

Dopamine D₂ Receptor Levels in Striatum, Thalamus, Substantia Nigra, Limbic Regions, and Cortex in Schizophrenic Subjects

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Background: Studies in schizophrenic patients have reported dopaminergic abnormalities in striatum, substantia nigra, thalamus, anterior cingulate, hippocampus, and cortex that have been related to positive symptoms and cognitive impairments.

Methods: [¹⁸F]fallypride positron emission tomography studies were performed in off-medication or never-medicated schizophrenic subjects ($n = 11$, 6 men, 5 women; mean age of 30.5 ± 8.0 [SD] years; 4 drug-naïve) and age-matched healthy subjects ($n = 11$, 5 men, 6 women, mean age of 31.6 ± 9.2 [SD]) to examine dopamine D₂ receptor (DA D_{2r}) levels in the caudate, putamen, ventral striatum, medial thalamus, posterior thalamus, substantia nigra, amygdala, temporal cortex, anterior cingulate, and hippocampus.

Results: In schizophrenic subjects, increased DA D_{2r} levels were seen in the substantia nigra bilaterally; decreased levels were seen in the left medial thalamus. Correlations of symptoms with ROI data demonstrated a significant correlation of disorganized thinking/nonparanoid delusions with the right temporal cortex ROI ($r = .94, p = .0001$), which remained significant after correction for multiple comparisons ($p < .03$). Correlations of symptoms with parametric images of DA D_{2r} levels revealed no significant clusters of correlations with negative symptoms but significant clusters of positive correlations of total positive symptoms, delusions and bizarre behavior with the lateral and anterior temporal cortex, and hallucinations with the left ventral striatum.

Conclusions: The results of this study demonstrate abnormal DA D_{2r}-mediated neurotransmission in the substantia nigra consistent with nigral dysfunction in schizophrenia and suggest that both temporal cortical and ventral striatal DA D_{2r} mediate positive symptoms.

Key Words: Delusions, dopamine D₂ receptors, fallypride, hallucinations, schizophrenia, substantia nigra, thalamus

Abnormal dopaminergic neurotransmission has been implicated in the positive symptoms and cognitive deficits seen in schizophrenia (1–5). Recent studies suggest abnormal function of γ -aminobutyric acid (GABA)ergic/glutamatergic cortical microcircuits in schizophrenia, resulting in dysfunction of cortical pyramidal glutamatergic neurons (6), which provide a major excitatory afferent projection to the substantia nigra (7). Dysfunction of this projection results in nigral dysfunction and increased striatal dopamine (DA) release (8–10), which has been positively correlated with positive symptoms (11). Prefrontal cortical glutamatergic afferents to the ventral tegmental area (VTA) synapse directly on mesocortical DA neurons; it has been hypothesized that dysfunction of this projection leads to decreased cortical DA release (12), which is believed to be a factor in the cognitive impairments seen in schizophrenia (4). Because dopamine D₂ receptors (DA D_{2r}) directly modulate cortical GABAergic interneurons (13,14), ventral midbrain DA neurons (15,16), and DA release in striatal and extrastriatal regions (17), DA D_{2r} are of considerable interest in schizophrenia.

Consistent with the hypothesis of decreased cortical DA release in schizophrenia, postmortem studies have reported

decreased dopaminergic innervation in medial temporal cortex, dorsolateral prefrontal cortex, and hippocampus (18–20) and dopamine metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC) levels in the anterior cingulate (21). Some imaging studies of extrastriatal DA D_{2r} in schizophrenic subjects have reported decreased DA D_{2r} levels in the anterior cingulate and temporal cortex, but most have not (22–27); the most frequent finding is decreased medial thalamic DA D_{2r} levels (24–26). Although there have been variable results, a recent study of DA D_{1r} in schizophrenic subjects reported increased frontal cortical levels that were negatively correlated with performance on a working memory task (28–30). The increased DA D_{1r} levels were interpreted as being consistent with decreased frontal cortical DA levels. Postmortem studies of dopaminergic function in the substantia nigra in schizophrenic subjects have reported increased levels of tyrosine hydroxylase (31), tyrosine hydroxylase messenger RNA (mRNA) (32), homovanillic acid (31), and DA D_{2r} (33) consistent with nigral dysfunction. Imaging studies have largely failed to examine substantia nigra DA D_{2r}. Both postmortem and imaging studies have reported increased striatal DA synthesis, DA levels, and DA release, which has been correlated with positive symptoms (34–41). In contrast to postmortem studies that have reported increased striatal DA D_{2r} levels (42,43), most but not all imaging studies of striatal DA D_{2r} have reported unaltered levels in schizophrenia (44–46). However, one imaging study of striatal DA D_{2r} performed before and after DA depletion with alphas-methylparatyrosine demonstrated normal levels before DA depletion but increased DA D_{2r} levels after depletion consistent with both increased striatal DA release and increased total DA D_{2r} levels (36). The discrepancy between postmortem studies and imaging studies with benzamide radioligands might be due to the occupancy of striatal DA D_{2r} by increased levels of extracellular DA. Overall, the available post-

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mortem and imaging data are consistent with the hypothesis of decreased cortical DA release, nigral DA neuronal dysfunction, and increased striatal DA release in schizophrenia.

Previous imaging studies of DA D₂r in medication-free schizophrenic subjects have evaluated either striatal or extrastriatal DA D₂r levels (22–27,44,45). In the current study, positron emission tomography (PET) with [¹⁸F]fallypride was used. [¹⁸F]Fallypride is a very high-affinity, specific benzamide PET radioligand for the DA D₂ receptor (K_D = .03 nmol/L) and is the only currently available radioligand that allows estimation of both striatal and extrastriatal DA D₂r levels (22,24,27,44–48). Given the hypothesis of nigral dysfunction in schizophrenia (1,8–10,12), the lack of previous imaging studies of the substantia nigra DA D₂r, post-mortem findings consistent with nigral dysfunction (31–33), and the ability of PET [¹⁸F]fallypride studies to estimate nigral DA D₂r levels (48,49), we specifically examined this region. Other regions previously reported to have altered DA D₂r levels—the anterior cingulate, temporal cortex, and medial thalamus (22–26)—were examined. Because significant correlations of symptoms with regional DA D₂r levels have been reported (22–27), correlations of positive and negative symptoms with regional DA D₂r levels were assessed.

Methods and Materials

Subjects

This study was conducted under protocols approved by the Vanderbilt University and Centerstone Mental Health Center institutional review boards. All subjects were judged capable of giving informed consent by a senior research psychiatrist and provided informed consent for this study. Subjects meeting the DSM-IV criteria (American Psychiatric Association, 1994) and Research Diagnostic Criteria (50) for the diagnosis of schizophrenia between the ages of 18 and 45 were recruited. The diagnosis of schizophrenia was established by the Structured Clinical Interview for DSM IV Axis I disorders (51) and checklist. Schizophrenic subjects ($n = 11$, 6 men, 5 women; mean age of 30.5 ± 8.0 [SD] years and age range of 20–45 years) were either never treated ($n = 4$) or were off-medication for at least 3 weeks (Table 1). The Brief Psychiatric Rating Scale (BPRS) (6 item scales), Scale for the Assessment of Positive Symptoms (SAPS), and Scale for Assessment of Negative Symptoms (SANS) were administered to each subject; mean total BPRS, SAPS, and SANS scores were 28.8 ± 7.0 (SD), 9.8 ± 3.1 (SD), and 9.4 ± 4.0 (SD), respectively. Age-matched healthy subjects ($n = 11$, 5 men, 6 women, mean age of 31.6 ± 9.2 [SD] years and age range of

21–45 years) were recruited as well. Significant medical conditions and previous or current substance abuse were exclusion criteria for all subjects.

Data Acquisition and Analysis

Magnetic resonance imaging (MRI) scans of the brain were performed with a GE 1.5-T Signa LXi MRI scanner (GE Healthcare, Waukesha, Wisconsin). High-resolution T1-weighted gradient echo acquisitions in the sagittal plane (1.2–1.3-mm-thick slices) and coronal planes (1.4–1.5-mm-thick slices) and axial spin density-weighted and T2 weighted (3-mm-thick slices) acquisitions were obtained. The PET scans were performed with a GE Advance PET scanner in the three-dimensional acquisition mode. [¹⁸F]Fallypride (4–5 mCi, specific activity >2000 Ci/mmol, maximum mass dose of <2.5 nmol) was injected intravenously over a 20-sec period; serial scans of increasing duration were obtained for 210 min, allowing stable estimates of binding potentials in all regions (47–49). A measured attenuation correction was used.

Serial PET scans were co-registered to each other and to thin section T1-weighted MRI images with a rigid-body, mutual information algorithm (52,53) and reoriented to the anterior commissure–posterior commissure (ACPC) line. Regions of interest (ROIs) were identified on thin section T1 weighted MRI images and transferred to co-registered PET studies. The putamen and caudate were manually drawn by a neuroradiologist (RMK) on axial slices from 2 to 12 mm above the ACPC line. The ventral striatum was defined with the criteria of Mawlawi *et al.* (54). Sobel filtering was performed on high-resolution gradient echo MRI images of the brain (55) but did not provide reliable boundaries for delineation of the dorsomedial thalamus and pulvinar. We used anatomic landmarks to delineate the medial thalamus and posterior thalamus, which approximated the boundaries of the dorsomedial thalamus and pulvinar (56). The medial thalamus was delineated on slices from 2 to 12 above the ACPC line; the posterior border was the coronal plane of the posterior commissure, the medial border was the midline, the anterior boundary was the foramen of Monro, and the lateral border extended up to 1 cm from the midline. The anterior border of the posterior thalamus was the coronal plane of the posterior commissure, the medial and posterior borders were the edge of the thalamus as it projects into the quadrigeminal plate cistern, and the lateral border was the posterior limb of the internal capsule. The substantia nigra/VTA is located in the ventral midbrain 9–14 mm below the ACPC line (56) and can be readily visualized in the midbrain on PET [¹⁸F]fallypride scans (57). Substantia nigra ROIs were manually drawn to adjust for inter-individual variability by a neuroradiologist (RMK); the intersubject coefficient of variation for the substantia nigra region was 8.7% (57). The amygdala can be visualized on MRI scans just anterior to the tip of the temporal horn of the lateral ventricle and deep to the uncus (57); the amygdala is located 6–20 mm below the ACPC line, 12–28 mm lateral to the midline, and from 2 to 12 mm behind the plane of the anterior commissure (56). To decrease partial voluming from the striatum, amygdala ROIs were drawn on MRI images from 10 to 16 mm below the plane of the ACPC. Temporal cortical ROIs were manually drawn on axial MRI images from 35 to 25 mm below the ACPC. Our previous studies have shown excellent inter-subject reliability for these ROIs (i.e., inter-subject coefficients of variation of 6.8%–15.9%) (57). The anterior cingulate was delineated as extending from superior to the axial plane through the ACPC in the pregenual region superiorly and

Table 1. Demographic Data for Off-Medication Schizophrenic Subjects

Subject Number	Gender	Age	Medication-Free Period	Previous Medications	BPRS Score (6-item scale)
1	F	36	3 weeks	quetiapine	30
2	F	32	9 weeks	quetiapine	32
3	M	22	5 weeks	olanzapine	38
4	M	20	Never Medicated	NA	27
5	F	36	21 weeks	olanzapine	40
6	F	39	10 weeks	olanzapine	19
7	M	22	Never Medicated	NA	32
8	F	35	Never Medicated	NA	18
9	M	23	40 weeks	olanzapine	30
10	M	45	Never Medicated	NA	29
11	M	26	3 weeks	olanzapine	22

BPRS, Brief Psychiatric Rating Scale.

Table 2. Binding Potentials for ROIs Sampled in 11 Unmedicated Schizophrenic Subjects and 11 Age-Matched Healthy Subjects

Region	Schizophrenic		Normal		Significance Level	
	R	L	R	L	R	L
Medial Thalamus	4.21 ± .58	4.17 ± .55	4.30 ± .62	4.55 ± .58	.51	.04
Posterior Thalamus	2.28 ± .41	2.40 ± .30	2.36 ± .32	2.54 ± .36	.41	.11
Anterior Cingulate	.79 ± .15	.75 ± .15	.78 ± .17	.77 ± .16	.52	.55
Substantia Nigra	2.87 ± .33	2.75 ± .34	2.44 ± .22	2.41 ± .19	.002	.009
Hippocampus	1.57 ± .41	1.68 ± .38	1.48 ± .26	1.59 ± .34	.59	.68
Temporal Cortex	1.52 ± .33	1.63 ± .33	1.59 ± .18	1.72 ± .24	.30	.20
Caudate	30.70 ± 3.30	31.81 ± 4.12	32.25 ± 2.08	32.33 ± 2.13	.19	.72
Putamen	36.52 ± 4.36	35.00 ± 4.46	37.02 ± 2.56	36.94 ± 2.77	.68	.18
Ventral Striatum	18.80 ± 3.66	19.49 ± 3.49	18.10 ± 2.81	18.36 ± 3.41	.60	.38
Amygdala	3.28 ± .43	3.20 ± .61	3.23 ± .27	3.26 ± .24	.85	.64

Significance level was estimated with an independent group, two-tailed *t* test covered for age. ROI, region of interest.

posteriorly to the coronal plane through the anterior commissure. The hippocampus was manually delineated on the coronal MRI images from the tip of the temporal horn anteriorly to the last coronal slice in which it would be reliably identified posteriorly. Regional DA D₂r levels were estimated with the reference region method with a cerebellar reference region (58). The cerebellum is an appropriate reference region, because <3% of cerebellar uptake is specific binding to DA D₂ receptors and reference region method estimates of binding potentials are highly correlated ($r > .99$) with modeled estimates with a metabolite corrected plasma input function (47,59–61). Parametric images of DA D₂r were co-registered across subjects with an elastic deformation algorithm (62).

Statistical Analysis

Region of interest data were analyzed with a repeated measures multivariate analysis of variance (MANOVA) with region and hemisphere as within subject factors and group (schizophrenic, healthy control) as a between subject factor with age as a covariate. Definition of the hippocampal ROI was problematic in one subject, and this subject was left out of the analysis. When the MANOVA was performed with this subject but without the hippocampus as a region, no conclusion was changed. Because age has a significant effect on DA D₂r levels, independent group two-tailed *t* tests covaried for age were used to test for group differences in regional binding potentials. To evaluate positive symptoms, the total SAPS scores and global SAPS scores for hallucinations, delusions, and bizarre behavior as well the BPRS positive symptom score and BPRS scores for suspiciousness (Item 11), hallucinations (Item 12), and disorganized thinking/nonparanoid delusions (Item 15) were measured. Negative symptoms were examined with the SANS. Correlations of symptom scores with ROIs were performed with a Pearson product moment correlation, and significance was evaluated with a two-tailed *t* test. Bonferroni correction was used to correct for multiple comparisons. Correlations of symptom scores with parametric DA D₂r images were calculated on a voxel basis with a Pearson product moment correlation, and significance was evaluated with a two-tailed *t* test. To assess the significance of clusters of significant correlations, corrections for multiple comparisons were made with the method of Forman as implemented in the AFNI program (63). The critical threshold for the voxelwise analysis was $p < .01$ and a minimum cluster size of 24 voxels. These clusters were significant at $p < .001$ corrected for multiple comparisons.

Results

A repeated measures MANOVA was performed with region and hemisphere as within subject factors, group (schizophrenic, healthy control) as a between subject factors, and age as a covariate. No significant main effect of hemisphere, group × hemisphere interaction, or group × hemisphere × region interaction was seen. There was a significant effect of region [$F(7,13) = 36.78$, $p < .00001$], reflecting the large differences in regional binding potentials (Table 2). There was no main effect of group. However, there was a significant region × group interaction [$F(7,13) = 6.00$, $p < .005$]. There was also a region × age interaction [$F(7,13) = 4.60$, $p < .010$], reflecting decreases in regional binding potentials with age that were greater for cortical than subcortical regions. To explore the regions responsible for the significant region × group interaction, independent group two-tailed *t* tests covaried for age were performed to examine which region(s) might account for this interaction. These tests demonstrated significantly increased DA D₂r levels in the substantia nigra/VTA bilaterally and decreased levels in the left medial thalamus (Table 2). No other ROI demonstrated a significant difference in DA D₂r levels between schizophrenic and healthy subjects.

Correlation of ROI data with SAPS scores, SANS scores, BPRS positive symptom score, and BPRS scores for suspiciousness (Item 11), hallucinations (Item 12), and disorganized thinking/nonparanoid delusions (Item 15) demonstrated one correlation that survived Bonferroni correction and a second trend level correlation. The DA D₂r levels in the right temporal cortex ROI were positively correlated with the BPRS score for disorganized thinking/nonparanoid delusions ($r = .94$, $p = .0001$ uncorrected for multiple comparisons, $p < .03$ after correction for multiple comparisons). The left temporal cortical ROI demonstrated a trend level correlation with the BPRS score for disorganized thinking/nonparanoid delusions after corrections for multiple comparisons ($r = .92$, $p = .0003$, uncorrected for multiple comparisons, $p < .08$, corrected for multiple comparisons).

Correlations of symptoms with regional DA D₂r levels performed with voxelwise analysis revealed no significant clusters of correlations of regional DA D₂r levels with either the total SANS score or individual SANS scores. Significant clusters of highly positive correlations of regional DA D₂r levels were seen with the total SAPS score and global SAPS scores for delusions, hallucinations, and bizarre behavior. Two clusters of highly positive correlations (146 voxels on the right, mean $r = .85$; 131 voxels on

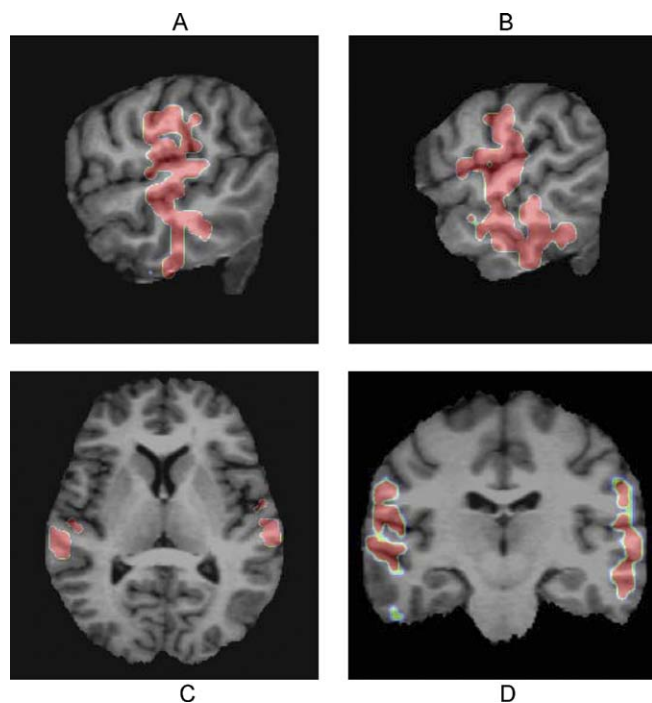


Figure 1. Sagittal (A,B), axial (C), and coronal (D) images through significant clusters of correlations of total Scale for the Assessment of Positive Symptoms (SAPS) scores with regional dopamine D_2 receptor ($DA D_{2r}$) levels. Two significant clusters are seen involving the posterior portions of the inferior, middle, and superior temporal gyri with extension superiorly into the supramarginal gyrus of the parietal lobe in both cerebral hemispheres. The cluster on the right (146 voxels, mean $r = .85$) was similar in size to the cluster on the left (131 voxels, mean $r = .86$).

the left, mean $r = .86$) were seen with total SAPS scores; these clusters involved the posterior portions of the inferior, middle, and superior temporal gyri and extended superiorly into the supramarginal gyrus of the parietal lobe in both cerebral hemispheres (Figure 1). Significant clusters of correlations of SAPS global delusions scores with $DA D_{2r}$ levels were seen in the lateral aspects of the right and left anterior temporal cortex extending into the temporal tips laterally (50 voxels on the right, mean $r = .84$; 80 voxels on the left, mean $r = .86$) (Figure 2). Similarly, correlations of the BPRS score for disorganized thinking/nonparanoid delusions (Item 15) with $DA D_2$ receptor levels demonstrated a similar cluster of positive correlations in the left anterior temporal cortex (80 voxels, mean $r = .85$). The SAPS global bizarre behavior scores demonstrated bilateral clusters of positive correlations (184 voxels on the right, mean $r = .85$; 179 voxels on the left, mean $r = .84$). The cluster on the left involved the posterior portions of the inferior and superior temporal gyri as well as the mid to posterior portions of the middle temporal gyrus with extension into the inferior parietal lobule. The cluster on the right also involved the inferior, middle, and superior temporal gyri and inferior parietal lobule; it extended further anteriorly in the sulcus between the superior and middle temporal gyrus but had less extension into the posterior superior temporal gyrus and inferior parietal lobule than the cluster on the left (Figure 3). In contrast, the SAPS global scores for hallucinations demonstrated positive correlations with the left ventral striatum (31 voxels, mean $r = .84$) but not with cortical regions (Figure 4). The BPRS scores for hallucinations demonstrated a similar left ventral striatal cluster of positive correlations (41 voxels, mean $r = .87$).

Discussion

The results of this study indicate that there are increased $DA D_{2r}$ levels in the substantia nigra/VTA and decreased $DA D_{2r}$ levels in the left medial thalamus. The increased levels of nigral/VTA $DA D_{2r}$ seen in the current study are consistent with the one postmortem study of nigral $DA D_{2r}$ in schizophrenic patients, which also reported increased levels (33). The $DA D_{2r}$ in the substantia nigra are largely inhibitory autoreceptors on nigral DA neurons (15,16). As discussed in the preceding text, postmortem studies have also reported increased nigral levels of tyrosine hydroxylase, tyrosine hydroxylase mRNA, and homovanillic acid (31,32) in the substantia nigra of schizophrenic subjects. The findings in both the current study and previous postmortem studies demonstrate both increased inhibitory nigral $DA D_2$ autoreceptor levels and increased DA synthesis and release, suggesting dysregulation of midbrain dopaminergic neurons in schizophrenic subjects. Similar findings (i.e., increased total $DA D_{2r}$ levels and increased DA synthesis and release) (34–43) have been reported in the striatum of schizophrenic subjects and suggest that similar dysregulation of dopaminergic neurotransmission occurs in both nigra and striatum. The factor(s) responsible for increased nigral and striatal $DA D_{2r}$ levels when increased extracellular DA levels are present are unclear.

The VTA, dorsal tier of the zona compacta of the substantia nigra and retrorubal fields, provide dopaminergic innervation to limbic and cortical regions and so are of considerable interest in schizophrenia (64,65). The resolution of the PET scanner used in this study is insufficient to distinguish changes in these areas from the ventral tier of the zona compacta, which provides dopaminergic innervation to the striatum.

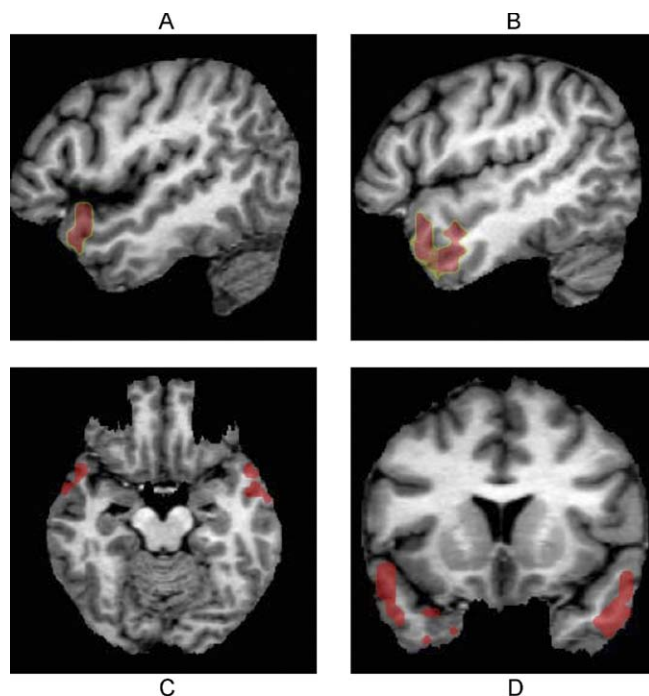


Figure 2. Two significant clusters of correlations of the Scale for the Assessment of Positive Symptoms global score for delusions with dopamine D_2 receptor levels are seen in the right (A) and left (B) sagittal planes in the anterolateral temporal cortex extending into the temporal tips. Clusters are shown in the axial (C) and coronal planes (D) through the temporal poles. The cluster on the left (80 voxels on the left, mean $r = .86$) is larger than the cluster on the right (50 voxels on the right, mean $r = .84$).

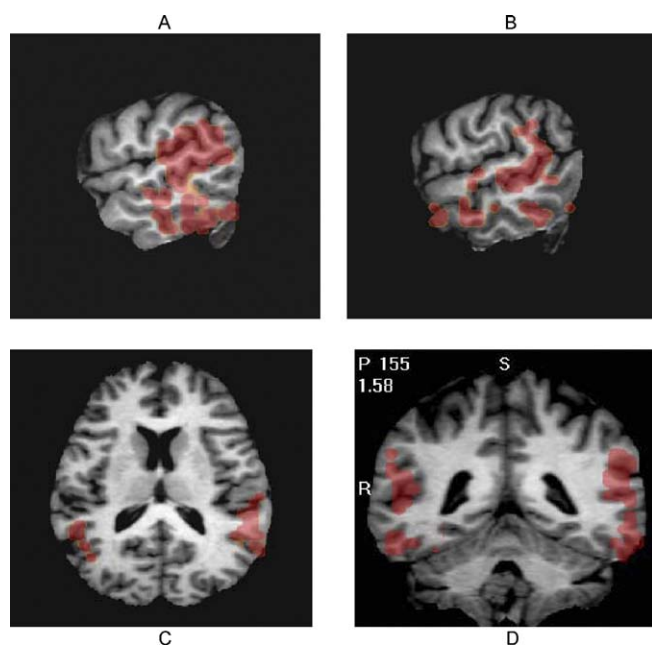


Figure 3. Sagittal left (A) and right (B), axial (C), and coronal (D) images through significant clusters of correlations of Scale for the Assessment of Positive Symptoms (SAPS) global scores for bizarre behavior with regional dopamine D_2 receptor (DA D_{2r}) levels. Two significant clusters of highly positive correlations (184 voxels on the right, mean $r = .85$; 179 voxels on the left, mean $r = .84$) involve the mid to posterior lateral aspects of the temporal lobes with extension into the inferior parietal lobule.

Although the PET scanner used in this study does not have sufficient resolution to provide complete quantitative recovery of DA D_{2r} levels in the substantia nigra, published calculated estimates of quantitative recovery for the substantia nigra indicate that the 5–6-mm resolution of the scanner does allow substantial recovery of quantitation (66). Consistent with these calculations are studies that indicate the ability of the scanner used to estimate SN DA D_{2r} occupancies by a number of antipsychotic drugs as well as the changes in apparent SN DA D_{2r} levels after DA release and DA depletion (49,57,59,67). There has been one recent [123 I]epidepride SPECT study that has reported decreased levels of midbrain uptake in schizophrenic subjects (68). The low resolution of SPECT relative to the size of the substantia nigra does not allow separation of nigral DA D_{2r} from those in other structures. In addition, the lack of a scatter correction, the use of a ratio method with cerebellum as a reference region before the attainment of a transient equilibrium, and the variability in this ratio due to lipophilic metabolites of [123 I]epidepride in the cerebellum makes interpretation of these results difficult (69–71).

The results of this study confirm the previously reported finding of decreased left medial thalamic DA D_2 receptor levels in schizophrenic subjects (24–26). An autoradiographic study of human thalamic DA D_{2r} has reported a heterogeneous and nuclear specific distribution of DA D_{2r} with highest levels in the midline and intralaminar nuclei of the thalamus; levels in the dorsomedial nucleus were at least twofold lower than in the midline and intralaminar nuclei (72). Whereas the dorsomedial nucleus accounts for most of the medial thalamic ROI, the midline and intralaminar nuclei are included in this ROI. Because a number of cognitive functions and behaviors that are impaired in schizophrenia are mediated by prefrontal cortical/basal gan-

glia/medial thalamic circuits (73), a loss of DA D_{2r} in the dorsomedial nucleus of the thalamus might contribute to these impairments. The thalamic intralaminar nuclei project to frontal cortex, striatum, and limbic regions, providing feedback from the thalamus to these regions (74,75); this feedback is affected by DA D_{2r} in these nuclei providing an additional site for modulation of prefrontal cortical/basal ganglia/medial thalamic circuit function. The apparent reduction in medial thalamic DA D_{2r} levels might reflect loss of medial thalamic neurons expressing DA D_{2r} consistent with imaging and postmortem studies reporting decreased medial thalamic volume and neuronal numbers (55,76–79), a loss of autoreceptors on medial thalamic dopaminergic projections, or an increase in thalamic DA release (80). However, increases in thalamic DA release are unlikely to cause the decrease in apparent left medial thalamic DA D_2 receptor levels, as d-amphetamine administration produces only a 3% decline in medial thalamic [18 F]fallypride binding potentials in humans (57).

The current results suggest that different positive symptoms are mediated by DA D_{2r} in different regions. Scores for delusions and bizarre behavior are positively correlated with anterior temporal/parietal tip and lateral temporal/inferior parietal cortical DA D_{2r} , respectively, whereas hallucinations are positively correlated with left ventral striatal but not cortical DA D_{2r} . Consistent with these correlations are cerebral blood flow studies in schizophrenic subjects that found positive correlations of left ventral striatal and left temporal tip blood flow in schizophrenic subjects with a reality distortion factor principally related to hallucinations and delusions (81). A comprehensive review of neurophathological lesions producing schizophrenic symptoms reported an association of striatal lesions with auditory hallucinations, whereas left temporal lobe lesions were associated with delusions (82). The differences in regional correlations for hallucinations and delusions raise the possibility that hallucinations and delusions might be differentially affected by antipsychotic drugs that produce preferential occupancy of temporal cortical versus striatal DA D_{2r} (60,67,83,84). The lack of significant clusters of correlations with negative symptoms suggests that these symptoms might not be mediated by DA D_{2r} neurotransmission.

The positive correlations of positive symptoms with cortical DA D_{2r} levels are similar to a recent [123 I]epidepride SPECT study that reported a positive correlation of positive symptoms with frontal cortical DA D_{2r} levels in male subjects but not female subjects (27). In subjects with bipolar disorder psychosis has been correlated with increased striatal DA D_{2r} (85) consistent

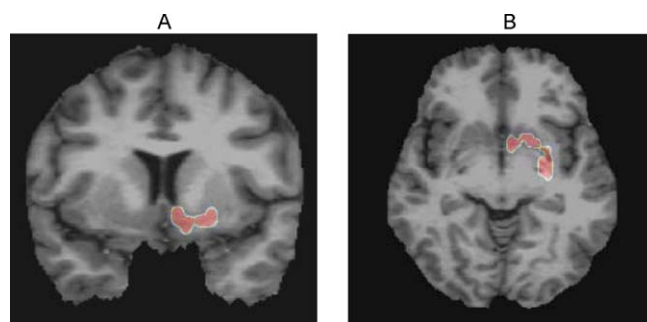


Figure 4. A significant cluster of correlations (31 voxels, mean $r = .84$) of the Scale for the Assessment of Positive Symptoms (SAPS) global score for hallucinations with dopamine D_2 receptor (DA D_{2r}) levels is seen in the left ventral striatum in the coronal (A) and axial (B) planes. No other significant clusters of correlations were seen.

with the results of the current study. Although previous studies (23–26) have reported negative correlations of medial, lateral, and/or total thalamic DA D₂ receptor levels with positive symptoms as measured by the BPRS or with the Positive and Negative Syndrome Scale general psychopathological scores, no significant correlations of symptom scores with medial thalamic ROIs were seen.

There are a number of potential limitations in this study. These include the small number of subjects studied and the fact that 7 of the 11 subjects studied had received previous neuroleptic treatment. Although the number of schizophrenic subjects examined in the current study is similar to other PET studies of extrastriatal DA D₂r, which have studied 7 to 15 subjects, a larger cohort might provide more reliable estimates of DA D₂r levels in schizophrenia (22–26). The largest study of extrastriatal DA D₂r in unmedicated schizophrenic patients, a SPECT study of 25 subjects, did not evaluate the regions found to be abnormal in the current study (27). Because increased, decreased, and unchanged levels of DA D₂r are seen in the current study, it is unlikely that the increased levels seen reflect receptor upregulation due to previous therapy or the decreased levels reflect residual antipsychotic drug effects. Although subjects were not carefully matched for smoking status, it is unlikely that the current results were affected by smoking status, because extrastriatal DA D₂r levels are not affected by smoking status (86). Although female subjects were not carefully matched for menstrual status, one study of the effect of menstrual status on DA D₂r levels in humans (87) found no statistically significant effect, whereas a second, older study (88) reported a small effect, but no statistical significance was reported; the effect, if any, is small. Finally, extracellular DA levels might be altered in schizophrenia and affect the apparent levels of DA D₂r, because [¹⁸F]fallypride has been shown to be sensitive to extracellular DA levels (49,57).

In conclusion, the results of this study demonstrate increased substantia nigra and decreased left medial thalamic DA D₂r levels in off-medication schizophrenic subjects. Positive correlations of positive symptoms with temporal cortical and left ventral striatal DA D₂r levels were found. The increased substantia nigra DA D₂r levels are consistent with the hypothesized nigral dysfunction in schizophrenia. The positive correlations of hallucinations with ventral striatal DA D₂r levels and delusions and bizarre behavior with temporal cortical receptor levels provides additional evidence for the role of DA D₂r mediated neurotransmission in these key psychotic symptoms and suggests that these symptoms might be mediated by DA D₂r in different brain regions.

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