

Association of Low Striatal Dopamine D₂ Receptor Availability With Nicotine Dependence Similar to That Seen With Other Drugs of Abuse

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Objective: All drugs of abuse induce a phasic dopamine release within the striatum that does not undergo habituation. Prolonged substance consumption impairs the natural function of the mesolimbic dopamine system, as shown by a decrease in the availability of striatal dopamine 2 (D₂) receptors in patients suffering from cocaine, heroin, amphetamine, and alcohol dependence. However, it is unclear whether similar changes can also be observed in heavy-smoking nicotine-dependent smokers.

Method: In vivo D₂/D₃ receptor availability was determined with [¹⁸F]fallypride positron emission tomography in 17 heavy-smoking nicotine-dependent subjects and in 21 age-matched never-smoking comparison subjects. The smokers were scanned twice: first, during a period

of usual consumption and second, 24 hours after smoking cessation.

Results: Independent of the withdrawal status, the nicotine-dependent smokers displayed significantly less availability of D₂/D₃ receptors within the bilateral putamen functionally covering parts of the dorsal striatum, as compared to the never-smoking subjects. Nicotine craving under the consumption condition correlated positively with D₂/D₃ receptor availability within the ventral striatum but negatively with D₂/D₃ receptor availability within the anterior cingulate and inferior temporal cortex.

Conclusions: Similar to other types of substance abuse, nicotine dependence is associated with low availability of dorsal striatal D₂/D₃ receptors. In contrast to previous findings on abstinent alcohol-dependent patients, nicotine craving seems to be maintained by a region-specific shift in D₂/D₃ receptor availabilities, with higher availability within the ventral striatum but lower availability within the anterior cingulate and inferior temporal cortex.

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Despite recent public health efforts, regular smoking is still the most frequent attributable cause of premature disability and death in Western societies (1). Nicotine as the primary addictive compound of tobacco smoke binds at nicotinic acetylcholine receptors located at neurons facilitating γ -aminobutyric acid (GABA) and dopamine transmission within different brain regions, such as the prefrontal cortex, thalamus, ventral tegmental area, and nucleus accumbens (2, 3). Like other drugs of abuse, nicotine provokes a sustained dopamine release in the nucleus accumbens, as shown by rat microdialysis experiments, that is important for the development of substance dependence (4).

Positron emission tomography (PET) provides a powerful tool to monitor pre- and postsynaptic changes within the dopamine system in the living brain (5). Consumption of a cigarette during a break from a [¹¹C]raclopride PET scan re-

sults in a prominent decrease of dopamine 2 (D₂) receptor availability in the left ventral striatum, potentially representing a nicotine-triggered dopamine release (6). In addition, striatal uptake of the dopamine precursor [¹⁸F]fluorodopa was 16%–29% higher among regular smokers than among nonsmoking comparison subjects (7). However, the nicotine-induced displacement of [¹¹C]raclopride by endogenous dopamine could not be confirmed in another study (8).

Given the provisional evidence that short-term use of nicotine releases dopamine within the ventral striatum in subjects who smoke for pleasure on a nonregular basis, it remains unclear whether prolonged nicotine intake and sustained dopamine release in dependent smokers might trigger hypofunctionality of the mesolimbic dopamine system. A significantly lower D₁ binding potential in the ventral striatum and caudate of chronic smokers than in

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nonsmoking subjects implies such a conclusion (9). Significantly lower striatal D₂ receptor availability, another marker for a hypofunctional dopaminergic state, has been observed in patients with alcohol (10), heroin (11), cocaine (12), and methamphetamine (13) dependence. In the case of alcohol-dependent subjects, the lower D₂ receptor availability persisted even 6 weeks after alcohol detoxification (10, 14, 15), and it only slowly recovered several weeks after detoxification (10, 14). Given the high relapse rates during early abstinence, the low striatal D₂ receptor availability, either as a cause or a consequence of prolonged substance consumption, might therefore trigger relapse into compulsive substance consumption. This hypothesis is supported by the finding of an inverse correlation of striatal D₂ receptor availability with alcohol craving and cue-induced activation of several brain regions, such as the medial prefrontal cortex and anterior cingulate cortex, in a group of recently detoxified alcohol-dependent patients (15).

In the present study, D₂ receptor availability was measured in nicotine-dependent smokers at two time points (in consumption and withdrawal conditions) and in never-smoking subjects, by means of the high-affinity D₂/D₃ receptor ligand [¹⁸F]fallypride. In contrast to [¹¹C]raclopride, [¹⁸F]fallypride has a very high affinity for D₂/D₃ receptors that allows the quantification of extrastriatal, e.g., fronto- or temporocortical, D₂ receptors (16, 17). We hypothesized that nicotine-dependent smokers would display less availability of striatal and potentially extrastriatal D₂/D₃ receptors than would the never-smoking subjects, i.e., differences similar to those observed in patients suffering from alcohol, amphetamine, cocaine, or opioid dependence. Furthermore, if the lower availability would rely only on the nicotine-induced displacement of the radioligand by endogenous dopamine, an increase in D₂ receptor availability should be observed during nicotine withdrawal.

Method

Ethical Approval

This study was carried out in agreement with the Helsinki Declaration and was approved by the local ethics committee, the Federal Health Administration (BfArM), and the radiation protection authorities (BfS).

Study Inclusion and Exclusion Criteria

Study participants were recruited by public advertisement. The never-smoking comparison subjects had a maximum lifetime cigarette consumption of 20 cigarettes. The smokers were recruited on the basis of their current heavy smoking, i.e., more than 15 cigarettes per day within the last 4 weeks. They fulfilled at least three DSM-IV criteria for nicotine dependence and had seriously attempted to quit smoking at least once. Before entering the study, subjects were screened with a standard psychiatric interview (Composite International Diagnostic Interview) (18), medical history, electrocardiography, blood tests, and clinical examination including a screening test for illicit drugs. The smokers and the never-smokers had no current or previous history of relevant physical illness, no current or past psychiatric or substance

abuse disorders, no family history of major psychiatric disorder in first-degree relatives, and no regular use of medication. After complete description of the study to the subjects, written informed consent was obtained.

Study Schedule and Nicotine Withdrawal

After study inclusion, a baseline assessment was done. This included a detailed neuropsychological examination and personality tests for both smokers and never-smokers; those results were not part of the current investigation. Nicotine dependence severity and nicotine craving in the dependent smokers were assessed with the Fagerström Test for Nicotine Dependence (19), a visual analogue scale for smoking desire, and the Questionnaire on Smoking Urges (20). To specifically test smoking withdrawal, the Wisconsin Smoking Withdrawal Scale (21) was completed. The never-smoking subjects were asked for their personal reasons for abstaining from smoking.

Among the dependent smokers, D₂/D₃ receptor availability was determined twice (technical details appear in the following section): first, during average cigarette consumption and second, 24 hours after smoking cessation. In the condition of uninterrupted consumption the study participants were asked to smoke their average number of cigarettes on the study day and not to stop with their smoking until lying in the PET scanner. The time interval between the last cigarette and the start of the ligand infusion was limited to 15 minutes. The smoking-specific questionnaires were completed immediately before the PET scan started. For the purpose of nicotine withdrawal, the subjects were asked to stop smoking at 3:00 p.m. and to stay at the psychiatric ward for subsequent supervision. The smoking-specific assessments were done at the beginning of the withdrawal and at hours 3, 6, 9, 12, and 24 after smoking cessation. The second PET scan was done 24 hours after smoking withdrawal started. The never-smokers were scanned only once, at the same time of the day when the smokers were scanned.

Data Acquisition

PET scans were acquired under resting conditions in dimmed ambient light with eyes closed by means of a Siemens ECAT EXACT scanner (CTI, Knoxville, Tenn.) operating in the three-dimensional mode (22). Images were reconstructed by filtered back projection using a ramp filter and a Hamming filter (4 mm width). To correct for tissue attenuation, transmission scans were acquired with three rotating ⁶⁸Ge sources before injection of [¹⁸F]fallypride. Data acquisition comprised 39 time frames initiated immediately after the bolus intravenous injection of a mean of 187 (SD=19) MBq of [¹⁸F]fallypride. The scan duration increased progressively from 20 seconds to 10 minutes, resulting in a total scanning time of 180 minutes. The study participants remained in the PET scanner for the whole data acquisition time without a break. Further methodological details, including synthesis, physiologic behavior, and kinetics of the ligand, can be found in earlier publications (16, 17).

Image Analysis

From the images of [¹⁸F]fallypride, binding potential was calculated on a voxelwise basis by using the simplified reference tissue model of Lammertsma and Hume (23). The cerebellum was chosen as a reference region since it is generally considered to be free of dopamine receptors. Prior to statistical analysis, the binding potential images were spatially normalized into Montreal Neurological Institute space (McGill University, Montreal) to remove intersubject anatomical variability. For this purpose, integral images (sum of frames between 4 and 8 minutes after infusion) were calculated and spatially normalized by using SPM99 routines (Wellcome Department of Cognitive Neurology, London) and a ligand-specific D₂ template. Subsequently, transfor-

mation parameters of normalization were applied to respective individual images. An isotropic Gaussian filter was used to smooth the spatially normalized images with a full width at half maximum (FWHM) 12-mm kernel.

Statistical Analysis

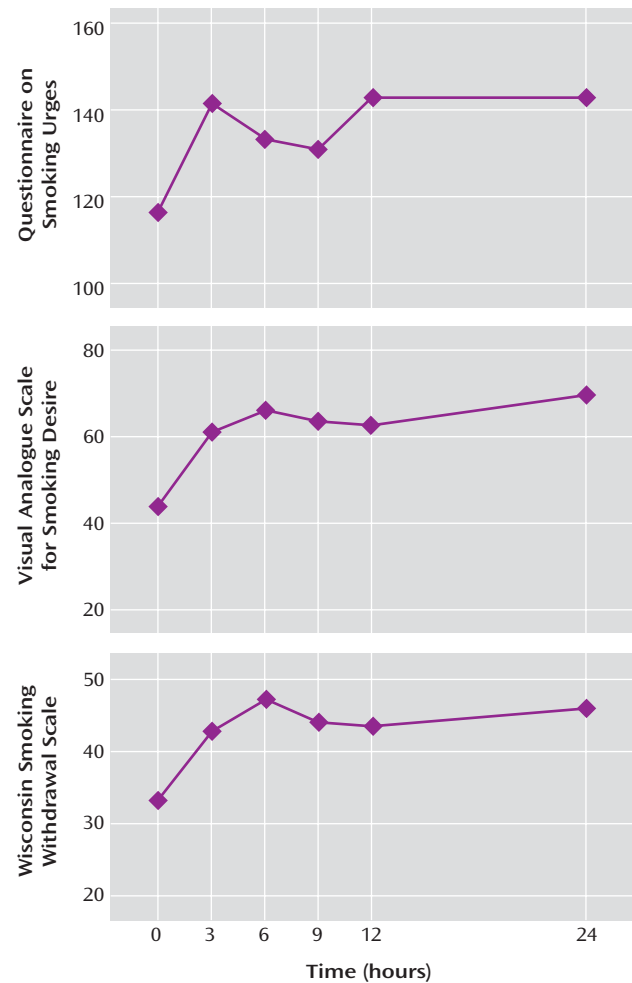
Statistical analysis of the data was performed by using SPM2 implemented in Matlab 6.5 (MathWorks, Sherborn, Mass.). The analysis included several steps. First, one-way analysis of covariance (ANCOVA), controlling for global [^{18}F]fallypride binding potential and followed by post hoc unpaired t tests, was used to identify significant differences in binding potential between the comparison subjects and the smokers in the consumption condition as well as between the comparison subjects and the smokers after withdrawal. The influence of the overnight withdrawal on D_2/D_3 receptor availability among the smokers was evaluated by paired t test. The final step was the investigation of the functional association between the symptoms specific to nicotine dependence and the D_2/D_3 receptor availability. The total score on the Questionnaire on Smoking Urges, the scores on the intention and withdrawal relief subscales, and the score on the Wisconsin Smoking Withdrawal Scale were correlated as external covariates to the corresponding PET data, with controls for global binding potential. In all statistical analyses, the global value was introduced as a nuisance variable to account for interindividual differences in the whole brain D_2 receptor availability (15). The global value was defined as the average for all voxels within the brain where any [^{18}F]fallypride binding potential was detected. The resulting set of values for each contrast constituted a statistical parametric map of t statistics (SPM_t). The SPM_t values were transformed to the unit normal distribution SPM_z . The statistical parametric maps for intra- and intergroup comparisons were based on a threshold for uncorrected probability of $p < 0.001$, but they were corrected for multiple comparisons at the cluster level with a probability level of $p < 0.05$. The threshold for covariate effects of nicotine craving (Questionnaire on Smoking Urges), nicotine withdrawal (Wisconsin Smoking Withdrawal Scale), and nicotine dependence severity (Fagerström Test for Nicotine Dependence) was set at an uncorrected probability level of $p < 0.005$, but correction for multiple comparisons was implemented at the cluster level with a probability value of $p < 0.05$. The extent threshold of 30 voxels (i.e., $2 \times \text{FWHM}$) was applied. The local maxima of each cluster are reported with the respective stereotactic coordinates. MRIcro software (C. Rorden and M. Brett, <http://www.sph.sc.edu/comd/rorden/micro.html>) was used for image display.

Results

Study Participants

Seventeen male nicotine-dependent smokers and 21 men who had never smoked were included in the study. Thirty-six (94.7%) of the 38 study participants were Caucasian, one (2.6%) participant was African, and one (2.6%) was Asian. The nicotine-dependent smokers and the never-smokers did not differ in mean age (smokers: 31.1 years, $\text{SD}=7.7$; never-smokers: 30.6 years, $\text{SD}=4.5$) or mean years of education (smokers: 12.2 years, $\text{SD}=1.6$; never-smokers: 12.7 years, $\text{SD}=1.0$). The mean verbal IQ was significantly higher for the never-smokers (smokers: 107.5, $\text{SD}=7.9$; never-smokers: 115.6, $\text{SD}=9.2$) ($t=2.7$, $\text{df}=30$, $p=0.02$). The smokers were heavily nicotine dependent; their mean score on the Fagerström Test for Nicotine Dependence was 5.7 ($\text{SD}=1.4$), and they fulfilled a mean of 5.4

FIGURE 1. Time Course of Nicotine Withdrawal for 17 Nicotine-Dependent Smokers

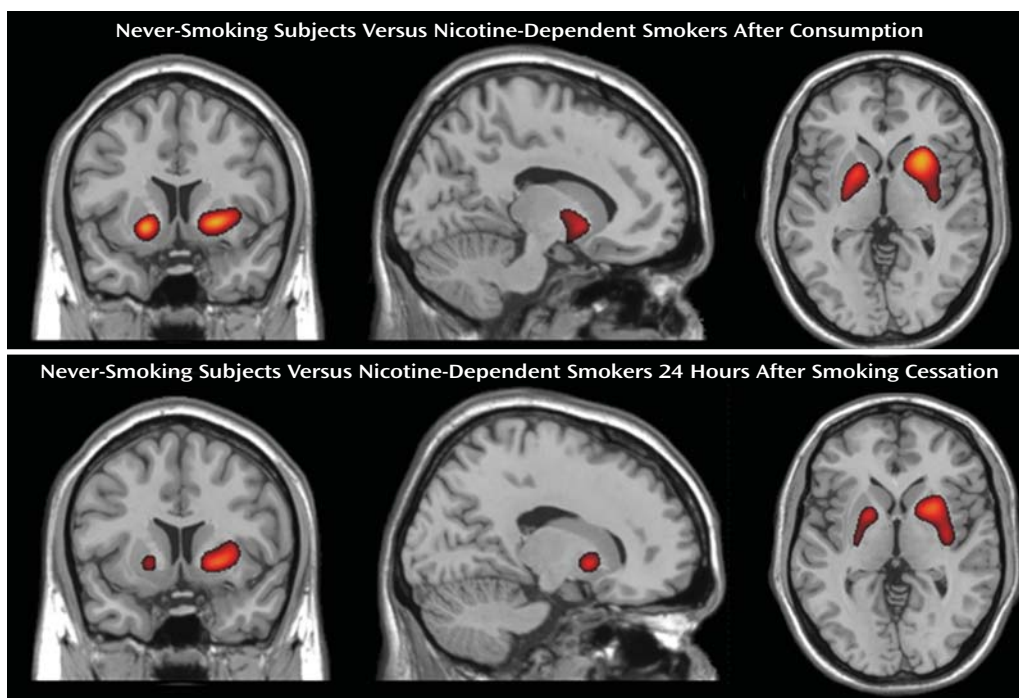


($\text{SD}=1.6$) DSM-IV criteria for nicotine dependence. They had started regular consumption at a mean age of 17.4 years ($\text{SD}=2.2$) and had smoked for 13.7 years ($\text{SD}=8.0$). During the 4 weeks preceding study inclusion they had smoked a mean of 19.5 ($\text{SD}=5.9$) cigarettes per day.

Nicotine Withdrawal

The time course and clinical symptoms of nicotine withdrawal are summarized in Figure 1. During the consumption period, the smokers had a moderate desire to smoke, as reflected in a mean summary score on the Questionnaire on Smoking Urges of 116.1 ($\text{SD}=25.8$) and a mean score on the visual analogue scale of 41.8 ($\text{SD}=21.9$), but they experienced almost no withdrawal, as indicated by a mean score on the Wisconsin Smoking Withdrawal Scale of 33.1 ($\text{SD}=16.4$). After the beginning of smoking cessation, scores on the Wisconsin scale indicated that the self-reported withdrawal escalated from mild to at least moderate during the withdrawal day, resulting in a significant effect of time ($F=3.4$, $\text{df}=5$, $p=0.01$; general linear model repeated measurement) (Figure 1). Parallel to that,

FIGURE 2. Differences in Dopamine D₂/D₃ Receptor Binding Potential Between 21 Never-Smoking Subjects and 17 Nicotine-Dependent Smokers After Consumption and Withdrawal^a



^a Colored voxels indicate regions with significantly higher availability of D₂/D₃ receptors among never-smoking subjects than among smokers. Differences were significant at $p < 0.001$ uncorrected but were corrected for multiple comparisons at the cluster level with $p < 0.05$.

the mean carbon monoxide content of the expiratory air declined from 22.5 (SD=8.6) parts per trillion at hour 0 to 2.4 (SD=2.3) parts per trillion at hour 24 ($t=11.7$, $df=16$, $p < 0.001$; paired t test), thus ensuring study compliance. Nicotine withdrawal achieved a maximum at hour 24 (Figure 1). Smoking desire also changed significantly during the course of withdrawal, as shown by significant effects of time (with general linear model repeated measures) on scores on the visual analogue scale ($F=2.9$, $df=5$, $p=0.02$) and Questionnaire on Smoking Urges ($F=2.9$, $df=5$, $p=0.02$) (Figure 1).

D₂/D₃ Receptor Availability Among Smokers and Never-Smokers

The categorical comparisons of D₂/D₃ receptor availability in the nicotine-dependent smokers and the never-smokers revealed significantly lower D₂/D₃ receptor availability in the bilateral putamen among the nicotine-dependent subjects, both immediately after consumption and after the overnight nicotine withdrawal (Figure 2, Table 1). However, the low D₂/D₃ receptor availability seemed to be independent of the severity of nicotine dependence, as we were unable to find any correlation between the smokers' striatal D₂/D₃ receptor availability and scores on the Fagerström Test for Nicotine Dependence under either condition (data not shown). The low D₂/D₃ receptor availability did not extend to extrastriatal regions, such as the prefrontal cortex, orbitofrontal cortex, cingu-

late cortex, or temporal cortex (Figure 2). The categorical comparison did not detect any brain region where the nicotine-dependent smokers exhibited higher D₂/D₃ receptor availability than the never-smokers (data not shown).

D₂/D₃ Receptor Availability After Nicotine Withdrawal

The categorical comparisons of D₂/D₃ receptor availability between the smokers after consumption and the smokers after overnight withdrawal did not detect any brain region with an either significantly higher or lower D₂/D₃ receptor availability (data not shown).

Nicotine Desire and D₂/D₃ Receptor Availability

It seemed reasonable to us that the observed variations in D₂/D₃ receptor availability were associated with differences in nicotine craving. Therefore, we looked at the relationship between the desire to smoke and D₂/D₃ receptor availability among the nicotine-dependent smokers under both the consumption and withdrawal conditions.

Contrary to our expectations, the overall desire to smoke in the consumption condition (sum score on the Questionnaire on Smoking Urges) was positively correlated with D₂/D₃ receptor availability in the lower parts of the bilateral putamen and the nucleus accumbens with extension to the orbitofrontal cortex (Table 2, Figure 3). In contrast, the desire to smoke after consumption was negatively correlated with the D₂/D₃ receptor availability in

TABLE 1. Bilateral Putamen Regions Showing Lower Dopamine D₂/D₃ Receptor Binding Potential in 17 Nicotine-Dependent Smokers Than in 21 Never-Smoking Subjects^a

Condition for Smokers	MNI Coordinates of Cluster Maxima ^b			Cluster Extent (number of voxels)	z Score
	x	y	z		
After nicotine consumption	24	16	-4	893	4.10
	-18	8	-6	770	3.92
24 hours after smoking cessation	24	10	-2	1034	3.75
	-18	6	-2	417	3.53

^a Difference between smokers and comparison subjects was significant at $p < 0.001$ uncorrected but was corrected for multiple comparisons at the cluster level with $p < 0.05$.

^b Based on the standard coordinate system of the Montreal Neurological Institute. See also Figure 2.

TABLE 2. Brain Regions With Dopamine D₂/D₃ Receptor Binding Potential Correlated With Questionnaire on Smoking Urges Score for 17 Nicotine-Dependent Smokers After Consumption^a

Direction of Correlation and Brain Region	MNI Coordinates of Cluster Maxima ^b			Cluster Extent (number of voxels)	z Score
	x	y	z		
Positive correlation					
Bilateral putamen and nucleus accumbens	-12	-10	-10	995	3.07
Negative correlations					
Right gyrus temporalis medius and gyrus fusiformis	52	-42	-12	3506	4.00
Left gyrus temporalis medius/superior and gyrus fusiformis	-64	-46	-14	2457	3.86
Bilateral gyrus cinguli anterior	2	48	-4	337	3.71
Right gyrus cinguli	10	-12	36	245	3.63

^a Correlations were significant at $p < 0.005$ uncorrected but were corrected for multiple comparisons at the cluster level with < 0.05 .

^b Based on the standard coordinate system of the Montreal Neurological Institute. See also Figure 3.

large areas of the left medial and superior temporal cortex and the left gyrus fusiformis, a substantial part of the right medial temporal cortex, the right gyrus fusiformis, both sides of the anterior cingulate cortex, and parts of the right cingulate cortex (Table 2, Figure 3).

As the Questionnaire on Smoking Urges comprises two empirically derived subscales, with one representing rather emotionally positive expectations from smoking or the intention to smoke (intention subscale) and the other representing the anticipation of withdrawal relief and relief from negative affects (withdrawal relief subscale), we also tested for correlation between the score on each subscale and D₂/D₃ receptor availability among the same subjects. As in the analysis of the smoking urge as a whole, the intention to smoke and the anticipation of withdrawal relief both correlated positively with D₂/D₃ receptor availability in the bilateral putamen and negatively with D₂/D₃ receptor availability in the bilateral medial temporal cortex, fusiform cortex, and anterior cingulum (data not shown).

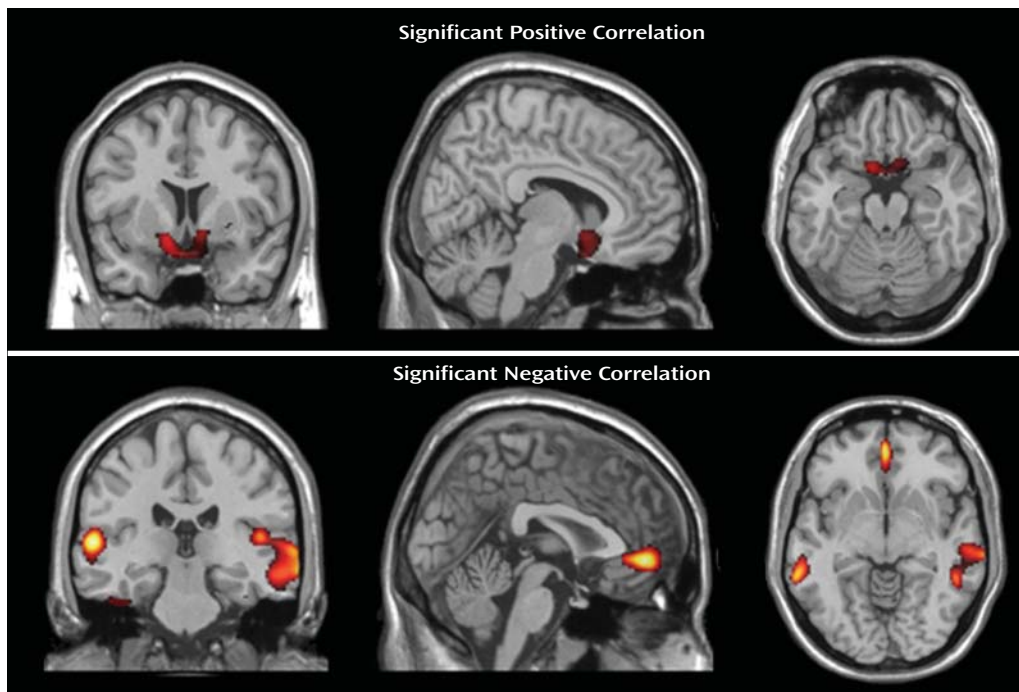
However, when the correlation analyses were repeated among the subjects withdrawn from nicotine, neither the positive correlation between the Questionnaire on Smoking Urges sum score and D₂/D₃ receptor availability within the striatum nor the negative correlation between smoking desire and D₂/D₃ receptor availability within the temporal cortex, fusiform cortex, or cingulate cortex could be confirmed (data not shown). In addition, we did not find any significant correlation between D₂/D₃ receptor availability and nicotine withdrawal as measured with the Wisconsin Smoking Withdrawal Scale (data not shown).

Discussion

A major finding of the present study was the significantly lower D₂/D₃ receptor availability in the bilateral putamen covering a major part of the dorsal striatum in heavy-smoking nicotine-dependent patients. Similarly low dorsal striatal D₂ receptor availability has been measured in patients dependent on alcohol (10), heroin (11), cocaine (12), and amphetamine (13) during either consumption or early abstinence. However, a sustained deficit in D₂/D₃ receptor availability has been shown even when synaptic dopamine levels have returned to normal after stimulation (24–26). Thus, the low D₂/D₃ receptor availability after 24 hours of abstinence might not actually reflect a low level of synaptic dopamine at that time point but could result from sustained low receptor availability due to nicotine-induced dopamine release. Nevertheless, low D₂/D₃ receptor availability either during consumption or during early abstinence has been viewed as a characteristic endophenotype defining substance dependence and potentially triggering relapse risk (5). If confirmed among nicotine-dependent patients several weeks after smoking cessation, the low striatal D₂/D₃ receptor availability observed in our study might explain the frequently experienced difficulties in becoming or staying abstinent from nicotine.

However, these considerations have to be limited to heavy-smoking nicotine-dependent subjects, such as those investigated in our study. Striatal dopamine release in response to acute tobacco/nicotine consumption has been substantiated by a number of human and primate experiments using [¹¹C]raclopride (6, 27, 28). The magnitude of the reported alteration in D₂/D₃ receptor availabil-

FIGURE 3. Correlations Between Questionnaire on Smoking Urges Score and Dopamine D₂/D₃ Receptor Binding Potential in 17 Nicotine-Dependent Smokers After Consumption^a



^a Results from parametric correlation analyses were significant at $p < 0.005$ uncorrected but were corrected for multiple comparisons at the cluster level with $p < 0.05$.

ity varies substantially across these studies, but it seems to be smaller than that seen with amphetamine administration (28, 29). However, these studies are unable to answer the question of whether the low striatal D₂ receptor availability is a result of nicotine-induced dopamine release over time or whether it is a trait increasing the liability for nicotine dependence, as none of these studies investigated nonaddicted smokers, addicted smokers, and never-smokers simultaneously (30). Nonaddicted smokers might even display a high availability of striatal D₂ receptors that protects them against nicotine dependence, as shown for the nonaddicted first-degree relatives of alcohol-dependent patients (31).

In our study, a low availability of striatal D₂/D₃ receptors among nicotine-dependent smokers was found in large areas of the bilateral putamen covering different parts of the striatum, such as the limbic, associative, and sensorimotor striatum (32). Lesion experiments in rodents have implicated functional subdivisions in the midbrain dopamine system, with the nucleus accumbens shell mediating psychostimulant drug effects and the nucleus accumbens core being important for priming cue-induced drug craving (33, 34). Functional subdivisions have also been proposed for the human striatum (32); however, as in our study, low [¹¹C]raclopride binding among cocaine-dependent subjects was observed within all three parts of the striatum, i.e., the limbic, associative, and sensorimotor striatum (35). Thus, nicotine-induced alterations are not

limited to the regions mediating unconscious drug seeking; presumably they also affect neurobiological regions initiating drug-stimuli conditioning as well as the psychomotor effects of nicotine stimuli (5).

In our study, overnight nicotine withdrawal did not alter D₂/D₃ receptor availability among the nicotine-dependent subjects. As mentioned earlier, [¹⁸F]fallypride binding 24 hours after smoking cessation still might have remained low because of the effects of nicotine-induced dopamine release (24–26). Alternatively, the low striatal D₂/D₃ receptor availability after overnight withdrawal might be maintained by mechanisms that go beyond direct competition with endogenous dopamine.

In contrast to the observed differences in striatal D₂/D₃ receptor availability between the nicotine-dependent smokers and nonsmoking subjects, no significant differences in extrastriatal D₂/D₃ receptor availability could be detected between the two groups (Figure 2). Given the substantially lower [¹⁸F]fallypride binding potentials in the extrastriatal regions as compared to the striatum in healthy subjects studied by Siessmeier et al. (16) (mean binding potential in thalamus, 1.9–2.2, mean in striatum, 21.7–23.3), this could have resulted from a relatively large intersubject variability in extrastriatal D₂ receptor availability hampering the measurement of a statistically significant difference. Besides, there might not be any extrastriatal difference in D₂/D₃ receptor availability if the low striatal D₂ availability results only from the prolonged nic-

otine-induced dopamine release that is most prominent in the nucleus accumbens, as suggested by experiments using animal models (33, 34, 36).

Contrary to our primary expectations, nicotine craving as measured with the Questionnaire on Smoking Urges positively correlated with D₂/D₃ receptor availability in the ventral striatum. Given the likelihood that higher D₂/D₃ receptor availability during consumption is the indirect measure of lower striatal dopamine levels, one likely explanation is that a stronger desire to smoke results from impaired nicotine-induced dopamine release. This explanation is appealing, as behavioral experiments in animal models have repeatedly demonstrated the importance of the mesolimbic dopamine system for attributing incentive salience to drugs of abuse, finally leading into compulsive drug taking and drug wanting (37). Alternatively, the positive correlation between smoking desire and D₂/D₃ receptor availability could be a result of a sensitization process that might have occurred after numerous years of smoking. Consistent with that hypothesis, an increased sensitivity to the D₂ receptor agonist quinpirole triggering cocaine reinstatement has been described among withdrawn rats with high previous cocaine intake (38). It should be noted that some previous studies found no association (35) or a negative relationship (15, 39) between drug craving intensity and striatal D₂ receptor availability. The observed discrepancies between the studies may be explained by different substances investigated, variations in study protocols, or the perceived opportunity of drug use in the case of nicotine (40).

In contrast to the positive correlation between striatal D₂/D₃ receptor availability and craving, we observed a negative correlation between craving and the D₂/D₃ receptor availability in the anterior cingulate cortex, inferior temporal cortex, and fusiform cortex. This is of particular interest as cue-induced nicotine craving has been repeatedly shown to activate the anterior cingulate cortex (30). Our data also support findings from experimental studies on rats that have emphasized the role of the prefrontal dopamine system for the reinstatement of drug-seeking behavior (41). If confirmed by independent investigations, nicotine craving might therefore be maintained by a spatial shift in D₂/D₃ receptor availability, with a relatively high proportion of available D₂/D₃ receptors in the striatum and lower proportions of D₂/D₃ receptors available in the anterior cingulate cortex and inferior temporal cortex that may lead to disinhibition of frontocortical glutamatergic neurons (42).

In this study, nicotine-dependent heavy smokers displayed lower availability of striatal D₂/D₃ receptors than did subjects who had never smoked. Contrary to our primary hypothesis, we did not find a negative correlation between nicotine craving and ventral striatal D₂ receptor availability. Our results imply, rather, that nicotine craving in a condition of average consumption is maintained

by a region-specific shift in D₂/D₃ receptor availability, with greater availability within the striatum and less availability within the anterior cingulate cortex and inferior temporal cortex.

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