

# Alcohol Dependence Is Associated with Blunted Dopamine Transmission in the Ventral Striatum

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**Background:** A decrease in dopamine type 2 receptors ( $D_2$ ) and mesolimbic dopamine transmission predisposes animals to consume alcohol. This study measured  $D_2$  receptors and dopamine transmission in human alcohol-dependent (AD) subjects using positron emission tomography (PET) and [ $^{11}C$ ]raclopride.

**Methods:** Fifteen AD and 15 healthy control (HC) subjects were scanned before and after a psychostimulant challenge (amphetamine .3 mg/kg intravenous). The outcome measures for baseline  $D_2$  receptor availability were binding potential (BP) and the equilibrium partition coefficient ( $V_3$ ). Amphetamine-induced [ $^{11}C$ ]raclopride displacement was measured as the difference in  $V_3$  between the two scans.

**Results:** [ $^{11}C$ ]raclopride BP was significantly reduced by 16.6% in the limbic striatum, 19.2% in the associative striatum, and 21.3% in the sensorimotor striatum in AD subjects compared with HC. The alcohol-dependent subjects showed a blunting of amphetamine-induced dopamine release in the limbic striatum: [ $^{11}C$ ]raclopride displacement was  $-5.2\% \pm 3.6\%$  in AD subjects compared with  $-13.0\% \pm 8.8\%$  in HC. However, no significant difference in [ $^{11}C$ ]raclopride displacement was seen in the associative ( $-4.6\% \pm 5.8\%$  in AD subjects vs.  $-6.7 \pm 5.4\%$  in HC) and sensorimotor ( $-12.3\% \pm 7.3\%$  in AD subjects vs.  $-13.7 \pm 7.5\%$  in HC) subdivisions of the striatum between the two groups.

**Conclusions:** Alcohol dependence was associated with a decrease in  $D_2$  receptors in each striatal subdivision, whereas amphetamine-induced dopamine release was reduced in the limbic striatum only.

**Key Words:** Alcohol dependence, amphetamine, dopamine, mesolimbic, positron emission tomography (PET), ventral striatum

Studies in rodents have reported a decrease in  $D_2$  receptor density in the caudate–putamen and nucleus accumbens of alcohol-preferring rats compared with non-alcohol-preferring rats (McBride et al 1993). Furthermore, lower dopamine concentrations in the mesolimbic terminals have also been measured in alcohol-preferring compared with alcohol-nonpreferring rodents (Murphy et al 1982). These studies suggest that a deficit in mesolimbic dopamine function, either presynaptic (low dopamine levels) or postsynaptic (low  $D_2$  receptor density), may be associated with alcohol dependence. Previous imaging studies in alcohol-dependent human subjects have reported a decrease in  $D_2$  receptor availability (Heinz et al 2004; Hietala et al 1994; Volkow et al 1996, 2002). However, alterations in presynaptic dopamine release have not yet been reported in alcohol-dependent subjects.

The goal of this study was to investigate  $D_2$  receptor availability and presynaptic dopamine function in alcohol dependence.  $D_2$  receptor availability was measured with positron emission tomography (PET) and the  $D_2$  receptor radiotracer [ $^{11}C$ ]raclopride. Presynaptic function was measured as the change in  $D_2$  receptor availability induced by amphetamine. Amphetamine administration results in an acute reduction in [ $^{11}C$ ]raclopride binding, and the magnitude of the decrease correlates with the change in extracellular dopamine (Breier et al 1997). The comparison of the pre- and post-amphetamine

[ $^{11}C$ ]raclopride scans provides a noninvasive measure of changes in dopamine concentration in the human brain.

Subjects underwent two scans with [ $^{11}C$ ]raclopride: baseline and following amphetamine (.3 mg/kg, intravenous). The scans were obtained with a high-resolution PET camera (ECAT EXACT HR+) to measure [ $^{11}C$ ]raclopride binding in the functional subdivisions of the striatum (the limbic striatum (LST), associative striatum (AST), and sensorimotor striatum (SMST; Martinez et al 2003). The hypotheses were that alcohol dependence would be associated with reduced  $D_2$  receptor availability and a deficit in presynaptic dopamine function in the limbic striatum.

## Methods and Materials

### Subjects

The study was approved by the Institutional Review Boards of the New York State Psychiatric Institute and Columbia Presbyterian Medical Center. All subjects provided written informed consent. Inclusion criteria for the alcohol-dependent (AD) subjects were as follows: 1) aged 25–45 years; 2) DSM-IV criteria for alcohol dependence and no other current Axis I disorders (a history of major depression was allowed); 3) no past or current abuse or dependence on other drugs except for nicotine, with a negative urine toxicology (a history of marijuana use was allowed, but no use within the last 6 months); and 4) no significant medical illnesses. Study criteria for healthy control subjects (HC) included 1) aged 25–45 years; 2) no current or past DSM-IV Axis I disorder (except nicotine dependence); 3) no significant medical illness; 4) social drinking not exceeding 7 drinks per week. The alcohol-dependent subjects were recruited from advertisements and the emergency department at Columbia Presbyterian Medical Center. Healthy control subjects were recruited through advertisements.

The timeline follow-back interview (Maisto et al 1982) was used to estimate daily drinking over the 30 days before study entry. Severity of alcoholism was also assessed with the Alcohol Dependence Scale (ADS; Skinner and Allen 1982) and the Michigan Alcoholism Screening Test (MAST; Selzer 1971). Crav-

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ing was assessed with the Obsessive Compulsive Drinking Scale (OCDS; Anton et al 1995), administered at admission and on the day of the PET scans. All AD subjects underwent a 3-week inpatient stay, with a 3- to 5-day detoxification with chlordiazepoxide. The PET scans were performed 2 weeks after completion of detoxification. The AD subjects were allowed to smoke cigarettes and drink caffeine during their hospitalization, except on scan days. The HC subjects participated as outpatients and abstained from cigarette smoking and caffeine on PET scan days.

### Imaging Methods

The [<sup>11</sup>C]raclopride was delivered as a bolus plus constant infusion (Kbol of 105 min) as described previously (Martinez et al 2003; Mawlawi et al 2001). Emission data were collected as eight frames of 5 min each obtained over 40–80 min. Each subject underwent two scans: before and after amphetamine (.3 mg/kg; Martinez et al 2003). The second [<sup>11</sup>C]raclopride administration was initiated 2 min following the amphetamine, and subjects were under cardiovascular monitoring. Four venous samples (collected at 40, 50, 60, and 70 min) were obtained to measure the plasma concentration of [<sup>11</sup>C]raclopride and the free fraction ( $f_1$ ). A sample was obtained at 40 min to measure amphetamine levels. An MRI was acquired on a GE 1.5-T Signa Advantage system.

Image analysis was performed in MEDx (Sensor Systems, Sterling, Virginia) as described previously (Mawlawi et al 2001). The regions of interest (ROIs) were drawn on each individual's MRI and applied to the coregistered PET images. The striatum was divided into five anatomic ROIs and three functional subdivisions (Figure 1) and included the LST, AST, and SMST striatum as described previously (Martinez et al 2003). The ROIs included the ventral striatum (VST), the dorsal caudate rostral to the anterior commissure (AC; precommissural dorsal caudate, preDCA), the dorsal putamen rostral to the AC (precommissural dorsal putamen, preDPU), the caudate caudal to the AC (postcommissural caudate, postCA), and the putamen caudal to the AC (postcommissural putamen, postPU). Based on their cortical and subcortical connections, the ROIs were classified as belonging to the AST (preDCA, preDPU, postCA), the LST (VST), or the SMST (postPU). Activities from left and right regions were averaged.

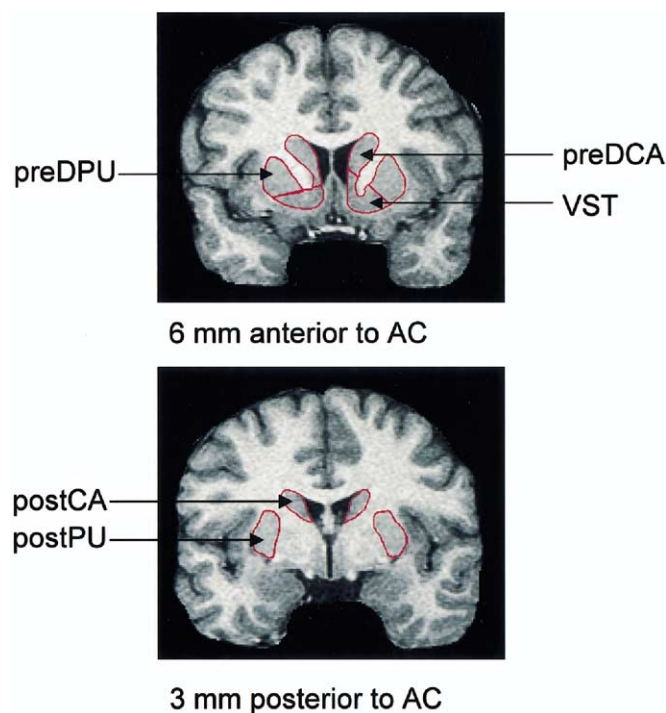
### Derivation of Outcome Measures

Baseline  $D_2$  receptor availability was estimated using the [<sup>11</sup>C]raclopride binding potential (BP) and specific to nonspecific equilibrium partition coefficient ( $V_3''$ ). [<sup>11</sup>C]Raclopride has a similar affinity for the  $D_2$  and  $D_3$  receptors (Sokoloff et al 1990), and  $D_2$  receptors is used to denote both receptors. Both outcome measures were obtained using an equilibrium analysis. The BP and  $V_3''$  for the AST were calculated from the weighted average of the ROI that make up this subdivision (weighted by size of the ROI) and BP and  $V_3''$  for the STR were calculated as the weighted average of all 5 ROIs.

The regional tissue distribution volume ( $V_T$ , mLg<sup>-1</sup>) is defined as the ratio of the ligand concentration in the ROI ( $C_T$ ,  $\mu\text{Ci g}^{-1}$ ) to the concentration of unmetabolized ligand in venous plasma ( $C_P$ ,  $\mu\text{C mL}^{-1}$ ) at equilibrium:

$$V_T = \frac{C_T}{C_P}$$

The concentration of  $D_2$  receptors is negligible in the cerebellum (Hall et al 1994), so that  $V_T$  in the cerebellum ( $V_{T\text{ CER}}$ ) was assumed to be equal to the nonspecific distribution volume ( $V_2$ ). BP can be derived from the difference between  $V_{T\text{ ROI}}$  and  $V_{T\text{ CER}}$ :



**Figure 1.** Striatal subregions drawn on a representative subject's magnetic resonance image. (Top) A coronal plane 6 mm anterior to the plane of the anterior commissure. The regions of interest on this plane include the ventral striatum (VST), the precommissural dorsal caudate (preDCA), and precommissural dorsal putamen (preDPU). (Bottom) A coronal plane 3 mm posterior to the plane of the anterior commissure. The regions of interest on this plane include postcommissural caudate (postCA) and postcommissural putamen (postPU). The regions are then categorized into the limbic (VST), associative (preDCA, preDPU, and postCA), and sensorimotor (postPU) subdivisions.

$$V_{T\text{ ROI}} * V_{T\text{ CER}} = BP = f_1 * \frac{B_{\text{MAX}}}{K_D'}$$

where  $f_1$  is the plasma free fraction,  $B_{\text{max}}$  is the concentration of  $D_2$  receptors (nmol/g of tissue), and  $K_D'$  is the in vivo equilibrium dissociation constant of the radiotracer (nmol/mL of brain water) in the presence of dopamine (Slifstein and Laruelle 2001).

$V_3''$  is the ratio of BP to  $V_{T\text{ CER}}$  and is related to receptor parameters by:

$$\frac{V_{T\text{ STR}} * V_{T\text{ CER}}}{V_{T\text{ CER}}} = V_3'' = f_2 * \frac{B_{\text{MAX}}}{K_D'}$$

where  $f_2$  is the free fraction of free plus nonspecifically bound ligand in brain ( $f_2 = f_1/V_2$ ).

The use of BP for between group comparisons assumes that  $f_1$  is not significantly different between groups, whereas  $V_3''$  assumes that  $f_2$  is not significantly different between groups. In this study,  $f_1$ , BP, and  $V_3''$  were measured to assess the validity of these assumptions.

The reduction in  $D_2$  receptor availability following amphetamine ( $\Delta V_3''$ ) was calculated as the relative reduction in  $V_3''$ :

$$\Delta V_3'' = (V_3 \text{ baseline} - V_3'' \text{ postamphetamine}) / V_3'' \text{ baseline}$$

### Partial Volume Effects Analysis

Because of limitations in PET camera resolution, the activity measured in a given ROI includes activity from adjacent regions,

**Table 1.** Region of Interest Volumes (mm<sup>3</sup>)

Functional Subdivision	Anatomic Subdivision	HC	AD	<i>p</i> <sup>a</sup>
LST	VST	2188 ± 853	2403 ± 755	.47
AST	preDPU	4836 ± 729	4661 ± 559	.47
	preDCA	5609 ± 819	5415 ± 858	.53
	postCA	1744 ± 416	1887 ± 555	.43
SMST	postPU	5685 ± 915	6048 ± 944	.29

Values are mean ± SD, *n* = 15 per groups.

AD, alcohol-dependent subjects; AST, associative striatum; HC, healthy control subjects; LST, limbic striatum; postCA, postcommissural caudate; postPU, postcommissural putamen; preDCA, precommissural dorsal caudate; preDPU, precommissural dorsal putamen; SMST, sensorimotor striatum; VST, ventral striatum.

<sup>a</sup>Unpaired *t* test.

which result in error due to partial volume effects (PVE). The PVE correction was performed as previously described using a full-width at half maximum of 5.1 mm at the center of the field of view (Mawlawi et al 2001). Briefly, the geometric transfer matrix (GTM; Rousset et al 1998) was formed by generating binary image sets of the ROI from each subject's magnetic resonance image, which were realigned to the location of the original PET in the camera field of view. Using this model to correct for PVE, the measured activity in the ROIs can be represented as a weighted average of the true activity in the ROIs and the background. The true activity in each ROI can then be estimated from the measured activity and the GTM.

### Statistical Analysis

Group comparisons were performed with unpaired *t* test. Outcomes related to D<sub>2</sub> receptor availability ([<sup>11</sup>C]raclopride BP, V<sub>3</sub><sup>''</sup>, and ΔV<sub>3</sub><sup>''</sup>) were analyzed by repeated-measures analysis of variance (ANOVA), with the region or subdivision as the repeated measure and group as the cofactor. Relationships between PET data and the clinical characteristics of the AD subjects were analyzed with the Pearson Product–Moment correlation coefficient. A two-tailed probability value of *p* < .05 was chosen as significant.

## Results

### Group Composition

Fifteen AD subjects (13 men/2 women, 34 ± 6 years) and fifteen HC subjects (12 men/3 women, 35 ± 6 years) were included in this study. Subjects were matched for ethnicity (AD subjects: 4 African American, 4 Caucasian, 5 Hispanic, and 2 Native American/Asian; HC subjects: 3 African American, 6 Caucasian, 4 Hispanic, and 2 Asian) and cigarette smoking (AD subjects smoked 13 ± 6 cigarettes/day and included 5 nonsmokers and 1 ex-smoker; HC smoked 11 ± 7 cigarettes/day and included 7 nonsmokers and 1 ex-smoker). The AD subjects consumed 20 ± 8 standard drinks per day and had been drinking for 18 ± 7 years. All met criteria for alcohol dependence before the age of 25. At screening, the AD subjects had an average MAST score of 25.7 ± 7.8 and average ADS score of 20.3 ± 8.7. Their average OCDS score was 22.2 ± 7.7 at screening and 11.4 ± 8.8 at scanning.

### Imaging Results

There was no significant difference in the [<sup>11</sup>C]raclopride injected dose between the HC and AD subjects at baseline (HC: 14.3 ± 3.0 mCi; AD: 14.5 ± 2.5 mCi, *p* = .8) or post-amphetamine

(HC: 13.0 ± 2.8 mCi; AD: 12.9 ± 3.2 mCi, *p* = .9). The average specific activity was 1679 ± 748 Ci/mmol for HC and 1561 ± 479 Ci/mmol for the AD (*p* = .6) at baseline and 1482 ± 708 Ci/mmol for HC and 1528 ± 474 Ci/mmol for the AD (*p* = .8) post-amphetamine. The injected mass of raclopride also did not differ between the groups in each condition (baseline HC: 3.4 ± 1.3 μg and AD: 3.4 ± .8 μg, *p* = .9; post-amphetamine HC: 3.4 ± 1.0 μg and AD 3.1 ± .8 μg, *p* = .3).

[<sup>11</sup>C]raclopride plasma clearance did not differ between groups both at baseline (HC: 12.9 ± 4.0 L h<sup>-1</sup>; AD: 13.5 ± 2.7 L h<sup>-1</sup>; *p* = .6) or post-amphetamine (HC: 12.4 ± 4.0 L h<sup>-1</sup>; AD: 13.1 ± 2.8 L h<sup>-1</sup>; *p* = .6). Likewise, plasma free fraction (f<sub>1</sub>) did not differ between groups at baseline (HC: 3.6 ± .5%; AD: 3.4 ± .6%; *p* = .31) or post-amphetamine (HC: 3.5 ± .4%; AD: 3.3 ± .5%; *p* = .2). No difference was seen in the plasma amphetamine levels between the two groups (HC: 45.0 ± 16.1 ng/mL, AD: 47.2 ± 12.7 ng/mL, *p* = .7). The volumes of the ROIs did not differ between the two groups (Table 1).

**Cerebellum V<sub>2</sub>.** The volume of distribution of the cerebellum (V<sub>2</sub>) was .40 ± .08 mL g<sup>-1</sup> in HC subjects and .39 ± .06 mL g<sup>-1</sup> in AD subjects (*p* = .7) at baseline and .36 ± .08 mL g<sup>-1</sup> in HC subjects and .36 ± .06 mL g<sup>-1</sup> in AD subjects (*p* = .8) post-amphetamine. The free fraction of the cerebellum (f<sub>2</sub>) was 9.2 ± 1.8% in HC subjects and 8.8 ± 1.7% in AD subjects (*p* = .5) and 9.9 ± 2.2% in HC subjects at baseline and 9.3 ± 1.7% in AD subjects (*p* = .4) post-amphetamine.

**Baseline D<sub>2</sub> Receptor Availability.** Two outcome measures were derived to assess D<sub>2</sub> receptor availability: [<sup>11</sup>C]raclopride binding potential (BP) and the specific to nonspecific partition coefficient (V<sub>3</sub><sup>''</sup>), as shown in Tables 2 and 3. Significant group differences in D<sub>2</sub> receptor availability for each subdivision of the striatum were found with both BP and V<sub>3</sub><sup>''</sup> (repeated-measures ANOVA for BP: subdivision factor: *p* < .001; group factor: *p* = .007; group by subdivision interaction: *p* = .0024; for V<sub>3</sub><sup>''</sup>: subdivision factor: *p* < .0001; group factor: *p* < .001; group by subdivision interaction: *p* = .0015). Within the associative striatum (AST), a significant decrease was found in all regions for BP (Table 2) and V<sub>3</sub><sup>''</sup> (Table 3; repeated-measures ANOVA for BP: region factor: *p* < .001; group factor: *p* = .008; group by region interaction: *p* = .04; for V<sub>3</sub><sup>''</sup>: region factor: *p* < .0001; group factor: *p* = .0003; group by region interaction: *p* = .02). Thus, in each subdivision, AD subjects had a lower D<sub>2</sub> receptor availability compared with HC subjects. The reduction in D<sub>2</sub> receptor availability was also observed at the voxel level, as depicted by the V<sub>3</sub><sup>''</sup> comparison map (Figure 2).

**Amphetamine Effect on [<sup>11</sup>C]Raclopride V<sub>3</sub><sup>''</sup>.** The effect of amphetamine on [<sup>11</sup>C]raclopride V<sub>3</sub><sup>''</sup> (denoted ΔV<sub>3</sub><sup>''</sup>) was similar between the HC and AD in the AST, SMST, but the AD subjects showed a significant decrease in ΔV<sub>3</sub><sup>''</sup> in the LST (repeated-

**Table 2.** [<sup>11</sup>C] Raclopride Binding Potential (Binding Potential, mL g<sup>-1</sup>)

Functional Subdivision	Anatomic Subdivision	HC	AD	Difference	<i>p</i> <sup>a</sup>
LST	VST	.84 ± .21	.70 ± .11	-16.6%	.03
AST	preDCA	1.04 ± .25	.84 ± .13	-19.2%	.009
	preDPU	.99 ± .23	.82 ± .12	-22.2%	.02
	postCA	1.21 ± .28	.97 ± .14	-20.1%	.006
SMST	postPU	.72 ± .19	.57 ± .11	-22.2%	.02
	STR	1.19 ± .27	.93 ± .12	-21.3%	.003
STR		1.06 ± .24	.85 ± .12	-20.0%	.01

Values are mean ± SD, *n* = 15 per groups. See Table 1 for abbreviations. <sup>a</sup>Unpaired *t* test.

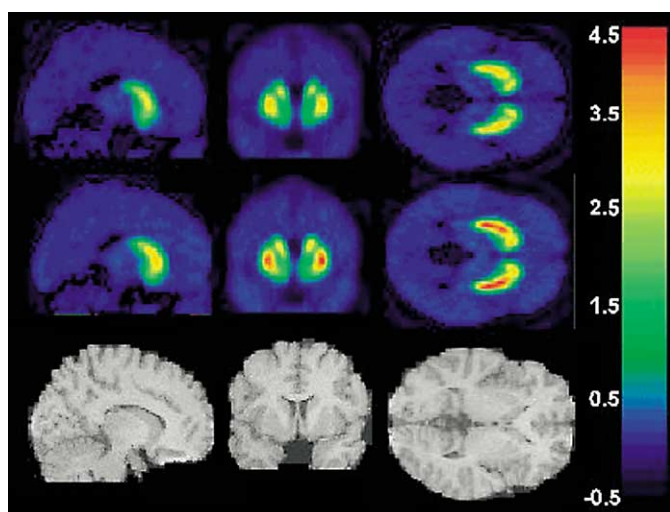
**Table 3.** [<sup>11</sup>C]Raclopride Specific to Nonspecific Partition Coefficient ( $V_3''$ , unitless)

Functional Subdivision	Anatomic Subdivision	HC	AD	Difference	$p^a$
LST	VST	2.09 ± .24	1.81 ± .27	-13.2%	.006
AST		2.60 ± .28	2.17 ± .27	-16.4%	<.001
	preDCA	2.47 ± .28	2.12 ± .25	-14.4%	.001
	preDPU	3.02 ± .32	2.50 ± .31	-17.3%	<.001
	postCA	1.80 ± .30	1.49 ± .30	-17.1%	.008
SMST	postPU	2.97 ± .31	2.42 ± .32	-18.5%	<.0001
STR		2.65 ± .27	2.21 ± .27	-16.7%	.0001

Values are mean ± SD,  $n = 15$  per groups. See Table 1 for abbreviations.  
<sup>a</sup>Unpaired  $t$  test.

measures ANOVA: subdivision factor:  $p < .0001$ ; group factor:  $p = .06$ ; group by subdivision interaction:  $p = .03$ ) as shown in Table 4. Within the ROIs that make up the AST, there was no significant between group difference in  $\Delta V_3''$  (repeated-measures ANOVA: region factor:  $p = .014$ ; group factor:  $p = .29$ ; group by region interaction:  $p = .72$ ). Similar results were seen with the reduction in BP ( $\Delta BP$ ) following amphetamine: a significant difference was seen between the two groups in the LST (HC =  $-19.9 \pm 7.8\%$ , AD =  $-11.5 \pm 6.4\%$ ,  $p = .003$ ), but not the AST (HC =  $-14.2 \pm 4.6\%$ , AD =  $-11.0 \pm 7.8\%$ ,  $p = .18$ ) or SMST (HC =  $-20.7 \pm 5.6\%$ , AD =  $-18.0 \pm 9.6\%$ ,  $p = .36$ ) subdivisions (repeated-measures ANOVA: subdivision factor:  $p < .0001$ ; group factor:  $p = .03$ ; group by subdivision interaction:  $p = .03$ ).

**PVE Correction.** The PVE-corrected values for baseline BP and  $V_3''$  are provided in Table 5. Correction resulted in a significant increase in the measured values of BP and  $V_3''$  for each ROI (one-sided  $t$  test,  $p < .001$  for all regions). Following PVE correction, the AD subjects still exhibited lower  $D_2$  receptor



**Figure 2.** Comparison of baseline mean  $V_3''$  maps within groups. Top row is mean ( $n = 15$ ) across patients. Middle row is mean ( $n = 15$ ) across control subjects. For each subject, a  $V_3''$  map was created on MR coregistered PET data according to the following formula:  $V_3''$  (voxel) = activity (voxel) / mean cerebellum value - 1. This formula was applied to each PET frame used in the ROI analysis and then averaged over frames. Analysis was restricted to voxels with reconstructed activity  $> 0$ . Maps were then normalized into a common template space (SPM software environment) to facilitate averaging across subjects. The bottom row is the SPGR magnetic resonance image of one subject normalized into the template space to show anatomic location of  $V_3''$  maps.

availability compared with HC subjects (repeated-measures ANOVA for BP: subdivision factor:  $p < .001$ ; group factor:  $p = .003$ ; group by subdivision interaction:  $p = .04$ ; for  $V_3''$ : subdivision factor:  $p < .0001$ ; group factor:  $p < .0001$ ; group by subdivision interaction:  $p = .03$ ).

The PVE-corrected data for  $\Delta V_3''$  are shown in Table 6. Correction resulted in a significant change in the value of  $\Delta V_3''$  in the rostral caudate (preDCA), the rostral putamen (preDPU) in both groups, and in the VST of the HC (there was no change  $\Delta V_3''$  in the VST of the AD subjects). For the preDCA and preDPU, PVE correction resulted in a small but significant decrease in  $\Delta V_3''$  for both groups; PVE correction did not significantly affect  $\Delta V_3''$  in the caudate or putamen caudal to the AC (postCA and postPU), nor did it affect  $\Delta V_3''$  in the striatum as a whole. Following PVE correction, decreases in  $\Delta V_3''$  were similar between groups in the AST and SMST, whereas  $\Delta V_3''$  in the LST was significantly reduced in the AD subjects (repeated-measures ANOVA: region factor:  $p < .001$ ; group factor:  $p = .02$ ; group by region interaction:  $p = .02$ ).

**Relationships Between Scan Data and Clinical Measures.** A negative association was observed between the baseline values of [<sup>11</sup>C]raclopride  $V_3''$  and daily alcohol consumption (STR:  $r = .65$ ,  $p = .008$ ; LST:  $r = .64$ ,  $p = .01$ ; AST:  $r = .62$ ,  $p = .015$ ; SMST:  $r = .67$ ,  $p = .006$ ), such that the AD subjects with the lowest values for  $V_3''$  were those with the highest alcohol intake. However, a negative association was also seen between baseline  $V_3''$  and the detoxification doses of chlordiazepoxide (STR:  $r = .72$ ,  $p = .002$ ; LST:  $r = .71$ ,  $p = .003$ ; AST:  $r = .74$ ,  $p = .001$ ; SMST:  $r = .64$ ,  $p = .01$ ). Furthermore, an association was seen between daily alcohol consumption and the detoxification dose of chlordiazepoxide ( $r = .67$ ,  $p = .006$ ). Thus, AD subjects who had been consuming greater amounts of alcohol before admission required higher doses of chlordiazepoxide during detoxification and had lower values for  $V_3''$ .

No association was seen between the baseline values of  $V_3''$  in each of the subdivisions and years of abuse or the MAST or ADS (data not shown). No association was seen between baseline values of  $V_3''$  and the OCDS at baseline (STR:  $r = .12$ ,  $p = .66$ ; LST:  $r = .15$ ,  $p = .60$ ; AST:  $r = .14$ ,  $p = .63$ ; SMST:  $r = .08$ ,  $p = .78$ ) or at scanning (STR:  $r = .01$ ,  $p = .90$ ; LST:  $r = .02$ ,  $p = .93$ ; AST:  $r = .11$ ,  $p = .71$ ; SMST:  $r = .14$ ,  $p = .62$ ).

No significant association was seen between  $\Delta V_3''$  and any of the clinical measures (quantity of alcohol, years of abuse, MAST, ADS, or OCDS scores) or with plasma amphetamine levels (data not shown). No association was seen between doses of chlordiazepoxide and amphetamine-induced [<sup>11</sup>C]raclopride displacement ( $\Delta V_3''$ ) as follows: STR:  $r = .23$ ,  $p = .41$ ; LST:  $r = .20$ ,  $p = .50$ ; AST:  $r = .18$ ,  $p = .51$ ; SMST:  $r = .33$ ,  $p = .23$ .

**Table 4.** Percent Change in Amphetamine-Induced [<sup>11</sup>C]Raclopride Displacement ( $\Delta V_3''$ )

Functional Subdivision	Anatomic Subdivision	HC	AD	$p^a$
LST	VST	$-13.0 \pm 8.8\%$	$-5.2 \pm 3.6\%$	.004
AST		$-6.7 \pm 5.4\%$	$-4.6 \pm 5.8\%$	.31
	preDCA	$-4.2 \pm 5.6\%$	$-3.1 \pm 5.6\%$	.60
	preDPU	$-8.8 \pm 6.7\%$	$-5.6 \pm 6.9\%$	.20
	postCA	$-7.8 \pm 8.3\%$	$-5.6 \pm 8.1\%$	.46
SMST	postPU	$-13.7 \pm 7.5\%$	$-12.3 \pm 7.3\%$	.59
STR		$-9.4 \pm 5.9\%$	$-7.2 \pm 5.3\%$	.28

Values are mean ± SD,  $n = 15$  per groups. See Table 1 for abbreviations.  
<sup>a</sup>Unpaired  $t$  test.

**Table 5.** Partial Volume Effects Corrected Baseline [<sup>11</sup>C]Raclopride Binding Potential (BP) and Specific to Nonspecific Partition Coefficient (V<sub>3</sub>'')

Functional Subdivision	Anatomic Subdivision	Binding Potential (BP, mL g <sup>-1</sup> )				Specific to Nonspecific Partition Coefficient (V <sub>3</sub> '', unitless)			
		HC	AD	Difference	p	HC	AD	Difference	p
LST	VST	1.34 ± .36	1.07 ± .16	-20.1%	.01	3.34 ± .49	2.79 ± .47	-16.7%	.003
AST		1.57 ± .37	1.24 ± .17	-20.8%	.004	3.93 ± .41	3.22 ± .40	-18.0%	<.001
	preDCA	1.48 ± .34	1.20 ± .18	-19.1%	.01	3.70 ± .40	3.09 ± .38	-13.2%	.0002
	preDPU	1.71 ± .40	1.33 ± .18	-21.9%	.003	4.27 ± .45	3.46 ± .41	-19.1%	<.001
	postCA	1.50 ± .42	1.17 ± .23	-21.9%	.01	3.75 ± .68	3.06 ± .74	-18.3%	.014
SMST	postPU	1.97 ± .50	1.51 ± .20	-23.4%	.002	4.94 ± .64	3.93 ± .56	-20.4%	<.001
STR		1.66 ± .38	1.30 ± .17	-21.3%	.003	4.14 ± .41	3.38 ± .42	-18.4%	<.001

See Table 1 for abbreviations.

## Discussion

The results of this study show that striatal D<sub>2</sub> receptor availability is decreased in the limbic, associative, and sensorimotor regions of the striatum in recently detoxified AD compared with HC subjects. Following an amphetamine challenge, the AD subjects were found to have a selective blunting of amphetamine-induced dopamine release in the limbic striatum compared with HC subjects.

### Baseline D<sub>2</sub> Receptor Availability and Alcohol Dependence

In this data set, alcohol dependence was associated with a reduction in D<sub>2</sub> receptor availability measured with both BP and V<sub>3</sub>''. No between-group differences were observed in nonspecific binding (V<sub>2</sub>), free fraction in the plasma (f<sub>1</sub>), or free fraction in the brain (f<sub>2</sub>), such that the decrease in these binding parameters can be attributed to a decrease in the D<sub>2</sub> receptor Bmax/KD' ratio (Slifstein and Laruelle 2001). Furthermore, no difference in the size of the regions of interest was seen between the two groups, and the decrease in D<sub>2</sub> receptors could not be attributed to partial volume effects.

Previous PET and single photon emission computed tomography (SPECT) studies in alcohol dependence have shown both a decrease (Hietala et al 1994; Volkow et al 1996) and no change (Guardia et al 2000; Kuikka et al 2000; Repo et al 1999) in D<sub>2</sub> receptor availability in the striatum. Because of camera resolution, these studies were performed measuring the striatum as a whole rather than its subdivisions. Volkow et al (2002) recently reported a decrease in D<sub>2</sub> receptor availability in both the caudate and putamen using [<sup>11</sup>C]raclopride and a high-resolution PET camera. Alcohol-dependent subjects were scanned at two time points: within 6 weeks of detoxification and at 1–4 months later, with no recovery of D<sub>2</sub> receptors within this time frame (Volkow et al 2002). This study did not measure D<sub>2</sub> receptor availability in the ventral striatum, however. On the other hand,

**Table 6.** Partial Volume Effects—Corrected Percent Change in Amphetamine-Induced [<sup>11</sup>C]Raclopride Displacement (ΔV<sub>3</sub>'')

Functional Subdivision	Anatomic Subdivision	HC	AD	p <sup>a</sup>
LST	VST	-15.2 ± 10.4%	-4.9 ± 5.3%	.002
AST		-6.2 ± 5.3%	-4.1 ± 6.2%	.31
	preDCA	-3.5 ± 5.9%	-2.4 ± 5.8%	.60
	preDPU	-8.2 ± 6.6%	-4.7 ± 7.7%	.20
	postCA	-8.1 ± 9.5%	-5.7 ± 9.0%	.48
SMST	postPU	-13.9 ± 7.8%	-12.3 ± 7.7%	.59
STR		-9.5 ± 5.9%	-7.0 ± 5.4%	.24

Values are mean ± SD, n = 15 per groups. See Table 1 for abbreviations.  
<sup>a</sup>Unpaired t test.

Heinz et al reported a decrease in D<sub>2</sub> receptor availability measured with [<sup>18</sup>F]desmethoxyfallypride in the ventral striatum and putamen but reported no difference in the caudate (Heinz et al 2004). Thus, our results support the previous reports of a 15%–20% reduction in D<sub>2</sub> receptor availability in alcohol dependence and show that this reduction involves the caudate, putamen, and ventral striatum.

Human autoradiography studies have shown that alcohol dependence is associated with a reduction in striatal D<sub>2</sub> receptor density (Tupala et al 2003, 2001). In type 1 alcoholics, D<sub>2</sub> receptors were reduced 22%–32% in the dorsal striatum (caudate and putamen) and 20% in the nucleus accumbens compared with control subjects (Tupala et al 2001, 2003). Decreases in D<sub>2</sub> receptor availability were also seen in the dorsal striatum and nucleus accumbens in type 2 alcoholics, but these differences did not reach significance (Tupala et al 2003; Tupala et al 2001). Although the alcohol-dependent subjects in our study reported onset of alcohol dependence before the age 25, they could not be clearly categorized as type 2 alcoholics based on their past behavior. Nevertheless, the results from this PET study are largely consistent with the human autoradiography data showing a moderate decrease in striatal D<sub>2</sub> receptors.

Studies in animals show that the D<sub>2</sub> receptors appear to be important in mediating the reinforcing effects of alcohol. Alcohol-preferring rats have decreased D<sub>2</sub> receptor density in both the caudate-putamen and nucleus accumbens compared with non-alcohol-preferring rats, even before exposure to alcohol (McBride et al 1993). Overexpression of the D<sub>2</sub> receptor in rats trained to self-administer alcohol reduced both their preference and intake of alcohol (Thanos et al 2001). Decreases in D<sub>2</sub> receptor availability of a similar magnitude have been shown in PET studies of other addictive behaviors, such as heroin (Wang et al 1997) and cocaine dependence (Volkow et al 1990), methamphetamine abuse (Volkow et al 2001), and even obesity (Wang et al 2001), showing that this finding is not specific to a particular substance of abuse. Thus, the findings from this study add to a growing body of evidence demonstrating that substance abuse is associated with abnormal transmission at the striatal D<sub>2</sub> receptor.

### Baseline D<sub>2</sub> Receptor Availability and Behavioral Data

No correlation was seen between baseline D<sub>2</sub> receptor V<sub>3</sub>' and the OCDS, which has been shown to reliably measure craving (Anton 2000). This is in contrast to the finding of Heinz et al (2004), who showed that low D<sub>2</sub> receptor availability correlated with craving for alcohol. The reason behind this discrepancy is not clear because both studies imaged a similar number of subjects who were of comparable severity, and imaging occurred after a similar period of abstinence. Both

studies used radiotracers and methods shown to measure striatal D<sub>2</sub> receptors reliably, and both studies used V3'' as the outcome measure. Thus, the main difference between these studies were the scales to measure craving (the OCDS in this study and the Alcohol Craving Questionnaire in the study of Heinz et al). A recent study showed a significant correlation between the Alcohol Craving Questionnaire and the obsessive and compulsive subscales of the OCDS (Raabe et al 2005). Thus, we performed a post hoc analysis comparing these subscales of the OCDS and baseline D<sub>2</sub> receptor V3'' but found no significant association between these subscales and V3'' in any region (all  $p > .6$ ).

In this study, we found a negative correlation between [<sup>11</sup>C]raclopride binding and the average daily quantity of alcohol consumed. We also found a similar correlation between D<sub>2</sub> receptor availability and the doses of chlordiazepoxide used for detoxification. Not surprisingly, the magnitude of the AD subjects' alcohol intake correlated with the dose of chlordiazepoxide needed for detoxification. Based on previous imaging studies, chlordiazepoxide is not expected to decrease measures of D<sub>2</sub> receptor availability. Hietala et al (1997) demonstrated that lorazepam (2 mg taken orally for 1 week) did not affect [<sup>11</sup>C]raclopride binding in healthy human subjects, whereas Dewey et al demonstrated an increase [<sup>11</sup>C]raclopride BP in nonhuman primates following gamma-vinyl-GABA and lorazepam (Dewey et al 1992). Thus, the administration of GABA-enhancing agents should result in either an increase or no change in the [<sup>11</sup>C]raclopride BP, rather than a decrease. Nevertheless, it cannot be stated with certainty that the correlation between D<sub>2</sub> receptor availability and quantity of alcohol is not confounded by the detoxification with chlordiazepoxide.

### Amphetamine-Induced Dopamine Release and Alcohol Dependence

To our knowledge, this study is the first published report measuring dopamine release in the striatum in alcohol dependence. Blunted amphetamine-induced dopamine release was observed in the limbic striatum in AD compared with HC subjects. Amphetamine-induced dopamine release was slightly reduced in the associative and sensorimotor striatum of AD subjects compared with HC, but these differences did not reach significance. This finding is in agreement with rodent studies showing a reduction in dopamine and its metabolites in the nucleus accumbens (Murphy et al 1982) and studies showing a reduction in midbrain dopamine projections to the nucleus accumbens (Casu et al 2002; Zhou et al 1995).

In human subjects, the etiology behind the reduction in amphetamine-induced dopamine release is not clear. Tiihonen et al (1998) demonstrated an increase in 6-[<sup>18</sup>F]-fluoroDOPA uptake in the putamen and caudate in AD subjects compared with HC subjects, a finding that suggests that alcoholics should have increased presynaptic dopamine function rather than a decrease. Alternatively, using PET and the radioligand (+)[<sup>18</sup>F]dihydrotrabectedazine, Gilman et al (1998) reported a decrease in striatal type 2 vesicular monoamine transporters (VMAT2) in the caudate (6%) and putamen (13%) of AD subjects, although this only reached significance in the putamen. Levels of VMAT2 may affect the magnitude of the amphetamine effect on extracellular dopamine (Patel et al 2003) such that a loss of VMAT2 would be consistent with a decrease in amphetamine-induced [<sup>11</sup>C]raclopride displacement. In the study of Gilman et al, VMAT2 was not specifically measured in the ventral striatum, so it is unclear whether this factor could explain the reduction in dopamine release seen in this study.

Mesolimbic dopamine has been shown to play a crucial role in mediating the reinforcing effects of alcohol. Ethanol has been shown to increase mesolimbic dopamine release in rodents (Imperato and Di Chiara 1986), nonhuman primates (Bradberry 2002), and human healthy control subjects (Boileau et al 2003). Alcohol-preferring rodents have a greater dopamine release in the nucleus accumbens following their initial exposure to alcohol compared with non-alcohol-preferring rats (Katner and Weiss 2001), and a reduced response to ethanol following repeated exposure (Murphy et al 1988). Acute alcohol withdrawal has been shown to reduce mesolimbic dopamine function (Diana et al 1993), and it has been postulated that a deficit in dopamine activity may play a critical role in relapse (Wise 1988). Thus, the results of these animal studies suggest that individuals who become alcohol dependent may initially have an exaggerated dopamine response to ethanol that is reinforcing. With time and the onset of dependence, however, alcohol-dependent subjects may lose dopamine tone in the ventral striatum. Insofar as dopamine in the nucleus accumbens is thought to serve as a behavioral switching device (Pennartz et al 1994), this deficit in dopamine release may represent an impaired ability of alcohol-dependent individuals to shift from the compulsive, maladaptive patterns of behavior that are indicative of addiction.

### Partial Volume Effects Correction

The PVE correction of the baseline [<sup>11</sup>C]raclopride images resulted in a significant increase in the values of BP and V3'', from 40% in the rostral putamen (an area with less contact with the background) to 106% in the caudal caudate (a long, thin region that is largely surrounded by background). These results are consistent with previous reports (Martinez et al 2003; Mawlawi et al 2001) and reflect the dilution of signal experienced by these regions due to low activity in the surrounding background tissue. On the other hand, PVE correction resulted in little or no effect on  $\Delta V_3''$ , even when correcting for adjacent regions with large differences in activity, consistent with previous studies (Martinez et al 2003; Slifstein et al 2004). The effect of PVE correction on  $\Delta V_3''$  in a given ROI can be understood by looking at the geometry of the striatum and  $\Delta V_3''$  of the adjacent ROIs. The PVE correction had no effect on  $\Delta V_3''$  in the caudate or putamen caudal to the AC; (postCA and postPU) or the striatum as a whole. These are regions that are largely surrounded by background, and we have previously shown that PVE correction has a negligible effect in this setting (Martinez et al 2003; Slifstein et al 2004).

The subdivisions of the striatum can be distinguished from each other based on their response to amphetamine: the limbic and sensorimotor subdivisions have a greater [<sup>11</sup>C]raclopride displacement compared with the associative subdivision (see Martinez et al 2003, and Table 4). Thus, PVE correction slightly decreased  $\Delta V_3''$  in the caudate and putamen anterior to the AC (preDCA and preDPU) because these regions displace less [<sup>11</sup>C]raclopride following amphetamine and are adjacent to regions that have a greater amphetamine effect (VST and postPU). Interestingly, PVE correction increased  $\Delta V_3''$  in the VST of the HC subjects but did not affect  $\Delta V_3''$  in the LST of the AD subjects. This is because  $\Delta V_3''$  in the VST of the HC was affected by the lower  $\Delta V_3''$  of the adjacent preDCA and preDPU. However,  $\Delta V_3''$  in the VST of the AD subjects was blunted and of a similar magnitude to the  $\Delta V_3''$  of the preDCA and preDPU.

Overall, PVE correction did not alter the primary findings in this study: AD subjects still had a lower D<sub>2</sub> receptor availability compared with HC subjects, and  $\Delta V_3''$  was reduced in the limbic

striatum only. These findings suggest that PVE correction may not be necessary when comparing between-subject differences of this magnitude when no difference in ROI size is seen between groups.

### Limitations

Several limitations of this study should be recognized. 1) The number of subjects per group is relatively small. 2) Changes in baseline D<sub>2</sub> receptor availability could result from either a decrease in receptor concentration or in receptor affinity for the radiotracer. 3) The amphetamine challenge provides information about the increase in dopamine transmission induced by amphetamine, but not about the baseline synaptic dopamine levels. Studies using rapid dopamine depletion techniques are required to assess this (Laruelle et al 1997). 4) The amphetamine challenge measures changes in D<sub>2</sub> receptor availability secondary to changes in endogenous dopamine. Thus, the difference between AD and HC subjects could be due to a smaller increase in synaptic dopamine or lower affinity of D<sub>2</sub> receptors. Studies with the radiolabeled agonist [<sup>11</sup>C]N-propyl-apomorphine are needed to clarify this issue (Hwang et al 2004).

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