Article

Elevated Putamen D_2 Receptor Binding Potential in Major Depression With Motor Retardation: An [^{11}C]Raclopride Positron Emission Tomography Study

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Objective: Several antidepressants raise striatal dopamine, but the role of striatal dopamine during major depressive episodes is unclear. Striatal [^{11}C]raclopride binding potential measured with positron emission tomography is an index of D_2 type receptors and is sensitive to extracellular dopamine levels (higher D_2 binding potential occurs when dopamine is lower). It was hypothesized that putamen D_2 binding potential would be higher during major depressive episodes featuring motor retardation.

Method: Drug-free, nonsmoking subjects experiencing a major depressive episode (N=21) underwent [^{11}C]raclopride PET imaging as did 21 healthy age-matched comparison subjects. Motor retardation was measured with the finger tapping test.

Results: The depressed subjects exhibiting motor retardation had significantly higher D_2 binding potential in both the left and right putamen than did healthy subjects, and putamen D_2 binding potential correlated significantly with motor speed in the depressed subjects.

Conclusions: The results argue that extracellular dopamine is lower in subjects experiencing a major depressive episode that features motor retardation. This depression subtype should preferentially benefit from dopamine-increasing medications and should be targeted in future clinical trials of dopamine reuptake inhibitors.

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It is generally believed that pathophysiological processes implicated in major depressive disorder are reversed by antidepressant treatment. Most antidepressants raise monoamines, and the majority of these antidepressants raise serotonin and/or norepinephrine. However, a number of commonly prescribed antidepressants also have dopamine-increasing properties, the most prominent being sertraline, bupropion, and the entire class of monoamine oxidase A and A/B inhibitors (1–4). Sertraline has a moderately high affinity for the dopamine transporter (1, 2). Bupropion has its highest known affinity for the dopamine transporter, and the entire class of monoamine oxidase A and A/B inhibitors robustly increase striatal dopamine in animal models (1, 3, 4). Even though these treatments are often used, the role of dopamine during major depressive episodes is not clear.

Pathological putamen dopamine neurotransmission is associated with motor retardation in a number of illnesses such as Parkinson's disease, multisystem atrophy, and progressive supranuclear palsy (5, 6). Motor retardation is frequently a symptom of major depressive episodes (7), and striatal dopamine may also be low during major depressive episodes when motor retardation is present, since a very indirect measure of brain dopamine—CSF levels of the dopamine metabolite homovanillic acid (HVA)—is often low during major depressive episodes with motor retardation (8, 9).

Striatal dopamine concentrations cannot be directly measured in vivo in humans. However, [^{11}C]raclopride positron emission tomography (PET) is a useful noninvasive method for investigating disease processes that may lower extracellular dopamine. [^{11}C]Raclopride is a validated PET radiotracer that is selective for D_2 type receptors with a modest preference for D_2 receptors over D_3 receptors (10–12). The index of D_2 type receptors found with this method, referred to in this article as D_2 receptor binding potential, is inversely proportional to extracellular dopamine levels in animal paradigms of acute and chronic dopamine depletion as well as acute increases in dopamine (13). Moreover, the D_2 binding potential is elevated in human conditions associated with dopamine loss such as AMPT (alpha-methyl-paratyrosine) treatment (14) and untreated Parkinson's disease (15–17). The D_2 binding potential is lower after acute increases in dopamine in humans (13). Thus, [^{11}C]raclopride PET should be useful for investigating abnormalities of striatal dopamine during major depressive episodes.

To our knowledge there have been no studies to date that have used [^{11}C]raclopride PET in depressed subjects. [^{123}I]IBZM single photon emission computed tomography (SPECT) is a similar method because IBZM binds to D_2

type receptors, and the D_2 binding potential found with [^{123}I]IBZM SPECT shows a similar inverse relationship to extracellular dopamine levels (13). However, all previous investigations of striatal D_2 binding potential during major depressive episodes using [^{123}I]IBZM SPECT are confounded by antidepressant use (18–22). Four (18–21) of the five studies recruited subjects who had taken antidepressants within 2 weeks of scanning. This is a critical issue, since large magnitude changes in D_2 binding potential during acute administration of serotonin-increasing medications have been reported in humans (23). The one study that recruited some drug-free subjects (22) cannot be considered conclusive because it did not compare the drug-free subjects to the healthy subjects. Of the five studies, only one (20) measured both striatal D_2 binding potential and motor speed with neuropsychological testing. This study is also not definitive because most of the subjects were taking antidepressant medication, subjects with bipolar disorder were included, and the effects of age were not addressed. Striatal D_2 binding potential declines with age (24), and motor speed declines with age (25). Therefore, controlling for the effect of age on both variables is essential or else a spurious association between the two is possible.

The underlying hypothetical model for the present study was that extracellular dopamine would be low in the putamen during major depressive episodes when motor retardation is present. The evidence supporting this model is that CSF concentration of the dopamine metabolite, HVA, is low during depression with motor retardation (8, 9) and that low dopamine neurotransmission in the putamen is associated with motor retardation in several other diseases (5, 6). Extracellular striatal dopamine cannot be measured directly in vivo in humans; however, the D_2 binding potential found with [^{11}C]raclopride PET is inversely correlated with extracellular dopamine levels (13, 14, 16). Therefore, our specific hypothesis was that putamen D_2 binding potential would be elevated in depressed subjects exhibiting motor retardation.

Method

Subjects

Twenty-one depressed subjects (nine men and 12 women; mean age=35 years [SD=10]) experiencing a current major depressive episode and 21 age-matched healthy subjects (nine men and 12 women; mean age=34 years [SD=11]) were recruited. All subjects were physically healthy, nonsmoking, and had no history of neurotoxin or neuroleptic use. Subjects who smoked were excluded because cigarette smoking in humans acutely lowers [^{11}C]raclopride PET measurement of D_2 binding potential in ventral striatum (26). All subjects received a urine drug screen on the day of the [^{11}C]raclopride PET scan.

Diagnoses of major depressive episode secondary to major depressive disorder were determined with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) and confirmed by a psychiatrist (J.H.M.). For subjects experiencing a major depressive episode, the minimum severity for study enrollment was a score of 17 on the 17-item Hamilton Depression Rating Scale. Additional clinical details are presented in Table 1. The SCID also was used to rule out comorbid axis I disorders in the depressed subjects. Subjects whose major depressive episode included psychotic symptoms were also excluded. All depressed subjects received blood tests (thyroid function, electrolytes, complete blood cell count) to rule out medical causes of disturbed mood.

TABLE 1. Demographic and Clinical Characteristics of Major Depressive Disorder Subjects Currently Experiencing a Major Depressive Episode

Characteristic	Subjects Experiencing a Major Depressive Episode (N=21)	
	Mean	SD
Age (years)	35	10.35
Hamilton Depression Rating Scale (17-item) score	20.43	3.25
Number of episodes	2.57[a]	1.50
Length of current episode (years)	1.90[b]	2.93
	N	%
Gender		
Male	9	42.86
Female	12	57.14
Antidepressant treatment history		
None	12	57.14
Within previous 6 months	0	0.00
Within previous year	4	19.05
Not within previous year	5	23.81

[a] Median number of episodes: 2.
[b] Median length of episodes: 0.5 years.

Healthy subjects were screened with the SCID to rule out any axis I disorders. All subjects were screened to rule out axis II disorders using the SCID for axis II disorders (27).

For each subject, written consent was obtained after the procedures had been fully explained. The study and recruitment procedures were approved by the research ethics board for human subjects at the Centre for Addiction and Mental Health.

PET Scanning

For each PET scan, 370 MBq of [^{11}C]raclopride was administered intravenously as a bolus. Frames were acquired as follows: five frames of 1 minute, 20 frames of 2 minutes, and three frames of 5 minutes. [^{11}C]Raclopride was of high radiochemical purity (>95%) and high specific activity (32 GBq/μmol [SD=15] at the time of injection). PET images were obtained using a GEMS 2048–15B camera (intrinsic resolution=5.5 mm full width at half maximum). All images were corrected for attenuation using a ^{68}Ge transmission scan and reconstructed by filtered back projection (Hanning filter).

To derive D_2 binding potential, the simplified reference tissue model (12) was applied to time activity curve data from [^{11}C]raclopride PET scanning (28). The binding potential found with this noninvasive method represents the ratio of specifically bound radiotracer to radiotracer in free and nonspecific compartments at equilibrium state. This binding potential is equal to $(1/V_2)*(B_{max}/K_d)$ (12). B_{max} represents receptor density, K_d is the dissociation constant (which is inversely proportional to affinity), and V_2 is the ratio of free and nonspecifically bound radiotracer in tissue relative to plasma concentration if they were at an equilibrium state (which is an index of free and nonspecific binding in tissue).

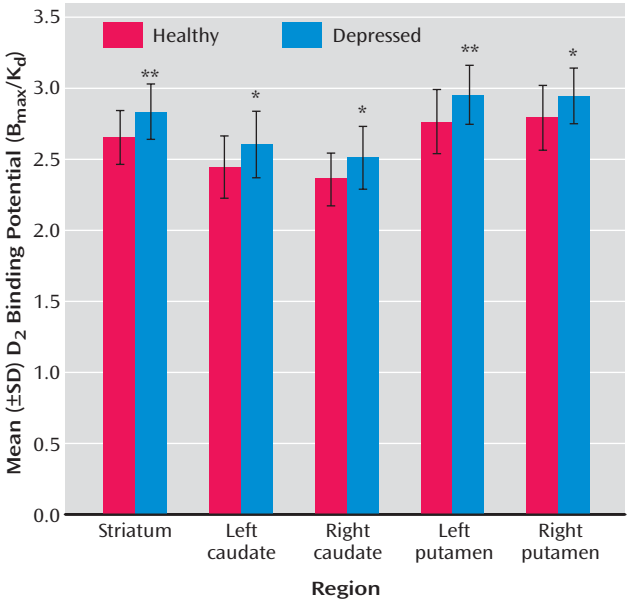
For the region of interest method, each subject underwent MRI scanning (GE Signa 1.5-T scanner, spin-echo sequence, T_1 weighted image; x, y, z voxel dimensions 0.78, 0.78, and 3 mm, respectively). Regions of interest were drawn on MRI scans that were coregistered to each summated [^{11}C]raclopride PET image using a mutual information algorithm (29). The location of the region of interest was verified by visual assessment of the region of

TABLE 2. Correlations Between Whole Striatum D_2 Binding Potential and Neuropsychological Test Performance in Depressed and Healthy Subjects

	Correlation With D_2 Binding Potential[a]			
	Depressed Subjects		Healthy Subjects	
Task Domain and Neuropsychological Test	r (df=17)	p	r (df=19)	p
Motor: Finger Tapping Test[a, b]	–0.53	0.02	–0.33	0.15
Attention				
Continuous Performance Test: commissions[c]	–0.18	0.44	–0.04	0.88
WAIS–R digit symbol subtest[a, b, d]	0.41	0.08	–0.03	0.89
Executive function				
Wisconsin Card Sorting Test: perseveration[e]	–0.24	0.31	0.26	0.26
Stroop Color-Word Test: interference[a, b]	0.17	0.49	0.06	0.79
Trail Making Part A: total time[a]	0.27	0.25	0.16	0.48
Trail Making Part B: total time[a, d]	–0.42	0.07	0.03	0.90
Memory				
Brief Visual-Spatial Memory Test: discrimination[e]	0.28	0.23	–0.03	0.90
Hopkins Verbal Learning Test: total recalled[e]	0.17	0.49	–0.15	0.51
Estimated IQ: North American Reading Test[e]	–0.19	0.42	0.23	0.33
Visual-spatial: Judgment of Line Orientation[c]	0.34	0.14	–0.32	0.16

[a] Age effect controlled.
[b] Gender effect controlled.
[c] Gender effect controlled, no age effect evident.
[d] Test has a major motor component.
[e] No clear age or gender effect, therefore raw scores used.

FIGURE 1. Striatal D_2 Receptor Binding Potential in Depressed (N=21) and Healthy (N=21) Subjects[a]



[a] D_2 binding potential values were normalized to a 30-year-old subject using the slope of the age-related decline. Between-group differences assessed by means of independent sample t tests.
*p≤0.05. **p≤0.005.

interest upon the summated [^{11}C]raclopride PET image. Left and right caudate and putamen regions of interest were drawn on two adjacent slices and the cerebellum region of interest (the reference region) was drawn bilaterally on two adjacent slices as described previously (30).

D_2 binding potential was found in individual voxels using the basis function application of the simplified reference tissue model (11). Images were spatially normalized to a common brain shape using statistical parametric mapping (31) and ligand specific templates (32).

Neuropsychological Testing

All healthy subjects and 19 of 21 depressed subjects completed neuropsychological testing that covered several domains of function (Table 2). The finger tapping test was selected as a measure of motor speed for several reasons. First, this test is sensitive to motor retardation in a number of illnesses, including major depressive disorder (7, 25). Second, the test is extremely reliable because the test itself involves at least five consecutive measures of finger tapping (25). Third, test performance has been associated with disturbances in dopaminergic neurotransmission in several conditions and illnesses, including neuronal loss of aging (24), [^{18}F]-dopa uptake in Parkinson's disease (33), and dopamine transporter binding potential during major depressive episodes (34). All neuropsychological tests were administered according to standardized procedures and blind to measurement of D_2 binding potential.

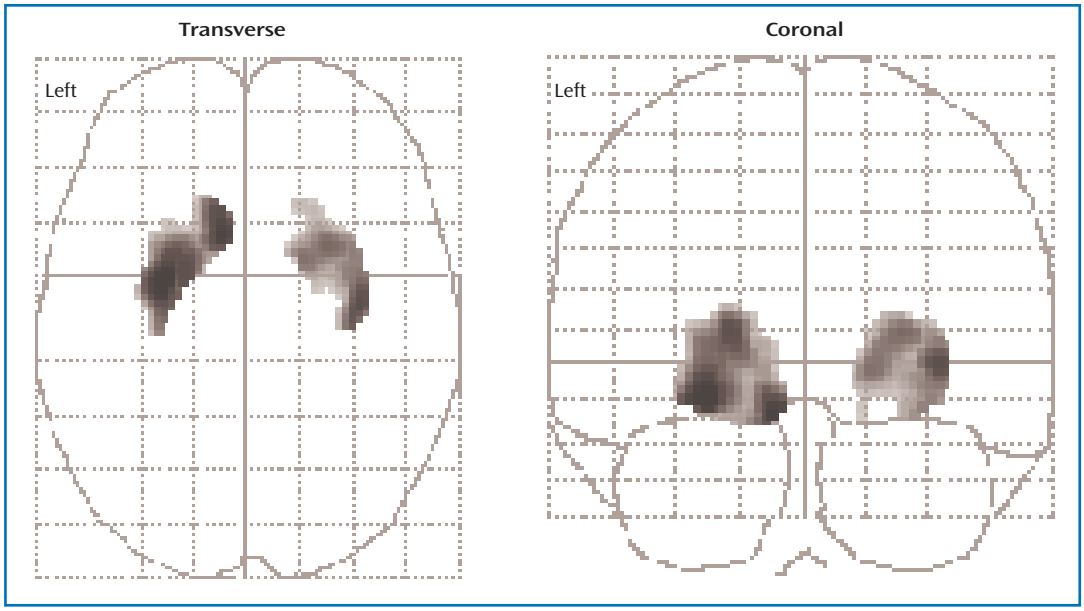
Statistical Methods

First, we determined the relationship between D_2 binding potential and age in each striatal region using an analysis of covariance (ANCOVA) so that we could control for age effects in our region of interest analyses. It is well known that striatal D_2 receptor density declines with age (24). For other region of interest analyses, the effect of age was removed from the D_2 binding potential using the slope of the linear regression between regional D_2 binding potential and age such that the regional D_2 binding potential for each subject was normalized to the D_2 binding potential for a 30-year-old subject. The spatial extent of the relationship between age and D_2 binding potential in striatum was assessed using an analysis of covariance for each voxel.

Given that there have been no investigations of striatal D_2 binding potential in drug-free, nonsmoking, depressed subjects, the next step was comparing striatal D_2 binding potential between depressed and healthy subjects using an analysis of variance for each region of interest. The spatial extent of this relationship in the striatum was also assessed using an analysis of variance for each voxel to assess the effect of diagnosis while controlling for age.

To test the primary hypothesis, a subgroup of depressed subjects exhibiting motor retardation was generated. First, the variance related to demographic variables of age and gender was re-

FIGURE 2. Voxel-Based Comparison of Striatal D_2 Receptor Binding Potential in Depressed (N=21) and Healthy (N=21) Subjects[a]



[a] After correction for cluster significance, ANCOVA with age as a covariate revealed two significant clusters depicting the effect of a major depressive episode (left striatum: N=1278 suprathreshold voxels, p<0.001 [corrected for cluster size]; right striatum: N=1020 suprathreshold voxels, p<0.001 [corrected for cluster size]). Threshold for display, p≤0.05.

moved from the measurement of motor retardation using the slopes of linear regression to remove the effects of these variables, normalizing the scores to a 30-year-old male subject. We have used these approaches previously (34, 35). An important reason to use this method is that the potential for a spurious correlation between D_2 binding potential and motor retardation based upon the common covariation of each variable with age is removed. Next, the subgroup of depressed subjects exhibiting motor retardation was found by selecting those subjects with motor speed less than or equal to the median finger tapping test score of all depressed subjects.

We then tested the primary hypothesis by comparing putamen D_2 binding potential between the subgroup of depressed subjects with motor retardation and healthy subjects using an analysis of variance (ANOVA). The spatial extent of this relationship in the striatum was also assessed using an analysis of variance for each voxel to assess the effect of group (while controlling for age). We also examined the relationship between motor speed and putamen D_2 binding potential in the depressed group using Pearson correlation coefficients, since this information is also relevant to the primary hypothesis. The spatial extent of this relationship in the striatum was also assessed using an analysis of covariance for each voxel to assess the effect of motor speed (while controlling for age).

Last, we investigated the relationship between striatal D_2 binding potential and other neuropsychological and clinical measures using Pearson correlation coefficients. In these analyses, for neuropsychological measurements in which there are known relationships to age or gender, the variance related to these demographic variables was removed from the measurement using the slopes of linear regression for the effects of these variables, normalizing scores to a 30-year-old male subject. With the exception of the finger tapping test, the correlations found were not directly related to the primary hypothesis and were not corrected for number of comparisons, so they should be viewed as exploratory.

Results

Effect of Age and Gender Upon Striatal D_2 Binding Potential

We found that in each region of interest (whole striatum, left and right caudate, left and right putamen), D_2 binding potential declined with age (ANCOVA F=11.0–21.0, df=1, 40, p≤0.002). The voxel analysis showed that D_2 binding potential within the entire striatum correlated significantly with age (left striatum: N=1765 suprathreshold voxels, p<0.001 [corrected for cluster size]; right striatum: N=1332 suprathreshold voxels, p<0.001 [corrected for cluster size]). There was no effect of gender upon striatal D_2 binding potential (ANCOVA F=2.3, df=1, 39, p=0.13).

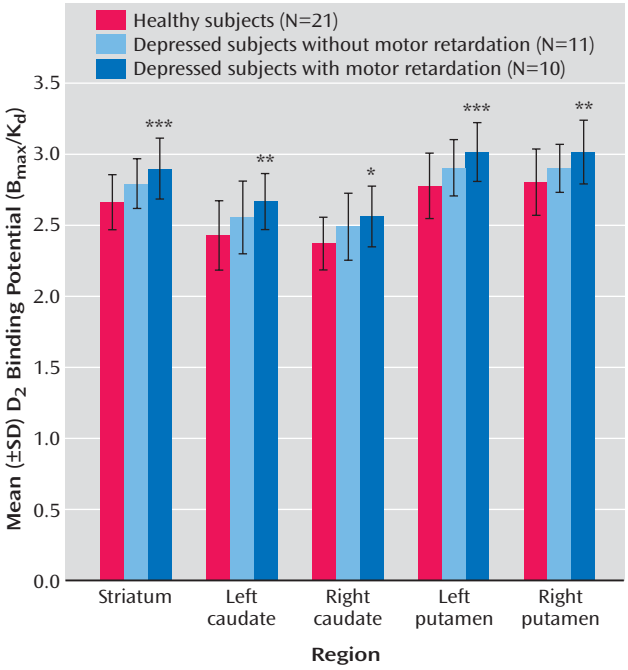
Effect of Major Depressive Episode on Striatal D_2 Binding Potential

As seen in Figure 1, D_2 binding potential in depressed subjects was significantly elevated in every striatal region (ANOVA F=4.99–10.23, df=1, 40, p=0.03–0.002; magnitude: 6% to 8%). Somewhat more motor retardation was seen in the depressed subjects (mean=42.6 taps in 10 seconds) than in the healthy subjects (mean=47.0 taps in 10 seconds) (t=1.8, df=38, p=0.08). In the voxel analysis, D_2 binding potential in the depressed subjects was elevated in the entire striatum (Figure 2).

Striatal D_2 Binding Potential in Depressed Subjects With Motor Retardation

The subgroup of depressed subjects with motor retarda-

FIGURE 3. Striatal D_2 Receptor Binding Potential in Healthy Subjects and Depressed Subjects With Versus Without Motor Retardation[a]



[a] D_2 binding potential values were normalized to a 30-year-old subject using the slope of the age-related decline. Differences between the healthy group and the depressed subjects with motor retardation assessed by means of independent sample t tests.
*p≤0.05. **p≤0.01. ***p≤0.005.

tion (mean=37.3 taps in 10 seconds) than did the healthy subjects (mean=47.0 taps in 10 seconds) (t=3.37, df=29, p=0.002). No differences between depression subgroups was found with respect to age, gender, or number of depressive episodes.

As seen in Figure 3, the depressed subgroup with motor retardation had significantly higher D_2 binding potential in each putamen region than the healthy subjects (left putamen: F=10.54, df=1, 29, p=0.003 [magnitude 10%]; right putamen: F=6.86, df=1, 29, p=0.01 [magnitude 8%]). In the voxel analysis, D_2 binding potential was elevated throughout the striatum in the depressed subjects with motor retardation (Figure 4).

Analysis of the entire group of depressed subjects showed a significant correlation between the measurement of motor speed with the finger tapping test and the D_2 binding potential in the left putamen (r=–0.50, df=17, p=0.03) and right putamen (r=–0.50, df=17, p=0.03) (Figure 5). In addition, motor speed measured with the finger tapping test tended to be associated with D_2 binding potential in the left caudate (r=–0.44, df=17, p=0.06) and the right caudate (r=–0.43, df=17, p=0.07). It was evident that the D_2 binding potential among regions was significantly correlated within the depressed individuals: the various correlations in age-normalized D_2 binding potential between the left and right caudate and left and right putamen ranged from 0.52 to 0.79 (p=0.02 to p≤0.001). Similar results were found in the voxel analysis: the D_2 binding potential in the entire striatum was correlated with finger tapping scores (Figure 6).

Secondary Neuropsychological and Clinical Measures and Regional D_2 Binding Potential in Depressed Subjects

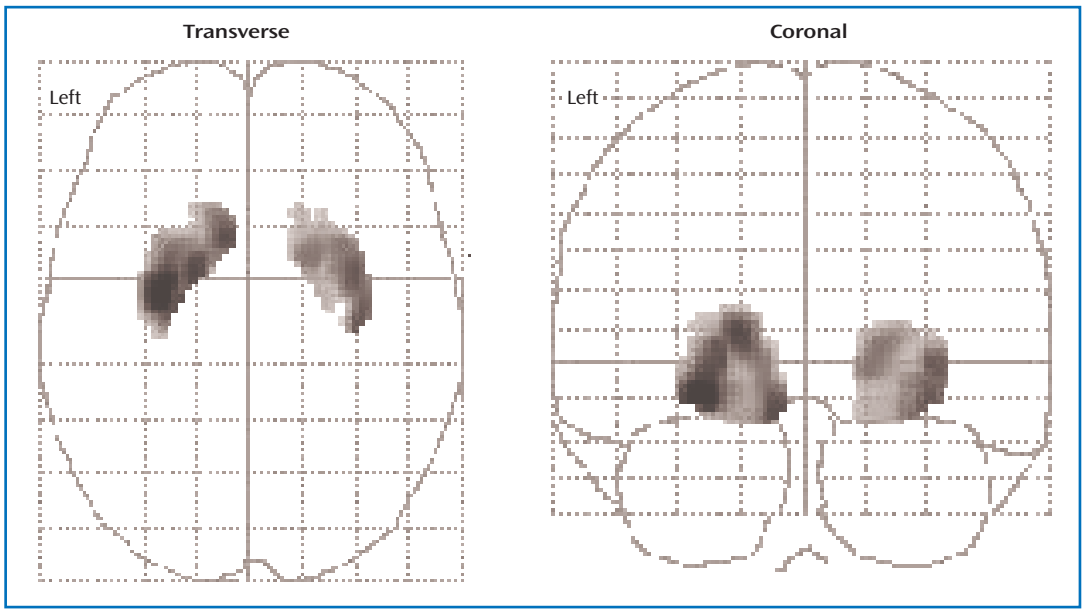
Since the D_2 binding potential among regions was correlated within individuals, the correlations between other neuropsychological measures and whole striatal D_2 binding potential was examined first (Table 2). There were no significant correlations between individual neuropsychological tests and regional D_2 binding potential in either group (except for the finger tapping test). In addition, post hoc analyses of clinical measures showed that no other clinical variable (including number of previous episodes, length of current episode, history of antidepressant treatment) was significantly correlated with regional D_2 binding potential.

Discussion

This is the first study to investigate striatal D_2 binding potential in medication-free, nonsmoking depressed subjects. The main findings were that caudate and putamen D_2 binding potential were elevated in the depressed group as compared with the healthy group, and that putamen D_2 binding potential was most significantly elevated in the depressed subgroup with motor retardation. Moreover, there was a significant correlation between putamen D_2 binding potential and motor speed in the depressed group. These findings are important for understanding the pathophysiology of depression because they represent a striatal dopaminergic disturbance during depression that is most prominent when motor retardation is present. This has implications for the monoamine theory of depression. In addition, these findings have important implications for treatment, since this dopamine abnormality may be targeted by dopamine-increasing antidepressants.

The best interpretation of these findings is that putamen dopamine is low in depression with motor retardation. Elevations in D_2 binding potential measured with [^{11}C]raclopride PET may occur when dopamine is low (13, 14), and the most significant elevations in putamen D_2 binding potential were observed in the depressed subjects with motor retardation (Figure 3). These results are consistent with previous reports of lower CSF metabolite of dopamine in depressed subjects with motor retardation (8, 9) and the general disease model associating motor retardation with impaired dopaminergic neurotransmission in the putamen (5, 6). These results are also consistent with our previous finding of lower dopamine transporter binding potential in a similar group of medication-free depressed subjects (34), since dopamine transporter density can decrease during chronic dopamine-depleting para-

FIGURE 4. Voxel-Based Comparison of Striatal D_2 Receptor Binding Potential Between Depressed Subjects With Motor Retardation (N=10) and Healthy Subjects (N=21)[a]



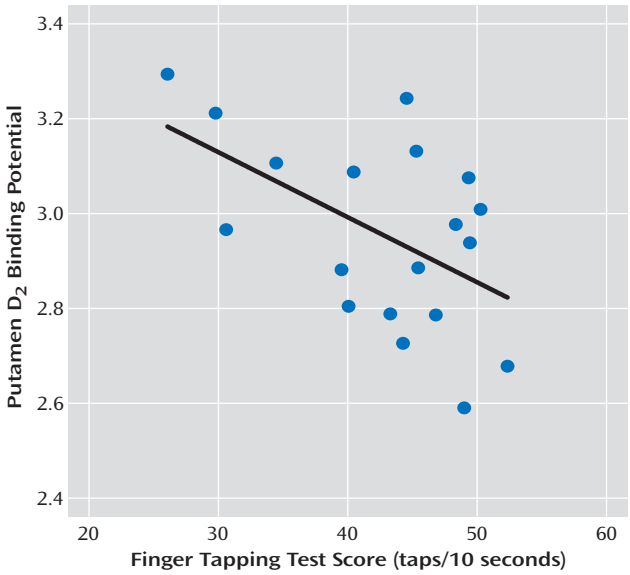
[a] After correction for cluster significance, ANCOVA with age as a covariate revealed two significant clusters depicting the effect of a major depressive episode with motor retardation (left striatum: N=1277 suprathreshold voxels, p<0.001 [corrected for cluster size]; right striatum: N=1174 suprathreshold voxels, p<0.001 [corrected for cluster size]). Threshold for display, p≤0.05.

digms (36, 37). The other investigation of striatal dopamine transporter in medication-free depressed subjects sampled those with seasonal affective disorder and also found lower striatal dopamine transporter binding potential (38).

The results of the present study have important implications for understanding the neurochemistry of major depressive disorder. In many versions of the monoamine theory of depression, major depressive disorder is viewed as having a pathology of homogenous monoamine loss. A contrasting view is that specific monoamines are lowest when specific symptoms of depression are most severe (35). Although putamen D_2 binding potential was elevated in the depressed group as compared with the healthy group, the data in Figure 3 show that the elevation in putamen (and striatal) D_2 binding potential was driven by the depressed group with motor retardation. Since putamen D_2 binding potential is highest in the depressed subjects with motor retardation and since measurement of D_2 binding potential with [^{11}C]raclopride PET is inversely correlated with extracellular dopamine levels (13, 14, 16), the results argue for heterogeneous monoamine loss in depression (with greater specific monoamine loss when specific symptoms are more severe).

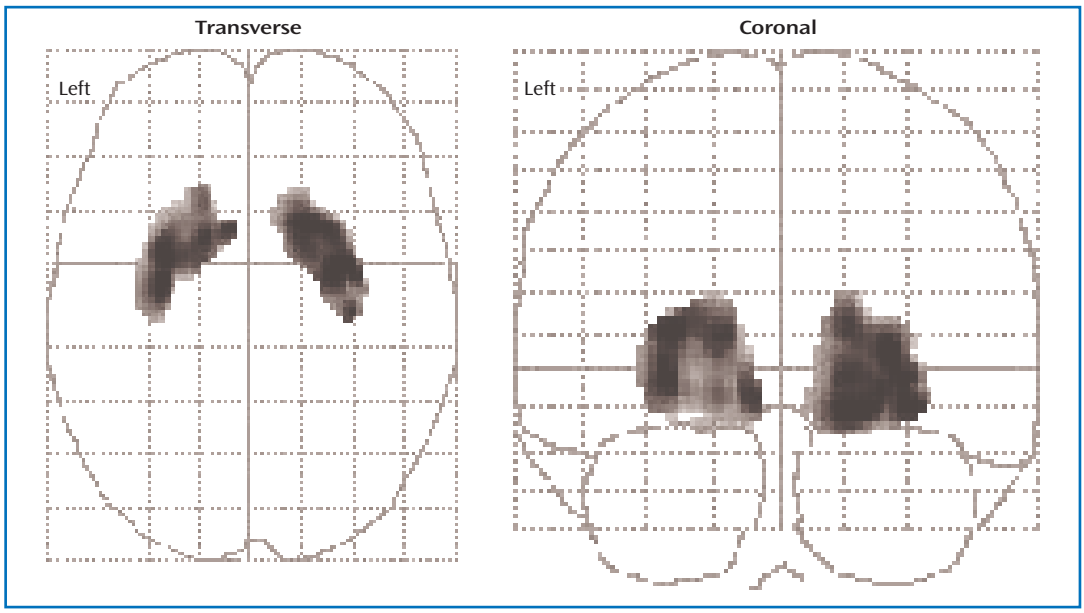
The interpretation that extracellular dopamine is low in depressed subjects with motor retardation has substantial implications for treatment because it argues for a preferential response in this subtype to antidepressants that induce sustained dopamine agonist effects such as dopamine reuptake inhibitors (i.e., bupropion and sertraline) and monoamine oxidase A and A/B inhibitors (1–4). Moreover, it is likely that further dopamine reuptake inhibitor development will occur, since current treatments are unlikely to

FIGURE 5. Correlation Between Bilateral Putamen D_2 Receptor Binding Potential and Motor Speed in Depressed Subjects (N=19)[a]



[a] In order to reduce variance related to age and gender, individual putamen D_2 binding potential values were normalized to a 30-year-old subject using the slope of the age-related decline. Individual finger tapping scores were normalized similarly to a 30-year-old male subject. The correlation was significant (r=–0.53, df=17, p=0.02).

FIGURE 6. Correlation Between Voxel Measurement of D_2 Receptor Binding Potential in Striatum and Motor Speed in Depressed (N=19) Subjects[a]



[a] After correction for cluster significance, ANCOVA with age as a covariate revealed two significant clusters depicting the effect of motor speed (left striatum: N=1665 suprathreshold voxels, p<0.001 [corrected for cluster size]; right striatum: N=1523 suprathreshold voxels, p<0.001 [corrected for cluster size]). Threshold for display, p≤0.05.

be optimally therapeutic at this target site. For example, in contrast to the 80% or greater occupancy of serotonin transporters typically found at therapeutic dosing of serotonin reuptake inhibitors (35), dopamine transporter blockade with sustained-release bupropion has been estimated between 0% and 26% (39–41). The other commonly used antidepressant with dopamine reuptake inhibitor properties, sertraline, has approximately two orders of magnitude higher affinity for the serotonin transporter over the dopamine transporter (1, 2), and it is probable that a closer affinity ratio between these two sites would be more optimal for therapeutic effect. A related class, dopamine-releasing medications, is available, but their mechanism is dependent upon intact dopamine storage (42), making them less clinically relevant. It is well known that serotonin-releasing medications like *d*-fenfluramine are not therapeutically relevant for treating depression. It is also theoretically possible that dopamine agonists that stimulate dopamine receptors in a similar manner to dopamine itself could also prove to be therapeutically useful in treating motor retardation during major depression. The results of the present study argue for 1) the use of existing dopamine-increasing medications to treat depression with motor retardation and 2) the development of antidepressants with higher dopamine reuptake inhibitor blockade for depression with motor retardation.

Striatal D_2 binding potential was 9% higher in the putamen of depressed subjects with motor retardation as compared with the healthy subjects. Although this elevation of putamen D_2 binding potential in depressed subjects with motor retardation was significantly higher than healthy subjects, it is less than what occurs in early untreated Parkinson's disease (estimates with [^{11}C]raclopride PET measurement typically range from 7% to 30% [15–17], averaging at 20%) or after a severe acute dopamine depletion with alpha-methyl-paratyrosine (18% [14]). This is not surprising: the loss of dopamine neurons in Parkinson's disease is generally considered a large magnitude effect, and the version of the alpha-methyl-paratyrosine challenge used by Verhoeff et al. (14) was a drastic paradigm tolerated for only a brief period under inpatient supervision.

This study has limitations inherent in the measurement of D_2 binding potential that are common with in vivo imaging studies of disease states. Striatal D_2 binding potential as measured with [^{11}C]raclopride reflects a combination of D_2 receptor density, affinity, and accessibility of the radioligand to D_2 receptor sites. While D_2 binding potential can certainly increase under conditions of acute and chronic dopamine depletion (13, 14), there are a number of other potential explanations for a greater striatal D_2 binding potential. Therefore, our interpretation of low extracellular dopamine is also dependent upon other dopamine-related investigations in major depressive disorder. We did not measure hedonia, since neuropsychological measurements of hedonia need to be developed for major depressive disorder. Self-report of hedonia is potentially prone to biases of severely negativistic thinking (where every experience is viewed pessimistically, resulting in underreporting) and anxiety (where people are hesitant to incorrectly report and therefore underreport).

Some PET study designs also measure D_2 binding potential after dopamine depletion and assume that the dopamine depletion would result in similar final dopamine levels in patients and healthy comparison subjects (13). This assumption seems contradictory to our hypothesized model of abnormally regulated extracellular dopamine levels in depression, so we did not apply a dopamine-depleting paradigm. Our previous work found that the striatal dopamine transporter binding potential is lower in depression (34)—as would be expected during a dopamine-lowering process (36, 37)—and when it is lowest, it is actually protective against motor retardation. We surmised that a lower striatal dopamine transporter binding potential would result in less clearance of extracellular dopamine and would be protective against a different dopamine-lowering process. Promising mechanisms for a major dopamine lowering process include dysregulations of enzymes of dopamine synthesis or dopamine metabolism, and these will be studied in future research.

This study was the first investigation of striatal D_2 binding potential in drug-free, nonsmoking, currently depressed subjects with a reasonably large patient group size. We found that depressed subjects with motor retardation had a significantly elevated striatal D_2 binding potential relative to healthy volunteers. Moreover, among depressed subjects, higher striatal D_2 binding potential was correlated with more severe motor retardation. The best explanation for these findings is that lower extracellular dopamine occurs in depressed subjects with motor retardation, since this explanation is consistent with reports of low CSF HVA in depression with motor retardation (8, 9), low dopamine transporter binding potential in depression (34), and an association between putamen dopaminergic pathology and motor retardation in other disease models (5, 6, 15). Low dopamine pathology in depression with motor retardation has important implications for the treatment of motor retardation in depression. This subtype of depression should benefit from dopamine-increasing medications, and future clinical trials of dopamine reuptake inhibitor treatments should be conducted in depression with motor retardation.

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