

Decreased Prefrontal Cortical Dopamine Transmission in Alcoholism

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Objective: Basic studies have demonstrated that optimal levels of prefrontal cortical dopamine are critical to various executive functions such as working memory, attention, inhibitory control, and risk/reward decisions, all of which are impaired in addictive disorders such as alcoholism. Based on this and imaging studies of alcoholism that have demonstrated less dopamine in the striatum, the authors hypothesized decreased dopamine transmission in the prefrontal cortex in persons with alcohol dependence.

Method: To test this hypothesis, amphetamine and [^{11}C]FLB 457 positron emission tomography were used to measure cortical dopamine transmission in 21 recently abstinent persons with alcohol dependence and 21 matched healthy comparison subjects. [^{11}C]FLB 457 binding potential, specific compared to nondisplaceable uptake (BP_{ND}), was measured in subjects with kinetic analysis

using the arterial input function both before and after 0.5 mg kg^{-1} of *d*-amphetamine.

Results: Amphetamine-induced displacement of [^{11}C]FLB 457 binding potential ($\Delta\text{BP}_{\text{ND}}$) was significantly smaller in the cortical regions in the alcohol-dependent group compared with the healthy comparison group. Cortical regions that demonstrated lower dopamine transmission in the alcohol-dependent group included the dorsolateral prefrontal cortex, medial prefrontal cortex, orbital frontal cortex, temporal cortex, and medial temporal lobe.

Conclusions: The results of this study, for the first time, unambiguously demonstrate decreased dopamine transmission in the cortex in alcoholism. Further research is necessary to understand the clinical relevance of decreased cortical dopamine as to whether it is related to impaired executive function, relapse, and outcome in alcoholism.

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Prefrontal cortical dopamine modulates executive functions such as attention, working memory, and risk/reward decision making (1, 2), all of which are impaired in alcoholism (3–6). Based on this, it is tempting to postulate decreased dopamine transmission in the prefrontal cortex in alcoholism. However, the preclinical literature on this topic is mixed and inconclusive, with studies suggesting increased (7), decreased (8, 9), and no changes (10–12) in prefrontal cortical dopamine transmission in alcoholism. Nevertheless, the ability of prefrontal cortical dopamine to modulate alcohol consumption has been demonstrated in microinjection studies using dopamine $\text{D}_{2/3}$ antagonist and agonist drugs (13, 14). In humans, the displacement of the $\text{D}_{2/3}$ specific positron emission tomography (PET) radiotracer [^{11}C]raclopride following an acute amphetamine (or methylphenidate) challenge has been validated as a noninvasive measure of the change in extracellular dopamine concentration induced by the challenge (15). Using this approach, two research groups have reported decreased striatal dopamine transmission in individuals with alcohol dependence compared with healthy comparison subjects (16, 17). A limitation of these studies was that measurements of dopamine transmission

were restricted to the striatum and its subdivisions (i.e., the caudate, putamen, and ventral striatum). Studies were limited to the striatum because [^{11}C]raclopride does not provide sufficient signal-to-noise ratio to quantify $\text{D}_{2/3}$ receptors in extrastriatal areas, such as the cortex, where the concentration of $\text{D}_{2/3}$ receptors is much lower than it is in the striatum. Thus, no previous studies, to our knowledge, have reported on the *in vivo* status of dopamine in the prefrontal cortex in alcoholism.

We previously validated the high-affinity $\text{D}_{2/3}$ PET radioligand [^{11}C]FLB 457 as a tool to image amphetamine-induced dopamine transmission in the human cortex (18). The results of our validation studies demonstrate 1) low test-retest variability ($\leq 15\%$) for [^{11}C]FLB 457 binding potential, specific compared to nondisplaceable uptake (BP_{ND}), under both baseline and postamphetamine conditions (19, 20); 2) no carryover mass-induced decrease in BP_{ND} in the imaging paradigm used to measure dopamine (19); 3) a relatively small fraction of $\text{D}_{2/3}$ receptor specific binding for [^{11}C]FLB 457 in the cerebellar reference region compared with cortical regions of interest (21); and 4) a linear relationship between the amphetamine-induced decreases in [^{11}C]FLB 457 BP_{ND} and increases in

This article is featured in this month's AJP **Audio** and is discussed in an **Editorial** by Dr. Smith (p. 814)

extracellular dopamine as measured with microdialysis (22). In the present study, we used amphetamine and [^{11}C]FLB 457 PET to contrast cortical dopamine transmission in 21 recently abstinent persons with alcohol dependence and 21 healthy comparison subjects matched on age, gender, race, and nicotine smoking status.

Method

Participants

Seventy-seven individuals with alcohol dependence and 36 healthy comparison subjects were enrolled in the study, and 21 individuals from each group completed the study. The study was approved by the University of Pittsburgh Institutional Review Board and the Radioactive Drug Research Committee. All participants provided written, informed consent. The alcohol-dependent and healthy comparison groups were largely recruited through advertisements displayed at local community centers, on buses, in newspapers, and on websites. Additionally, addiction medicine clinics and hospital emergency departments in the community also referred alcohol-dependent patients. Study criteria for inclusion in the alcohol-dependent group were 1) male or female aged 18–40 years of any ethnic/racial origin; 2) fulfillment of DSM-IV criteria for alcohol dependence as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders; 3) no current or past DSM-IV axis I disorder other than alcohol abuse or dependence, including abuse of or dependence on other recreational drugs (nicotine dependence was allowed); 4) no current use of cocaine, opiates, cannabis, sedative-hypnotics, amphetamines, 3,4-methylenedioxy-*N*-methylamphetamine, or phencyclidine (as confirmed by urine drug screen at the study screening); 5) not currently taking any prescription or over-the-counter medications; 6) no current or past chronic medical or neurological illnesses (including glaucoma, seizure disorders, a focal finding on MRI such as stroke or tumor, chronic obstructive pulmonary disease or respiratory disease, renal problems, and liver problems) as assessed by a complete physical examination and laboratory examination; 7) no resting systolic blood pressure >140 mm Hg and no diastolic blood pressure >90 mm Hg; 8) no more than one risk factor for coronary artery disease (e.g., smoking, obesity, cholesterol >240 mg dl $^{-1}$, sedentary lifestyle, etc.); 9) no first-degree relative with a psychotic or mood disorder; 10) not currently pregnant; 11) no history of radioactivity exposure from nuclear medicine studies or occupation; and 12) no metallic objects in the body that are contraindicated for MRI.

Participants in the alcohol-dependent group completed a minimum of 14 days of outpatient abstinence monitored with witnessed urine toxicology. They were monitored for alcohol and recreational drug use with urine alcohol metabolites (ethyl glucuronide and ethyl sulfate) and urine drug screens three times per week for 2 consecutive weeks. Since alcohol metabolites and common drugs of abuse can be detected for 2–3 days after use, individuals in this group were informed that they should not use alcohol or street drugs for the 14 days before the PET study. In order to promote abstinence from alcohol during this 2-week period, they were paid \$75.00 for each urine sample that was negative for ethyl glucuronide and ethyl sulfate. They were scheduled for the PET scans after successful completion of the abstinence monitoring protocol. Individuals who tested positive for ethyl glucuronide and ethyl sulfate were offered up to three attempts to restart the abstinence monitoring protocol. This abstinence monitoring protocol ensured that all persons in the alcohol-dependent group were abstinent for a minimum of

2 weeks before the PET scan. This group was also monitored for alcohol withdrawal signs and symptoms three times during the first week of abstinence using the Clinical Institute Withdrawal Assessment for Alcohol Scale (23). Those who were at risk of severe withdrawal (i.e., scored >19 on the Clinical Institute Withdrawal Assessment for Alcohol Scale and had a history of alcohol withdrawal seizures or delirium tremens) were excluded from the research protocol. The severity of alcohol dependence was assessed with the Michigan Alcoholism Screening Test (24) and the Alcohol Dependence Scale (25).

Healthy comparison subjects, matched for age, gender, ethnicity, and smoking status, had no past or present neurological or psychiatric illnesses, including substance abuse (as confirmed by urine drug screen, at both the study screening and the day of the PET scan). Both the healthy comparison and alcohol-dependent groups underwent the PET scans as outpatients. Following the completion of the PET scans, those in the alcohol-dependent group were scheduled for a follow-up visit, during which they were debriefed of the risks of alcohol abuse and provided with a referral for outpatient treatment.

Image Acquisition and Analysis

Following a structural MRI, participants underwent a baseline and a postamphetamine [^{11}C]FLB 457 PET scan in the same experimental session using procedures previously described (18).

Briefly, [^{11}C]FLB 457 was synthesized using the methodology reported by Halldin et al. (26). PET imaging sessions were conducted with the ECAT EXACT HR Plus camera (CTI-Siemens, Munich, Germany). Following a transmission scan, participants received an intravenous bolus injection of [^{11}C]FLB 457, and emission data were collected for 90 minutes. Arterial blood samples were collected to measure the plasma free fraction (f_p) for [^{11}C]FLB 457 and to derive a metabolite-corrected arterial input function for modeling using methods previously described (18). The maximum injected mass for [^{11}C]FLB 457 was restricted to 0.6 μg (27). The postamphetamine [^{11}C]FLB 457 scan was performed 3 hours after the administration of 0.5 mg kg $^{-1}$ of oral *d*-amphetamine. During this scan, amphetamine blood levels were measured in three arterial samples drawn at 0 minutes, 45 minutes, and 90 minutes and analyzed using methods described by Reimer et al. (28).

PET data were reconstructed and processed with the image analysis software MEDx (Sensor Systems, Sterling, Va.) and SPM2 (www.fil.ion.ucl.ac.uk/spm) as previously described (18). Frame-to-frame motion correction for head movement and MR-PET image alignment were performed using a mutual information algorithm implemented in SPM2. MRI segmentation was performed using the automated segmentation tool in Functional MRI of the Brain Software Library (29). Cortical (medial temporal lobe, dorsolateral prefrontal cortex, orbital frontal cortex, medial prefrontal cortex, anterior cingulate cortex, temporal cortex, parietal cortex, and occipital cortex) and subcortical (midbrain and cerebellum) regions of interest were defined on the MRI using a segmentation-based and direct identification method previously described (19, 30, 31). Regional volumes and time activity curves were then generated in MEDx as outlined by Abi-Dargham et al. (30, 31). Primary analysis included the eight cortical regions that had been validated in our previous [^{11}C]FLB 457 human studies (18–21). Secondary analysis included the midbrain as a region of interest to test whether there is convergence between the midbrain dopamine cells and terminal fields. Derivation of [^{11}C]FLB 457 volumes of distribution expressed relative to total plasma ligand concentration (V_T) in the regions of interest ($V_{T\text{ ROI}}$) and cerebellum ($V_{T\text{ CER}}$) was performed using a two-tissue compartment kinetic analysis with the arterial input function we previously described (18).

PET outcome variables are defined in accordance to the consensus nomenclature for in vivo imaging of reversibly binding radioligands (32). The $D_{2/3}$ receptor availability at the baseline and postamphetamine conditions was estimated using BP_{ND} , which was derived as follows:

$$BP_{ND} = \frac{V_{T\ ROI} - V_{T\ CER}}{V_{T\ CER}} = f_{ND} * \frac{B_{avail}}{K_D} \quad \text{Equation 1}$$

In this equation, f_{ND} (which equals $f_P/V_{T\ CER}$) is the free fraction of [^{11}C]FLB 457 in the nondisplaceable compartment, B_{avail} is the density of $D_{2/3}$ receptors (nmol L^{-1}) available to bind to [^{11}C]FLB 457 in vivo, and K_D is the in vivo equilibrium dissociation constant of [^{11}C]FLB 457 (nmol L^{-1}).

The amphetamine-induced change in BP_{ND} (ΔBP_{ND}) was calculated as the difference between BP_{ND} measured in the postamphetamine condition ($BP_{ND\ AMPH}$) and BP_{ND} measured in the baseline condition ($BP_{ND\ BASE}$) and expressed as a percentage of $BP_{ND\ BASE}$ as follows:

$$\Delta BP_{ND} = 100 * \frac{BP_{ND\ AMPH} - BP_{ND\ BASE}}{BP_{ND\ BASE}} \quad \text{Equation 2}$$

Finally, because our validation work with [^{11}C]FLB 457 demonstrated $D_{2/3}$ specific binding in the cerebellum, there was concern that any amphetamine-induced change in $V_{T\ CER}$ could bias the dopamine-release outcome measure, ΔBP_{ND} (BP_{ND} is dependent on $V_{T\ CER}$; see Equation 1). Therefore, to arrive at a dopamine-release measurement in the cortex (i.e., $D_{2/3}$ receptor occupancy following amphetamine administration) that is independent of $V_{T\ CER}$, we analyzed the baseline and postamphetamine V_T values from the eight cortical regions of interest with Lassen plots as described by Cunningham et al. (33). Briefly, the equation for the line [$y=mx+b$], where $y=[V_{T\ BASELINE}-V_{T\ AMPHETAMINE}]$ and $x=V_{T\ BASELINE}$, produced a linear relationship with the slope of line equal to the receptor occupancy (m). This approach assumed that there is uniform receptor occupancy across the cortical regions.

Statistical Analysis

Comparisons between scan conditions (baseline and postamphetamine) were performed with paired t tests. Comparisons between groups (alcohol-dependent and healthy comparison subjects) were performed with unpaired t tests (regions-of-interest level) and repeated-measures of analysis of variance (ANOVA) (amphetamine blood levels). Furthermore, to test for a global effect of diagnosis (alcohol-dependent and healthy comparison) on baseline cortical BP_{ND} and ΔBP_{ND} , a linear mixed-model analysis was performed with cortical regions of interest as a repeated measure and diagnostic group as the fixed factor (IBM SPSS Statistics, IBM, Armonk, N.Y.). Relationships between PET data and clinical characteristics (years of drinking, amount of drinks consumed per day, and Alcohol Dependence Scale and Michigan Alcohol Screening Test scores) were assessed using the Pearson product-moment correlation coefficient. A two-tailed probability (p) value <0.05 was selected as the significance level for all analyses. A false discovery rate correction with an alpha set at 0.05 was applied to correct for multiple comparisons in the regions of interest (34).

Results

Twenty-one individuals with alcohol dependence were matched with 21 healthy comparison subjects on age, gender, ethnicity, and smoking status (including the number of cigarettes smoked per day rounded to the nearest one-half pack, i.e., 10 cigarettes). The demographic variables for both

TABLE 1. Demographic and Clinical Parameters for Healthy Comparison and Alcohol-Dependent Subjects

Characteristic	Healthy Comparison Group (N=21)		Alcohol-Dependent Group (N=21)	
	N	%	N	%
Gender				
Male	16	76.2	16	76.2
Female	5	23.8	5	23.8
Ethnicity				
African American	2	9.5	4	19.0
Asian	2	9.5	0	0.0
Caucasian	17	81.0	17	81.0
Smoking status				
Yes	12	57.1	12	57.1
No	9	42.9	9	42.9
Positive family history for alcoholism	0	0.0	18	85.7
	Mean	SD	Mean	SD
Age (years)	28	4	28	5
Weight (kg)	74	12	77	14
Duration of abuse (years)			11	6
Alcohol frequency (days per week)			5.7	1.5
Alcohol amount (standard number of drinks per day)			13	5
Michigan Alcohol Screening Test score (range: 0–22)			13	4
Alcohol Dependence Scale score (range: 0–47)			21	6
Abstinence before scans (days)			33	18

groups and the measures of alcohol use in the alcohol-dependent group are summarized in Table 1.

Scan Parameters

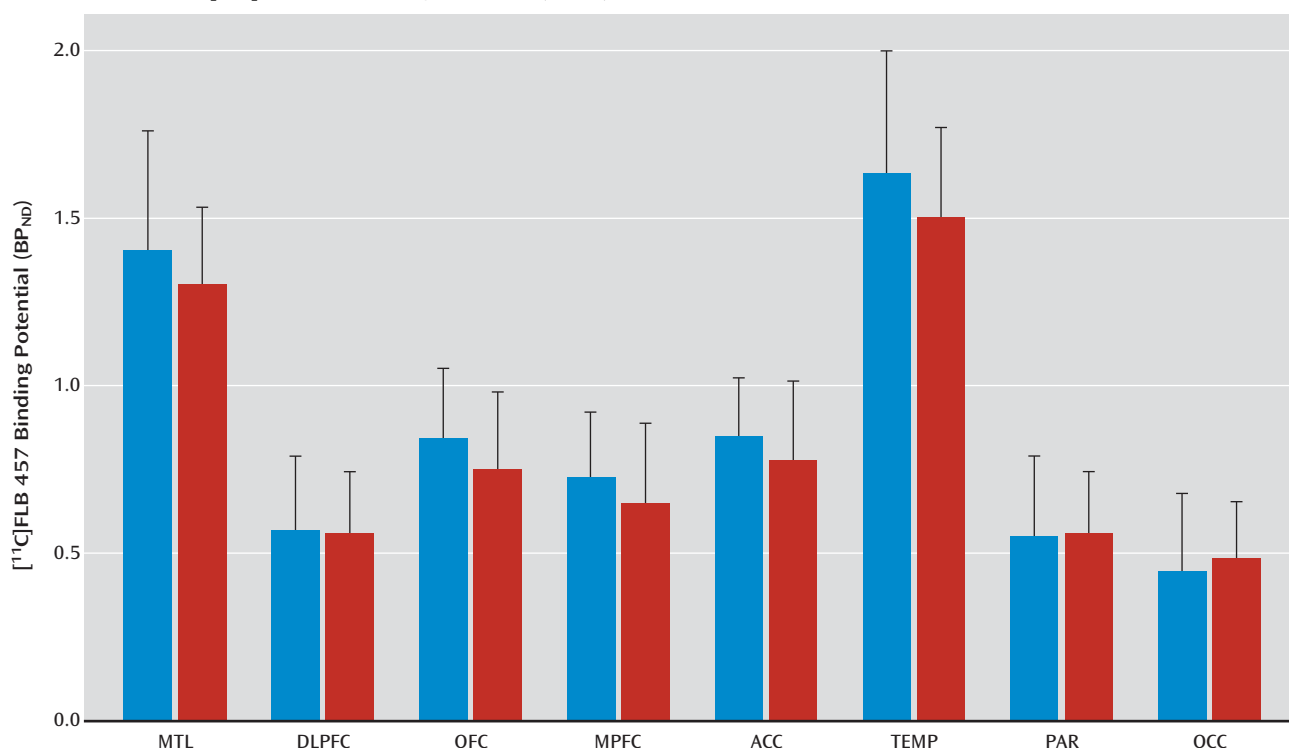
The [^{11}C]FLB 457 scan parameters for the healthy comparison and alcohol-dependent groups under baseline and postamphetamine conditions are presented in Table 2. No significant differences between the baseline and postamphetamine conditions were observed in any of these scan parameters in either group. Notably, there was no significant change in $V_{T\ CER}$ following amphetamine administration in both groups ($\Delta V_{T\ CER}$: healthy comparison = -2.5% [$SD=15.1$]; alcohol-dependent = -0.9% [$SD=10.8$]; $t=0.41$, $df=40$, $p=0.68$). This justified the use of ΔBP_{ND} to contrast differences in amphetamine-induced dopamine transmission between the two groups (see Equation 1, also see reference 35).

The amphetamine blood levels measured at 0, 45, and 90 minutes during the postamphetamine [^{11}C]FLB 457 scan in the healthy comparison group (80 ng mL^{-1} [$SD=10$], 73 ng mL^{-1} [$SD=9$], and 70 ng mL^{-1} [$SD=10$]) were not significantly different from the amphetamine levels measured in the alcohol-dependent group (75 ng mL^{-1} [$SD=8$], 69 ng mL^{-1} [$SD=7$], and 66 ng mL^{-1} [$SD=7$]; repeated measures of ANOVA, effect of diagnosis: $F=3.08$, $df=1$, 40, $p=0.09$; effect of time: $F=57.20$, $df=2$, 39,

TABLE 2. [^{11}C]FLB 457 Positron Emission Tomography Scan Parameters^a

Group and Condition	Injected Dose (mCi)		Specific Activity (Ci mmol ⁻¹)		Injected Mass (μg)		Free Fraction in Plasma (%)		Nondisplaceable Volume of Distribution (mL cm ⁻³)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Healthy comparison										
Baseline	7.1	1.7	8,891	5,689	0.39	0.17	34.7	5.9	4.27	1.23
Postamphetamine	7.7	1.4	8,741	4,307	0.39	0.13	34.3	5.1	4.04	0.86
Alcohol-dependent										
Baseline	7.6	1.4	11,369	8,871	0.36	0.17	38.9	7.6	4.43	1.01
Postamphetamine	6.8	1.9	6,995	4,736	0.46	0.16	39.3	7.3	4.37	0.97

^a Comparison between scan conditions was performed with paired t tests (statistical significance, $p < 0.05$).

FIGURE 1. Baseline [^{11}C]FLB 457 Binding Potential (BP_{ND}) in Healthy Comparison and Alcohol-Dependent Subjects^a

^a The bar graph shows the lack of difference in $\text{D}_{2/3}$ receptor availability in cortical regions of interest in the alcohol-dependent group (red bars) compared with the healthy comparison group (blue bars). MTL=medial temporal lobe; DLPFC=dorsolateral prefrontal cortex; OFC=orbital frontal cortex; MPFC=medial prefrontal cortex; ACC=anterior cingulate cortex; TEMP=temporal cortex; PAR=parietal cortex; and OCC=occipital cortex.

$p < 0.001$; diagnosis-by-time interaction: $F = 0.07$, $df = 2, 39$, $p = 0.93$).

Regional Volumes

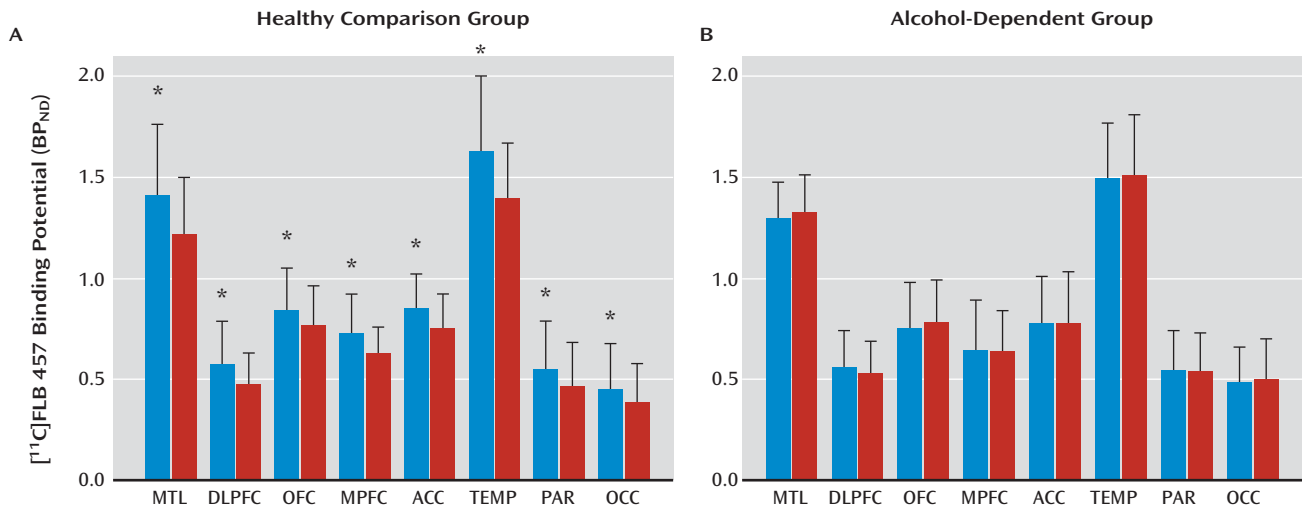
No between-group differences were found in volumes in the cortical regions, midbrain, and cerebellum determined from the MRI scans, suggesting a lack of measurable volumetric changes in alcohol dependence.

Cortex

$\text{D}_{2/3}$ receptor availability (BP_{ND}) under baseline conditions. As shown in Figure 1, no differences in baseline [^{11}C]FLB 457 BP_{ND} were observed in the alcohol-dependent group

compared with the healthy comparison group (linear mixed model: effect of diagnosis: $F = 0.89$, $df = 1, 40$, $p = 0.35$; effect of region: $F = 332.65$, $df = 7, 280$, $p < 0.001$; region-by-diagnosis interaction: $F = 1.71$, $df = 7, 280$, $p = 0.11$). Additionally, unpaired t tests conducted at the level of the individual regions of interest did not show any significant differences between the two groups.

Amphetamine-induced reduction in $\text{D}_{2/3}$ receptor availability ($\Delta\text{BP}_{\text{ND}}$). Amphetamine led to a significant reduction in [^{11}C]FLB 457 BP_{ND} in healthy comparison subjects (Figure 2A) but not in those with alcohol dependence (Figure 2B). The amphetamine-induced Δ [^{11}C]FLB 457 BP_{ND} was significantly lower in the alcohol-dependent group compared with the

FIGURE 2. [^{11}C]FLB 457 Binding Potential (BP_{ND}) at Baseline and Following Amphetamine Administration in Healthy Comparison and Alcohol-Dependent Subjects^a

^a The bar graphs show [^{11}C]FLB 457 BP_{ND} under baseline (blue bars) and postamphetamine (red bars) conditions in the healthy comparison group (panel A) and the alcohol-dependent group (panel B). Amphetamine led to a significant decrease in [^{11}C]FLB 457 BP_{ND} in healthy comparison subjects but not in the alcohol-dependent group ([*] represents $p < 0.05$, following the false discovery rate correction for multiple comparisons). MTL=medial temporal lobe; DLPFC=dorsolateral prefrontal cortex; OFC=orbital frontal cortex; MPFC=medial prefrontal cortex; ACC=anterior cingulate cortex; TEMP=temporal cortex; PAR=parietal cortex; and OCC=occipital cortex.

TABLE 3. Amphetamine-Induced Displacement of [^{11}C]FLB 457 Binding Potential

Region	Healthy Comparison Group (N=21)		Alcohol-Dependent Group (N=21)		Analysis ^a		
	Mean	SD	Mean	SD	t	df	p
Medial temporal lobe	-11.1	16.2	3.1	15.9	2.88	39.98	0.006 ^b
Dorsolateral prefrontal cortex	-13.7	14.7	-3.9	12.7	2.30	39.12	0.03 ^b
Orbital frontal cortex	-8.6	12.4	8.5	18.6	3.50	34.87	0.001 ^b
Medial prefrontal cortex	-11.6	15.1	5.4	27.3	2.48	31.62	0.02 ^b
Anterior cingulate cortex	-9.0	17.7	1.1	19.6	1.75	39.61	0.09
Temporal cortex	-12.2	13.4	0.4	10.4	3.39	37.80	0.002 ^b
Parietal cortex	-11.7	18.6	-1.6	12.2	2.09	34.65	0.04
Occipital cortex	-10.6	19.2	1.3	17.2	2.11	39.52	0.04

^a Analysis was conducted using two-tailed, unpaired t tests.

^b Values were significant following multiple corrections using false discovery rate.

healthy comparison group (linear mixed model: effect of diagnosis: $F=11.03$, $df=1$, 40, $p=0.002$; effect of region: $F=1.99$, $df=7$, 280, $p<0.056$; region-by-diagnosis interaction: $F=0.65$, $df=7$, 280, $p=0.71$). The inclusion of mean amphetamine blood levels as a covariate in the model did not change the significance of the results (linear mixed model: effect of diagnosis: $F=9.44$, $df=1$, 39, $p=0.004$). Unpaired t tests conducted at the level of the individual regions of interest were significant in all of the cortical regions except the anterior cingulate cortex (Table 3). All significant comparisons, except in the parietal and occipital cortices, survived the false discovery rate correction. Furthermore, consistent with the $\Delta\text{BP}_{\text{ND}}$ results, the amphetamine-induced dopamine release occupancy of $\text{D}_{2/3}$ receptors (derived using Lassen plots independent of V_{T} CER) was significantly lower in the alcohol-dependent group compared with the healthy comparison group (healthy comparison=16.0% [SD=15.6]; alcohol-dependent=-1.2% [SD=19.5]; $t=-3.16$, $df=40$, $p=0.003$).

Midbrain

$\text{D}_{2/3}$ receptor availability (BP_{ND}) under baseline conditions. No significant differences were observed in the midbrain [^{11}C]FLB 457 BP_{ND} in the alcohol-dependent group compared with the healthy comparison group (BP_{ND} : healthy comparison=2.50 [SD=0.62]; alcohol-dependent=2.23 [SD=0.38]; $t=-1.67$, $df=40$, $p=0.10$).

Amphetamine-induced reduction in $\text{D}_{2/3}$ receptor availability ($\Delta\text{BP}_{\text{ND}}$). Amphetamine led to a significant reduction in [^{11}C]FLB 457 BP_{ND} in the midbrain in the healthy comparison group (baseline=2.50 [SD=0.62]; postamphetamine=2.09 [SD=0.37]; $t=3.16$, $df=20$, $p=0.005$) but not in the alcohol-dependent group (baseline=2.23 [SD=0.38]; postamphetamine=2.35 [SD=0.63]; $t=-1.49$, $df=20$, $p=0.15$). The amphetamine-induced Δ [^{11}C]FLB 457 BP_{ND} in the midbrain was significantly lower in the alcohol-dependent group compared with the healthy comparison group ($\Delta\text{BP}_{\text{ND}}$:

healthy comparison = -13.2% [$SD=15.2$]; alcohol-dependent = 5.0% [$SD=14.6$]; $t=3.91$, $df=40$, $p=0.0003$). This comparison survived the false discovery rate correction.

Clinical Correlations

Correlation analyses revealed no significant associations between ΔBP_{ND} in the regions of interest (the cortex and midbrain) and mean amphetamine blood levels in the healthy comparison and alcohol-dependent groups. Additionally, there was no significant association between ΔBP_{ND} and any of the clinical measures (alcohol frequency, amount of consumption, duration of abuse, and Michigan Alcohol Screening Test and Alcohol Dependence Scale scores) in the alcohol-dependent group.

Discussion

In this PET study, we found less displacement of [^{11}C]FLB 457 BP_{ND} in the cortex and midbrain after amphetamine administration in recently abstinent alcohol-dependent subjects compared with healthy comparison subjects. In a previous study using PET and microdialysis, it was shown that 1% displacement of [^{11}C]FLB 457 BP_{ND} in the cortex corresponds to a 57% increase in extracellular dopamine concentration (22). Extending this relationship to the present data set (mean ΔBP_{ND} : healthy comparison group: -9% to -14% ; alcohol-dependent group: -4% to $+9\%$ [Table 3]) suggests that cortical dopamine in the healthy comparison and alcohol-dependent subjects increases by approximately 513%–798% and 0%–228%, respectively, following the same dose of amphetamine. This result, for the first time to our knowledge, unequivocally demonstrates that there is decreased dopamine transmission in the cortex in alcoholism. Also for the first time, these data show convergence between the midbrain dopamine cells and terminal fields with respect to decreased dopamine transmission in alcoholism. Such a blunting in mesocortical dopamine transmission in persons with alcohol dependence is consistent with previously reported findings in the nigrostriatal system that includes the limbic-related nucleus accumbens (16). Decreased dopamine transmission in the mesolimbic regions, such as the ventral striatum and medial temporal lobe, likely contributes to anhedonia, amotivation, and decreased reward sensitivity in alcohol dependence. This has led to the conceptualization of alcohol dependence as a reward-deficit disorder with a higher reward threshold for both natural and drug/alcohol reinforcers (36, 37). The fact that there is also less dopamine in the prefrontal cortex, which governs executive functions, is important because it could impair the addicted person's ability to learn and utilize informational/behavioral strategies critical to relapse prevention. This is supported by literature that links prefrontal cortical dopamine with executive functions, such as attention, working memory, behavioral flexibility, and risk/reward decision making, all of which are impaired in addictive disorders such as

alcoholism (3, 38). In a study using a rodent version of the Iowa Gambling Task (a task that measures risk-preference decision making), Floresco and Magyar (38) demonstrated that blocking dopamine transmission in the prefrontal cortex leads to a response decision that fails to integrate the consequences of conditioned punishment. Based on this study, it is tempting to speculate that the failure to incorporate past negative consequences in a decision to drink alcohol during abstinence is related to decreased prefrontal cortical dopamine in alcoholism. If this hypothesis were confirmed, it would support a role for medications that increase prefrontal cortical dopamine to prevent relapse in alcoholism.

Alcohol-induced potentiation of GABA, the major inhibitory transmitter in the brain, inhibits GABA-ergic interneurons in the ventral tegmental area and substantia nigra and leads to increased phasic (or synaptic) dopamine transmission (39, 40). However, chronic and repeated use of alcohol leads to decreased phasic dopamine through adaptations in the tonic (or extracellular) dopamine and glutamatergic systems in the cortico-limbic pathways (for a detailed review, see reference 39). If decreased dopamine transmission is the result of an adaptation in the cortico-limbic circuits, it might be possible to reverse this deficit in persons with alcohol dependence with prolonged abstinence. On the other hand, alcohol-dependent persons also demonstrate signs of inflammation (i.e., greater activated microglia and proinflammatory cytokines) and a reduction of dopamine neuronal markers in the brain (41, 42). Therefore, the possibility of a toxic irreversible loss of dopamine neurons in alcoholism cannot be ruled out. This may explain the persistent and enduring cognitive impairments that have been reported in abstinent persons with alcohol dependence (43). Also unclear is whether decreased dopamine transmission in alcoholism represents a premorbid trait or alcohol-induced state. Future dopamine imaging studies of individuals recovering from alcoholism with prolonged periods of abstinence and nonhuman primates that can be imaged both pre- and postalcohol exposure are necessary to evaluate these issues.

Another interesting observation in the present study is the lack of differences in baseline $D_{2/3}$ receptor binding potential in both the cortex and midbrain in the alcohol-dependent group compared with the healthy comparison group (Figure 1). This is in contrast to previous [^{11}C]raclopride imaging studies that have reported a decrease in $D_{2/3}$ receptor BP_{ND} of approximately 10%–20% in the striatal subdivisions in persons with alcohol dependence (16). The exact reason and physiological relevance for decreased $D_{2/3}$ receptor BP_{ND} in the striatum, but not in the extrastriatal regions, in alcoholism is not clear. Reasons that may have contributed to the inability to detect group differences in our study include diminished power because of greater between-subject variability in cortical $D_{2/3}$ receptor binding potential and/or a more pronounced reduction in baseline dopamine levels (i.e., before amphetamine

stimulation) in the cortex compared with in the striatum in the alcohol-dependent group. PET studies in alcohol-dependent individuals using alpha-methyl-para-tyrosine that can deplete baseline dopamine in the striatal and extrastriatal regions are necessary to further understand this issue.

The strengths of this study are inclusion of relatively young individuals (≤ 40 years old) with mild to moderate alcohol dependence; exclusion of individuals with comorbid medical illness, psychiatric illness, or drug abuse; monitoring of abstinence before imaging; use of a validated imaging paradigm to measure cortical dopamine transmission; use of compartmental modeling with an arterial input function to derive PET outcome measures; ruling out changes in [^{11}C] FLB 457 nonspecific binding (nondisplaceable volume of distribution) as a significant contributor to $\Delta\text{BP}_{\text{ND}}$ in both alcohol-dependent and healthy comparison subjects; and measurement of amphetamine blood levels. However, this study does have some limitations, including the exclusion of older individuals with severe alcohol dependence and no identification of a relationship between $\Delta\text{BP}_{\text{ND}}$ and alcohol measures such as the frequency, amount, severity, and duration of abuse. One possible reason for the failure to demonstrate a relationship between $\Delta\text{BP}_{\text{ND}}$ and alcohol measures is the limited range of values observed in the alcohol abuse measurements (see Table 1). This is likely an unintended consequence of excluding individuals with more severe alcoholism and comorbid disorders. In conclusion, we found decreased dopamine transmission in abstinent persons with alcohol dependence in several of the cortical regions that have been implicated in addiction, including the prefrontal cortex and medial temporal lobe. The results of this study suggest that dopamine dysfunction in alcohol dependence is more widespread than previously conceptualized and not restricted to the striatum. Further studies are necessary to understand the mechanisms that contribute to blunted dopamine transmission and its clinical relevance in alcoholism.

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