
Striatal Dopamine Transporter Imaging Correlates with Anxiety and Depression Symptoms in Parkinson's Disease

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We studied the correlation of striatal dopamine transporter (DAT) imaging with anxiety and depression symptoms in Parkinson's disease (PD). **Methods:** Patients with idiopathic PD ($n = 76$) and age-matched healthy volunteers ($n = 46$) underwent SPECT brain scans with ^{99m}Tc-TRODAT-1, a radiolabeled tropane that selectively binds to the DAT. TRODAT-1 distribution volume ratios, a reflection of DAT availability, were calculated from the SPECT scan data for 6 regions of interest (ROIs) in the caudate and putamen. The association between neuropsychiatric symptoms (anxiety, depression, and fatigue) and DAT availability was explored for both subject groups, and the impact of disease severity on this association was examined in the PD group. **Results:** PD patients showed lower DAT availability than did healthy volunteers in all examined regions (for all ROIs, $P < 0.001$). In PD patients, higher individual affective measures (for anxiety, $r = -0.30$ and $P = 0.01$; and for depression, $r = -0.24$ and $P = 0.05$) and total affect scores ($r = -0.31$; $P = 0.01$) were associated with diminished left anterior putamen DAT availability. The association between total affect scores and DAT availability was present only in the subset of patients with less severe PD ($r = -0.35$; $P = 0.04$), but subjects with the highest DAT availability did not show high total affect scores. No association between neuropsychiatric measures and DAT availability was found in the controls. **Conclusion:** These preliminary findings suggest that decreased DAT availability may be necessary for but not invariably associated with the development of affective symptoms in PD. This suggestion is consistent with previous research showing a link between depression and basal ganglia impairment, particularly involving the left hemisphere, and extends this finding to include anxiety.

Key Words: TRODAT-1; dopamine transporter; anxiety; depression; Parkinson's disease

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P sychiatric and other nonmotor symptoms are common in Parkinson's disease (PD). Prevalence estimates for clinically significant depression and anxiety are 30%–40% each, and these conditions are frequently comorbid (1,2). Although the etiologies of depression and anxiety in PD are likely multifactorial, specific brain regions and neurotransmitters have been implicated.

Regional brain changes have been revealed for depression, with an association between striatal deficits and depression in non-PD patients, by structural and functional neuroimaging (3–9). Depressed PD patients were found to have reduced basal limbic system echogenicity by transcranial sonography and MRI (10). An association between abnormal bilateral caudate, putamen, and frontal lobe metabolism and either a depression diagnosis (11) or depression symptoms (12) was revealed for PD by PET.

Some studies with non-PD patients have found that depression is more common with left hemispheric striatal changes (13,14). Most studies reporting an association between laterality and affective changes in PD patients have found a link between right-sided symptoms (i.e., left hemisphere dysfunction) and depression (15,16).

In addition to serotonin and norepinephrine, dopamine is thought to be an important neurotransmitter in the pathophysiology of depression. One study with non-PD patients reported higher dopamine transporter (DAT) availability in several striatal regions in patients with major depression than in healthy controls. The authors speculated the presence of upregulation of the dopamine system in depression (9). Dopaminergic deficiency has been associated with depression in PD in some (17,18) but not all (19) studies. However, there is no published research examining the relationship between depression and DAT integrity in PD.

Research on the pathophysiology of anxiety has focused on the prefrontal cortex and the amygdala, 2 regions that

project to the striatum. Increased prefrontal cortex dopamine release has been demonstrated with stress (20,21), and a PET study with non-PD patients found an association between higher scores on anxiety-related personality scales and lower ^{18}F -fluorodopa uptake in the caudate (22). A PET study with PD patients found a paradoxical, highly significant positive correlation between an anxiety- and depression-related personality score and 6- ^{18}F -fluorodopa uptake in the right caudate nucleus (23).

We hypothesized that increasing severity of depression symptoms, as measured with a standardized instrument, would be associated with decreased nigrostriatal dopamine function in PD patients but not in healthy volunteers, and that the association between depression and dopamine function would be more pronounced in the left striatum.

MATERIALS AND METHODS

Subjects

Patients with clinically diagnosed idiopathic PD ($n = 76$) underwent $^{99\text{m}}\text{Tc}$ -TRODAT-1 SPECT as part of a study measuring DAT availability in PD. They were referred from 2 large movement-disorders clinics in the greater Philadelphia metropolitan area and a third research clinic at a nearby university medical center. As a result, all diagnoses of PD were confirmed by specialists in the field. In addition to having at least 2 of the 4 cardinal features of PD, all patients included in this study had a history of a favorable response to dopamine replacement therapy. Patients with an Axis I psychiatric disorder were excluded; the presence or absence of an Axis I disorder was based on a structured clinical interview that was conducted with all potential subjects and that focused on psychiatric symptoms and treatment (24).

Because studies with rats and baboons showed that antiparkinsonian drug regimens that act on postsynaptic receptors do not affect the uptake of TRODAT-1 (25), the design allowed patients to be studied while they were taking most of their usual medications. Specifically, all patients were on dopamine replacement therapy. Drugs that act or could act on presynaptic transporters (e.g., tricyclic antidepressants) were discontinued for 7 half-lives before the study. Prospective patients taking selective serotonin reuptake inhibitors were excluded, because the half-lives of these medications are too long.

Healthy volunteers (an age-matched subset of a larger comparison population; $n = 46$) were recruited by investigators at the Division of Nuclear Medicine, Department of Radiology, University of Pennsylvania, to participate in the establishment of a normative database for $^{99\text{m}}\text{Tc}$ -TRODAT-1 SPECT studies. The

comparison subjects were found to have no axis I diagnosis when interviewed with a structured clinical interview (24). All were free from psychotropic medications, and none had a history of central nervous system disease. PD patients were more likely than healthy volunteers to be male and white (Table 1).

All subjects were provided with a detailed description of the study purpose and procedures in accordance with the ethical standards set forth by the institutional review board of the University of Pennsylvania. All subjects provided written informed consent before enrolling in the study.

Imaging Acquisition, Processing, and Analysis

The TRODAT-1 imaging protocol was previously described in detail (26). All individuals in the study were injected with a single bolus dose of 740 MBq (20 mCi) of $^{99\text{m}}\text{Tc}$ -TRODAT-1. Brain SPECT images were obtained from 3 to 4 h after injection at a framing rate of 5 min per scan with a triple-head camera equipped with fanbeam collimators (Picker 3000; Picker International). All image data were acquired in a 128×128 matrix through 40 projection angles over a 120° arc with a pixel width of 2.11 mm and a slice thickness of 3.56 mm. A simple, low-pass filter was applied with an order of 4 and a cutoff of 0.351 cm^{-1} . Photon attenuation correction was performed with Chang's first-order correction method (27).

Standardized templates representing various structures of the striatum were superimposed on the acquired images. Six primary regions of interest (ROIs) were assessed: right and left caudate, right and left anterior putamen, and right and left posterior putamen. The putamen was selected because it shows the most severe TRODAT-1 abnormalities in early PD. Each ROI on a template was slightly smaller than the actual structure it represented and was placed only on the 2 slices with the highest activity to minimize problems with ill-defined edges and effects of volume averaging (Fig. 1).

Supratentorial areas (at least 5 slices above the last slice containing the basal ganglia) other than the occipital cortex or cerebellum were used to model nonspecific activity because previous experience showed that the occipital cortex and cerebellum might have low counting rates that could destabilize kinetic analyses. The total number of counts in each ROI were divided by the total number of corresponding pixels for that region. Mean distribution volume ratios (DVRs) were calculated with the following equation from the ratios for the ROI and the reference region: $(\text{ROI} - \text{reference region})/\text{reference region}$.

All analyses of imaging parameters were conducted without knowledge of nonmotor test results. Intrarater reliability for analyses of the manually defined ROIs was estimated with intraclass correlation coefficients. The procedures were implemented with a

TABLE 1
Demographic and Clinical Characteristics of Study Subjects

Characteristic	Value for:		χ^2 or <i>t</i> test (<i>P</i> value)
	PD patients ($n = 76$)	Healthy volunteers ($n = 46$)	
Age (mean \pm SD)	62.8 \pm 10.8	60.2 \pm 11.7	0.9 (0.38)
Sex (% male)	75.0	52.2	6.7 (0.01)
Race (% white)	97.4	71.7	17.5 (<0.001)
Education (mean \pm SD no. of years)	15.1 \pm 2.9	14.9 \pm 3.2	0.3 (0.76)
Duration of PD (mean \pm SD no. of years)	7.5 \pm 5.5		

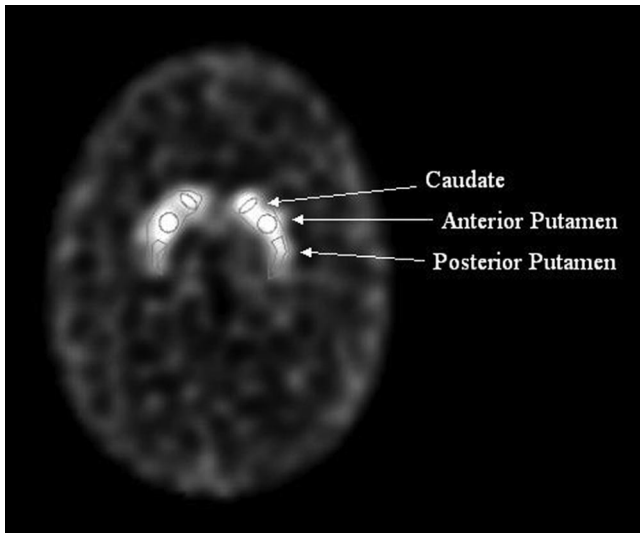


FIGURE 1. TRODAT-1 SPECT image of healthy volunteer (control) demonstrating ROI analysis for caudate, anterior putamen, and posterior putamen (shown within a larger region outlining the striatum).

commercial statistical package (StatS; Think Point Software). This procedure resulted in a high correlation because the high-contrast images were particularly amenable to “punch biopsy” approaches to image analysis and the “large” ROIs were difficult to misplace. The reliability of the image analysis techniques was found to be high, with intraclass correlations consistently above 0.95.

TRODAT-1 DVRs were used as surrogate measures of PD severity because previous research showed that both 6-¹⁸F-fluorodopa PET and ¹²³I-β-CIT SPECT of the DAT correlate with symptom severity in PD (28–30). For the purposes of this study, subjects were placed into groups representing less and more severe cases of PD by use of the median TRODAT-1 DVR (0.48) for the left anterior putamen (i.e., less severe cases with higher TRODAT-1 DVRs and more severe cases with lower TRODAT-1 DVRs).

All procedures were approved by the institutional review boards of all of the participating clinics as well as by the U.S. Food and Drug Administration.

Psychiatric Assessments

The State–Trait Anxiety Scale (31) and the Profile of Mood States (POMS) (32) instruments were administered to all subjects at the time of SPECT. The State–Trait Anxiety Scale is a 40-item self-administered instrument that contains 20 items pertaining to the current level of anxiety symptoms and 20 items inquiring about enduring anxiety symptoms. The POMS is a 65-item self-administered instrument that is well validated and widely used for rating mood and other affective symptoms. The POMS has 6 subscales: tension (commonly equated with anxiety), depression, fatigue, anger, confusion, and vigor. Higher scores on the State–Trait Anxiety Scale and the POMS indicate increasing severity of psychiatric symptoms. For the purposes of this study, we chose to include only the tension (or anxiety), depression, and fatigue subscales, as each of these symptoms is commonly reported in PD.

For secondary analyses, a composite affect score was created by use of an anxiety score (Trait Anxiety Scale score) and a depression measure (POMS depression subscale); these 2 measures were

highly correlated in our population ($r = 0.55$; $P < 0.001$). The raw score for each of these measures was transformed to a z score to provide equal weighting, and then an average z score for the 2 measures was calculated. This composite score (hereafter referred to as the total affect score) was used in subsequent analyses. Similar composite psychiatric scores are commonly used in the study of neuropsychiatric diseases (33). For the purposes of this study, an elevated total affect score was defined as ≥ 1 SD above the mean (i.e., a z score of ≥ 1).

Statistical Analyses

Group comparisons of demographic characteristics, neuropsychiatric measures, and DAT availability for each ROI were analyzed by use of the χ^2 statistic, multiple ANOVA, or the unpaired Student t test. The association between neuropsychiatric measures and DAT availability for each ROI was calculated by use of the Pearson correlation, controlling for age, sex, and duration of PD (when applicable). As the goal of this study was to probe for an association between DAT availability and neuropsychiatric symptoms in PD, corrections for multiple comparisons were not made. Statistical significance was defined as $P \leq 0.05$.

RESULTS

There were significant differences between the entire PD population and healthy volunteers in TRODAT-1 DVRs across the 6 ROIs [Wilks $\lambda(6,115) = 0.4$; $P < 0.001$] and for each ROI (Table 2). Consistent with previous research, the deficits for PD patients were more pronounced in the putamen, particularly the posterior region, than in the caudate.

There were significant differences between the PD patients and controls across the 5 neuropsychiatric measures [Wilks $\lambda(5,115) = 0.8$; $P < 0.001$], including significant differences between the groups on 2 of the 3 anxiety measures (State Anxiety Scale and POMS tension subscale). There was a trend for a difference on the POMS depression subscale (Table 2).

Increasing severity of both anxiety symptoms and depression symptoms was correlated with decreased DAT availability in the left anterior putamen region in PD patients (Table 3). This significant association remained when the total affect score was substituted for individual measures. There was no significant correlation in healthy volunteers between any neuropsychiatric measure and DAT availability in any ROI (data not shown).

When the PD sample was divided into less or more severely impaired groups based on DAT availability in the left anterior putamen, the total affect scores for the groups with less and more severe PD were similar ($t = 0.9$; $P = 0.37$). However, only the group with less severe PD showed a significant association between the total affect score and DAT availability (Table 4).

When the PD sample was divided into groups with higher (total affect z score of ≥ 1) or lower (total affect z score of < 1) severity of affective symptoms, all 10 subjects with higher total affect scores had left anterior putamen TRODAT-1 DVRs lower than the 80th percentile (i.e., a

TABLE 2
TRODAT-1 DVRs and Neuropsychiatric Measures

Parameter	Mean \pm SD value for:		P value
	PD patients (n = 76)	Healthy volunteers (n = 46)	
TRODAT-1 DVRs			
Right caudate	1.03 \pm 0.34	1.47 \pm 0.28	<0.001
Left caudate	1.02 \pm 0.31	1.49 \pm 0.30	<0.001
Right anterior putamen	0.61 \pm 0.31	1.26 \pm 0.32	<0.001
Left anterior putamen	0.55 \pm 0.30	1.23 \pm 0.27	<0.001
Right posterior putamen	0.33 \pm 0.18	0.75 \pm 0.29	<0.001
Left posterior putamen	0.33 \pm 0.20	0.75 \pm 0.24	<0.001
Neuropsychiatric measures			
State anxiety	37.5 \pm 9.0	32.0 \pm 7.6	<0.01
Trait anxiety	37.0 \pm 7.6	34.4 \pm 10.2	0.13
POMS tension	9.3 \pm 5.6	4.7 \pm 4.9	<0.001
POMS depression	6.0 \pm 7.4	3.7 \pm 7.0	0.09
POMS fatigue	6.0 \pm 4.9	4.6 \pm 4.5	0.11

DVR of <0.76). These data suggest that PD patients with relatively intact DAT availability do not develop higher levels of depression and anxiety symptoms (Figure 2).

DISCUSSION

We found evidence for an inverse correlation between severity of anxiety and depression symptoms and left anterior putamen DAT availability in PD patients; no such correlation was found in healthy volunteers. This research is the first to report an association between specific nigrostriatal dopamine system deficits and multiple neuropsychiatric symptoms in PD, and the results suggest that decreased DAT availability may be necessary for but not invariably associated with the development of affective symptoms in PD. If so, then this relationship may be mediated by impairment in frontal-subcortical circuits, as has been posited for PD-associated depression (34).

A significant association between decreased DAT availability and psychiatric symptoms was found for the anterior putamen only. Although putamen dysfunction is typically linked with motor impairment in PD (29), previous research

with non-PD patients found an association between depression and putamen changes (4,8,14), and one previous PET study of PD found an association between depression symptoms and altered putamen metabolism (12). It is possible that the lack of an association between neuropsychiatric symptoms and caudate function was attributable to the relative sparing of the caudate compared with the putamen in PD, especially early in the disease process.

The association between striatal impairment and affective symptoms was specific to the left hemisphere, a result consistent with previous research with both non-PD (13,14,35) and PD (15,16) subjects. Because of limitations in the data set, we were unable to determine whether there was an association between laterality of motor symptoms and psychiatric symptoms.

Using the total affect score, we found that the association between dopamine function and affective symptoms was present only in patients with less severe PD. It is possible that the pathophysiology of depression and anxiety in PD changes as the disease progresses; therefore, dopamine or striatal dysfunction may be associated with affective symp-

TABLE 3
Association Between Neuropsychiatric Symptoms and DAT Availability in PD

Parameter	r value* (P value) for the following striatal region:					
	Right caudate	Left caudate	Right anterior putamen	Left anterior putamen	Right posterior putamen	Left posterior putamen
State anxiety	-0.01 (0.93)	0.01 (0.95)	0.06 (0.62)	-0.24 (0.04)	-0.09 (0.46)	-0.09 (0.45)
Trait anxiety	0.01 (0.94)	-0.04 (0.74)	-0.05 (0.65)	-0.30 (0.01)	0.03 (0.78)	-0.15 (0.20)
POMS anxiety	0.05 (0.67)	0.11 (0.34)	0.09 (0.47)	-0.09 (0.47)	-0.07 (0.55)	-0.02 (0.89)
POMS depression	-0.01 (0.96)	-0.05 (0.68)	-0.12 (0.33)	-0.24 (0.05)	-0.06 (0.96)	-0.11 (0.35)
POMS fatigue	-0.02 (0.90)	-0.05 (0.66)	-0.12 (0.30)	-0.19 (0.11)	-0.01 (0.95)	-0.03 (0.77)
Total affect score	0.01 (0.99)	-0.06 (0.61)	-0.12 (0.30)	-0.30 (0.01)	0.02 (0.90)	-0.14 (0.25)

*Pearson correlation, controlling for age, sex, and duration of PD.

TABLE 4

Association Between Total Affect Score and Left Anterior Putamen DAT Availability in Relation to Severity of PD

PD severity (no. of patients)	Mean ± SD				<i>r*</i> (<i>P</i>)
	Age (y)	PD duration (y)	Total affect score (z score)	Left anterior putamen TRODAT-1 DVR	
Less severe (37)	59.9 ± 10.8	5.8 ± 5.4	-0.1 ± 0.8	0.8 ± 0.3	-0.35 (0.04)
More severe (39)	63.9 ± 10.5	9.0 ± 5.2	0.1 ± 0.9	0.3 ± 0.1	-0.22 (0.21)

*Pearson correlation, controlling for age, sex, and duration of PD.

toms in earlier stages only. Alternatively, the significant impairment in putamen function seen early in the course of PD (23) may have led to a floor effect in DAT availability in patients with more severe disease, a scenario that would have precluded finding an association between neuroimaging results and affective symptoms.

In addition, all 10 PD subjects with elevated (i.e., defined as ≥1 SD above the mean) total affect scores had left anterior putamen DVRs lower than the 80th percentile. These data indicate that PD subjects with the highest DAT availability did not show elevated total affect scores, suggesting that diminished DAT availability may be necessary for the development of affective symptoms in PD.

A limitation of this study was that the scores for PD patients indicated low overall levels of depression and anxiety symptoms in comparison with the results of previous research with the POMS in PD patients (36) and in psychiatric outpatients (32), because patients were excluded if they had a psychiatric diagnosis. Therefore, it is possible that we could have demonstrated a more robust correlation or associations with other striatal regions had our sample included patients with more severe neuropsychiatric symptoms. Another limitation of this study was the lack of available standardized ratings of motor performance, disease severity,

and side predominance of motor symptoms. Finally, although a significant association was found, DAT availability in the left anterior putamen explained only 12.3% of the total variance in the total affect score in patients with less severe PD.

These findings may have treatment implications. For instance, dopamine agonists, which help compensate for nigrostriatal dopamine deficiencies in PD and which have been reported to have antidepressant effects (37,38), may be of particular use in depressed PD patients with less severe disease and left brain hemisphere involvement. In addition, depression and anxiety were highly correlated with each other in our sample, suggesting a common neurobiologic basis for these symptoms. If so, then it is possible that a given treatment may be effective for both symptoms, consistent with existing research in non-PD patients showing that newer antidepressants have both antidepressant and anti-anxiety effects (39).

CONCLUSION

The results of this study suggest an inverse correlation in PD between severity of depression and anxiety symptoms and basal ganglion DAT availability, specifically in the left anterior putamen. Diminished DAT availability may be necessary for but not invariably associated with increasing severity of affective symptoms in the population with PD.

Further studies are needed with a better-defined patient cohort, including patients with formal anxiety and depression diagnoses, to truly establish the existence of a relationship between the integrity of the nigrostriatal dopamine system and the occurrence of psychiatric symptoms in PD. Confirmation of these findings may improve the understanding of the pathophysiology of anxiety and mood disorders in PD and assist clinicians in diagnosing and treating them.

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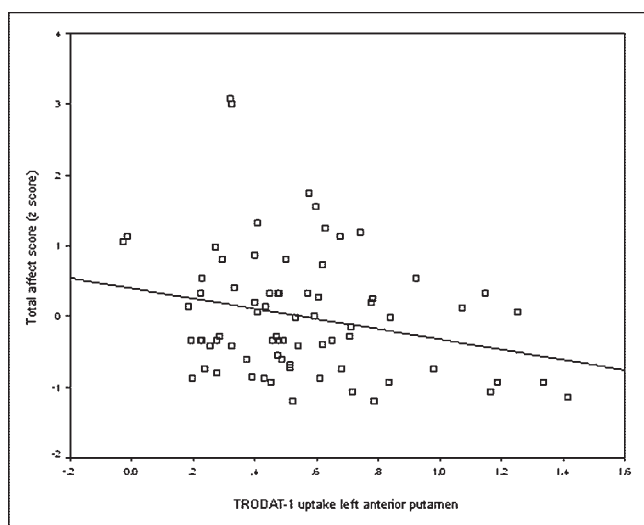


FIGURE 2. Association between total affect score and left anterior putamen DAT availability.

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