Article

Correlation of Alcohol Craving With Striatal Dopamine Synthesis Capacity and $D_{2/3}$ Receptor Availability: A Combined [^{18}F]DOPA and [^{18}F]DMFP PET Study in Detoxified Alcoholic Patients

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Objective: In abstinent alcoholic patients, a low availability of dopamine $D_{2/3}$ receptors in the ventral striatum and adjacent putamen was associated with a high level of craving for alcohol. Alcohol craving may also depend on presynaptic dysfunction of striatal dopamine production, which may contribute to the risk of relapse. In this study, positron emission tomography (PET) was used to compare dopamine synthesis capacity in the striatum in alcoholic patients and healthy comparison subjects.

Method: Positron emission tomography (PET) was used to map the net blood-brain clearance of the dopa decarboxylase substrate 6-[^{18}F]fluoro-L-dopa, an index of dopamine synthesis capacity, in the striatum of 12 detoxified male alcoholic patients and 13 age-matched healthy men. The parametric maps were correlated with results of an earlier [^{18}F]desmethoxyfallypride PET study of dopamine $D_{2/3}$ receptor availability in the same 12 alcoholic patients and in 12 of the healthy volunteers. Alcohol craving was measured with the Alcohol Craving Questionnaire. Patients were followed for 6 months, and alcohol intake was recorded.

Results: The magnitude of net blood-brain clearance in the striatum did not differ significantly between detoxified alcoholic patients and the comparison subjects. However, a voxel-wise correlation analysis of net blood-brain clearance in the alcoholic patients linked low levels of dopamine synthesis capacity in the bilateral putamen with high levels of alcohol craving. After normalization of net blood-brain clearance maps to the voxel-wise estimates of dopamine $D_{2/3}$ receptor availability, there was still a negative correlation with alcohol craving. Alcohol craving at the time of scanning was associated with high level of alcohol intake in the 6-month follow-up period.

Conclusions: Simultaneous assay by PET of pre- and postsynaptic markers of dopamine neurotransmission indicated that a striatal dopamine deficit correlated with alcohol craving, which was associated with a high relapse risk.

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Results of a cerebral microdialysis study in rats (1) and a positron emission tomography (PET) study of healthy volunteers (2) indicated that acute and chronic alcohol intake stimulates dopamine release in the ventral and dorsal striatum. Chronic alcohol intake, however, reduced the availability of striatal dopamine $D_{2/3}$ receptors (3, 4), which may represent a compensatory down-regulation that ensures homeostasis of central dopaminergic neurotransmission (5). Precipitous withdrawal from alcohol during detoxification results in a rapid decrease in dopamine release (6), whereas the availability and sensitivity of central dopamine $D_{2/3}$ receptors increase during the first week of abstinence (4, 7, 8). In alcoholic subjects, delayed recovery of central dopamine D_2 receptors was associated with an increased risk of relapse (7, 8) and may be associated with persistent presynaptic dopaminergic dysfunction during early abstinence (5, 9). However, striatal dopamine transporter availability was reduced during acute detoxification but did not differ from control levels after several weeks of abstinence (3, 10). To our knowledge, only one study has examined presynaptic dopamine production in detoxified alcoholic subjects, in whom changes in the net uptake of the dopa decarboxylase substrate [^{18}F]fluoro-L-dopa ([^{18}F]DOPA) were reported in restricted subregions of the striatum (11).

We recently reported reduced availability of dopamine $D_{2/3}$ receptors in the ventral striatum and adjacent putamen of abstinent alcoholic subjects, which was associated with a high level of craving for alcohol and an increase in brain activation elicited by alcohol-associated (as opposed to control) cues (12). To explore further the interaction between presynaptic striatal dopamine production and dopamine $D_{2/3}$ receptor availability in recently detoxified alcoholic patients, we measured [^{18}F]DOPA uptake in

the same alcoholic patients and comparison subjects, who also underwent assessment of dopamine $D_{2/3}$ receptors with [^{18}F]desmethoxyfallypride ([^{18}F]DMFP). We tested the following hypotheses: 1) [^{18}F]DOPA influx to the striatum is lower in alcoholic subjects, relative to healthy comparison subjects; 2) this lower level of influx correlates with higher levels of craving for alcohol; and 3) alcohol craving is associated with a risk of relapse during a 6-month follow-up period. Lower levels of [^{18}F]DOPA influx, a marker of impaired presynaptic dopamine production, may predict alcohol craving if it coincides spatially with a low availability of dopamine $D_{2/3}$ receptors. Because low striatal dopamine $D_{2/3}$ receptor availability was inversely correlated with alcohol craving in abstinent alcoholic subjects (12), we also explored whether low [^{18}F]DOPA influx, when normalized to the local availability of dopamine $D_{2/3}$ receptors, is associated with alcohol craving.

Method

Subjects and Instruments

The local ethics committee approved the study, and written, informed consent was obtained from all participants after the procedures had been fully explained. Twelve male alcoholic patients (mean age=42.5 years, SD=7.5, range=32–57) and 13 age-matched healthy comparison subjects (mean age=43.2 years, SD=9.5, range=32–60) were included in the investigation. The patients met the ICD-10 and DSM-IV criteria for alcohol dependence and had no other axis I psychiatric disorders and no past history of drug dependence or current drug abuse, according to assessment with random urine drug testing and the Structured Clinical Interview for DSM-IV-TR (SCID) (13). The patients had abstained from alcohol in a supervised inpatient treatment program for a mean of 36 days (SD=22) (verified by random administration of an alcohol breath test and urine analysis) (12). The healthy comparison subjects had no psychiatric axis I or II disorders (according to assessment with the SCID) (13, 14). The severity of alcoholism was assessed with the Alcohol Dependence Scale (15). The lifetime amount of alcohol intake was measured with the Lifetime Drinking History questionnaire (16). The severity of current alcohol craving was measured with the Alcohol Craving Questionnaire (17) on the morning before the subject underwent functional brain imaging. The Alcohol Craving Questionnaire is a widely and internationally used instrument with good test-retest reliability (kappa=0.85, $p<0.001$; tested in 46 alcoholic subjects on 2 separate days) and high internal consistency (Cronbach's alpha=0.96, $p<0.001$, N=243).

PET investigations with [^{18}F]DOPA and [^{18}F]DMFP were performed in all patients and volunteers within a period of 5 days. In six patients and six volunteers, the [^{18}F]DOPA PET preceded the [^{18}F]DMFP PET. Patients were released from the ward 1 week after scanning. They were then seen biweekly by one of the researchers (J.W.) over the following 6 months, and alcohol consumption was recorded with the Form 90, a standard tool for the retrospective assessment of alcohol intake (18). The researcher was blind to the imaging data during these biweekly visits. In accordance with procedures for standard clinical trials (8, 19), relapse was defined for the male patients as the consumption of more than 60 g of alcohol during the assessment period. Random alcohol blood and breath tests were performed, and plasma levels of carbohydrate-deficient transferrin and γ-glutamyltransferase were evaluated. In addition, relatives or members of patient self-help groups were contacted to verify the patients' abstinence.

Correlation of Dopamine Synthesis Capacity With Alcohol Craving

We used PET and [^{18}F]DOPA to reveal the capacity for dopamine synthesis in living brain by calculating the net blood-brain clearance (20, 21). All subjects were given carbidopa (2.5 mg/kg of body weight) orally 60 minutes before scanning to block extracerebral dopa decarboxylase activity. Subjects reclined on the scanning bed with eyes closed and the head positioned within the aperture of the ECAT EXACT PET scanner (Siemens/CTI, Knoxville, Tenn.) operating in three-dimensional mode. To correct for tissue attenuation, transmission scans were acquired with a ^{68}germanium rod source before [^{18}F]DOPA injection. A dynamic emission recording consisting of 28 frames (four 1-minute, three 2-minute, three 3-minute, 15 5-minute, and three 10-minute frames) lasting 120 minutes was initiated after intravenous administration of a mean of 198 MBq (SD=38) of [^{18}F]DOPA. Arterial blood samples were collected at intervals during the emission recording, and the total radioactivity concentration in the plasma samples was measured with a well counter cross-calibrated to the PET. The fraction of untransformed [^{18}F]DOPA in plasma was measured by high-performance liquid chromatography at selected time points, and the continuous arterial [^{18}F]DOPA input function was calculated by biexponential fitting of the measured fractions (22). On the basis of the multiple-time graphical analysis (23, 24), the net influx of [^{18}F]DOPA from plasma to brain (K_{in}^{app}) (ml/[g × min]) was calculated voxel-wise by linear graphical analysis, after subtraction of the radioactivity measured in the cerebellum, and by using frames recorded in the interval 20–70 minutes after the injection (24).

Summed early emission frames (2–8 minutes) were coregistered to individual T_1-weighted magnetic resonance (MR) images of the brain and normalized to Montreal Neurological Institute (MNI) standard stereotaxic space by using an automated coregistration procedure and a fine 12-parameter affine transformation. During the subsequent analysis, the MNI coordinates were transformed to Talairach coordinates (25). After careful inspection of the PET-to-MR registrations, the individual net blood-brain clearance maps were resampled by using the calculated transformation parameters and then smoothed with a Gaussian filter with isotropic 12-mm full width at half maximum before further statistical analysis with SPM 99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College, London).

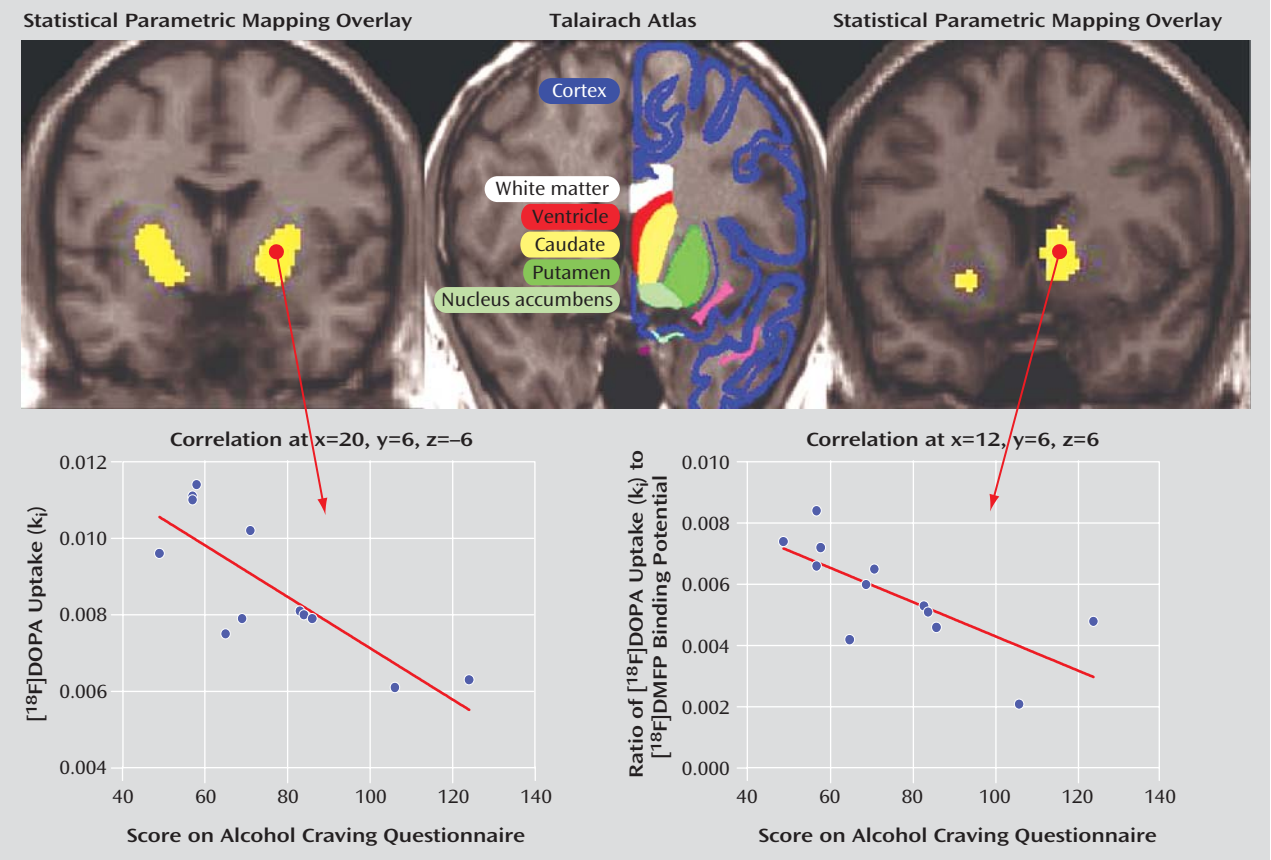
Dopamine $D_{2/3}$ Receptor Availability Measured by PET

Study procedures have been described in detail elsewhere (12, 26). In brief, we used PET to measure the uptake of the benzamide radioligand [^{18}F]DMFP, which binds with high selectivity to D_2 and D_3 dopamine receptors. Dynamic PET data consisting of 28 time frames (four 1-minute, three 2-minute, three 3-minute, 15 5-minute, and three 10-minute frames) were recorded with the same ECAT EXACT PET scanner after administration of a mean of 194 MBq (SD=27) of [^{18}F]DMFP (specific activity at time of injection: mean=267 GBq/μmol (SD=283); injected tracer mass <1 μmol). A simplified reference tissue model using the cerebellum as a dopamine receptor-free reference region was fitted to the dynamic PET data, which yielded parametric images of the binding potential (27), corresponding to the ratio of B_{max} (the total concentration of specific binding sites) to the apparent K_d (the equilibrium dissociation constant), i.e., the K_d observed in the presence of competition from endogenous dopamine.

Statistical Analysis

A categorical comparison between the two groups (alcoholic patients versus comparison subjects) was performed with statistical parametric mapping (SPM 99) (28). We tested the hypothesis that the net influx of [^{18}F]DOPA to the striatum is lower in al-

FIGURE 1. Correlation of Alcohol Craving With Striatal Dopamine Production and Striatal [^{18}F]DOPA Influx Normalized to Local Dopamine $D_{2/3}$ Receptor Availability[a]



[a] Craving for alcohol was significantly and negatively correlated with [^{18}F]fluoro-L-dopa ([^{18}F]DOPA) net influx (net blood-brain clearance) and with the ratio of net blood-brain clearance to the [^{18}F]desmethoxyfallypride ([^{18}F]DMFP) binding potential ratio in the bilateral striatum of alcoholic patients after 5 weeks of abstinence, but not in healthy comparison subjects. For illustrative purposes, a significance threshold of $p<0.01$ was applied. Upper left: Coronal images showing correlation of [^{18}F]DOPA net influx (net blood-brain clearance) and acute alcohol craving, as measured by the Alcohol Craving Questionnaire. Upper center: The areas of significant correlation correspond well to the (ventral) putamen (as identified in the standardized anatomic brain atlas of Talairach and Tournoux [25]). Upper right: Coronal images showing correlation of alcohol craving with the ratio of the magnitude of [^{18}F]DOPA net influx to the magnitude of [^{18}F]DMFP binding potential in the same voxel. Lower left: The scatter plot shows the correlation between [^{18}F]DOPA net influx in the right putamen and acute alcohol craving ($r=–0.80$, $N=12$, $p<0.05$, corrected for the bilateral striatal voxel of interest). Lower right: The scatter plot shows the correlation between acute alcohol craving and the magnitude of the ratio of [^{18}F]DOPA net influx to the magnitude of [^{18}F]DMFP binding potential in the same voxel in the right putamen ($r=–0.73$, $N=12$, $p<0.05$, corrected for the bilateral striatal voxel of interest).

coholic patients, compared to healthy comparison subjects. A linear regression analysis was performed with SPM 99 to test the hypothesis that [^{18}F]DOPA influx in the striatum correlated inversely with the severity of alcohol craving. Because the comparison subjects reported almost no alcohol craving, the correlations were computed separately for the alcoholic patients and the comparison subjects. The input matrices in this analysis were the PET parametric images of the net blood-brain clearance for each voxel and the alcohol craving score as a covariate. The SPM approach can entail a global search without an a priori hypothesis about spatial localization of between-group differences or covariances. However, in the present study, on the basis of a prior hypothesis, we restricted the search volume to the striatum (8.5 cm^3), with the threshold for significance set at $p<0.05$. Pearson's linear correlation coefficient was used to test the hypothesis that the severity of alcohol craving was significantly correlated with the amount of subsequent alcohol intake during the 6-month follow-up period. Bonferroni's correction was applied for multiple testing of the three previously mentioned a priori hypotheses.

In the exploratory part of the present analysis, we intended to obtain information on the relationship between [^{18}F]DOPA influx and the availability of dopamine $D_{2/3}$ receptors in the same subjects. To do so, we calculated the ratio between [^{18}F]DOPA net blood-brain clearance and [^{18}F]DMFP binding potential, and used SPM to test for an inverse correlation between the magnitude of this ratio and the severity of alcohol craving as measured with the Alcohol Craving Questionnaire in the patient group. We also explored whether the main outcome variables (severity of alcohol craving, mean net blood-brain clearance in the striatum) correlated with potentially confounding variables such as smoking, age at onset of alcohol dependence, severity of alcoholism, lifetime alcohol intake, and length of time between last drink and scanning. In this exploratory analysis, p values are presented only for illustrative reasons.

Results

Contrary to our hypothesis [^{18}F]DOPA net influx did not differ between the alcoholic patients and the healthy

comparison subjects (p>0.05, corrected for the striatal voxel of interest). However, as hypothesized, the severity of alcohol craving measured with the Alcohol Craving Questionnaire was significantly and negatively correlated with [^{18}F]DOPA net influx in the bilateral putamen (right: x=20, y=6, z=–6 [Talairach coordinates]; r=–0.80, N=12) (left: x=–22, y=8, z=–10; r=–0.80, N=12) (p<0.05, corrected for striatal voxel of interest and after Bonferroni's correction for multiple testing). For illustrative purposes, only the scatter plot of the right side is shown in Figure 1 (lower left).

Although [^{18}F]DOPA can also label cortical catecholamine fibers, there was no correlation between alcohol craving and the magnitude of net blood-brain clearance in the cerebral cortex. In the healthy comparison subjects, no significant correlation was observed between alcohol craving and the magnitude of net blood-brain clearance. Five alcoholic patients remained abstinent and seven relapsed during the 6-month follow-up period (mean alcohol intake=14.5 kg, SD=22.8). As hypothesized, the severity of alcohol craving measured with the Alcohol Craving Questionnaire was positively and significantly correlated with subsequent alcohol intake during the 6-month observation period (Pearson's r=0.76, N=7, p<0.05, after Bonferroni's correction for multiple testing).

As previously reported (12), dopamine $D_{2/3}$ receptor availability was significantly lower in the alcoholic patients than in the healthy comparison subjects in the bilateral putamen and adjacent ventral striatum (right: x=20, y=12, z=–6 [Talairach coordinates]; t=2.39, df=9) (left: x=–28, y=10, z=–8; t=2.21, df=9) (p<0.05, corrected for the striatal voxel of interest). No significant correlation was found between [^{18}F]DOPA net blood-brain clearance and [^{18}F]DMFP binding potential. [^{18}F]DOPA net influx per voxel was normalized to the availability of dopamine $D_{2/3}$ receptors in the same voxel (net blood-brain clearance/binding potential ratio). In the alcoholic patients, we observed a negative correlation between the severity of alcohol craving and the magnitude of this ratio throughout the bilateral putamen and the right ventral striatum and caudate (right: x=12, y=6, z=6 [Talairach coordinates of the voxel with maximum significance]; r=–0.73, N=12) (left: x=–22, y=10, z=–8; r=–0.68, N=12) (p<0.05 corrected for striatal voxel of interest). For illustrative purposes, only the scatter plot for the right side is shown in Figure 1 (lower right). No significant correlation between this ratio and alcohol craving was found in the healthy men.

We did not observe significant correlations between the main outcome variables (severity of alcohol craving, mean [^{18}F]DOPA net influx in the striatum) and potentially confounding variables, such as smoking, age at onset of alcohol dependence, severity of alcoholism, lifetime alcohol intake, and length of time between last alcohol intake and scanning (Pearson's r range=–0.44 to 0.01, N=12, all p>0.15).

Discussion

This study shows that in abstinent alcoholic patients, striatal [^{18}F]DOPA net influx in the striatum correlated inversely with the severity of alcohol craving as assessed with the Alcohol Craving Questionnaire (17). Alcohol is known to stimulate dopamine release in the striatum in humans and experimental animals (1, 3, 5, 29), and alcohol consumption may be specifically rewarding in subjects with a striatal dopamine deficit. After detoxification, synaptic dopamine release was found to decrease rapidly in microdialysis studies of experimental animals (6). Thus, we hypothesized that alcoholic patients with a persistent striatal dopamine deficit may experience stronger cravings for alcohol. In support of this hypothesis, the results of our study suggest that low capacity for dopamine production in nigrostriatal fibers predicts severity of alcohol craving in detoxified alcoholic patients. However, contrary to our hypothesis, we did not observe a significant group difference in [^{18}F]DOPA net influx between detoxified alcoholic patients and healthy comparison subjects. This observation indicates that dopamine synthesis capacity per se may not be affected in detoxified alcoholic patients. Rather, a low level of dopamine synthesis may contribute to alcohol craving if it coincides with other factors, such as a local reduction in the availability of dopamine $D_{2/3}$ receptors.

In a previous study of striatal dopamine $D_{2/3}$ receptor availability in the same group of alcoholic patients, we observed a significant negative correlation between alcohol craving and the availability of dopamine $D_{2/3}$ receptors, specifically in the ventral striatum (12). Therefore, in the present study we used SPM analysis to search for regions in which the [^{18}F]DOPA net influx, relative to the local availability of dopamine $D_{2/3}$ receptors, correlated with the severity of alcohol craving in abstinent alcoholic patients. In accordance with the prediction that the relationship between dopamine synthesis capacity and $D_{2/3}$ receptor availability is altered in alcoholic patients, we observed a negative correlation between alcohol craving and the magnitude of the net blood-brain clearance/binding potential ratio, indicating that the alcoholic patients who exhibited the most severe craving had a low capacity for dopamine synthesis, relative to the number of available $D_{2/3}$ receptors in the putamen and adjacent ventral striatum.

However, in the context of the receptor competition binding model (30), low availability of binding sites for benzamide radioligands could indicate high basal occupancy by dopamine. Indeed, the availability of $D_{2/3}$ binding sites in this group of detoxified alcoholic patients was lower than in age-matched healthy men. Given the present finding of reduced dopamine synthesis capacity in alcoholic patients, we suggest that the lower availability of dopamine receptors cannot readily be attributed to increased occupancy by dopamine. However, the effects of occupancy on the magnitude of binding potential cannot

be ascertained from single PET studies. Although the ventral striatum/nucleus accumbens is most strongly linked to the rewarding properties of drugs (5, 9, 29), we found the highest correlation between the net blood-brain clearance/binding potential ratio and alcohol craving in the dorsal striatum. Although this observation must be qualified by the spatial resolution of the tomography, the results of some previous studies suggest that dopamine release in the dorsal striatum is involved in habit formation, which may play a preeminent role in stereotypical drug and alcohol intake and relapse (31, 32).

The relevance of alcohol craving for the relapse risk of detoxified alcoholic patients remains a topic of debate. Some studies suggested that relapse is triggered by habit formation and automatic drug intake rather than by conscious drug-craving (32, 33). However, in the present study, conscious alcohol craving, as measured by the Alcohol Craving Questionnaire, was significantly and positively correlated with the subsequent amount of alcohol intake during the 6-month follow-up period, whereas no significant correlations were found between subsequent alcohol intake and the severity of alcoholism (15), lifetime alcohol intake (16), or the number of cigarettes smoked per day. This observation supports the hypothesis that alcohol craving is associated with the risk of relapse in detoxified alcoholic patients (5, 9, 34). Furthermore, we found that low [^{18}F]DOPA net influx, which was correlated with craving, served as an independent predictor of relapse in the present group of alcoholic patients. In conjunction with our earlier study of [^{18}F]DMFP binding in the same subjects, we conclude that an insufficiency of dopamine transmission in the striatum underlies the propensity to relapse.

Some potential limitations of the study should be considered. The patients lie in the scanner with their eyes closed, and although they were instructed to relax, some of them may have experienced various degrees of alcohol craving, which might have interacted with the PET measures. Moreover, the observed correlations between [^{18}F]DOPA net influx and craving do not imply causation. The nature of the interaction between striatal dopamine synthesis capacity, $D_{2/3}$ receptor availability, and alcohol craving might be elucidated in PET studies in which the sensitivity of dopamine receptor availability to pharmacologically evoked dopamine release is compared in abstinent alcoholic patients and healthy comparison subjects.

In conclusion, the results of this study show that alcohol craving is associated with high risk of relapse and a low level of striatal [^{18}F]DOPA net influx, an index of dopamine synthesis capacity. In this context, we speculate that alcohol-induced dopamine release during relapse may compensate for a relative deficit in dopamine neurotransmission. The [^{18}F]DOPA net influx normalized to the local availability of dopamine $D_{2/3}$ receptors correlated negatively with alcohol craving in abstinent alcoholic patients. Thus, the full spectrum of perturbed dopamine transmission in alcoholism reflects presynaptic changes in dopamine synthesis and postsynaptic changes in receptor availability, assessed by combined [^{18}F]DOPA/[^{18}F]DMFP PET studies. The results of our study support the hypothesis that a deficit in striatal dopamine neurotransmission contributes to alcohol craving.

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