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Smoking, Reward Responsiveness, and Response Inhibition: Tests of an Incentive Motivational Model

Jane Powell, Lynne Dawkins, and Robert E. Davis

Background: Incentive–motivation models of addiction suggest impairment of functional activity in mesocorticolimbic reward pathways during abstinence. This study tested implications for subjective and behavioral responses to nondrug incentives, cue-elicited craving, and prefrontal cognitive functions, particularly response inhibition.

Methods: We tested 26 smokers after smoking and after overnight abstinence in counterbalanced order; 26 nonsmokers were also tested twice. Measures included a simple card-sorting test performed with and without financial incentive (the CARROT), the Snaith Hamilton Pleasure Scale as an index of subjective reward responsiveness, ratings of subjective craving and withdrawal before and after exposure to a cigarette, an index of oculomotor response inhibition (saccadic vs. antisaccadic eye movements), verbal fluency, and reversed digit span.

Results: Compared with the smoking condition, and independently of withdrawal severity, abstinence was associated with reduced cue reactivity, pleasure expectancies, responsiveness to financial incentive, and response inhibition (antisaccadic eye movements). Verbal fluency and reversed digit span were unaffected, contrary to findings elsewhere with heavier smokers. Nonsmokers' scores either fell between those of abstainers and recent smokers or approximated those of recent smokers.

Conclusions: The data were in general consistent with behavioral predictions derived from the incentive–motivational model of addiction and suggest that abstinence may be associated with impairments of motivation and response inhibition, which are independent of other subjectively experienced withdrawal symptoms.

Key Words: Nicotine, abstinence, reward, response inhibition, cue reactivity

Introduction

It is now widely argued that compulsive drug use is more clearly driven by the achievement of pleasurable states than by the relief of aversive physical and/or emotional states (e.g., Stewart et al 1984; reviews by Lyvers, 1998, and Robinson and Berridge, 1993). Consistent with this formulation, contemporary neurobiological models of addiction strongly implicate the mesocorticolimbic brain system comprising projections from the ventral tegmental area (VTA) to structures including the nucleus accumbens, amygdala, anterior cingulate, and prefrontal cortex. Functionally, this circuitry corresponds to the so-called reward pathways of the brain because its activation is associated with appetitive behaviors directed at obtaining a wide range of reinforcers including brain electostimulation, food, and sex (e.g., Wise, 1998). In relation specifically to smoking, Stein et al (1998), using functional magnetic resonance imaging (fMRI), found intravenous nicotine injections in smokers to induce subjective drug effects in parallel with elevated activity in the above-mentioned structures. The subjective correlate of the activation of reward pathways is, arguably, a state of heightened desire, wanting, or craving (e.g., Robinson and Berridge, 1993, 2000). Exposing addicts to drug-related stimuli elicits both subjective craving (e.g., Carter and Tiffany 1999) and activation of mesocorticolimbic structures (e.g., Childress et al 1999; Grant et al 1996; Volkow et al 1999).

Activation of brain reward pathways by a single drug dose or exposure to drug-related stimuli may explain rapid reinstatement of addiction following a period of abstinence. Thus, for example, rats show reinstatement of previously extinguished nicotine seeking and consumption when given "priming" injections of nicotine (Shaham et al 1997). Such priming effects are, however, dose dependent: Markou et al. (1999) recently showed that preadministering rats cocaine doses below those self-administered during training increased instrumental responding for more cocaine, whereas priming doses similar to

training doses reduced responding, possibly reflecting satiation. Effects depended also on whether the priming dose was "expected" by the animal (i.e., contingent vs. noncontin-gent) and on the type of behavioral paradigm used. Similar dose-dependent priming effects have been observed in relation to reinstatement of nicotine administration (Chiamulera et al 1996).

In addition, small priming doses of one addictive drug have been shown to result in heightened subjective and behavioral reactions toward cues signalling the availability of a different drug ("cross sensitization"; see review by Self 1998). Nicotine shares the ability to cross-sensitize: in a double-blind placebo-controlled study with abstaining cocaine addicts, Reid et al (1998) found cue-elicited cocaine craving to be strongly enhanced by a dose of transdermal nicotine. Further evidence of associations between smoking, exposure to smoking-related cues, subjective craving, and neural activity in brain reward structures comes from a recent electroencephalographic study (Zinser et al 1999) showing heightened electrical activity in frontal cortex during both smoking and cue exposure. Interestingly, cue exposure, but not smoking itself, was associated with increased asymmetry of electrocortical activity, a putative physiologic marker of approach motivation.

Smoking and Brain Reward Pathways: Implications for Cognitive Functioning

The anterior cingulate (AC) and prefrontal cortex (PFC), cortical projection sites of the reward pathways, have been strongly associated with the executive cognitive functions involved in strategic problem solving and response planning (e.g., Jahanshahi and Frith 1998; Lezak 1995). In particular, PFC has been implicated in working memory (D'Esposito et al 1995; Goldman-Rakic 1995), response generation (Frith et al 1991), planning (e.g., Shallice and Burgess 1991) and suppression of reflex responses (e.g. Guitton et al 1985), whereas AC has been linked with executive attention (Posner and Petersen 1990), detection of erroneous responding (e.g., Dehaene et al 1994), oculomotor response inhibition (Gaymard et al 1996), and overcoming habitual responses (e.g., Crawford et al 1996).

Theoretically, therefore, activation of reward pathways via either drug ingestion or perception of incentive stimuli is likely to modulate information-processing functions subserved by PFC and AC. This could be of biological value in facilitating the organization and execution of an effective plan of action directed at acquisition of the desired reinforcer. It might also be expected to have a general facilitative effect on executive functions that could be detected on a range of more abstract problem-solving task. Interestingly, Ashby et al (1999) have recently reviewed evidence that activation of PFC via positive mood induction is associated with enhanced performance on a range of "frontal" tests.

Until fairly recently, there was little convincing evidence that even chronic use of addictive drugs was associated with cognitive dysfunction, with few gross impairments seen in long-term cocaine or heroin users (e.g., Horner 1999; Selby and Azrin 1998). Evidence is accumulating for the existence of more subtle impairments, however, particularly of specific executive functions such as decision making and judgment (e.g., Bechara et al 2001; Grant et al 2000; Rogers et al 1999). These findings are complemented by neuroimaging studies showing abnormalities of the structure and function of frontal cortex in drug users (e.g., Liu et al 1998; London et al 2000). Different drugs may, however, produce subtly different effects depending on how they impact neurochemically on the pathways innervating different regions of PFC. For instance, Ornstein et al (2000) compared addicts whose primary drug was either heroin or amphetamine (although most also used a variety of other drugs) with matched non–drug-using control subjects on a variety of neuropsychologic tests sensitive to fronto-striatal and temporal damage. Addicts showed selective and partially drug-specific patterns of impairment, with the heavy stimulant users showing more difficulty than the heavy opiate users on some fronto-striatal indices and the pattern reversing on others.

Consistent with an impact of nicotine on executive functions, there is robust evidence that it enhances sustained, divided, and focused attention (Kassel 1997); conversely, abstinence has been associated with impaired working memory (e.g., Blake and Smith 1997). Conflicting results were reported by Park et al (2000): contrary to the authors' predictions, recent nicotine consumption by smokers was associated with a *decline* in performance on a test of spatial working memory, selected specifically as a measure of dorsolateral PFC function. Spatial selective attention was unaffected. Although these findings await replication, they suggest that the effects of smoking and abstinence on cognitive functions are complex. This point emerges again from an experimental positron omission tomographic study (Ernst et al 2001), in which, although abstaining and ex-smokers scored equivalently on a test of

working memory, their patterns of regional cerebral blood flow during the task differed, suggesting that abstinence did affect the information-processing strategies used on the task.

Importantly, nicotine dependence, as with other addictions, has also been associated with poor inhibitory response control, a key function associated with PFC (e.g.. Hatsukami et al 1989). Addicts also show poor decision making on gambling tasks, tending to favour responses that produce short-term gains but long-term losses (e.g., Grant et al 2000). Jentsch and Taylor (1999) suggested that this impulsive response style increases the risk of relapse.

Effects of Smoking and Abstinence on Functioning of Brain Reward Circuitry in Chronic Smokers

The preceding review suggests that activation of brain reward pathways may be associated with modulation of executive cognitive functions and with various aspects of incentive motivation. By implication, if addiction is indeed associated with abnormalities of reward mechanisms, then some or all of these functions might be compromised.

Withdrawal from addictive drugs has been linked experimentally with reductions in incentive motivation. For instance, Epping-Jordan et al (1998) found that across four days of nicotine withdrawal, rats showed markedly increased thresholds for intracranial stimulation. Similar findings have been reported in relation to other addictive drugs (e.g., Kuhar and Pilotte, 1996; Wise and Munn 1995), and Wise and Munn (1995) have suggested that dysfunction of brain reward pathways during withdrawal might underlie the characteristic subjective reports of anhedonia and dysphoria.

There is growing evidence for addiction-related changes in the functional activity of dopamine (DA), the neurotransmitter that has been most strongly linked with functioning of the brain reward pathways (e.g., Fung and Lau 1988; Fung et al 1986). In smokers, for instance, Geracioti et al (1999) found abnormally low levels of a DA metabolite in cerebrospinal fluid. Reviewing an international symposium on this topic, Altmann et al (1996) concluded that "withdrawal from various drugs of abuse is associated with a reduction in dopamine transmission in the ventral striatum, an effect that is opposite to the common property of drugs of abuse to stimulate dopamine transmission."

Our study tests a number of predictions deriving from the above literature review concerning the effects of acute abstinence and smoking on cognitive and behavioural functions believed to be mediated by activity in brain reward pathways. Although not all of the predictions are unique to an incentive-motivational model of addiction, we are unaware of any other framework that would predict the same pattern of performance across the range of measures.

1. APPETITIVE RESPONSES FOR NONDRUG INCENTIVES WILL BE IMPAIRED DURING ABSTINENCE.

Evidence has been reviewed that response to incentives of most kinds is mediated by activity in brain pathways that nicotine and other addictive drugs appear to activate directly, that such drug-induced activation increases appetitive behaviors directed at further drug intake (priming and cross-priming), and that in animals acute abstinence is associated with elevated reward thresholds. If addiction indeed compromises mechanisms that mediate general incentive responses, then abstaining smokers should show reduced instrumental responding and subjective desire for a range of "normal" rewards compared with non-smokers. Furthermore, if nicotine consumption enhances functioning of these reward mechanisms, then their responses should be elevated after smoking.

These predictions are investigated firstly using a behavioural measure of responsiveness to financial incentive, the Card Arranging Reward Responsivity Objective Test (CARROT; Powell et al 1996) in which participants sort cards under conditions of nonreward and reward. Reward responsiveness (acceleration in sorting rate under reward) has been found to correlate highly with measures of executive functioning and with clinical ratings of motivation during rehabilitation in patients with brain injury (Al-Adawi et al 1998); these indices all showed concomitant recovery during a period of treatment with bromocriptine, a dopamine agonist (Powell et al 1996). In a previous study with heavy smokers, reward responsiveness was impaired during abstinence and restored after a single cigarette (Al-Adawi and Powell 1997). Because nonrewarded sorting speed in these studies was unrelated to executive function and insensitive to drug manipulations, reward responsiveness effects cannot readily be interpreted as secondary to generalized psychomotor slowing.

To complement this experimental behavioral measure of reward responsiveness, the self-report Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al 1995) is used here to quantify respondents' expectations of enjoying a range of naturalistic reinforcers (e.g., social events, a favourite meal).

2. SMOKING-RELATED STIMULI WILL ELICIT GREATER INCREASES IN SUBJECTIVE CRAVING FOLLOWING SMOKING THAN DURING ACUTE ABSTINENCE AND WILL BE ASSOCIATED WITH DECREASES IN WITHDRAWAL SYMPTOMS.

If the responses elicited by drugrelated stimuli reflect conditioned activation of brain reward pathways as indicated by Robinson and Berridge's (1993) incentive–sensitization model of addiction, cue reactivity should be reduced during abstinence when these pathways are putatively relatively unreactive but enhanced immediately after drug consumption. Insofar as the conditioned response thus mimics direct drug effects, subjective withdrawal should tend to decrease during cue exposure.

A competing argument is that abstinence might increasecue reactivity by inducing a deprivation state and thus enhancing the salience of cues of drug availability (e.g., Baker et al 1987; Stewart et al 1984). Whereas some studies have found no effect of abstinence on cue-elicited craving or physiological responses (e.g., Drobes and Tiffany 1997), in a study by Payne et al (1996) cue-elicited increases in craving were greater within 90 min of smoking than after 180 min of abstinence, despite the fact that preexposure craving was not at ceiling.

Our present study employs a brief test of cue reactivity, measuring participants' subjective craving and symptoms before and after they held and smelled a cigarette. Participants were permitted to smoke immediately after the test because drug availability has been shown elsewhere to enhance appetitive states and responses during cue exposure (e.g., Juliano and Brandon 1998; Powell, 1995).

3. PERFORMANCE ON COGNITIVE TASKS TAPPING THE EXECUTIVE FUNCTIONS OF PREFRONTAL CORTEX, PARTICULARLY RESPONSE INHIBITION, SHOULD BE BETTER FOLLOWING SMOKING THAN DURING ACUTE ABSTINENCE.

The clearest predictions for the effects of smoking and abstinence concern the inhibition of dominant or reflexive responses, a fundamental control function of PFC. Activation in various regions of PFC and AC tends to be associated with the execution of inhibitory responses on go/no-go tasks (e.g, Rubia et al 2001). If, as empirical data indicate, drug dependence is associated with lowered levels of frontal functioning, then smokers should show reduced ability to inhibit automatic responses except shortly after smoking when the immediate enhancement of frontal activity by nicotine should restore inhibitory control.

Our measure of response inhibition is an oculomotor task in which participants are required to inhibit reflexive eye movements (prosaccades or reflexive saccades) toward a peripheral stimulus and instead to make movements away from it (antisaccades). This task has previously been linked directly to activation of PFC and AC (e.g., Everling and Fischer 1998; Gaymard et al 1996; Guitton et al 1985); patients with frontal lesions are impaired on this task (e.g., Gooding et al 1997) and the probable involvement of executive cognitive processes is widely recognized (Findlay and Waler 1999; Gooding 1999). The effects of nicotine on eye movements has been little studied, although smoking has been observed to decrease intrusive reflexive saccades during smooth pursuit tracking (Klein and Andresen 1991; Olincy et al 1995). Here, we predict that abstinence will impair accuracy on the antisaccade but not on the reflexive saccade task.

We also administered two other tests commonly used clinically to tap other aspects of executive function. Verbal fluency (Benton 1968) is often interpreted as a measure of strategic response generation or willed action (e.g., Jahanshahi and Frith 1998), whereas digit span (Wechsler 1981) taps working memory. Al-Adawi and Powell (1997) found both to be enhanced in smokers after smoking compared with during abstinence.

Methods and Materials

Design

Twenty-six smokers were each tested twice, a week apart, once when they had been requested to abstain from smoking overnight and up to the time of the test session (at least 10 hours in total) and once just after smoking a cigarette; half were randomly allocated to the order abstinent/cigarette (Group AB/CIG) and half to the order cigarette/abstinent (Group CIG/AB). Twenty-six "never-smokers" (Group NOSMOKE) were also tested twice to provide normative data against which to compare the absolute levels of performance of the smoking groups on each occasion separately.

Exhaled CO levels were measured before each test session, and any smoker whose level in the just-smoked condition fell within the range shown by the nonsmokers (0–5 parts per million [ppm]) or whose level in the abstinent condition was less than 4 ppm lower than their reading in the just-smoked condition was excluded. Five participants were excluded for one or both of these reasons, leaving 26 (13 in AB/CIG and 13 in CIG/AB).

Ethical Issues

Our study was approved by Goldsmiths College Ethics Committee. All participants were volunteers recruited through advertisements on college noticeboards. They received no financial renumeration other than their earnings (less than £2) on the CARROT, although some undergraduates received course credits as part of an experimental participation course. "Oral and written explanations of the experimental protocol were given to participants, and their verbal informed consent was required before an appointment was made for their first experimental assessment. They were told that they could withdraw from the study at any time. All participants were independent adults capable of giving informed consent."

Assessment Measures

The measures described below were administered in the following order: demographic and smoking information (time 1 only), reflexive saccade task, verbal fluency, antisaccade task, cue exposure, CARROT, and reversed digit span.

Demographics and Smoking Related Variables

The Fagerström Test of Nicotine Dependence (FTND; Heatherton et al 1991) is a six-item self-report scale concerning various indicators of dependence. Scores range from 0 (*low dependence*) to 10 (*high dependence*). Expired carbon monoxide was recorded before each session using a breath CO monitor. The half-life of CO is 2–5 hours, and therefore 10 hours of abstinence should be associated with markedly reduced CO levels. Here, no nonsmoker showed a difference exceeding 3 ppm between the two occasions, whereas for smokers the differences between abstinence and smoking conditions ranged from 4–22 ppm (M 11.5, ± 5.1).

Responsiveness to Nondrug Incentives

In the CARROT (Powell et al 1996), participants are given a stack of cards, each showing five digits of which one, and one only, is a 1, 2, or 3. The cards have to be sorted into corresponding numbered piles. In both testing sessions, there is first a baseline trial (T1) in which the participant is required to sort exactly 60 cards as quickly as possible. The time taken is then used as the individualized time limit in the subsequent three experimental trials (T2, T3, T4), for which a larger stack of cards is provided. In T3, the rewarded condition (REW), the participant is informed that s/he will receive 10 pence for every five cards sorted, and a 10 pence coin (15 cents) is placed on the table in full view after every fifth card. In T2 and T4, there is no reward, but the instruction is still to sort as rapidly as possible. Performance in these two trials is averaged to yield a nonreward (NONREW) index. Rate of sorting (cards per second) is computed for each individual trial, and a reward responsiveness index (REWRESP) is derived by subtracting the NONREW rate from the REW rate.

The SHAPS (Snaith et al 1995) is a 14-item self-report scale designed to assess state dependent hedonic tone in healthy and psychiatric populations. Subjects indicate whether they agree that they

would enjoy each of 14 normally pleasurable events or activities; each item is scored 0 (*disagree*) or 1 (*agree*).

Cue Reactivity

Smokers, but not nonsmokers, rated their urge to smoke and withdrawal symptoms before and after being given a cigarette of their preferred brand to hold and smell. They were asked to take the cigarette out of a packet, sniff it, and then hold it in their hand while completing the ratings for the second time. Total exposure duration was approximately 2 min.

Desire to smoke was assessed using a shortened version of the Questionnaire of Smoking Urges (QSU; Tiffany and Drobes 1991), a 32-item instrument comprising two factor-analytically derived subscales, A and B. For brevity, we used an abbreviated scale comprising those items loading higher than 0.55: six on A relating to immediate desire/urge/intention to smoke a cigarette and expected pleasantness of doing so, and three on B (beliefs that smoking will reduce depression and improve control and that "nothing would be better than a cigarette right now"). Items were rated between 1 and 7, and mean item scores were computed for the two subscales separately and for the combined scale.

The severity of seven nicotine withdrawal symptoms (depression, irritability, anxiety, drowsiness, restlessness, hunger, poor concentration) were rated on 5-point scales (Hughes and Hatsukami 1986).

Indices of Prefrontal Cognitive Function

Response inhibition—antisaccadic oculomotor responding involves measuring the accuracy of prosaccadic and antisaccadic eye movements. Findlay and Walker (1999) described the antisaccadic task as involving "the voluntary inhibition of a reflexive saccade and the cognitive manipulation of the spatial parameters to produce a response in the opposite direction." Participants were tested in a quiet, darkened room where they were seated in front of a 35-cm computer monitor and fitted with eye-tracking headgear. A chin rest 25 cm from the screen minimized head movement. The equipment was calibrated for each participant before each task by asking them to look at a white dot subtending a visual angle of < 0.25 against a dark background at three positions (central fixation, +24° and -4°) for 5 sec each. Horizontal eye movements were measured for the right eye only using an infrared reflection technique (IRIS IR 6500 by Skalar Medical, Delft, Netherlands) with a sampling rate of 120 Hz. Incoming eye-movement recordings were digitized using a Brain Boxes 12-bit analogue to digital conversion card. This in turn was connected to the data-logging IBM-compatible desktop computer.

In the experimental task, a central fixation target was presented for a period varying randomly between 2 and 4 sec; 200 msec after it was extinguished, one of six peripheral targets was illuminated for 500 msec. The central fixation point was then reilluminated. Peripheral targets varied in both direction (left or right of the fixation point) and amplitude (i.e., 8°, 12°, or 24°) and were presented in a randomized order. We presented 60 peripheral stimuli, 10 in each of the six positions.

This procedure was conducted first with prosaccades, when participants were instructed to look at the peripheral target as quickly and accurately as possible, and then, after a 5-min break, with antisaccades, when they were told instead to look in the opposite direction as quickly as possible and at approximately equal distance from the fixation point. Within each condition, responses were classified as incorrect if the initial movement was in the wrong direction regardless of whether it was subsequently corrected. Mean number of correct responses was calculated for each of the six stimulus positions.

The Controlled Oral Word Association Test (Benton 1968) was used to measure verbal fluency. Participants were required to generate as many words as possible beginning with each of three letters excluding proper nouns or the same word with different suffixes. Equivalent letter combinations (FAS and DOT) were used for times 1 and 2, and the order of presentation was counter-balanced. Score is the total number of acceptable words over all three letters.

Reversed Digit Span (e.g., Wechsler 1981) is a test of working memory in which participants listen to sequences of numbers that gradually increase in length and then repeat them in reverse order. Testing is terminated after two consecutive failures at the same sequence length. Equivalent number sequences

were used for times 1 and 2, and the order of presentation was counter-balanced. One point is given for each sequence of numbers correctly reversed.

Statistical Analysis

All experimental variables were analyzed in two stages. First, the smoking groups (CIG/AB, AB/CIG) were compared with each other in a repeated measures analyses of variance (ANOVA) with the within-subject factor of Time (first vs. second occasion of testing). In each case it is the Group _ Time interaction that is of theoretical interest because the CIG/AB group was tested first after smoking and second after abstaining, whereas the AB/CIG group was abstinent at time 1 and had smoked at time 2. If smoking status affects performance on the experimental measures in the predicted manner, then crossover interactions are predicted with CIG/AB subjects performing better at time 1 than at time 2 and the AB/CIG group performing better at time 2 than time 1. Where significant interactions were found, the possible impact of withdrawal symptomatology was assessed by covarying out change-in-withdrawal scores across the two test sessions.

The second state of analysis investigated how the test scores of acutely abstinent and recent smokers compared with those of nonsmokers. This was achieved by comparing the two smoking groups with the nonsmoking group in one-way ANOVAs conducted separately at time 1 and time 2. A priori contrasts were specified to restrict the analysis of between-groups effects to these two comparisons (abstinent smokers vs. nonsmokers and recent smokers vs. nonsmokers). The main omnibus effect of group is not of direct interest and is therefore not reported; when contrasts are specified a priori, it is not necessary for the omnibus effect to be significant (e.g., Keppel 1991). Because the two contrasts are not orthogonal, however, Bonferroni corrections have been applied, adjusting the significance level to $p < .025$. This two-stage approach provided the most economic way of addressing the contrasts specified within the present hypotheses.

Results

Participants

Descriptive statistics are shown in Table 1. The groups did not differ from one another in age or sex ratio. All smokers smoked more than 10 cigarettes a day and had done so for at least 1 year; the AB/CIG and CIG/AB groups did not differ significantly in this respect or in their Fagerström nicotine dependence scores, which were low in both groups.

For both smoking groups, the difference in CO levels between abstaining and smoking conditions was highly significant (CIG/AB: $t_{12} = 9.6$, $p < .001$; AB/CIG; $t_{12} = 7.0$, $p < .001$), and the two groups did not differ in this respect ($t_{24} = 1.4$, *ns*). By contrast, and as expected, the nonsmokers had lower CO levels than both smoking groups on both occasions, and showed no change in CO levels from the first to the second occasion of testing ($t_{25} < 1.0$, *ns*).

Responsiveness to Nondrug Incentives

CARROT REWARD RESPONSIVENESS. Table 2 shows sorting rates (cards per second) for the nonrewarded

Table 1. Demographic and Smoking Variables for the Three Groups

	NOSMOKE (n = 26)	CIG/AB (n = 13)	AB/CIG (n = 13)
Age			
× (*SD*)	24.5 (*7.2*)	21.8 (*2.3*)	26.2 (*7.4*)
Range	18–43	19–26	19–38
Sex ratio (M:F)	12:14	5:8	8:5
No. cigarettes per day			
× (*SD*)	0	16.3 (*3.4*)	19.2 (*4.6*)
Range	0	10–20	12–25
Fagerström nicotine dependence score			
× (*SD*)	n/a	3.5 (*1.7*)	3.9 (*2.6*)
Range		1–6	1–9
CO level			
time 1 × (*SD*)	1.8 (*1.1*)	18.9 (*7.6*)	8.9 (*6.0*)
	1–5	9–35	2–20
time 2 × (*SD*)	1.9 (*1.0*)	8.8 (*4.5*)	21.9 (*8.4*)
	1–5	3–17	9–37

AB/CIG, abstinent/cigarette group; CIG/AB, cigarette/abstinent group; NOSMOKE, "never-smoker" group.

and rewarded trials separately, whereas Figure 1 gives a graphic representation of the derived reward responsivity variable (rate in rewarded minus rate in non-rewarded trials).

Contrasting the AB/CIG and CIG/AB groups, there was a significant Group x Time x Reward interaction [$F(1,24) = 7.5$, $p = .01$] as predicted: both showed lower reward responsiveness (i.e., rewarded–nonrewarded rate) when abstinent than when they had just smoked. This effect remained significant when change in withdrawal symptoms was covaried out [$F(1,23) = 6.3$, $p = .02$].

There was no main effect of GROUP [$F(1,24) < 1$, *ns*], and none of the two-way interactions (Group x Reward, Group x Time, Reward x Time) reached significance [$F(1,24) < 1.5$, *ns*, in each case]. There was a main effect of Time [$F(1,24) = 31.2$, $p = .001$] with both groups sorting faster on the second occasion than the first, and the main effect of Reward was close to significance [$F(1,24) = 4.0$, $p < .06$] with sorting rate being elevated in the rewarded trial.

To test the hypothesis that abstinent but not recent smokers would show lower reward responsiveness than nonsmokers, one-way ANOVAs were conducted at time 1 and time 2 separately with a priori contrasts to compare the scores of nonsmokers with those of the two smoking groups separately, as explained in the Analysis section above. The pattern was almost identical on the two occasions: recent smokers did not differ significantly from nonsmokers ($t49 < 1$, *ns*, both times), whereas abstaining smokers showed significantly lower reward responsiveness than nonsmokers at time 1 ($t49 = -2.3$, $p < .025$) and a trend in the same direction at time 2 ($t49 = -1.4$, $p = .08$).

Table 2. CARROT Sorting Rates for Each Group across the Two Occasions of Testing

	NOSMOKE (n = 26)	CIG/AB (n = 13)	AB/CIG (n = 13)
Time 1			
Rate of sorting under nonreward (mean of trials 2 and 4) × *(SD)*	1.25 (.17)	1.22 (.16)	1.26 (.18)
Rate of sorting under reward × *(SD)*	1.28 (.19)	1.25 (.16)	1.24 (.21)
Time 2			
Rate of sorting under non-reward (mean of trials 2 and 4) × *(SD)*	1.35 (.18)	1.32 (.15)	1.36 (.18)
Rate of sorting under reward × *(SD)*	1.39 (.18)	1.33 (.18)	1.40 (.18)

AB/CIG, abstinent/cigarette group; CARROT, Card Arranging Reward Responsivity Objective Test; CIG/AB, cigarette/abstinent group; NOSMOKE, "never-smoker" group.

SNAITH HAMILTON PLEASURE SCALE. One statistical outlier (>2 SDs from the mean) in the CIG/AB group was excluded from this analysis. Data for the remaining participants are summarized graphically in Figure 2.

For the two smoking groups, there was a significant Group x Time crossover interaction [$F(1,23) = 4.8$, $p < 0.05$], with both groups showing elevated scores (indicative of low responsiveness to pleasurable stimuli) when abstinent and low scores (high responsiveness) after smoking. There was no main effect of either Group or Time [$F(1,23) < 1.0$, *ns*, for both).

Neither of the smoking groups differed significantly from the nonsmokers at either time 1 or time 2 ($t49 < 1.5$, *ns*, for every comparison).

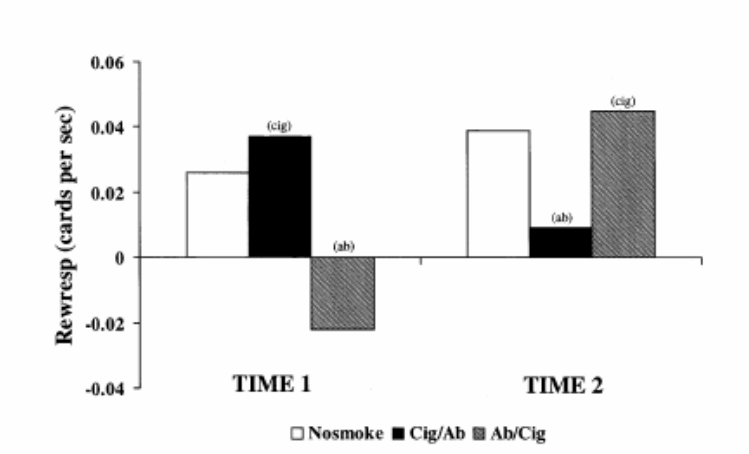


Figure 1. The Card Arranging Responsivity Objective Test reward responsiveness (increase in card-sorting rate from nonreward to reward) for the three groups separately on the two assessment occasions. (cig) indicates score when tested just after smoking. (ab) indicates score when tested during abstinence.

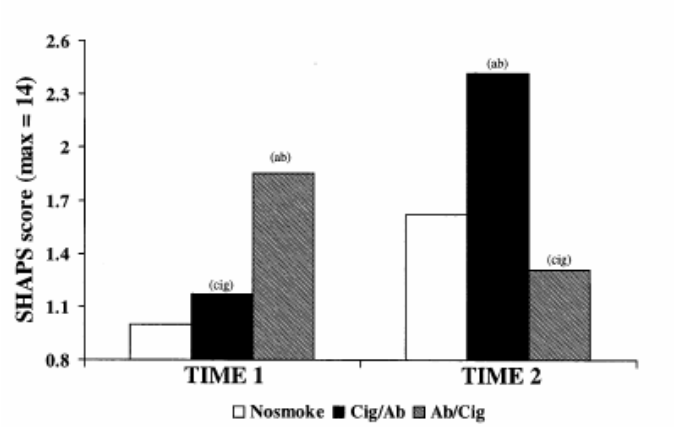


Figure 2. Snaith-Hamilton Pleasure Scale scores for the three groups separately on the two assessment occasions. High scores indicate low pleasure capacity. Data exclude one outlier from the cigarette/abstinent group. (cig) indicates score when tested just after smoking. (ab) indicates score when tested during abstinence.

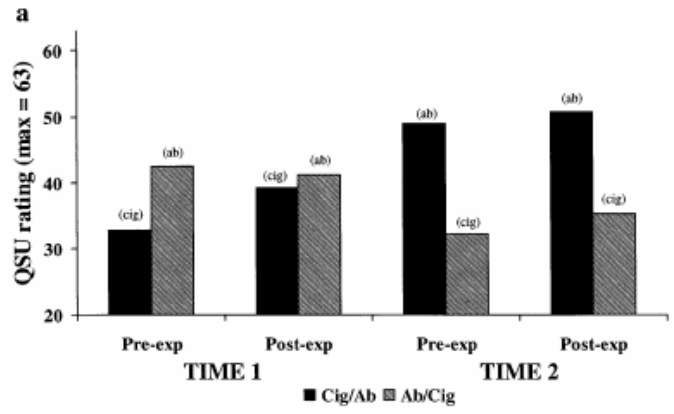
Cue Reactivity

These data were not collected for nonsmokers, so the following analyses therefore compare the two smoking groups only. An additional within-subjects factor of Exposure (preexposure vs. postexposure ratings) was included in all analyses. Summary data for total QSU and withdrawal ratings are shown in Figures 3(a) and (b) respectively.

QUESTIONNAIRE OF SMOKING URGES SCORES. For total QSU scores, there was, as expected, a significant main effect of EXPOSURE [$F(1,24) = 5.4$ $p < .03$], with average craving ratings increasing from before to after stimulus exposure. The Group x Time interaction was likewise significant [$F(1,24) = 27.8$, $p < .001$], with both groups reporting higher craving when abstinent. Most important, there was also a significant Group x Time x Exposure interaction [$F(1,24) = 6.0$, $p < .025$]. Inspection of Figure 3(a) shows that this reflected minimal alteration in craving following exposure to a cigarette for both groups when abstinent, contrasting with a much larger increase in the just-smoked condition. This three-way interaction remained significant when change-in-withdrawal symptoms across the two testing occasions was covaried [$F(1,23) = 4.7$, $p < .05$]. None of the other main effects or two-way interactions was significant.

When the two subscales were analyzed separately, the pattern of results was very similar for both except that for Scale B the Group x Time x Exposure interaction, although of the same form as described above, fell short of statistical significance [$F(1,24) = 2.1$, $p = .15$].

WITHDRAWAL SYMPTOMS. As can be seen from Figure 3(b), there was a trend toward an overall reduction



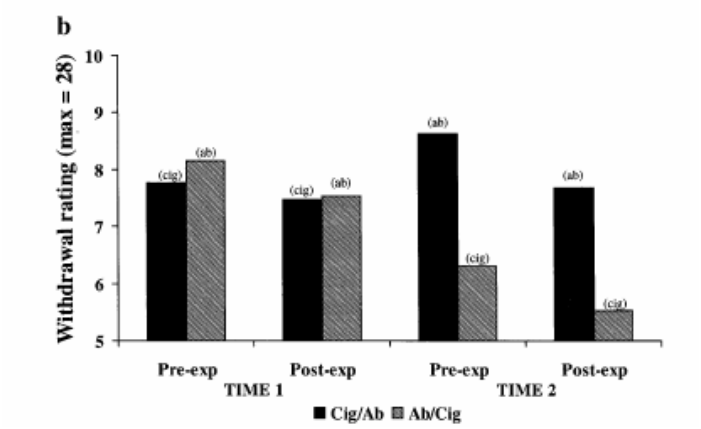


Figure 3. **(A)** Craving (total Questionnaire of Smoking Urges) ratings for the abstinent/cigarette and cigarette/abstinent groups separately, pre- and postexposure, on the two assessment occasions. **(B)** Withdrawal symptom ratings for the abstinent/cigarette and cigarette/abstinent groups separately, pre- and postexposure, on the two assessment occasions. (cig) indicates ratings when tested just after smoking. (ab) indicates ratings when tested
during abstinence.

in the level of self-reported withdrawal symptoms following exposure to a cigarette, although this fell short of significance [$F(1,24) = 2.9$, $p = .10$]. There were no significant interactions involving either Time or Group, although there was a weak trend for a Group x Time interaction [$F(1,24) = 2.6$, $p = .12$], which reflected slightly more elevated symptoms in the abstinent as opposed to the just-smoked condition for both groups.

To explore further the relationship between cue-elicited craving and cue-elicited withdrawal symptoms, change (pre- to postexposure) scores were computed. During abstinence, the change scores correlated negatively although nonsignificantly ($r26 = -.30$, $p = .14$); after smoking, when subjective withdrawal symptoms were in any case very low, there was no hint of an association ($r26 = -.04$, *ns*). By contrast, prior to cigarette exposure, those participants who were abstaining showed a significant positive association between craving and withdrawal symptoms ($r26 = .44$, $p < .03$).

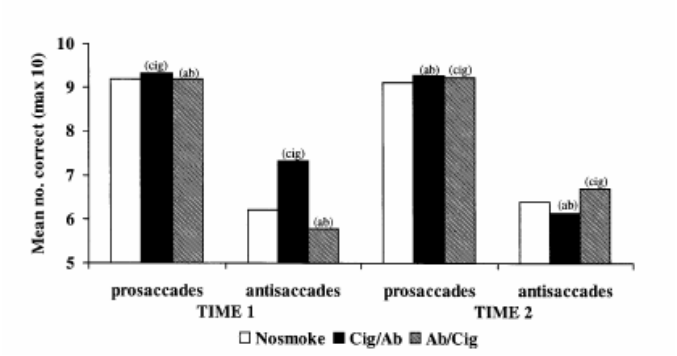


Figure 4. Saccadic and antisaccadic eye movements: number correct, averaged across stimulus positions, for the three groups separately on the two assessment occasions. Participants with incomplete data and one outlier are excluded, leaving 22 in "never-smoker" group, 11 in the cigarette/abstinent group, and 12 in abstinent/cigarette group. (cig) indicates ratings when tested just after smoking. (ab) indicates ratings when tested during abstinence.

Indices of Prefrontal Cognitive Function

RESPONSE INHIBITION: SACCADIC AND ANTISACCADIC EYE MOVEMENTS. Data were incomplete for one participant in the AB/CIG group, one in the CIG/AB group, and four in the

NOSMOKE group because of sudden movements or excessive blinking that disrupted calibration. One further CIG/AB participant was excluded because he was an extreme outlier on number of correct prosaccades on the second occasion (3.8 against an overall mean of 9.2 ± 0.6). The following analyses are thus based on 12 participants in AB/CIG, 11 in CIG/AB, and 23 in NOSMOKE; the number of correct responses for these participants are shown graphically in Figure 4.

Tasktype (prosaccaadic vs. antisaccadic) was included as a within-subject factor. Data were averaged across the six stimulus positions; separate analyses, not reported here, confirmed that the pattern of results was almost identical when each position was considered individually.

First comparing the two smoking groups within a repeated measures ANOVA, there were no main effects of Time or Group [$F(1,21) < 1$, *ns*], although there was a highly significant effect of TASKTYPE [$F(1,21) = 80.2$, $p < .001$], with many more errors being made in the antisaccadic than in the saccadic task. Both the Time x Group and Time x Group x Tasktype interactions were significant [$F(1,21) = 21.9$ and 15.5, $p < .001$], reflecting the fact that both groups made more errors on the antisaccadic task when they were abstinent; as can be seen from Figure 4, few errors were made on the saccadic task by any group on either occasion. When the ANOVA was repeated including change in withdrawal symptoms across the two occasions as a covariate, the critical three-way interaction remained highly significant [$F(1,20) = 12.6$, $p < .005$].

Table 3. Scores on Verbal Fluency and Reversed Digit Span for Each Group across the Two Occasions of Testing

	NOSMOKE (n = 26)	CIG/AB (n = 13)	AB/CIG (n = 13)
Time 1			
Verbal fluency × (*SD*)	44.62 (11.41)	41.08 (10.93)	49.08 (14.22)
Reversed digit span × (*SD*)	7.19 (1.86)	8.54 (2.47)	7.92 (2.10)
Time 2			
Verbal fluency × (*SD*)	48.65 (13.12)	43.54 (16.42)	56.00 (20.00)
Reversed digit span × (*SD*)	7.65 (2.74)	8.46 (3.07)	7.85 (2.34)

AB/CIG, abstinent/cigarette group; CIG/AB, cigarette/abstinent group; NOSMOKE, "never-smoker" group.

Comparing smokers with nonsmokers, inspection of Figure 4 shows that on the antisaccadic task nonsmokers scored somewhat better than abstaining smokers and somewhat worse than recent smokers on both occasions. These differences fell short of statistical significance, however ($t42 < 1.8$, *ns*, for all four contrasts). There was no indication of differences between smokers and nonsmokers on accuracy of prosaccades ($t42 < 1.0$, *ns*, in every contrast).

VERBAL FLUENCY. These data are given in Table 3. Comparing the two smoking groups across the two occasions, there was an overall effect of Time [$F(1,24) = 4.6$, $p < .05$), with both groups generating more words on the second occasion than on the first. Although the data show a tendency for the improvement to be more pronounced in the ABCIG group as predicted, this Group x Time interaction fell well short of significance [$F(1,24) = 1.05$,*ns*].

At neither time 1 nor time 2 did either of the smoking groups differ from the nonsmokers ($t49 < 1.5$, *ns*, in every case).

REVERSED DIGIT SPAN. Scores are shown in Table 3. Comparing the two smoking groups, there was no significant Group x Time interaction, nor main effects of either Time or Group [$F(1,24) < 1$, *ns*, in every case]. At neither time 1 nor time 2 did either of the smoking groups differ from the nonsmokers ($t49 < 1.25$, *ns*, in every case).

Discussion

Despite a compelling literature linking the addictive properties of nicotine to activity within distributed brain reward pathways, to date there has been little systematic exploration of the behavioral, cognitive,

and subjective implications of the involvement of this neurobiological system in human smokers. Our study therefore tested a set of related hypotheses arising from an integration of existing data concerning the effects of addiction and abstinence. Specifically, it was predicted that during acute abstinence, smokers would show weakened incentive motivation and deficits on tests of prefrontal executive functions, especially response inhibition (Jentsch and Taylor 1999), reflecting low levels of activity in mesocorticolimbic pathways.

The predictions concerning incentive motivation received strong support. Thus, on a simple card-sorting task (the CARROT), smokers who had recently smoked showed responsiveness to financial incentive that was equivalent to that of nonsmokers; by contrast, abstinence was associated with significantly lower reward responsiveness. Most important, in the absence of financial incentive all groups (abstinent smokers, recent smokers, and nonsmokers) sorted at similar rates. Impaired reward responsiveness during abstinence therefore cannot reflect either a generalized reduction in psychomotor speed or the operation of a ceiling effect.

The above pattern was paralleled by changes in smokers' subjective expectations of enjoying a range of normally pleasurable events; thus, on the SHAPS (Snaith et al 1995), abstaining smokers rated themselves as expecting significantly lower pleasure than did those who had just smoked. Again, abstaining smokers (but not recent smokers) showed reduced expectancies relative to nonsmokers; this effect was significant on one testing occasion and showed a nonsignificant trend in the same direction on the other. Both the reward responsiveness and the SHAPS effects remained significant when we controlled for subjectively rated withdrawal symptoms, suggesting that they are not simply secondary to the general malaise associated with acute abstinence. Further evidence for a dissocation between withdrawal symptoms and functional activity of brain reward pathways comes from a preclinical study by Carboni et al (2000) in which naloxone-precipitated withdrawal symptoms were not associated with alteration of central transmission of dopamine, the neurotransmitter most closely associated with reward processes (e.g., Fung et al 1986).

On the test of cue reactivity, abstaining smokers showed virtually no increase in subjective craving following exposure to the sight, smell, and handling of a cigarette, whereas when tested just after smoking, they showed a pronounced increase. However, preexposure craving was markedly higher in the abstaining than in the smoking condition, albeit not at the ceiling of the scale. The observed interaction may therefore reflect to some extent the more restricted range for further increases in craving during abstinence. It is methodologically difficult if not impossible to eliminate this problem, and the observed pattern therefore remains ambiguous; however, there is clearly no support here for the alternative view that abstinence actually heightens cue reactivity by enhancing cue salience. The present findings are consistent with other reports that prior nicotine administration sensitizes subjective responses to cocaine-related cues (e.g., Reid et al 1998) and that heroin addicts show greater relative activation of prefrontal cortex and amygdala during exposure to heroin-related cues immediately following administration (under double-blind conditions) of an intravenous dose of heroin rather than placebo (Sell et al 1999).

Interestingly, cue-elicited craving was not predicted by the severity of preexposure subjective withdrawal symptoms. This is incompatible with models asserting that the incentive salience of drug-related cues is enhanced by withdrawal symptoms (e.g., Baker et al 1987, Stewart et al 1984) or which view craving primarily as a subjective correlate of withdrawal-like symptoms (e.g., Siegel 1979; Wikler 1965). Indeed, during cue exposure there was a trend for self-reported withdrawal symptoms to decrease, contrasting with the simultaneous increase in craving. In abstaining smokers, cue-elicited craving correlated negatively with cue-elicited withdrawal ($r26 = -.30$), although this association fell just short of statistical significance. Thus, far from being associated with exacerbation of withdrawal, cue-elicited craving was weakly associated with improvements in physical state as would be expected if it is an appetitive rather than a withdrawal-related response. These findings have some interesting parallels in an experimental study of methadone consumption in which five opiate-dependent patients consumed more methadone if they had previously either smoked ad libitum or chewed 4 mg of nicotine gum than if they were nicotine-abstinent, despite reporting higher levels of nicotine craving and appetite in the abstinent condition (Spiga et al 1998).

The present results therefore add to the evidence that craving has at least two facets that respectively relate to severity of subjective withdrawal symptoms and to the strength of a more positive, appetitive, state. Consistent with the predictions of the incentive–motivation model, appetitive effects appear more

likely than withdrawal-like effects to be elicited by exposure to drug-related cues and to be depressed during abstinence. The two subscales of the QSU (Tiffany and Drobes 1991) were not sensitive to this possible dissociation, both following the same pattern in the present study; however, inspection of the item content of the abbreviated versions of the scales used here suggests that both include items that could be construed as appetitive and neither include items that are unambiguously related to relief of withdrawal symptoms.

Turning finally to prefrontal cognitive functions, it was hypothesized that abstinence would be associated with impairments in inhibition of dominant responses (tested here using an oculomotor task), working memory (reversed digit span), and response generation (verbal fluency) and that smoking a cigarette would restore normal function. The prediction concerning the effect of smoking on response inhibition was strongly supported: not only was the mean accuracy of antisaccades strikingly lower during abstinence than after smoking, but of the 24 smokers for whom complete data were available, this pattern was shown by all but five.

In contrast to the effect of smoking status on antisaccadic responses, it did not affect accuracy of prosaccadic responding, which was close to ceiling on both occasions. This overall pattern is consistent with the idea that smoking specifically increases the ability to inhibit the reflexive (dominant) response and that abstinence is associated with a reduction in the efficiency of inhibitory processes rather than in the ability to initiate or make oculomotor responses per se. As with the other measures, the effect remained strong after changes in withdrawal symptoms across the two testing sessions were taken into account, suggesting that the observed enhancement after smoking is not attributable to alleviation of general malaise.

Interestingly, however, there was no support for the prediction that abstainers would be impaired relative to nonsmokers. In fact, although nonsmokers were marginally but nonsignificantly more accurate than abstaining smokers, they were slightly (although again nonsignificantly) outperformed by smokers who had just had a cigarette, especially on the first testing occasion. Although there were no obvious demographic differences between the groups, it is possible that some unmeasured difference between the smokers and nonsmokers could account for the nonsmokers' failure to outperform abstaining smokers on the antisaccadic task; however, the trends in these data may also suggest that smoking can enhance response inhibition directly rather than simply by reversing a dependence-related deficit. Consistent with such an interpretation, a recent review of the complex empirical literature on neurochemical modulation of frontal-executive functions (Robbins 2000) concluded that drugs that enhance activity in pathways projecting to different regions of frontal cortex can have direct but mixed and dosedependent effects on executive cognitive tasks, varying as a function of the specific circuitry affected by the drug and involved in the task and on individual differences in baseline levels of performance. Thus, in some cases, dopamine agonists may enhance performance on executive tasks in people who perform them relatively poorly beforehand while having no effects in those who initially score highly (e.g., Kimberg et al 1997). Neuroimaging techniques have verified the activation of frontal cortexfollowing administration of dopamine agonists such as bromocriptine (e.g., Kimberg et al 2001). Such findings are particularly salient here because there is now an extensive literature demonstrating the close involvement of dopamine both in the functioning of brain reward circuitry and in the associated behavioral phenomena of addiction such as priming, incentive–sensitization, and cue reactivity (e.g., Robinson and Berridge 2000). Furthermore, there is clear evidence that nicotine consumption triggers, among other biochemical effects, release of dopamine in the shell of nucleus accumbens (Gamberino and Gold 1999), one of the structures at the heart of the reward circuitry projecting to frontal cortex. Thus, it is biologically as well as conceptually plausible that ingestion of nicotine by smoking could simultaneously modulate responses to incentive and enhance performance of executive tasks.

The data reported here extend and substantially replicate our earlier finding (Al-Adawi and Powell 1996) of reduced reward responsiveness in abstaining smokers; however, the previous study also showed significant effects of abstinence on verbal fluency and digit span, effects that did not emerge here. This may reflect the much higher level of dependence of Al-Adawi and Powell's participants; in addition to smoking more cigarettes per day, their mean score on the Fagerström test of nicotine dependence (Heatherton et al 1991) was 7.9 ± 1.8, contrasting with 3.7 ± 2.2 here. It may be that the antisaccadic task is more sensitive than the other two indices of frontal function to relatively subtle aspects of executive cognitive functioning, and it would be of interest to assess a group of more heavily

dependent smokers on this and other tests used in the present study to see whether they indeed demonstrate more pronounced impairments relative to nonsmokers on the various measures used here.

The significant effects seen here for reward responsiveness and antisaccadic responses were small in absolute terms, and their functional significance is by no means clear. Nonetheless, a small effect of financial incentive on the intrinsically meaningless card-sorting task used here (compared with virtually no effect in abstaining smokers) could in principle predict willingness to put effort into significant work-related, domestic, or social activities; indeed, such a relationship was observed in our study with brain-injured patients (Powell et al 1996). Jentsch and Taylor (1999) suggested that impairments of response inhibition might be particularly important because of their potential for increasing the risk of impulsive drug use and thus of relapse. As far as we are aware, our study represents the first focused investigation of response inhibition per se in human drug users, and, although it does not show response inhibition to be worse in abstainers than in nonsmokers, it does confirm that smokers find it more difficult to inhibit responses when they are abstinent than when they are smoking. We are currently planning a prospective study that will investigate directly whether impairments of either reward responsiveness or response inhibition seen during acute nicotine abstinence predict either relapse or other aspects of social functioning.

The dissociation between subjective withdrawal symptoms and the observed effects of smoking and abstinence on incentive motivation and cognitive functioning is of both theoretical interest and potential clinical importance. A reduction in the capacity to enjoy alternative sources of reward may undermine attempts at abstinence and thus contribute to relapse. Treatment with dopamine-enhancing drugs during this phase might counteract this effect, but, paradoxically, simultaneously increase reactivity to smoking- related cues. This would suggest that a combined pharmacologic and psychologic approach, which explicitly identifies the possible dual effects of drug treatment and which helps abstaining smokers to develop strategies for avoiding or coping with cue-elicited craving, might be the optimal way forward.

Finally, our study does not illuminate either the aetiology or the time course of the observed deficits during smoking abstinence. They may have preceded onset of smoking or have developed during chronic smoking; they might be reversible, and they might not. If they are reversible, the time course of recovery is as yet unexplored. These represent important issues for future research as they would inform the provision of appropriate treatment and advice and might also provide a basis for predicting individual differences in liability to addiction or relapse.

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