PET imaging of the dopamine transporter in progressive supranuclear palsy and Parkinson's disease

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Article abstract—*Objective:* To differentiate the patterns of dopamine transporter loss between idiopathic PD and progressive supranuclear palsy (PSP). *Methods:* We used the radiotracer [^{11}C]-WIN 35,428 and PET. Regional striatal dopamine transporter binding was measured in the caudate, anterior putamen, and posterior putamen of six patients with L-dopa–responsive stage 2 PD, six patients with PSP, and six age-comparable healthy controls. *Results:* In patients with idiopathic PD, the most marked abnormality was observed in the posterior putamen (77% reduction), whereas transporter density in the anterior putamen (60% reduction) and the caudate (44% reduction) was less affected. Unlike the patients with PD, the PSP group showed a relatively uniform degree of involvement in the caudate (40% reduction), anterior putamen (47% reduction), and posterior putamen (51% reduction). When posterior putamen/caudate ratios were calculated, these values were significantly lower in patients with PD than they were in patients with PSP ($p = 0.0008$) and the control group ($p < 0.0001$). *Conclusions:* Patients with PD have a more pronounced loss of dopamine transporters in the posterior putamen due to a subdivisional involvement of nigrostriatal dopaminergic projections in idiopathic PD. This technique is useful in the determination of neurochemical changes underlying PD and PSP, thus differentiating between them.

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The evaluation of PD is often difficult because similar symptoms may present in drug-induced parkinsonism, multiple system atrophy, and progressive supranuclear palsy (PSP). It would also be useful to identify individuals at risk for these movement disorders, such as those with a significant family history who have not yet developed clinical symptoms. This is especially relevant because novel therapies emerge that may offer some neuroprotective effects. Although the clinical diagnostic criteria for the differential diagnosis of PD have been well formulated,[1-3] PSP may be mistaken for PD. Recently two postmortem studies of patients diagnosed with PD showed that one-quarter of cases diagnosed with idiopathic PD did not have the disease.[4-5] These data indicate a need for improved clinical diagnostic accuracy.

The diagnostic value of functional brain imaging techniques is now being investigated for use in determining disease progression and early differential diagnosis of movement disorders. Degeneration of the dopaminergic pathways in PD and PSP has been evaluated by a number of pre- and postsynaptic biochemical markers. Among these, imaging with 6-L-(F-18-fluorodopa) (^{18}F-dopa) and PET is the most frequently employed tool, reflecting in vivo human striatal L-dopa decarboxylase activity[6] and dopamine (DA) turnover rates.[7] One of the disadvantages of this technique is the complexity of the kinetics and metabolism of this radiotracer, which, in spite of more than a decade of use, is still being evaluated.[8] In addition, dopa decarboxylase enzyme activity may be due to a reflection of both disease progression and the disease-associated modulation of enzyme kinetics.

Recently, ligands that bind to the DA transporter (DAT) have been used to determine presynaptic dopaminergic degeneration.[9-10] Prior studies in our laboratory have shown marked reductions in [^{11}C]-WIN 35,428 binding in the striatum of patients with mild bilateral PD, providing a definite discrimination from healthy individuals. We attempted to determine the feasibility of using this technique for the determination of differential patterns of dopaminergic terminal loss in PD in comparison with PSP using [^{11}C]-WIN 35,428 and PET imaging of the DAT.

Methods. *Patients.* Six patients with PSP (age 63 ± 6 years, duration of symptoms 5.5 ± 1 years) and six patients with bilateral idiopathic PD (age 62 ± 2 years, duration of symptoms 6.6 ± 3.2 years) were recruited from the Movement Disorders Clinic at The Johns Hopkins University School of Medicine. Patients with other movement disorders, primary psychiatric disorders, substance abuse or

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Table 1 *Clinical characteristics of patients with PD*

Patient no.	Age, y	Duration of symptoms, y	Hoehn & Yahr score	Symmetry	Antiparkinson medication (total daily dose)
1	62	5	2.0	R = L	Carbidopa/levodopa 150/600 mg
2	62	13	2.0	R = L	Carbidopa/levodopa 150/600 mg, trihexyphenidyl 14 mg, bromocriptine 15 mg
3	66	7	2.0	R > L	Carbidopa/levodopa 75/300 mg, bromocriptine 15 mg
4	66	6	2.0	L > R	Carbidopa/levodopa 125/500 mg
5	64	5	2.0	R = L	Carbidopa/levodopa 50/200 mg, bromocriptine 22.5 mg
6	61	4	2.0	R > L	Carbidopa/levodopa 150/300 mg, selegiline 25 mg

current illicit substance use, neuroendocrine disorders, history of closed head trauma, or dementias were excluded.

The clinical characteristics of the patients are presented in tables 1 and 2. The diagnostic criteria for PSP were a gradually progressive disorder with supranuclear limitation of downgaze and onset after age 40 as well as any three of the following: 1) symmetric akinesia or rigidity, proximal more than distal, 2) retrocollis, 3) poor or absent response of parkinsonism to levodopa therapy, 4) early dysphasia and dysarthria, 5) early onset of cognitive impairment and personality change suggesting frontal lobe dysfunction, and 6) inhibition of eyelid elevation. Six healthy volunteers (mean age 62 ± 2.5 years) with a normal neurologic examination and normal CTs also underwent PET imaging using [^{11}C]-WIN 35,428. The study was approved by the Institutional Review Board, and all patients provided written informed consent and agreed on withdrawal of therapy that could possibly affect dopaminergic function (24 hours for L-dopa, 2 weeks for amantadine). Because of the long half-life of monoamine oxidase inhibitors, patients were scanned while taking selegiline because chronic treatment with this medication causes no change in [3H]-WIN 35,428 binding in the mouse striatum.[11]

PET imaging. Before PET imaging, a thermoplastic face mask was constructed for each participant as previously described.[10] Although the MRI data for patients were not available at the time of the study, a limited radiograph CT was performed to visually identify a slice passing through the center of the head of the caudate nucleus and the putamen, parallel to the glabellar-inion line. This CT study was important for both the assessment of atrophy to avoid potential partial volume effects and correct alignment of the slices obtained in PET for each individual. On the day of the PET study, the mask was placed on the patient's face, and the PET laser was positioned on the mask-alignment line. A 10-minute transmission scan using a ^{68}Ge source was performed before each study for subsequent attenuation correction. [^{11}C]-WIN 35,428 was synthesized as previously described.[12] Approximately 20 mCi of [^{11}C]-WIN 35,428 (mean specific activity 6,000 mCi/μmol) was administered IV. Imaging was performed with a GE 4096 Plus scanner (GE, Milwaukee, WI), which acquires 15 simultaneous slices separated by 6.5 mm. Thereafter, a series of 25 PET images was acquired, ranging from 30 seconds to 8 minutes, over a 90-minute period. The gantry and bed positions were continuously monitored and adjusted to ensure accurate positioning on the mask-alignment line. Images were reconstructed using a ramped filtered back projection and smoothed by a nine-point neighborhood averaging filter to a final resolution of 7.7 mm in plane at full width half-maximum.

Table 2 *Clinical characteristics of patients with progressive supranuclear palsy*

Patient no.	Age, y	Duration of symptoms, y	Symmetry	Antiparkinson medication (total daily dose)
1	61	5	R = L	Carbidopa/levodopa 150/600 mg
2	55	6	R = L	Carbidopa/levodopa 150/600 mg, selegiline 25 mg
3	70	4	R = L	Carbidopa/levodopa 150/600 mg
4	64	6	R = L	Carbidopa/levodopa 150/600 mg
5	56	5	R = L	Amantadine 100 mg
6	70	7	R = L	None

PET data analysis. Paired regions of interest (ROIs) (4 × 4 pixels) were drawn on four summed (34 to 82 minutes) and smoothed PET images in each hemisphere using the coregistered CT as a guide. Eight ROIs were placed throughout the cerebellar cortex in the lowest summed PET slice. Two consecutive summed images were used to cover a greater extent of the striatum. On each of these two summed images, and in each hemisphere, one ROI was placed in the caudate and two in the putamen, the first one in the anterior putamen and the second one more posteriorly. These ROIs, which were all drawn on summed PET images, were then placed on the corresponding PET images covering the 25 time points to generate the time-activity curves. For each region, the mean ROI values covering the 34- to 82-minute time period were calculated from the corresponding time-activity curves. For the striatal regions, this mean was composed of data from two adjacent slices. To obtain semi-quantitative [^{11}C]-WIN 35,428 binding data, we computed a (region-cerebellum)/cerebellum (Rcb) ratio, as previously described.[10] The cere-

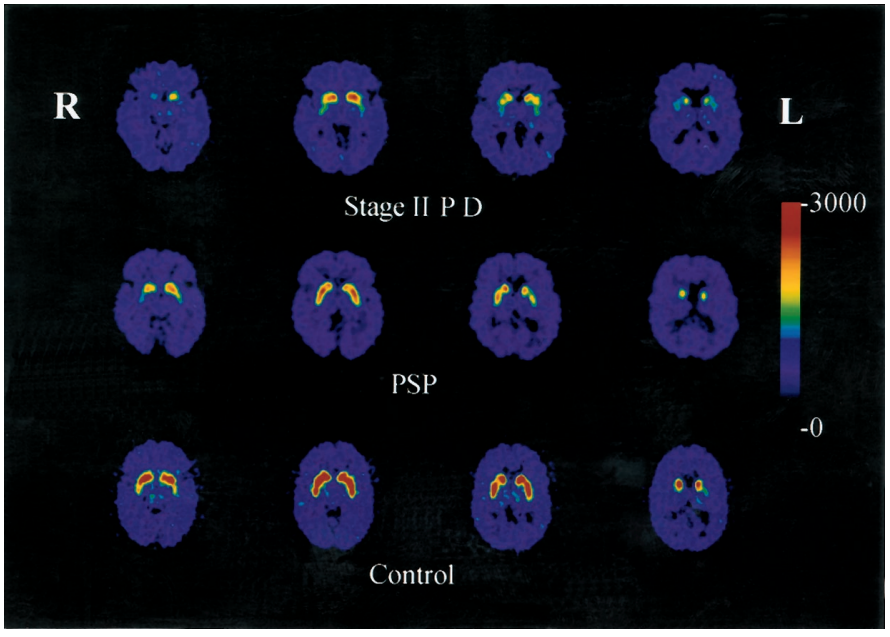

Figure 1. Images of [^{11}C]-WIN 35,428 binding at four different levels throughout the striatum of a stage 2 PD patient, a patient with progressive supranuclear palsy (PSP), and a healthy control. The images are formed by averaging the data acquired 34 to 82 minutes after administration of the tracer (six time frames of 8 minutes each) and are normalized to the cerebellar activity. The images demonstrate lower binding in the basal ganglia of patients diagnosed with PD and PSP compared with the control subject. In PD, there is reduced [^{11}C]-WIN 35,428 binding predominantly in the posterior putamen, whereas there is a more uniform reduction of specific binding throughout the striatum in PSP.

bellum was selected as a reference region because it contains negligible levels of DA and DA receptors, providing an estimate of nonspecific binding and free tracer concentration. Statistical analysis was performed by using the average of left and right Rcb ratios (analysis of variance with post hoc Bonferroni correction). We also used regression analysis to examine the relationship between the reductions in transport-related early [^{11}C]-WIN 35,428 activity and the specific [^{11}C]-WIN 35,428 transporter binding using the ROI/cer ratios obtained at early (0 to 10 minutes) and later time points (34 to 82 minutes).

Results. Figure 1 shows a representative [^{11}C]-WIN 35,428 study in a patient diagnosed with PD, in another with PSP, and in a healthy participant. Images show data averaged from 34 to 82 minutes post-tracer administration (six time frames of 8 minutes each) with image intensities normalized to the cerebellum. In the healthy participant, [^{11}C]-WIN 35,428 binding was high in the caudate nucleus and putamen and low in the cerebellum. Radiotracer binding is much lower in both patients. In the stage 2 PD patient, the reduction is most pronounced in the putamen, whereas the reduction of binding is uniform in all striatal structures in the PSP patient.

Reductions in [^{11}C]-WIN 35,428 binding were observed in patients with PD compared with the age-matched healthy control group in the caudate ($p = 0.0001$), anterior putamen ($p < 0.0001$), and posterior putamen ($p < 0.0001$) as well as in patients with PSP ($p < 0.0001$ for each). Using the Rcb ratios of the data acquired from 34 to 82 minutes after injection, binding in the posterior putamen was reduced by 77%, whereas the anterior putamen showed a reduction of 60% and the caudate nucleus showed a reduction of 44% in patients with PD (figure 2). [^{11}C]-WIN 35,428 binding in PSP patients was reduced by 40% in the caudate, 47% in the anterior putamen, and 51% in the posterior putamen.

Unlike the uniform pattern of decreased [^{11}C]-WIN 35,428 binding observed in PSP, the reduction in DAT binding in PD was stepwise, following a pattern of more severe putaminal involvement with relative sparing of the caudate. When compared with the control group, the percent reduction of specific binding in the posterior putamen was larger in the PD group than it was in the PSP group ($p < 0.05$). The degree of involvement in the caudate and anterior putamen, however, was similar in both groups.

Group analysis of the differences in the regional binding after computing anterior and posterior putamen/caudate ratios for PD versus PSP and controls (figure 3) showed that in PD, the posterior putamen/caudate ratios were significantly different than that observed in the PSP group ($p = 0.0008$) and the control group ($p < 0.0001$). For the PD group, the mean posterior putamen/caudate ratio was 0.35 ± 0.1, and the mean anterior putamen/caudate ratio was 0.72 ± 0.18. In patients with PSP these values were 0.71 ± 0.26 for the mean posterior putamen/caudate ratio

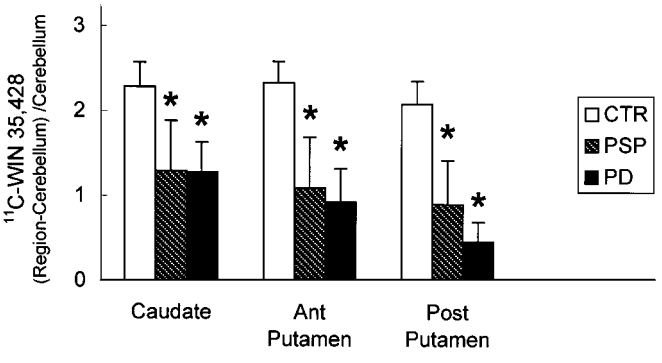

*Figure 2. [^{11}C]-WIN 35,428 binding differences measured by the ratio method in controls (CTR), patients with progressive supranuclear palsy (PSP), and PD patients. Data are expressed as (right-left) mean ± standard deviation of specific binding, measured as the ratio (region-cerebellum)/cerebellum, using data from 34 to 82 minutes post-tracer administration. *Significantly different from healthy controls (analysis of variance with post hoc* t*-test and Bonferroni correction,* p *< 0.05). Ant = anterior, Post = posterior.*

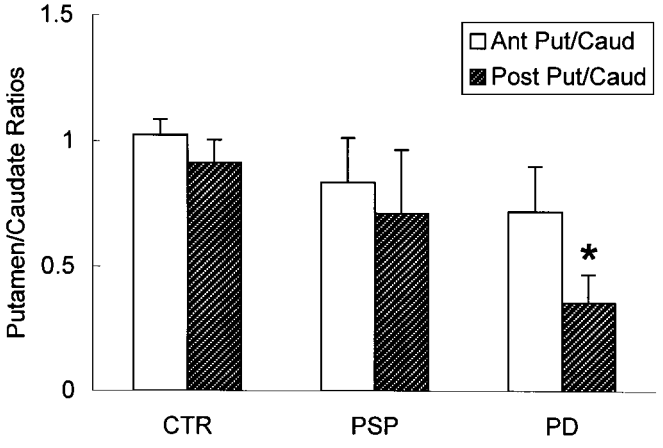

*Figure 3. Anterior putamen/caudate (Ant Put/Caud) and posterior putamen/caudate (Post Put/Caud) ratios in controls (CTR), patients with progressive supranuclear palsy (PSP), and patients with stage 2 PD. The Post Put/Caud ratio was reduced in the PD group compared with the PSP and control groups. *Significantly different from CTR and PD groups (analysis of variance with post hoc t-test and Bonferroni correction,* $p < 0.05$*).*

and 0.84 ± 11 mean anterior putamen/caudate ratio. In the control group the mean posterior putamen/caudate ratio was 0.9 ± 0.11, and the mean anterior putamen/caudate ratio was 1 ± 0.6.

It is important to ascertain that the ratio method of analysis employed for the quantification of [^{11}C]-WIN 35,428 binding is sensitive enough to detect small changes in regional receptor densities, and relatively insensitive to changes in tracer blood-brain transport that may be present in disease processes. Changes in regional cerebral blood flow (rCBF) have been shown in the basal ganglia of patients diagnosed with PSP.[13-14] To evaluate the potential effect of transport-related changes in PSP, regression analysis was used to examine the relationship between the reductions in transport-related early [^{11}C]-WIN 35,428 uptake and specific [^{11}C]-WIN 35,428 transporter binding, using the ROI/cer ratios obtained at early (0 to 10 minutes) and later time points (34 to 82 minutes). The percent reductions in transport-related and late specific [^{11}C]-WIN 35,428 binding in the PSP group were not correlated (r^2 values ranged from 0.02 to 0.11, $p > 0.05$). Thus, small changes in transport alone do not account for the large reductions in [^{11}C]-WIN 35,428-specific binding observed in PSP patients.

Discussion. Imaging with [^{11}C]-WIN 35,428 and PET can reliably differentiate the striatal neurodegenerative patterns associated with PSP and PD. Patients with PSP showed a more uniform degeneration of dopaminergic innervation throughout the striatum. In PD a relative sparing of the caudate nucleus was observed compared with the anterior and posterior putamen. Conversely, caudate [^{11}C]-WIN 35,428 binding was significantly lower in patients with PSP than it was in patients with PD, being reduced to the same level as that in the putamen.

Compared with other radiotracers, it appears that [^{11}C]-WIN 35,428 is more sensitive in the detection of DA terminal degeneration in PD. Reductions in the observed binding measure in patients with stage 2 PD were in the range of 60 to 80% in the present study. Previous studies using ^{18}F-dopa and PET revealed, however, approximately 20 to 55% reductions in tracer uptake in fully symptomatic patients with respect to control values.[15-18]

PSP is characterized by cell loss and neurofibrillary tangles mainly in the brainstem, globus pallidus, and subthalamic and dentate nuclei.[19] In PD the nerve cell parenchyma of the caudate nucleus and putamen remains morphologically intact. It has been reported that PD is characterized by severe neuronal loss in the substantia nigra.[19] It is believed that qualitative, quantitative, and topographic differences in the lesion pattern of the substantia nigra found in various forms of parkinsonism are due to different etiologic factors. Neuronal subpopulations of the substantia nigra pars compacta can be separated into two functionally distinct nigrostriatal projections—a poorly melanized ventral tier and a well melanized dorsal tier. The ventral portion appears more susceptible to degeneration than the dorsal tier.[19] The ventrolateral substantia nigra cells project primarily to the putamen, whereas dopaminergic input to the caudate arises primarily from the more dorsal and medial portions of the substantia nigra, which are affected later in the disease process.[20-22]

Therefore, more severe reduction in radiotracer binding observed in the posterior putamen of patients with PD is consistent with previous neuropathologic findings and other reported functional neuroimaging studies. Previous studies using PET and ^{18}F-dopa showed significantly reduced mean uptake of ^{18}F-dopa in the putamen in PD. Similar to the data obtained from this study, dopaminergic function in the posterior part of the putamen was the most severely affected (45% of normal) compared with that of the anterior part of the putamen and the caudate nuclei, which were relatively spared (62% and 84% of normal).[16] Unlike patients with PD, patients with PSP have shown an equally severe impairment of mean ^{18}F-dopa uptake in the anterior and posterior putamen. Recent findings in postmortem samples also show a pattern of nonselective reduction in striatal DAT density in patients with PSP.[23]

The putamen appears to be a part of a cortical-subcortical neuronal loop with a predominantly motor function. The caudate nucleus, in contrast, is closely connected to the frontal association cortex and other neocortical areas and appears involved in psychomotor function and complex cognitive functions.[24] The dorsolateral prefrontal cortex and medial prefrontal cortex have selective portions of the caudate to which they are connected. Based on these relationships, it is only in the late stages of PD that cognitive functions are affected, despite severe motor impairments occurring at early stages. In PD intact nigral projections to the caudate nucleus and limbic

and cortical areas are a prerequisite for normal cognitive functioning and their loss may lead to clinical dementia.[25]

In recent studies, DAT-related ligands have shown an age-related loss of presynaptic dopaminergic terminals,[26,27] where a 6% loss in the DAT is observed per decade. However, the relationship between the atrophy-related partial volume effects and the reduction in DAT binding has not been thoroughly investigated in PET and SPECT studies, and the age-related reductions in DAT binding need to be addressed after correction for atrophy. In this study, the highest reductions in [^{11}C]-WIN 35,428 binding were not coexistent with atrophy of the basal ganglia in PSP; the reductions in specific binding ratios were highest in patients with little or no evidence of basal ganglia atrophy observed by CT. Conversely, although radiograph CT achieves good spatial and contrast resolution, MRI is superior, particularly in the posterior putamen. Further analysis of these patient groups could be done with MRI to determine methods for partial volume correction. However, partial volume correction would likely not change the core conclusions of this study.

Other radiotracers have also been used to examine dopaminergic function in PSP. Striatal D2-receptor binding in PSP has been examined using PET and SPECT in a number of studies[28-31] that showed globally unaltered density of D1 and D2 receptors in the striatum and increased D2-receptor density in striatal areas where DA depletion exceeds 90%. To identify various parkinsonian disorders, more than 90% DA depletion may be needed to make a differential diagnosis by PET and SPECT imaging of the D2 receptors. Presynaptic DAT imaging provides an advantage over predominantly postsynaptic receptor ligands in clinical practice because it directly evaluates degeneration of the nerve terminals[32-34] and provides a single technique for the diagnosis and differentiation of PD from other clinical entities.

It is also important to determine the optimum in vivo PET-SPECT ligand for imaging the presynaptic DA markers in PD. In this regard, a recent study compared five different DA neuronal markers[35] to determine the extent to which different DA neuronal markers provide similar estimates of DA nerve terminal loss in idiopathic PD. These included DA itself, three DAT markers ([^{3}H])GBR 12,935, [^{3}H]WIN 35,428, and DAT protein immunoreactivity), and one VMAT2 marker ([^{3}H]DTBZ). Striatal levels of all examined DA markers in PD were significantly intercorrelated. However, the magnitude of marker reduction in PD relative to controls was unequal (DAT protein = DA > [^{3}H]WIN 35,428 > [^{3}H]DTBZ > [^{3}H]GBR 12, 935).

The fact that parkinsonian symptoms become apparent only when the DA concentration in the striatum is decreased by an average of 80% in PD suggests that the loss of dopaminergic neurons is compensated functionally, at least in the early stages of the disease. In PD, the degree of neuronal loss in the substantia nigra varies among patients (50 to 95%)[35] and may indicate that symptom appearance may be directly related to various pre- and postsynaptic compensatory mechanisms.[35] In animal models of parkinsonism, the ability to lose a substantial proportion of dopaminergic neurons without behavioral deficits does not apparently result from other systems taking over function of the dopaminergic pathway. The surviving nigrostriatal projections increase both the rate of synthesis and the release of DA as compensatory adjustments. This capacity allows at least a fivefold rise in DA delivery per neuron, and this enhancement is potentiated further by some receptor upregulation. Decreased reuptake caused by loss of nerve endings may also lead to augmented occupancy of DA receptors constituting yet another compensatory mechanism.[36]

Thus, if dopaminergic cell death is accompanied by concomitant neuronal plasticity, in vivo imaging by PET may show the loss of dopaminergic neurons during the process of functional compensation before the parkinsonian symptoms become apparent. Indeed, studies in various denervation models suggest that sprouting from axons or terminals of the surviving nigral dopaminergic neurons may take place after the neuronal loss in substantia nigra.[37] Although WIN 35,428 may be more closely related to the DA pools in the presynaptic terminals, F-dopa may overestimate this pool due to the compensatory increase in the tyrosine hydroxylase TH activity observed in early stages of PD. That the concentration of DA metabolites dihydroxyphenylacetic acid and homovanillic acid are less decreased than that of DA in the striatum[38] may explain the difference of the results obtained by F-dopa and [^{11}C]-WIN PET in patients with PD. Different levels of reductions in specific binding of these two tracers in a given patient group may be seen.

In the current study we selected a method of image analysis that is suitable for clinical utilization, the calculation of radiotracer binding ratios between striatal structures and the cerebellum. In the context of reductions in rCBF, and therefore tracer transport, this more simplified analysis may result in some inaccuracies. Although this is not an important issue in the study of PD, in which rCBF changes are not observed until very late in disease progression, they may represent a confounding variable in other conditions such as PSP, in which rCBF reductions have been described.[13-14] The analysis of early uptake compared with late specific transporter binding shows that the magnitude of the specific binding reductions in [^{11}C]-WIN 35,428 distribution in PSP exceeds the changes in tracer transport detected, confirming the clinical utility of this radiotracer.

The data presented confirm that DAT binding is reduced in PD and PSP and that the calculation of binding ratios between the putamen and caudate can differentiate these conditions. [^{11}C]-WIN 35,428 PET imaging of the DAT may be helpful in the early dif-

ferential diagnosis of PD with other neurodegenerative conditions such as PSP.

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