

The Hedonic Response to Cigarette Smoking Is Proportional to Dopamine Release in the Human Striatum as Measured by Positron Emission Tomography and [¹¹C]Raclopride

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ABSTRACT Positron emission tomography and [¹¹C]raclopride were used to assess the dopaminergic response to cigarette smoking in ten smokers. Nicotine-deprived smokers were scanned twice on separate days. In one condition, participants smoked their usual brand of cigarettes while in the scanner and in the other condition they remained nicotine abstinent. On each day, subjects monitored the hedonic properties of their experience as well as their levels of craving. Initial analyses revealed no significant differences between the conditions in [¹¹C]raclopride binding potential (BP) in the caudate, putamen, or ventral striatum. Because previous research suggested that drug-induced dopamine transmission is related to levels of craving and/or hedonic drug effects, the relationship between these variables and [¹¹C]raclopride BP was examined. Craving levels were reduced by smoking but were not systematically related to BP change. However, the hedonic response to smoking was correlated with BP reduction in the caudate ($P < 0.001$) and posterior putamen ($P < 0.05$) but not in the ventral striatum. Post hoc analyses revealed that only five of the ten smokers reported mood-elevating effects in response to the smoking procedure. In these subjects, smoking was associated with decreased [¹¹C]raclopride BP in the caudate. On the other hand, among subjects that reported a diminished mood response to smoking there was an increase in BP in the caudate and putamen. These results suggest that pleasurable drug experiences are associated with increased dopamine transmission in the dorsal striatum while unpleasant experiences may be related to decreased dopamine release in this region. **Synapse 54:65–71, 2004.** © 2004 Wiley-Liss, Inc.

INTRODUCTION

Cigarette smoking has been identified as the leading cause of preventable death in industrialized nations (Polin, 1984). While cigarette smoke contains several thousand compounds (Schmeltz and Hoffmann, 1976), tobacco dependence appears to be predominantly associated with the addictive properties of a solitary alkaloid, nicotine (e.g., Domino, 1998). Evidence in rodents suggests that important aspects of nicotine addiction may be mediated by central dopamine (DA) systems. For example, nicotine administration leads to increased DA cell firing in the ventral tegmental area (Corrigall et al., 1994) and increased DA release in the nucleus accumbens (Pontieri et al., 1996), actions thought to be critical to the reinforcing properties of

several addictive substances (Wise 1996; Di Chiara and Imperato 1988). In addition, disruption of DA function in rats has been shown to attenuate nicotine self-administration (Corrigall et al., 1994), nicotine-induced locomotor stimulation (Clarke et al., 1988), as well as the acquisition of nicotine-related place preference (Di Chiara, 2000). Despite evidence linking nicotine's ad-

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dictive properties with its central DA actions, nicotine's DA stimulating properties are relatively weak compared to other addictive substances such as amphetamine or cocaine (Yanagita et al., 1995; Tsukada et al., 2002; Marenco et al., 2004; see Cumming et al., 2003) and appear more akin to those produced by "natural" reinforcers such as food (Di Charia, 2000). Evidence linking nicotine administration to DA release in humans and in non-human primates is currently limited. In a PET study using anesthetized baboons, intravenous nicotine reduced the mean distribution volume ratio of the D2 tracer [^{11}C]raclopride, an action thought to reflect increased DA release (Dewey et al., 1999). While similar results have been reported in anesthetized pigs (Cumming et al., 2003) and anesthetized rhesus monkeys (Marenco et al., 2004) these findings have not been consistently replicated in fully conscious monkeys (Tsukada et al., 2002) and it is possible that the initial findings resulted from an interaction between nicotine and isoflurane anesthesia (Tsukada et al., 2002). In a functional magnetic resonance imaging study in humans, smokers that passively received intravenous nicotine displayed an increase in the blood oxygen level dependent signal in several DA rich regions including the nucleus accumbens (Stein et al., 1999). However, these findings should be interpreted with caution because the route of nicotine administration differed from that used by smokers and the methodology did not directly measure DA release.

The present investigation used PET and [^{11}C]raclopride to assess the dopaminergic response to acute cigarette smoking in humans. Experimental evidence indicates that drug-induced DA release in the striatum causes a reduction in [^{11}C]raclopride binding potential (BP) that is proportional to the increase in extracellular DA (Endres et al., 1997). Although the exact mechanism by which enhanced DA transmission leads to a reduction in [^{11}C]raclopride BP is likely more complex than what could be explained by a simple competition model (Tsukada et al., 2000), this technique has been successfully used to delineate the dopaminergic effects of several abused substances in humans, including cocaine (Schlaepfer et al., 1997), amphetamine (Drevets et al., 2001; Martinez et al., 2003; Leyton et al., 2002), methylphenidate (Volkow et al., 2003), and alcohol (Boileau et al., 2003). Previous PET data suggest that DA release in the striatum is related to various motivational and rewarding processes in humans. For example, decreased [^{11}C]raclopride BP in the ventral striatum (including the nucleus accumbens) is associated with the appetitive (Leyton et al., 2002) and euphoric (Martinez et al., 2003; Drevets et al., 2001) effects of amphetamine, while the pleasurable effects of food (Small et al., 2003) have been associated with decreased [^{11}C]raclopride BP in the dorsal striatum (caudate and putamen). Thus, a goal of this study was to

examine the DA properties of nicotine craving and the hedonic effects of smoking.

METHODS

Subjects

Ten right-handed, non-medicated smokers (5 males) with a mean age of 28.1 years ($SD = 9.45$) were recruited from the community using word of mouth and advertisement. All were regular smokers, smoking an average of 18 ($SD = 7.6$) cigarettes daily for an average of 11.2 years ($SD = 10.5$) and all were free from current or previous neurological or mental illness, including past or present substance use disorders other than nicotine dependence. None reported use of illegal drugs in the previous 30 days and all met a minimum of two DSM IV criteria for nicotine dependence. Following a complete description of the study, all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of the Montreal Neurological Institute.

Procedure

Each participant was scanned twice. In one condition, subjects smoked their usual brand of cigarettes while in the scanner, and in the second condition participants did not smoke. In both conditions, participants remained abstinent from cigarettes for a minimum of 12 hours, alcohol for a minimum of 24 hours, and from food and caffeine for a minimum of 4 hours prior to their scans. All scans were performed at the same time of day (mid-afternoon) following overnight cigarette abstinence. The sequence of scans was counterbalanced across subjects to avoid order effects. Abstinence from smoking was confirmed with a breath carbon monoxide analyzer (Vitalograph Breath CO, Lenexa, KS), using a maximum cutoff of 10 parts per million. Every 15 minutes while in the scanner, subjects were asked to verbally rate the hedonic value of their experience as well as their level of craving by numerically indicating their agreement with the following statements: "I feel elated or euphoric" and "I am craving a cigarette right now" (on a scale from 1 = strongly disagree, to 10 = strongly agree).

In the smoking condition, cigarette consumption began 15 minutes prior to [^{11}C]raclopride delivery. The average nicotine yield of each cigarette smoked by the subjects ranged from 1.9–2.4 mg (mean = 2.1; $SD = 0.1$). Subjects were asked to smoke at a rate of one cigarette every 12 minutes to a maximum of six cigarettes. In two cases, only five cigarettes were smoked due to complaints of adverse effects. In order to avoid additional unpleasant responses, the smoking regimen was altered for the final two subjects so that only three cigarettes were smoked. In each case, smoking was carefully monitored to ensure a steady pace of smoking

as well as minimal movement in the scanner. Head position was verified throughout the scans using a laser mounted on the camera.

PET image acquisition and analysis

Dynamic PET (63 slices, 26 time frames of 60 minutes total duration) was performed using the CTI/Siemens ECAT HR+ camera with lead septa removed, with a theoretical spatial resolution of 4.2 mm full width at half maximum. A transmission scan for attenuation correction was first performed using a ⁶⁸Ge source. Then, [¹¹C]raclopride (10 mCi in 10 ml of saline) was injected over 120 seconds into the antecubital vein and dynamic acquisition was begun. High-resolution 1.5 T T1-weighted MRI scans were obtained at a separate time for each subject for the purpose of anatomical co-registration.

PET frames were summed and co-registered with the MRI, and both images were transformed linearly into standardized stereotaxic space using the Montreal Neurological Institute template (Collins et al., 1994). Parametric maps of [¹¹C]raclopride BP were generated using a simplified reference region method (Lammertsma and Hume, 1996; Gunn et al., 1997). Regions of interest (ROI) were drawn in a two-step process using automated followed by manual anatomical segmentation. First, each subject's MRI was automatically segmented into predefined anatomical regions using the program ANIMAL (Collins et al., 1995). Then, the ROI for caudate, putamen (divided into an anterior and posterior part by the anterior commissural line), and ventral striatum were manually revised on the co-registered MRI following the anatomical segmentation suggested by Martinez et al. (2003), which is based on the known subdivision of the striatum in primates (Parent, 1990). BP values were extracted from each ROI and corrected for partial volume effects using a method that takes into account the noise and resolution characteristics of the scanner (Aston et al., 2002). It is feasible to perform the partial volume correction on the BP images rather than on the original radioactivity images since the simplified compartmental model is linear. Finally, the segmented MRI was used to generate a 4-dimensional template that was used for head motion detection and correction, using a previously described method (Zald et al., 2004). Only five of the scans exhibited head motion greater than 2 mm (range: 2.5 to 4 mm), and these were motion-corrected.

Because previous research has linked both craving and hedonic drug-related effects to changes in [¹¹C]raclopride BP (Drevets et al., 2001; Leyton et al., 2002; Martinez et al., 2003), analyses were also performed to examine the relationship between these variables and BP change. For the two behavioral variables, baseline and overall differences between the two scans were evaluated using paired-samples *t*-tests, and Pearson's correlations were used to examine the relationship be-

tween the average smoking-induced change in the variable and the percent change in [¹¹C]raclopride BP for each ROI.

In addition to ROI analysis, voxelwise estimation of the change in BP was also carried out to generate statistical parametric images as previously described (Aston et al., 2000). Two types of statistical maps were generated: a subtraction between smoking and non-smoking, and a regression map to assess the relationship of BP change to craving and hedonic measures. For the latter, a linear regression was performed at each voxel between the nicotine-induced increase in euphoria rating and the difference in [¹¹C]raclopride BP between the smoking and control scans.

RESULTS

Paired samples *t*-tests revealed no overall significant differences in [¹¹C]raclopride BP between the smoking and control conditions in any of the ROI (all $P > 0.05$) and this was confirmed by the statistical parametric subtraction map. The mean change in BP between the smoking and abstinence scans was 3.12% for the ventral striatum, -1.9 % for the caudate, 2.9% for the anterior putamen, and -1.59% for the posterior putamen.

Smoking-induced changes in elation/euphoria were found to be significantly correlated with changes in [¹¹C]raclopride BP in the caudate ($r = -0.859$; $P < 0.001$) and posterior putamen ($r = -0.679$; $P < 0.05$), but not in the ventral striatum ($r = -0.015$; $P = 0.967$) (Fig. 1). No significant relationships between BP and smoking-induced changes in craving were revealed by correlation analysis.

In order to determine if various demographic and smoking-related variables were associated with regional smoking-induced changes in [¹¹C]raclopride BP, stepwise linear regressions were performed using age, gender, number of cigarettes smoked daily, number of cigarettes smoked during the scan, duration of lifetime smoking, nicotine content of cigarettes, smoking-induced changes in elation/euphoria, and level of craving as potential predictor variables. In both the caudate and posterior putamen, smoking-related elation/euphoria was retained as the sole predictor of [¹¹C]raclopride BP change. No associations were found between any of the variables and change in [¹¹C]raclopride BP in the ventral striatum.

A post hoc inspection of the data revealed that in five subjects smoking produced an increase in elated/euphoric ratings, in four subjects it produced a decrease, and in the remaining subject there was no change (Table I, Fig. 2). Paired samples *t*-tests demonstrated that among subjects experiencing an increase in elation/euphoria in response to smoking, there was a significant 21.3% decrease in [¹¹C]raclopride BP in the caudate ($t(4) = -2.92$; $P = 0.043$) as well as a nonsignificant trend towards decreased BP in the posterior

putamen ($P > 0.05$). In those experiencing a decrease in elation/euphoria, there was a significant 11.3% increase in BP in the posterior putamen ($t(3) = 3.30$; $P = 0.046$) and trends toward increased BP in the cau-

date ($P > 0.05$) and anterior putamen ($P > 0.05$). The statistical parametric correlation map confirms the association between reduced [^{11}C]raclopride BP and euphoria (Fig. 3).

Additional analyses were performed to determine if there were systematic differences within or between the scans in levels of craving or elation/euphoria. Craving levels prior to the start of the scan did not significantly differ between the control and smoking conditions. Craving was reduced in the experimental condition following the initiation of smoking ($t(9) = -2.88$; $P = 0.018$) and overall greater levels of craving were reported during the control scan ($t(9) = 2.76$; $P = 0.022$). There were no significant baseline or overall differences between the smoking and control scans in reported levels of elation/euphoria ($P > 0.05$).

DISCUSSION

In this study, the effects of cigarette smoking on DA neurotransmission were dependent on and proportional to the hedonic response of each subject. Participants were required to smoke multiple cigarettes lying on their backs in the scanner. For some subjects, this was an enjoyable experience while others found it unpleasant. The participants' level of enjoyment appeared to be reflected in changes in DA neurotransmission in the dorsal striatum (Fig. 2).

However, we failed to detect a purely pharmacological effect of nicotine on DA transmission. Looking at the group of subjects as a whole, there was no overall reduction in [^{11}C]raclopride BP in any subdivision of the striatum in response to acute repeated cigarette smoking. These findings suggest that the pharmacological actions of cigarette smoking may not be in and of themselves sufficient to reduce [^{11}C]raclopride BP in human smokers. Although abundant animal research suggests that various aspects of nicotine addiction are mediated by DA systems (e.g., Di Ccharia, 2000), the present findings are consistent with observations that, relative to other abused substances, nicotine may only have relatively weak DA actions (e.g., Yanagita et al., 1995, Marengo et al., 2004). Alternatively, our failure to observe a significant overall reduction in [^{11}C]raclopride BP may have resulted from nicotinic receptor desensitization resulting from repeated administration. In rodents, nicotine increases DA transmission through stimulation of the nicotinic receptors on DA-containing neurons (Pontieri et al., 1996) and repeated nicotine administration results in a desensitization of these receptors (Pidoplichko et al., 1997). Thus, while

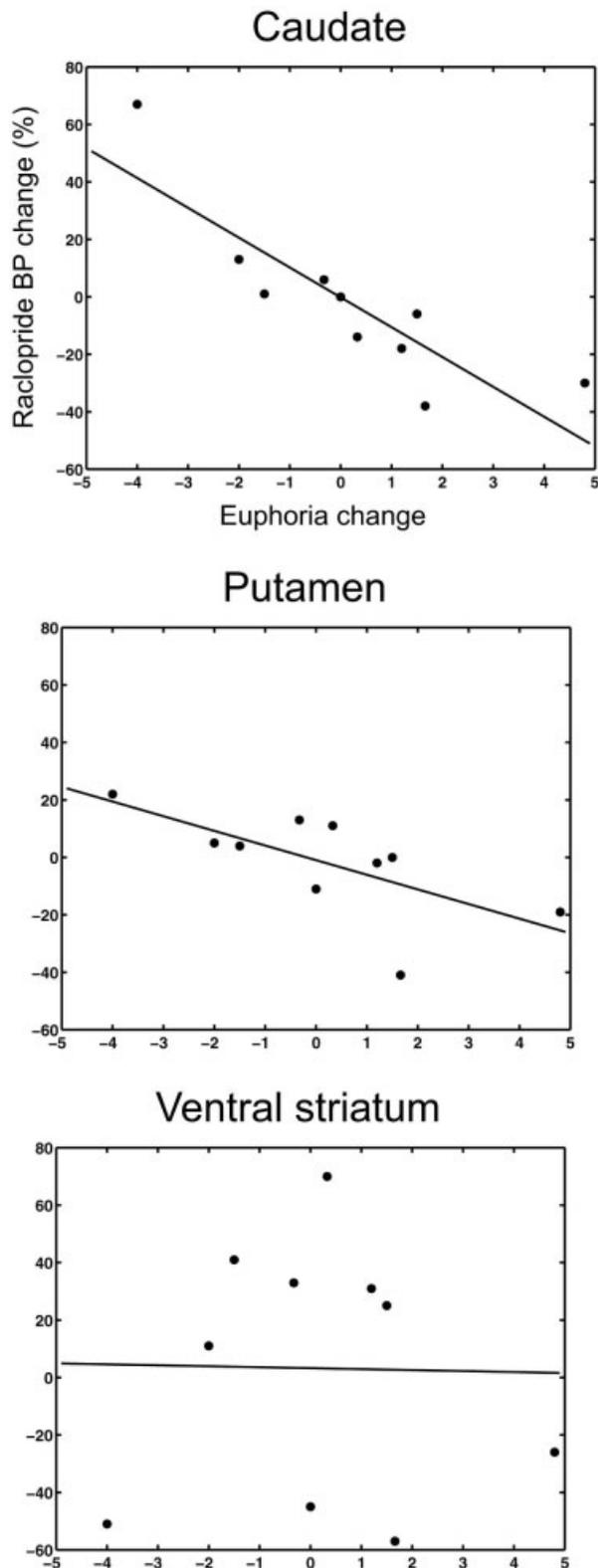


Fig. 1. Relationship between euphoria and dopamine release. Plots of the percent difference in [^{11}C]raclopride BP between the smoking and non-smoking scans versus the change in self-reported euphoria after smoking. A reduction in BP indicates an increase in dopamine transmission. In the caudate nucleus and posterior putamen, there was a statistically significant correlation between euphoria and dopamine release (see text for details) but not in the ventral striatum.

TABLE I. Tobacco-induced changes in euphoria and [¹¹C]raclopride BP for each participant[†]

Subject	Baseline euphoria	Post-smoking euphoria	Caudate (%)	Posterior putamen (%)	Anterior putamen (%)	Ventral striatum (%)
9	1	+4.8	-30	-19	-16	-26
8	3	+1.7	-38	-41	-26	-57
7	2	+1.5	-6	0	6	25
2	3	+1.2	-18	-2	16	31
10	4	+0.33	-14	11	13	70
6	1	0	0	-11	-7	-45
1	2	-.33	6	13	21	33
4	3	-1.5	1	4	12	41
5	4.5	-2	13	5	6	11
3	5	-4	67	22	4	-51

Euphoria was measured using a 10-point scale (1–10). The post-smoking euphoria value represents the change from baseline. The change in [¹¹C]raclopride BP represents the percent difference between the smoking and non-smoking scans.

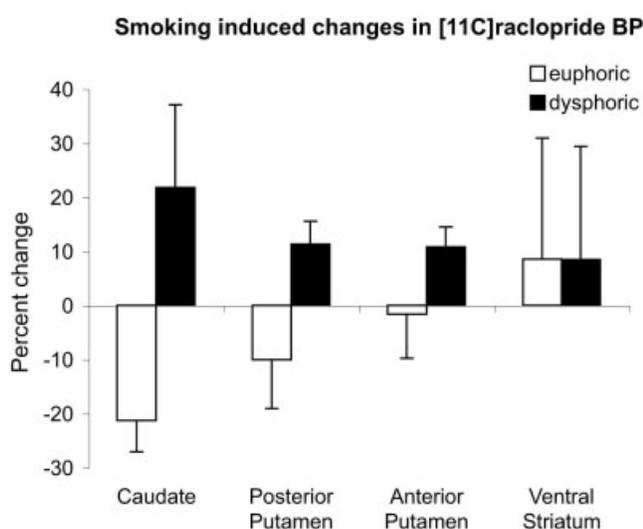


Fig. 2. Change in [¹¹C]raclopride BP in the striatum. Subjects who experienced the smoking/PET session as pleasant demonstrated increased dopamine release in the dorsal striatum. However, subjects who experienced decreased euphoria from smoking demonstrated evidence of reduced dopamine release in all striatal areas.

an initial cigarette may stimulate DA transmission, subsequent cigarettes may not cause further DA release unless there is an adequate refractory period (Pidoplichko et al., 1997). The cigarette smoking procedure utilized in this study required participants to smoke 3–6 cigarettes in 12-minute intervals, beginning 15 minutes prior to [¹¹C]raclopride administration. Although this smoking regimen was selected in order to maximize the nicotine response, it may have in fact resulted in desensitization, thereby reducing any nicotine-induced DA effects.

Another consideration concerns the possible effect of nicotine craving on DA transmission. Although there is currently no direct human evidence for a DA mediation of nicotine craving, animal models suggest that DA transmission in the ventral striatum mediates cravings for addictive substances that possess DA agonist actions (e.g., Robinson and Berridge, 1993; Wise, 1988). In the present study, levels of craving were not related

to [¹¹C]raclopride BP change in either the ventral or dorsal striatum. However, a ceiling effect may have been reached because all subjects were nicotine-deprived and displayed high levels of craving prior to each scan. Moreover, while craving levels significantly decreased following smoking in the experimental condition, they remained elevated throughout the control scan. Thus, if nicotine cravings are indeed associated with increased DA transmission, it is possible the persistently elevated level of craving during the control scan may have negated our ability to detect a nicotine-specific DA response in the experimental condition.

Nonetheless, a possible explanation for the absence of a detectable effect of smoking on DA release in the group as a whole may be that DA release is the result of an interaction between the pharmacological effects of nicotine and the hedonic response to the cigarette. Indeed, among those who found the smoking procedure pleasurable, there was evidence for DA release in the neostriatum, and in those who found it aversive there was decreased DA transmission in this region (Fig. 2). These findings are consistent with animal data that show increased DA cell firing in response to rewarding events but decreased DA neuronal activity in response to events that are less rewarding than expected (e.g., Schultz et al., 1997).

The relationship between DA activity and the hedonic effects of smoking was only apparent in the dorsal striatum, and not in the limbic ventral striatum (Figs. 1–3). A growing body of evidence has implicated the dorsal striatum as a key site for differentiating the hedonic value of rewarding and punishing events in humans. For example, in a recent fMRI study the dorsal striatum exhibited a differential response to monetary gains and losses (Delgado et al., 2003). Similarly, Small et al. (2001) reported that the pleasurable effects of eating chocolate correlated with regional cerebral blood flow increases in the dorsal caudate and putamen but not the ventral striatum. Finally, in two recent [¹¹C]raclopride PET studies, we showed that the pleasurable effects of eating a meal correlated with DA release in the dorsal but not ventral striatum (Small et

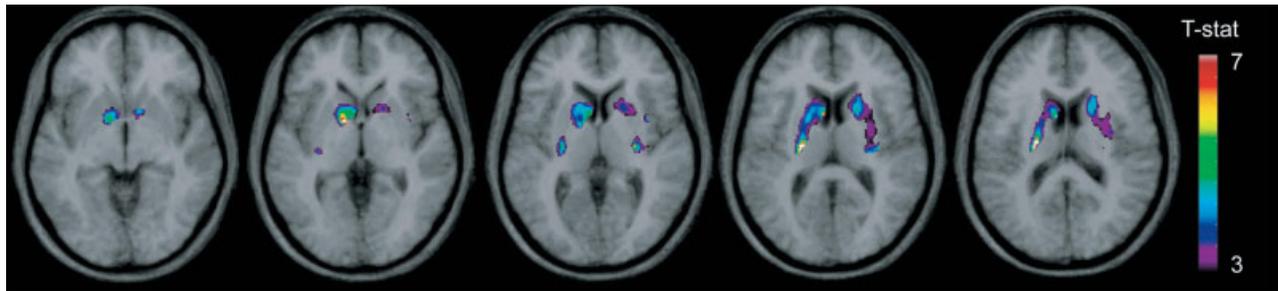


Fig. 3. Correlation between the reduction in [^{11}C]raclopride BP and euphoria. Statistical parametric map of the t -statistic of the linear regression of the reduction in [^{11}C]raclopride BP between smoking and non-smoking scans and the increase in euphoria resulting from smoking. The statistical map is overlaid on an average MRI

image of all subjects in stereotaxic space. Axial sections from $z = -5$ mm to $z = +15$ mm at 5-mm intervals are shown (relative to the anterior commissure). The correlation is greatest in the dorsal and posterior parts of the neostriatum. The left side of each image represents the left side of the brain.

al., 2003), and that monetary reward led to DA release in dorsal parts of the striatum (Zald et al., 2004). Human drug administration studies have produced less consistent results. The euphoric effects of amphetamine have been reported to correlate with the level of DA release in the ventral striatum (Drevets et al., 2001; Martinez et al., 2003) but this finding has not been consistently reported (Leyton et al., 2002). It should be noted, however, that while the present investigation examined the effects of tobacco self-administration in nicotine-dependent smokers, each of the amphetamine studies cited used drug-naïve participants who passively received the drug. Thus, disparities in the expression of hedonic drug effects between studies may reflect differences in the type of drug administered, the route and method of administration, or the previous drug-taking experiences of the participants. For example, there is evidence that expectation of a positive drug effect in humans is associated with DA release in the striatum (de la Fuente-Fernandez et al., 2001).

The present results should be interpreted in light of the following considerations. First, while participants were permitted to smoke their usual brand of cigarettes during the scan, the experimenters determined the frequency and rate of cigarette administration and this likely affected their hedonic value. An alternative design where participants were permitted to smoke ad lib might provide a superior index of how cigarette smoking affects DA transmission under “typical” smoking conditions. Second, variability in nicotine concentrations of the different brands of cigarettes smoked as well as potential individual differences in nicotine metabolism may have led to differences in plasma nicotine concentrations. Although plasma nicotine levels were not directly measured in this study, this is an unlikely explanation for our findings. Numerous cigarette-smoking parameters were found to be unassociated with changes in [^{11}C]raclopride binding including nicotine content of the cigarettes smoked, number of cigarettes smoked during the scan, and daily cigarette consumption, suggesting that the effect of differences

in plasma nicotine on our results was likely minimal. Finally, the sample size in this study was modest ($n = 10$), but was well within the norms for assessing within subject drug effects, and the overall associations between the hedonic effects of smoking and change in [^{11}C]raclopride BP in the caudate ($P < 0.001$) and posterior putamen ($P < 0.05$) were robust. Even when participants were divided into those experiencing euphoric and dysphoric effects, the reported [^{11}C]raclopride BP changes still exceeded $P < 0.05$ and small sample size is typically associated with increased incidence of type I but not type II error.

In conclusion, although cigarette smoking failed to consistently alter DA transmission in the group as a whole, a relationship was observed between smoking-induced hedonic effects and DA release in the dorsal striatum. In subjects experiencing a positive mood response to smoking, there was evidence for increased DA release, while decreased DA activity was associated with a negative mood response.

These findings suggest that changes in DA transmission in the dorsal striatum are related to the valence of affective responses to abused substances. However because of the correlational nature of the data, it is currently not possible to determine if changes in DA release are a cause or a consequence of drug-induced hedonic change.

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