFC dysfunction in chronic drug users is likely to lead to impairments in the inhibitory control of appetitive responses to drugs or drug-related stimuli, thereby increasing

their risk of relapse. Likewise, Goldstein and Volkow's (2002) Impaired Response Inhibition and Salience Attribution (I-RISA) model of addiction argues that dependence is associated with an overvaluing of drug reward, undervaluing of natural rewards, and deficits in inhibitory control over prepotent responses to drug-related stimuli; and Lubman et al. (2004) conceptualise addiction as a compulsive disorder and propose that the addict's characteristic loss of control over their drug use is underpinned by a failure of cortical inhibitory control mechanisms.

Our group has measured inhibitory control at a basic motor level via the ability to suppress reflexive saccades towards peripheral visual stimuli in favour of controlled 'antisaccades' in the opposite direction. Acutely abstinent smokers made significantly more errors on this task than either satiated smokers or non-smokers (Powell et al. 2002). Poor inhibitory response control in abstinent smokers has also been inferred by others based on evidence of: increased errors of commission on vigilance tasks (Hatsukami et al. 1989; Zack et al. 2001); less efficient inhibition of eye movements towards task irrelevant stimuli (Rycroft et al. 2005); and decreased inhibition of irrelevant material on a retrieval induced forgetting task (Edginton & Rusted, 2003). Using continuous performance and go/no-go tasks, Bekker et al. (2005), by contrast, recently reported only minimal enhancing effects of nicotine on response inhibition in abstinent smokers. Elsewhere, others have demonstrated that current smokers are also more likely than non-smokers to favour small but immediate monetary rewards over larger but delayed rewards, a pattern of responding often characterised as 'impulsive' (Bickel et al. 1999; Mitchell 1999).

The neurobiological theories of addiction outlined above have focused in particular on deficits of inhibitory control. There is rather inconsistent empirical evidence for other executive functioning deficits in smokers or people addicted to other substances. For example, whilst Al-Adawi and Powell (1997) found poorer verbal fluency (tapping volitional response generation) and reduced reversed digit span (tapping working memory) in abstinent compared with satiated smokers, these findings were not replicated in a subsequent study (Powell et al. 2002). Several researchers (e.g., Bekker et al., 2005; Harte and Kanarek, 2004; Sacco et al., 2005) have reported reduced accuracy on the continuous performance task, which involves working memory and attention, during abstinence; however, although Mendrek et al. (2006) found that relative to non-smokers abstinent smokers were impaired in working memory assessed by the n-back task, their deficits were not reversed by smoking a single cigarette. There are also other apparently contradictory reports. Using a spatial working memory (SWM) task designed specifically to tap PFC

function, Park et al. (2000) found smokers to show *superior* performance after 24 hours abstinence compared to following recent nicotine consumption. By contrast, Sacco et al. (2005) found that smokers with schizophrenia showed a SWM deficit after overnight abstinence, and that this was reversed by smoking. Using PET, Ernst et al. (2001) found that, although the working memory performance of abstaining- and ex-smokers was equivalent, there were differences in patterns of activation across brain regions, suggesting that abstinence may affect the nature of the underlying information-processing strategy.

Whether neural and cognitive dysfunctions develop as a consequence of chronic smoking, or predate (and possibly pre-dispose to) heavy smoking/substance use, they are most likely to be apparent, or unmasked, during early abstinence. The present study was designed to further investigate the impact of smoking abstinence and acute nicotine intake on dependent smokers' response inhibition and other executive functions, using a rigorously double-blinded placebo-controlled design and by delivering nicotine in pure form. Based on the preceding review, the study tested the hypotheses that, by comparison with performance following a nicotine lozenge, acute abstinence (placebo lozenge condition) would be associated with:

1. Decreased inhibitory control, assessed using the following measures: (a) accuracy of antisaccadic eye movements; (b) a criterion location measure (C) of response bias on a Continuous Performance Task (CPT); and (c) proportion of 'filler' (to-be-ignored) trials on which a response is made (pre-emptive 'motor errors') on the CPT.

2. Impairments of selected 'other' executive functions, specifically: (a) performance on the spatial working memory (SWM) task developed by Park et al. (2000); (b) accuracy on the CPT task (indexed by dprime), which taps the ability to discriminate targets from distractors ('catch' stimuli) and has a strong working memory component; and (c) verbal fluency, a widely used index of volitional response generation.

Materials and methods

Design

In this repeated measures design, 145 smokers were each tested on two occasions a week apart, following overnight (12 hours) abstinence from smoking on both occasions. On arrival, they received either a 4mg NiQuitin lozenge (the dose given

clinically to smokers who smoke within 30 minutes of waking, as did the majority of the present sample) or a placebo lozenge. Both preparations were provided by Glaxo Smith Kline and were identical in appearance and very similar in taste. When used as directed, 4mg nicotine lozenges take approximately one hour to produce maximum plasma concentrations averaging 10.8 ng/ml (sd: 4.7), and have a half life of approximately 2 hours (Choi et al. 2003). Order of the two lozenges was counterbalanced, and participants were required to suck them for 30 minutes before commencement of testing; this gives sufficient time for nicotine to reach the bloodstream. One hour into the testing session, a second 'top-up' lozenge, identical to the first, was given in order to maintain fairly stable blood nicotine levels across the 2-hour testing session. Both participant and experimenter were blind to experimental condition.

In addition to the experimental measures reported here, the test battery included a number of indices of reward motivation and incentive salience; these are processes which are also theoretically likely to be affected by nicotine abstinence and administration. That element of the study is fully described in another paper (Dawkins et al., in press). Table 1 gives a schematic representation of the overall study design and the order in which all tasks were administered.

Table 1 here

Participants

Participants were recruited through advertisements 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, reported smoking within the first hour of waking up in the morning, and had salivary cotinine levels (at a baseline screening) of at least 20ng/ml. Exclusion criteria included pregnancy, current diagnosis of psychiatric or neurological condition, and regular use of prescription drugs or other psychotropic drugs.

Expired CO samples were taken prior to each experimental testing session to verify compliance with the abstinence requirement, with CO levels ≤ 10ppm at both time points required for inclusion in the study (Hughes et al 1978).

Participants all gave written informed consent, and the study was approved by Goldsmiths College Ethics Committee.

Assessment Measures

Demographic information included age, gender, and years of education.

Smoking status

Self-reported use: Participants were asked how many cigarettes they smoked per day, how many years they had smoked, and how many quit attempts they had made.

Salivary Cotinine: Participants provided a saliva sample at a preliminary screening assessment. Cotinine, a metabolite of nicotine and the most sensitive marker of recent nicotine intake with a half-life of 48 hours, was analysed by gas chromatography. Regular smokers typically show salivary cotinine levels in the region of 330ng/ml, and non-smokers < 20ng/ml (Jarvis et al., 1987).

Expired carbon monoxide. Breath CO levels were taken at baseline and at the beginning of each testing session. The half life of CO is approximately 4 hours and scores of < 11ppm are expected in smokers who have abstained 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).

Craving and Withdrawal Symptoms: Craving for a cigarette and withdrawal symptoms were assessed towards the end of each session following exposure to a neutral stimulus in the context of a cue reactivity assessment (findings from which are reported in Dawkins et al., in press). Participants rated their craving ('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); and, on the Mood and Physical Symptoms Scale (MPSS; West and Hajek 2004), the severity of seven symptoms of nicotine withdrawal (depression, irritability, anxiety, drowsiness, restlessness, hunger, poor concentration) on a 5-point scale (0-4), yielding a maximum possible score of 28 (severe symptoms).

Mood state

Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983): The HADS was administered towards the end of each session. This instrument

assesses the presence and severity of symptoms of anxiety and depression over the preceding seven days. 7 items tap each mood state, with each item rated on a 4-point scale (0-3) to yield total scores of between 0 and 21 for both anxiety and depression (higher scores indicate greater disturbance).

Experimental Tasks

Oculomotor task of response inhibition (antisaccadic eye movements): Participants were required to suppress a reflexive glance towards a stimulus which appeared in the periphery of the visual field and instead to generate an eye movement of the same amplitude in the opposite direction (an antisaccade). In a control condition, participants were simply required to look towards the peripheral stimulus (prosaccades). The procedure used here was based on that employed by Fukushima et al. (1994) and Clementz et al. (1994). Participants were tested in a quiet, darkened room, seated 30cm in front of a 25cm computer monitor and fitted with eye-tracking headgear. A chin rest was used to minimise head movements. Horizontal eye movements were measured (for the left eye only) using an infra-red reflection technique (IRIS IR 6500 by Scalar Medical) with a sampling rate of 500 Hz. Recordings were then digitised using a Brain Boxes 12-bit analogue-to-digital converter.

Following calibration, participants were asked to fixate on a centrally located white dot subtending a visual angle of $< 0.25^{o}$ for a period varying randomly between 2 and 4 seconds. Following a 200 msec interval after extinction of the fixation point, one of four possible peripheral targets was illuminated for 500 msec. The central fixation point then re-appeared. Peripheral targets varied in both direction (left or right of central fixation) and amplitude (10° or 20°) and were presented in a randomised order. In the prosaccade condition, which was always first, participants were instructed to "look at the peripheral target as quickly and as accurately as you can"; a total of 60 peripheral stimuli were then presented, 15 at each of the four possible positions. After a 5-minute interval, 60 more stimuli were presented under antisaccade instructions ("don't look at the peripheral target but instead, look in the opposite direction, i.e., to the mirror image position").

A custom program, written in-house, was used to classify each eye-movement as correct (initial movement in the right direction) or incorrect (initial movement in the wrong direction regardless of whether it is subsequently corrected). Instances in which no eye movement was recorded (e.g. due to poor calibration, temporary eye closure or failure to elicit an eye movement of sufficient magnitude) were eliminated

from the analysis, and percentages correct were then computed for the remaining pro- and antisaccade trials. On average, only 3.85 trials out of 60 were eliminated for each participant (mode = 0); however, more than half of the trials were affected for 13 participants, because of calibration problems, and the data from these participants were entirely excluded on the basis that it was less likely to be reliable.

Continuous Performance Task (CPT; Dougherty et al. 1999). Versions of the CPT have been widely employed to study attentional control and response inhibition in a variety of patient groups, particularly schizophrenics (see Cohen and Servan-Schreiber 1992). In this version, adapted from Dougherty et al. (1999), 5-digit numbers were presented at a constant rate of two per second for a period of 5 minutes. Participants were instructed to respond by clicking the left button on a computer mouse whenever a 5-digit sequence was identical to the preceding one ('targets') and NOT to respond to either 'novel' stimuli (all 5 digits were different from those in previous stimulus) or 'catch' stimuli (where 4 of the 5 digits matched the preceding stimulus). Each presentation of a target, catch, or novel stimulus was separated from the next by three consecutive presentations of the fixed 'filler' sequence 12345 to which participants were told NOT to respond (see Figure 1). Two fixed sequences were used here, with the order counterbalanced across sessions.

Figure 1 here

The rate of impulsive, incorrect responses to catch stimuli (measured by commission errors) has been found to correlate positively with impulsive personality traits and to increase following consumption of alcohol (Dougherty et al., 1999). However, the probability of a commission error is influenced both by the ability to discriminate between target and catch stimuli and by response bias; we have therefore indexed these influences separately using signal detection theory. Our signal detection analysis, using responses to targets as hits and responses to catch stimuli as false positives, yields: (i) an index of accuracy ('dprime'), which taps the ability, strongly influenced by working memory, to discriminate targets from catch stimuli, with scores ranging from 0 (chance level performance) to 4 (effectively, perfect performance); and (ii) a criterion location measure of response bias (C) where a score of 0 reflects unbiased responding, a negative score reflects a liberal (and putatively impulsive) bias to respond on the basis of little evidence for the presence of a target (i.e. a high rate of both hits *and* false positives), and a positive score represents a cautious bias (fewer hits *and* fewer false positives). In addition we calculated the proportion of trials on which a pre-emptive response was made to at least one of the sequence of

three filler stimuli (12345s); because participants knew in advance that these three stimuli, occurring as they did immediately following the target stimulus, should never be responded to. We have labelled these as (impulsive) 'motor errors'.

Spatial Working Memory (SWM; Park et al. 1995). This delayed-response SWM task was adapted from Park et al. (1995) from a paradigm used by Funahashi et al. (1989) with rhesus monkeys and shown to be sensitive to DLPFC lesions. Similar impairments have been reported in patients with PFC lesions (Partiot et al., 1996), schizophrenics (e.g. Spitzer, 1993), and healthy individuals high in schizotypy (Park et al., 1995).

Participants were asked to focus on a central fixation point (a small red dot) throughout the task. A 'target' stimulus (a larger black dot) then appeared for 200msec. in one of eight possible locations each separated by 45 degrees on the circumference of an imaginary circle centred on the red dot. Participants were instructed simply to remember the position of this target. The location of the target dot varied from trial to trial in a pseudo-randomised order with each of the eight locations used four times. During a 10 second interval between target presentation and response, a distractor task was presented in which participants were required to decide whether or not each of eight successively presented words belonged to a particular semantic category (one of: fruits, vegetables, colours or household items). Participants made their category responses by pressing a key on the computer keyboard labelled 'Y' (Yes) or 'N' (No). This categorisation task served simply to prevent rehearsal of the spatial location, and to ensure that participants continued to focus on the centre of the screen; these data were therefore not of interest in their own right, and have not been analysed. After 10 seconds the eight (reference) black dots reappeared and participants were required to click the mouse on the dot occupying the position in which the target had previously appeared. The next trial then commenced. 32 such experimental (SWM) trials were interspersed with 32 sensorimotor control (SMC) trials in which the original target was displayed throughout the categorisation task and which thus imposed no demand on working memory. Percentage correct and reaction time were recorded for both SWM and SMC trials.

Verbal Fluency. This has consistently been found to be sensitive to prefrontal lesions and is believed to tap strategic response generation or 'willed action' (e.g. Jahanshahi and Frith, 1998). Here, participants were asked to generate as many words as they could beginning with either B or F (order counterbalanced across

conditions) in one minute, avoiding repetitions, proper nouns and the same word with different suffixes. This single-letter version has good test-retest reliability and correlates highly with the traditional three-letter version (Harrison et al., 2000).

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). Main effects or interactions involving LOZORDER are reported only where significant. These analyses were also repeated with just the heavier smokers ($\geq$ 15 cigarettes per day) for direct comparability with the participants in our earlier study (Powell et al., 2002a). In fact, however, we found no differences between the results for this sub-group and the full sample, thus here we present only those for the latter.

Between-groups analyses were also conducted for time 1 data only, given that the blinding procedure was less successful at time 2 (see below); these are presented only where they yield findings which differ substantively than those from the full repeated measures analysis.

Results

Unless otherwise indicated all variables were normally distributed.

Demographic and smoking-related variables: Summary statistics are shown in Table 2. The groups receiving nicotine and placebo lozenges in the two orders did not differ from each other in sex ratio (χ^2 = 0.31, df = 1, ns), age (t_{143} < 1, ns), years in education (after age 16; t_{142} < 1.5, ns), or any of the smoking-related variables (t_{143} < 1.6, ns in each case).

Table 2 here

Blinding: 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 not significantly different from chance level (χ^2 = 1.67, ns), whilst 69% guessed correctly at time 2 (χ^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

when participants had the benefit of mentally comparing the perceived effects of the lozenges across sessions.

Craving, withdrawal and mood state: As shown in Table 3, both craving and withdrawal symptoms (MPSS score) were lower in the nicotine than placebo condition (craving: $F_{1,143} = 21.95$, $p < 0.0001$; MPSS: $F_{1,143} = 6.65$, $p = 0.01$).

HADS Anxiety scores were significantly higher in the nicotine than placebo condition ($F_{1,143} = 4.31$, $p < 0.05$); although the scores were slightly elevated, in most cases they were well within the normal range (Zigmond and Snaith 1983). There was no effect of LOZTYPE on HADS Depression scores ($F_{1,143} < 1$, ns).

Table 3 here

Experimental tasks

Oculomotor task (antisaccadic eye movements): Saccade type (SACTYPE: prosaccade vs. antisaccade) was an additional within-subjects factor in the ANOVA. Summary data are shown in Figure 2.

Figure 2 here

The main effects of LOZTYPE ($F_{1,120} = 30.0$) and SACTYPE ($F_{1,120} = 370.9$) were both highly significant ($p < 0.0001$ in both cases), reflecting greater accuracy after nicotine than placebo, and in the prosaccade than antisaccade condition (see Figure 2). The LOZTYPE X SACTYPE interaction was also highly significant ($F_{1,120} = 20.97$, $p < 0.0001$), with nicotine improving performance more markedly in the antisaccade than in the prosaccade condition. This may be, to some extent, a function of ceiling level performance in the prosaccade trials.

Continuous Performance Task (CPT): Table 4 shows summary data for the indices of accuracy (dprime), response bias (C) and motor errors (impulsive motor responses to filler stimuli).

Table 4 here

There was no main effect of LOZTYPE on either accuracy or response bias ($F_{1,131} < 1.5$, ns, in each case). LOZTYPE interacted significantly with LOZORDER for

accuracy ($F_{1,131}$ = 10.49, p < 0.01) reflecting a strong practice effect from the first to the second testing session (time 1 mean dprime = 2.08, SD: 0.98; time 2 mean dprime = 2.28, SD: 1.03). This effect was also apparent, but less pronounced, for response bias ($F_{1,131}$ = 3.58, p = 0.06) with a slight negative bias in the first session changing in the direction of a more neutral bias in the second session.

Analysis of data at time 1 only revealed that participants receiving nicotine were more accurate than those receiving placebo (dprime: 2.22 $\pm$ 1.02 and 1.91 $\pm$ 0.90 respectively; t_{133} = 1.82, p < 0.05 for a 1-tailed test), though there was no effect of LOZTYPE on response bias (t_{131} < 1, ns).

For motor errors, there was a significant effect of LOZTYPE ($F_{1,132}$ = 7.270, p < 0.01) reflecting a greater number of impulsive mouse clicks under placebo than nicotine. These data were positively skewed, with half of the participants making 3 or fewer errors, and so were re-analysed using the nonparametric Wilcoxon's signed rank test. This confirmed the effect as highly significant (Z = -3.16, p < 0.005). Analysis of motor errors at time 1 only also revealed a highly significant effect (t_{133} = -3.18, p < 0.005).

Spatial Working Memory (SWM): Data were missing for two participants who had difficulty using the computer mouse. TRIALTYPE (SWM vs. sensorimotor control [SMC] trials) was an additional within-subjects factor. Summary data are shown in Table 5.

Table 5 here

For reaction time, there was a weak trend for responses to be faster after nicotine than placebo (LOZTYPE: $F_{1,139}$ = 2.98, p = 0.09), and there was a significant effect of TRIALTYPE ($F_{1,139}$ = 3.88, p = 0.05) with responses faster on SMC than SWM trials. However, there was no TRIALTYPE X LOZTYPE interaction ($F_{1,139}$ < 1, ns). LOZORDER interacted significantly with LOZTYPE ($F_{1,139}$ = 8.78, p < 0.005) reflecting a decrease in reaction time (i.e. a speeding of response) across testing sessions for both SMC and SWM trials. However, the analysis of time 1 data only revealed no main or interactive effects of LOZTYPE ($F_{1,140}$ < 1, ns).

For percentage correct (the measure of accuracy), the main effect of LOZTYPE was significant ($F_{1,139}$ = 6.26, p = 0.01) reflecting greater accuracy overall after nicotine. The main effect of TRIALTYPE was also significant ($F_{1,139}$ = 152.42, p < 0.0001), with

greater accuracy on SMC trials. There was, however, no significant LOZTYPE X TRIALTYPE interaction ($F_{1,139}$ < 1, ns). Again, the LOZORDER X LOZTYPE interaction was significant ($F_{1,139}$ = 8.97, p < 0.005) reflecting a greater enhancement by nicotine in the group receiving it second. The LOZTYPE X TRIALTYPE interaction also fell short of significance in the between-groups comparison at time 1 ($F_{1,140}$ = 1.96, ns).

Verbal Fluency: There was no significant effect of LOZTYPE ($F_{1,141}$ < 1, ns; nicotine, 14.95 ± 4.94 words, placebo 14.75 ± 5.25 words). A between-groups t-test at time 1 did however reveal a significant effect of LOZTYPE, but in the opposite direction from that predicted: performance was better in the placebo condition (t_{142} = -2.45, p < 0.05; placebo 15.8 ± 5.5 vs. nicotine 14.0 ± 4.4 words). This effect remained significant even when four outliers (± 2 sds from the mean) were excluded.

Associations between measures of smoking dependence and cognitive variables

In order to determine whether nicotine was more effective in enhancing performance in more severely dependent smokers, we computed correlations between two indices of nicotine dependence (baseline salivary cotinine and FTND scores) and change scores (nicotine minus placebo) on those cognitive tasks that showed a beneficial effect of nicotine lozenge (i.e. antisaccades percentage accuracy; CPT motor errors; SWM percentage correct; and SMC percentage correct).

Antisaccadic accuracy correlated significantly and positively with both baseline salivary cotinine (r = 0.23, p< 0.01) and FTND scores (*r* = 0.25, p < 0.01); that is, more heavily dependent smokers showed greater enhancement of performance by nicotine compared with placebo. All other correlations fell short of significance.

Discussion

The results from this placebo-controlled double-blind study are generally consistent with our first hypothesis, that acute smoking abstinence would be associated with impaired response inhibition relative to performance after nicotine, and corroborate our previous observations when nicotine was administered by smoking (Powell et al. 2002). The fact that in this study nicotine was administered in lozenge form under double-blind conditions, with guessing by participants at chance level in the first (but not the second) testing session, strongly suggests that the performance

enhancement seen both here and in our previous studies is attributable to nicotine and not either to some other constituent of tobacco or to expectancy effects.

On the oculomotor (antisaccade) task, as in our previous study (Powell et al. 2002) participants made more erroneous reflexive glances towards the peripheral stimulus during abstinence (placebo condition) than after nicotine. Furthermore, the extent to which nicotine ameliorated poor response inhibition was modestly correlated with degree of nicotine dependence as measured by salivary cotinine and FTND scores. This raises the interesting possibilities either that some individuals are more sensitive to the effects of nicotine and that this increases their susceptibility to developing dependence, or conversely that this effect of nicotine develops alongside – and reflects – increases in dependence.

The impaired inhibitory control of oculomotor responses during abstinence observed here is consistent with neuroimaging studies which have demonstrated reduced DA activity in PFC/ACG in chronic drug users, and with current neurobiological models of addiction (e.g. Jentsch & Taylor, 1999; Goldstein & Volkow, 2002. For instance, in their I-RISA model, Goldstein and Volkow describe addiction as a 'cortically regulated cognitive and emotional process' that manifests behaviourally in impaired inhibitory control over responses to drug-related stimuli. The present data suggest that such deficits may be part of a more generalised impairment which encompasses control over reflexive responses to non drug-related stimuli, and that they are particularly marked during acute abstinence. That nicotine lozenges can attenuate this deficit may contribute to the effectiveness of nicotine replacement therapy (NRT) in increasing abstinence rates. Whether poor inhibitory control resurfaces following withdrawal of NRT is an important clinical question, since this might help to explain the subsequent elevation in relapse risk.

Impaired response inhibition was also manifest on the continuous performance task (CPT) in that abstinent smokers made more motor errors (responses to to-be-ignored fillers) after placebo than nicotine. By contrast, however, we found no effect of nicotine/abstinence on our response bias measure (C), which has been argued to reflect the propensity to respond impulsively (Dougherty et al. 1999).

A few previous studies have explored the effects of nicotine and abstinence on indices of response inhibition, with rather mixed findings. In non-smokers, Levin et al. (1998) found nicotine to reduce the frequency of omission errors on the CPT without any increase in commission errors. In smokers, Hatsukami et al. (1989) found

increased rates of commission errors after 24 hours abstinence, though Bekker et al. (2005) found no benefit of nicotine following overnight abstinence on commission errors on two different versions of the CPT, or on successful 'stops' on a stop-signal task. On the other hand, in minimally (c. 2 hour) abstinent smokers Edginton & Rusted (2003) reported nicotine to enhance the inhibition of task-irrelevant material on a retrieval-induced forgetting task, whilst Rycroft et al. (2005) found a similar increase in efficiency on a visual search task which was attributable to better inhibition of eye movements towards distractor stimuli.

Discrepancies between studies could reflect a number of methodological variations, including for example route of nicotine administration or degree of nicotine dependence. One theoretically interesting possibility, however, is that tasks showing apparently contradictory results tap different facets of inhibitory control. Several authors have proposed conceptually important distinctions. For instance, Nigg (2000) has proposed a working taxonomy with the following classes of executive response inhibition: interference control (resource/response competition), cognitive inhibition (of irrelevant information in working memory), behavioural inhibition (of prepotent responses) and oculomotor inhibition (of reflexive saccades). Under this taxonomy, response bias on the CPT (C) might correspond most closely to interference control whilst impulsive motor errors (responses to the filler stimuli) represent a failure of behavioural inhibition. This analysis suggests that the inhibitory control deficits observed during nicotine abstinence may relate specifically to prepotent motor (including oculomotor) responses rather than extending more generally to cognitively mediated reactions. An interesting direction for future empirical research would be to compare the effects of abstinence and drug administration on a range of measures designed specifically to tap the different categories of response inhibition.

With respect to our second hypothesis, we found mixed evidence for the predicted effects of abstinence and nicotine on other tasks of executive functioning. Spatial working memory (SWM) was assessed using a delayed response task, performance on which has been associated with DLPFC activity (Funahashi et al. 1989), and was, as predicted, impaired during abstinence relative to the nicotine condition. However, the effect of nicotine was not specific to SWM trials but affected sensorimotor control (SMC) trials equally. This suggests that whilst nicotine did improve working memory performance in these abstinent smokers, it probably did so via a general effect on attention or efficiency of information-processing. Interestingly, the beneficial effect of nicotine on both SWM and SMC trials disappeared when five participants with very

poor performance (more than three standard deviations below the mean) were excluded. This observation is consistent with the conclusions of a review by Newhouse et al. (2004) which led the authors to conclude that any performance-enhancing effects of nicotine are likely to be greatest in individuals whose functioning is sub-optimal.

Previous studies using the SWM task have yielded rather inconsistent results. Thus Ernst et al. (2001) reported no difference in performance between abstaining- and ex-smokers, despite differential patterns of regional brain activity; whilst in direct contradiction to the present data, Park et al. (2000) found that smoking a single cigarette after 24 hour abstinence had an adverse effect on SWM in regular smokers. There were some differences between the two studies; for instance, in Park et al.'s study the duration of abstinence was longer, nicotine was given by cigarette rather than lozenge, and the SWM task was repeated under abstinent and nicotine conditions within a single session. It may be, for example, that the rapid and strong effect of a bolus of nicotine after rather 24 hours abstinence produces somatic and cognitive effects which are quite different from those achieved by the slower lozenge delivery mechanism used here (cf. Hukkanen et al., 2005).

The dprime index of accuracy on the CPT task can also be interpreted as tapping working memory. Here, there was some evidence that nicotine increased accuracy, though this effect emerged only when the analysis was restricted to scores on the first testing occasion; there is a strong practice effect on this task which may have weakened the ability to detect a nicotine effect on the second assessment. However, dprime is also sensitive to attention and general efficiency of information-processing; these findings, like those from the SWM task, can therefore be explained via an effect of nicotine on general alertness and information-processing efficiency, rather than specifically on executive functioning.

Finally, we found no support for the predicted beneficial effect of nicotine on another well-established aspect of executive functioning: verbal fluency. Indeed, counter to expectation, between-groups analysis of time 1 data only revealed superior performance during abstinence. This is difficult to explain, but may well be spurious as we have previously found inconsistent results for the effects of smoking vs. abstinence on this task: in one study performance improved after smoking (Al-Adawi and Powell, 1996) whilst in another there was no such effect (Powell et al. 2002).

To conclude, although this study has found little support for a broad deficit of executive functioning during nicotine abstinence in regular smokers, it has yielded

persuasive evidence for an impairment of inhibitory control over reflexive motor and oculomotor responses that can be reversed with nicotine administration. Since response inhibition is commonly attributed to anterior cingulate function (e.g. Volkow et al. 2004) it may be that functioning of this particular region more than neighbouring areas is disrupted in chronic smokers. Elucidation of the exact nature of the inhibitory deficits, their potential relevance to relapse, and the extent to which they also characterise addicts recently withdrawn from other substances (e.g. alcohol, cocaine, heroin) may prove to be fruitful avenues for future research.

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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 ≤ 10ppm)** ***Administration of lozenge + 30 minute wait*** **Spatial Working Memory Task** **Oculomotor (saccade) Task** **Verbal Fluency test** **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 [**craving** and **withdrawal symptoms**]
One week later	
Assessment 2 Following overnight (12 hours) abstinence Group 1: Placebo lozenge Group 2: Nicotine lozenge	**Expired carbon monoxide (must be ≤ 10ppm)** ***Administration of lozenge + 30 minute wait*** **Spatial Working Memory Task** **Oculomotor (saccade) Task** **Verbal Fluency test** **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 [**craving** and **withdrawal symptoms**]

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

* This task was not available for the first 12 subjects

Table 2

	All participants N = 145
Age	
Mean (SD)	31.90 (12.28)
Range	18-65
Sex ratio (M:F)	63:82
Years in education (post 16yrs)	
Mean (SD)	3.84 (3.28)
Range	0-22
No. of cigarettes per day	
Mean (SD)	18.05 (5.82)
Range	10-40
Years of regular smoking	
Mean (SD)	15.71 (12.33)
Range	1-52
No. of previous quit attempts	
Mean (SD)	2.75 (3.25)
Range	0-20
Baseline cotinine	
Mean (SD)	266.59 (151.39)
Range	43.60-940.30
FTND	
Mean (SD)	4.92 (1.83)
Range	1-9

FTND = Fagerstrom Test of Nicotine Dependence

Table 3

	Placebo Lozenge	Nicotine Lozenge
Craving		
Mean (SD)	3.99 (1.75)	3.29 (1.66)
Range	1-7	1-7
MPSS		
Mean (SD)	7.12 (5.12)	6.04 (4.32)
Range	0-42	0-21
HADS – Anxiety		
Mean (SD)	6.69 (3.50)	7.16 (3.92)
Range	0-17	0-20
HADS – Depression		
Mean (SD)	4.26 (2.93)	4.12 (2.95)
Range	0-13	0-16

MPSS: Mood and Physical Symptoms Scale

HADS: Hospital Anxiety and Depression Scale

Table 4

CPT task variable	Placebo Lozenge	Nicotine Lozenge
D' (dprime): Mean (SD)	2.15 (1.04)	2.21 (0.98)
C: Mean (SD)	-0.02 (0.41)	-0.05 (0.41)
No. of motor errors Mean (SD)	5.82 (5.73)	4.58 (4.85)

D': Measure of accuracy in discriminating targets from catch stimuli (range 0 to 4)

C: Criterion location index of response bias (0 = unbiased, negative = liberal/impulsive, positive = cautious)

Table 5

SWM Task variable	Placebo Lozenge	Nicotine Lozenge
RT SMC trials Mean (SD)	1326.56 (662.03)	1280.07 (483.00)
RT SWM trials Mean (SD)	1346.73 (723.62)	1300.48 (560.69)
% correct SMC trials Mean (SD)	97.66 (8.76)	98.76 (4.80)
% correct SWM trials Mean (SD)	86.14 (17.04)	88.03 (13.79)

RT = reaction time (msec)

SMC = sensorimotor control

SWM = spatial working memory

Figure 1

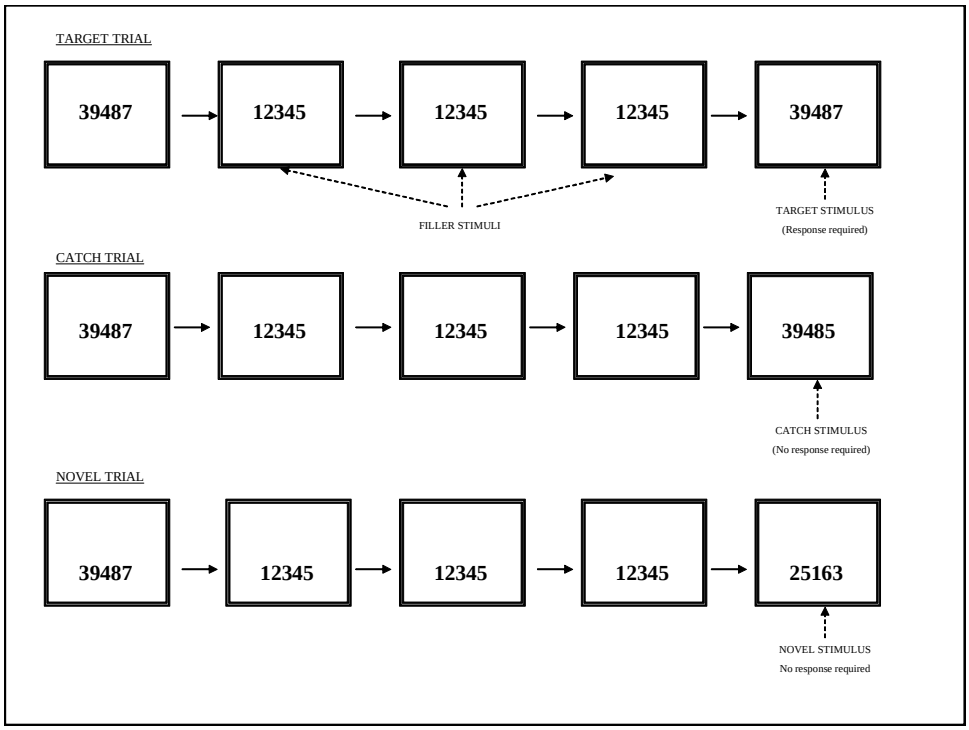
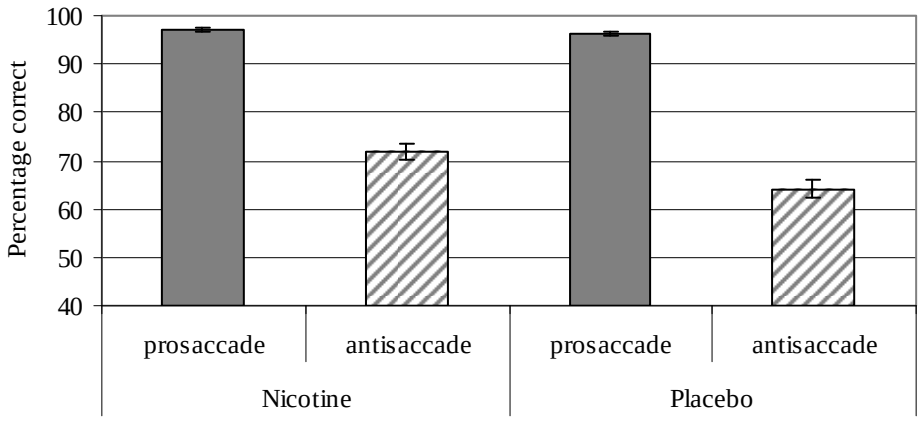

TARGET TRIAL
39487
12345
12345
12345
39487
FILLER STIMULI
TARGET STIMULUS
(Response required)
CATCH TRIAL
39487
12345
12345
12345
39485
CATCH STIMULUS
(No response required)
NOVEL TRIAL
39487
12345
12345
12345
25163
NOVEL STIMULUS
No response required

Figure 2


Percentage correct
100
90
80
70
60
50
40
prosaccade
antisaccade
prosaccade
antisaccade
Nicotine
Placebo

Legend for Tables and Figures

Table 1: Schematic overview of design and order of assessments

Table 2: Demographic and smoking-related information

Table 3: Mean (SD) self-reported craving, withdrawal symptoms (MPSS) and HADS Anxiety and Depression scores under nicotine and placebo lozenge conditions.

Table 4: Means for Continuous Performance Task (CPT) variables under nicotine and placebo lozenge conditions.

Table 5: Spatial Working Memory task means (SD) under nicotine and placebo lozenge conditions

Figure 1: CPT task experimental framework.

Figure 2: Percentage correct on the Antisaccade and Prosaccade Tasks under conditions of nicotine and placebo lozenge. Error bars are +/- 1SE