Topography of Dopamine Transporter Availability in Progressive Supranuclear Palsy

A Voxelwise [^{123}I]β-CIT SPECT Analysis

Klaus Seppi, MD; Christoph Scherfler, MD; Eveline Donnemiller, MD; Irene Virgolini, MD; Michael F. H. Schocke, MD; Georg Goebel, PhD; Katherina J. Mair, MD; Sylvia Boesch, MD; Christian Brenneis, MD; Gregor K. Wenning, MD; Werner Poewe, MD

Background: Dopaminergic loss can be visualized by means of iodine I 123–labeled 2β-carbomethoxy-3β-(4-iodophenyl)tropane ([^{123}I]β-CIT) single-photon emission computed tomography (SPECT) in several neurodegenerative parkinsonian disorders. Most previous SPECT studies have adopted region-of-interest methods for analysis, which are subjective and operator dependent.

Objective: To objectively localize the cerebral dopamine transporter status in the early stages of progressive supranuclear palsy (PSP).

Design: Prospective study.

Setting: Parkinson disease outpatient clinic.

Patients: Fourteen patients with PSP, 17 with Parkinson disease (PD), 15 with Parkinson-variant multiple-system atrophy (MSA-P), and 13 healthy control subjects, matched for age and disease duration.

Interventions: Statistical parametric mapping applied to [^{123}I]β-CIT SPECT.

Main Outcome Measures: Differences in [^{123}I]β-CIT uptake.

Results: All patients with the different parkinsonian disorders showed a significant decrease in striatal [^{123}I]β-CIT uptake without any overlap with the control group. In patients with MSA-P and PSP, an additional reduction in brainstem [^{123}I]β-CIT signal compared with controls and patients with PD was identified with statistical parametric mapping. Midbrain [^{123}I]β-CIT uptake discriminated atypical parkinsonian disorders from PD with an overall correct classification of 91.3%. On the other hand, [^{123}I]β-CIT SPECT failed to discriminate PSP and MSA-P.

Conclusion: By applying statistical parametric mapping to [^{123}I]β-CIT SPECT images of patients with PSP, a widespread decline of monoaminergic transporter availability including the striatum and brainstem was localized in PSP, discriminating patients with PSP from patients with PD, but not from those with MSA-P. Quantification of midbrain dopamine transporter signal may therefore enhance the utility of SPECT imaging in the differential diagnosis of patients with parkinsonism.

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Author Affiliations:
Departments of Neurology (Drs Seppi, Scherfler, Mair, Boesch, Brenneis, Wenning, and Poewe), Nuclear Medicine (Drs Donnemiller and Virgolini), Radiology 1 (Dr Schocke), and Medical Statistics, Informatics, and Health Economics (Dr Goebel), Medical University Innsbruck, Innsbruck, Austria.

DESPITE THE PUBLICATION of consensus operational criteria for the diagnosis of Parkinson disease (PD) and the various atypical parkinsonian disorders (APD), such as progressive supranuclear palsy (PSP) and the Parkinson variant of multiple-system atrophy (MSA-P),[1] the clinical differentiation of PD from APD may be challenging, especially during the early disease stages.[1-5] A considerable number of either radiotracer-based or magnetic resonance imaging–based brain imaging studies have been shown to be helpful in the differential diagnosis of PD vs APD based on morphologic and functional abnormalities of the basal ganglia or brainstem.[6-8] Early differentiation between APD and PD is important for a number of reasons, including differences in natural course and treatment response.[9-11] Furthermore, pharmacologic and neurosurgical treatment trials for PD require a correct diagnosis, avoiding inclusion of misdiagnosed patients with APD.[12-14]

Our group recently applied statistical parametric mapping (SPM), a technique that objectively localizes focal changes of the radiotracer throughout the entire brain volume without having to make an a priori hypothesis as to their location, to iodine I 123–labeled 2β-carbomethoxy-3β-(4-iodophenyl)tropane ([^{123}I]β-CIT), a cocaine derivative with a high affinity for dopamine (DAT) and serotonin (SERT) transporters.[15] That study had shown reductions in striatal DAT activity in early

MSA-P and PD similar to those detected with a standard region-of-interest (ROI) approach but, in addition, objectively localized focal reductions of [^{123}I]β-CIT signal in brainstem regions in patients with MSA-P compared with both control subjects and patients with PD that could not have been predicted by visual inspection or ROI analysis of [^{123}I]β-CIT single-photon emission computed tomographic (SPECT) images.

In the present study, we aimed to extend our previous findings by investigating the integrity of the dopaminergic system with SPM and [^{123}I]β-CIT SPECT within the entire brain volume in patients with PSP, a neuronal multisystem degeneration characterized by atypical parkinsonism associated with prominent subcortical tau pathologic features.[16,17] Patients with MSA-P and PD matched for age and disease duration served as control groups.

METHODS

SUBJECTS

Fifteen consecutive patients with MSA-P, 14 consecutive patients with PSP, and 17 consecutive patients with PD matched for age and disease duration were recruited at our Parkinson disease outpatient clinic. Clinical diagnosis of MSA-P, PSP, and PD was made according to established criteria[18-20] by movement disorder specialists experienced in parkinsonian disorders (G.K.W. and W.P.). A detailed clinical history and a careful neurologic examination were performed. All patients were followed up clinically for at least 2 years.

At the time of the SPECT study, 12 of the cases of MSA-P had been classified as "probable" and 3 as "possible"; these 3 were reclassified as "probable" at follow-up 1 year after SPECT examination. The PSP group comprised 9 patients satisfying the National Institute of Neurological Disorders and Stroke–Society for Progressive Supranuclear Palsy (NINDS-SPSP) criteria for "probable" PSP and 4 patients satisfying the NINDS-SPSP criteria for "possible" PSP at the time of the imaging study. Two of the 4 "possible" cases had disease durations of less than 1 year at the time of the SPECT study and progressed to probable PSP during subsequent clinical follow-up. The other 2 patients did not satisfy the criterion of "falls within the first year of symptom onset" to comply with the NINDS-SPSP diagnostic category of probable PSP but had otherwise typical symptoms of PSP.[21,22] An additional patient with unclassified atypical parkinsonism at the time of the SPECT examination progressed to "probable" PSP according to the NINDS-SPSP diagnostic criteria during subsequent clinical follow-up.

The [^{123}I]β-CIT SPECT findings in patients with PD, MSA-P, and PSP were compared with those of a group of 13 age-matched healthy control subjects (6 women and 7 men; mean±SD age, 61.0±8.3 years).[15] The study was approved by the Ethics Committee of the Innsbruck Medical University, Innsbruck, Austria. Informed consent was obtained from all patients. The SPECT data from all of the patients with MSA-P and the healthy controls and from 15 of the patients with PD were reported previously.[15] Clinical data of 8 of the patients with PSP were reported previously.[23]

Nine patients with PD, 8 with MSA-P, and 8 with PSP were receiving regular levodopa therapy. In addition, 12 of the patients with PD, 5 with MSA-P, and 2 with PSP were taking dopamine agonist medication. All patients with PD showed a marked sustained response to long-term dopaminergic therapy, while the clinical response in the patients with MSA-P and PSP was poor or minimal, leading to withdrawal of dopaminergic treatment in 4 of the patients with MSA-P and 5 of the patients with PSP before this study. None of the patients was taking selective serotonin reuptake inhibitors at the time of the [^{123}I]β-CIT SPECT imaging study.

RADIOPHARMACEUTICAL PREPARATION, SCANNING PROTOCOL, AND IMAGING DATA PROCESSING

The radiopharmaceutical preparation, the scanning protocol, and the computation of the specific-to-nondisplaceable equilibrium partition coefficient (V_3'') were extensively described in a previous report by our group.[15]

SPM ANALYSIS AND CALCULATION OF ROIs

The SPM analysis and calculation of striatal ROIs were extensively described in a previous report by our group.[15] For the SPM analysis, patient and control groups were subjected to a 1-way analysis of variance followed by applying t contrasts to compare groups. The SPM maps that survived a threshold of $P<.001$ were corrected for multiple comparisons. Because SPM analysis demonstrated significant decreases of [^{123}I]β-CIT V_3'' values in the brainstem of the MSA-P and PSP groups (see the "Results" section), a circular ROI (diameter, 16 mm) was positioned on the T1-weighted magnetic resonance image MNI (Montreal Neurological Institute) space on 6 consecutive planes in the midbrain and transferred onto the individual parametric DAT-SPECT image.

STATISTICAL ANALYSIS

Data were tabulated and analyzed with a commercial software package (SPSS for Windows 10.0; SPSS Inc, Chicago, Ill).

Group Comparisons of Clinical and Imaging Data

One-way analysis of variance followed by post hoc pairwise comparisons of groups calculated by unpaired, 2-tailed *t* tests and Bonferroni multiple test adjustment was used for comparison of the age at examination, disease duration, and mean ROI values between groups. For motor examination, the Unified Parkinson's Disease Rating Scale III "off" scores in patients with APD and PD were compared by the Kruskal-Wallis test followed by post hoc Mann-Whitney tests, setting the latter significance level at a lower threshold ($P<.05/3=.017$). The significance level was set at $P<.05$.

Discrimination Between Groups

To discriminate between PD and APD, forward- and backward-stepping logistic regression analysis followed by receiver operating characteristic (ROC) curve analysis was used to identify an optimal cutoff value. The stepwise logistic regression analysis included caudate, putamen, and midbrain mean V_3'' values, the caudate-putamen ratio, and the asymmetry index of the caudate and putamen, as well as age at SPECT examination, sex, and disease duration as independent variables.

The ROC curve plots "sensitivity" vs "specificity" for every possible cutoff point. Maximal discrimination of the ROC curve is reached at the cutoff level that has the highest sum of sensitivity and specificity. The positive predictive value, the negative predictive value, and the predictive accuracy (ie, overall correct classification) were calculated for the optimal cutoff value in the ROC curve.[23,24]

Table 1. Demographic and Clinical Data of Patients With PSP, MSA-P, and PD and Healthy Control Subjects

	PSP (n = 14)	MSA-P (n = 15)	PD (n = 17)	Controls (n = 13)
Age, mean ± SD, y*	66.7 ± 76.9	61.8 ± 9.3	61.9 ± 6.9	61.0 ± 8.3
Sex, No. M/F	6/8	8/7	10/7	7/6
Disease duration, mean ± SD, y*	2.2 ± 0.7	2.0 ± 0.8	2.0 ± 1.1	NA
UPDRS III, mean ± SD†	35.5 ± 6.5	38.9 ± 10.7‡	21.5 ± 7.2‡	NA
Levodopa response at time of imaging study, No. poor/moderate/good	11/3/0	9/6/0	0/2/15	NA
No tremor, No.	13	11	4	NA
Axial > limb rigidity, No.	5	2	1	NA

Abbreviations: MSA-P, multiple-system atrophy (Parkinson variant); NA, not applicable; PD, Parkinson disease; PSP, progressive supranuclear palsy; UPDRS, Unified Parkinson Disease Rating Scale.
*Not significant between patient groups, 1-way analysis of variance.
†$P<.001$, Kruskal-Wallis test.
‡$P<.001$, Mann-Whitney test, vs PD; not significant between PSP and MSA-P.

Table 2. ROI Analysis of Mean Regional Caudate, Putamen, and Midbrain [^{123}I]β-CIT V_3'' Values in Patients With PSP, MSA-P, and PD and Healthy Control Subjects*

	PSP (n = 14)	MSA-P (n = 15)	PD (n = 17)	Controls (n = 13)
Caudate	4.13 ± 2.05†	5.23 ± 2.25†	5.79 ± 1.00†	9.1 ± 1.8
Putamen	4.97 ± 2.11†	5.93 ± 2.64†	5.99 ± 1.04†	9.7 ± 1.8
AI, %				
Caudate	13.8 ± 6.6‡	12.1 ± 11.5‡	11.2 ± 7.7‡	3.7 ± 3.6
Putamen	10.2 ± 6.6	15.4 ± 12.2§	10.3 ± 8.2	4.0 ± 2.3
Ratio, caudate-putamen	0.79 ± 0.18‡‖	0.87 ± 0.07	0.97 ± 0.12	0.93 ± 0.04
Midbrain	1.37 ± 0.86†¶	1.45 ± 0.55†¶	2.67 ± 0.37	2.86 ± 0.30

Abbreviations: AI, asymmetry index; [^{123}I]β-CIT V_3'', specific-to-nondisplaceable equilibrium partition coefficient values on iodine I 123–labeled 2β-carbomethoxy-3β-(4-iodophenyl)tropane single-photon emission tomography; MSA-P, multiple-system atrophy (Parkinson variant); PD, Parkinson disease; PSP, progressive supranuclear palsy; ROI, region of interest.
*Values represent mean ± SD. Intergroup differences were calculated by 1-way analysis of variance with post hoc Bonferroni correction.
†$P<.001$ vs healthy controls.
‡$P<.05$ vs healthy controls.
§$P<.01$ vs healthy controls.
‖$P<.01$ vs PD.
¶$P<.001$ vs PD.

RESULTS

PATIENTS

Patients groups and control subjects were matched for age and disease duration (**Table 1**). Maximum disease duration was limited to 4 years. Maximum Hoehn and Yahr stage was III. The Unified Parkinson's Disease Rating Scale motor scores were higher in the APD group than the PD group.

ROI ANALYSIS OF [^{123}I]β-CIT SPECT

Regional mean [^{123}I]β-CIT V_3'' values of the study groups and the intergroup statistics are detailed in **Table 2** and displayed in **Figure 1**. Patients with PSP had levels of putaminal and caudate [^{123}I]β-CIT uptake similar to those of the patients with PD and MSA-P. The midbrain [^{123}I]β-CIT V_3'' values were significantly decreased in the patients with PSP (mean, –52% vs controls) when compared with patients with PD and controls, while patients with PSP had midbrain [^{123}I]β-CIT V_3'' values similar to those of the patients with MSA-P (mean, –49% vs controls).

[^{123}I]β-CIT SPECT SPM FINDINGS

The SPM of parametric [^{123}I]β-CIT V_3'' images confirmed the results of striatal ROI analysis (**Table 3**; **Figure 2**). When compared with values for patients with PD and controls, significant relative decreases in V_3'' values were additionally localized in the brainstem, including the ventral and dorsal midbrain and the pons, of patients with PSP (mean, –59% vs controls) and MSA-P (mean, –52% vs controls), comprising a volume of about 1200 mm^3. Furthermore, we found significant decreases in [^{123}I]β-CIT V_3'' values in the anterior striatum (caudate) of patients with PSP compared with the MSA, PD, and control groups.

DISCRIMINATION BETWEEN PATIENTS WITH PD, PSP, AND MSA-P

Patients with parkinsonism (PD, PSP, or MSA-P) could be easily discriminated from healthy controls by means of striatal [^{123}I]β-CIT V_3'' values (cutoff values: caudate V_3'' value, 7.6; putaminal V_3'' value, 7.8), because there was no overlap in putaminal and caudate [^{123}I]β-CIT V_3''

values between healthy controls and patients with parkinsonism. Therefore, we tested further discriminative ability of [^{123}I]β-CIT SPECT in the patient groups only. Since none of the [^{123}I]β-CIT SPECT variables were found to discriminate between MSA-P and PSP by forward- and backward-stepping logistic regression analysis, patients with MSA-P and PSP were grouped together and further analysis was performed between patients with PD and APD.

By means of forward- and backward-stepping logistic regression analysis, midbrain mean V_3'' values remained the only significant variables (coefficient [β], 6.6, SE of β, 2.5; P=.009) to discriminate between PD and APD. The optimal cutoff level in the ROC curve (with an area under the curve of 0.96) for midbrain mean V_3'' value to discriminate between APD and PD was 2.3, implying that a midbrain mean V_3'' value less than 2.3 is indicative of a diagnosis of APD and a midbrain mean V_3'' value of 2.3 or greater is indicative of a diagnosis of PD. Sensitivity for the cutoff level of 2.3 was 89.7%; specificity, 94.1%; positive predictive value, 96.4%; and negative predictive value, 84.2%. The predictive accuracy was 91.3%. In general, 1 patient with PD was classified as having APD, and 1 of the patients with MSA-P as well as 2 of the patients with PSP were classified as having PD (**Table 4**).

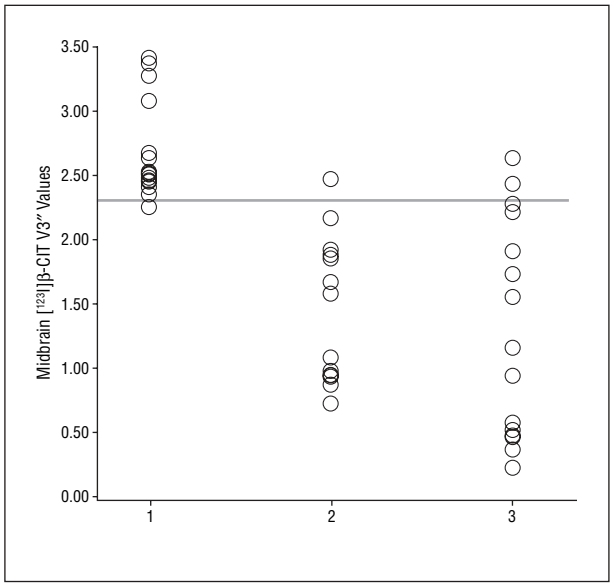

Figure 1. Scattergram of midbrain specific-to-nondisplaceable equilibrium partition coefficient (V3′′) values on iodine I 123–labeled 2β-carbomethoxy-3β-(4-iodophenyl)tropane [^{123}I](β-CIT) single-photon emission tomography from patients with Parkinson disease (1), the Parkinson variant of multiple-system atrophy (2), and progressive supranuclear palsy (3). The horizontal line corresponds to the cutoff level of 2.3.

COMMENT

This is the first SPECT study, to our knowledge, to characterize alterations in DAT availability within the entire brain volume in patients with PSP by using the radiotracer [^{123}I]β-CIT, a cocaine derivative with a high affinity for DAT and SERT. We have applied SPM to spatially normalized parametric images of [^{123}I]β-CIT V_3'' and localized reductions in striatal [^{123}I]β-CIT V_3'' in early PSP similar to those detected by means of a standard ROI approach. However, SPM enabled us to identify objectively focal [^{123}I]β-CIT V_3'' changes in the brainstem including midbrain and pontine regions in PSP, which could not have been predicted by visual inspection of [^{123}I]β-CIT SPECT images. The routinely performed ROI-based assessment of a [^{123}I]β-CIT SPECT image focuses primarily on the striatum as the brain area with the highest DAT uptake, whereas sections within extrastriatal regions of the brain with somewhat lower but still detectable [^{123}I]β-CIT uptake might be neglected by the investigator, since they are not properly visualized by most software packages for image analysis. Another drawback when outlining small brain volumes is the limited anatomic information provided by [^{123}I]β-CIT SPECT, forcing the investigator to generate an a priori assumption on the size and shape of the region to be evaluated. In contrast, no a priori hypothesis regarding the localization of SPECT signal is required by SPM.[15]

In line with the ROI analysis, SPM interrogation demonstrated a severe decline in caudate and putaminal [^{123}I]β-CIT uptake in the PSP group when compared with healthy controls, which corresponds with former SPECT studies using ROI techniques and the tracer [^{123}I]β-CIT.[25-27] Furthermore, we found significant decreases in [^{123}I]β-CIT V_3'' values in the anterior striatum (caudate) of patients with PSP compared with patients with PD by means of SPM interrogation. The higher degree of caudate involvement in the patients with PSP compared with PD is consistent with the underlying neuropathologic features of PSP, characterized by a more diffuse uniform involvement of the substantia nigra than in PD, where the pathologic degeneration mainly affects the ventrolateral part of the pars compacta of the substantia nigra projecting to the putamen.[28,29] Few studies have compared [^{123}I]β-CIT uptake between patients with PSP and MSA[25,27]; those studies that exist have reported no difference in [^{123}I]β-CIT binding between PSP and MSA groups, similar to our ROI results. By contrast, using the SPM approach, the present study found a significant decrease in caudate [^{123}I]β-CIT V_3'' values for patients with PSP compared with those with MSA, suggesting possibly a more severe nigral involvement in early PSP than in early MSA. A possible explanation for the failure of the ROI approach to detect the caudate decreases in DAT binding in PSP could be related to the fact that ROIs primarily sample the dorsal head of caudate, whereas SPM localizes relative reductions in the entire volume of this structure.

The brainstem area of reduced [^{123}I]β-CIT uptake as identified by SPM in PSP and MSA-P vs PD comprises a volume of about 1200 mm^3 including the ventral and dorsal midbrain and the pons. In the brainstem, [^{123}I]β-CIT has been reported to be taken up by DAT, SERT, and noradrenergic transporters.[30-33] A precise assignment of the [^{123}I]β-CIT signal loss in the involved brainstem region is precluded by the limited spatial resolution of about 10 mm full-width half-maximum and by the nonselective tracer-to-receptor binding of adjacent nuclei containing DAT-, SERT-, and noradrenergic transporter–bearing neurons.[30,34,35] Although highly significant decreases of [^{123}I]β-CIT uptake in the brainstem of patients with PSP cannot be assigned further to a single transporter system

Table 3. Between-Group SPM Findings Showing the Locations of Significant Decreases of [^{123}I]β-CIT V_3'' Values in Patients With MSA-P, PSP, and PD and Healthy Control Subjects

Brodmann Area	Talairach Coordinates* x	y	z	*z* Score	*P* Value (Corrected)	Height Threshold
Decreases in PSP vs PD						
Left striatum (caudate)	−12	4	9	5.73	<.001	.001
Right striatum (caudate)	8	12	9	5.14	<.001	
Midbrain	−8	−20	−9	5.2	<.001	
Pons	6	−14	−16	4.91	<.001	
Decreases in PSP vs MSA						
Left striatum (caudate)	−14	4	7	4.55	.001	.001
Right striatum (anterior putamen/caudate)	16	6	7	3.47	.001	.01
Decreases in PSP vs controls						
Left striatum (caudate)	−12	12	12	Inf	<.001	.001
Right striatum (caudate	10	18	8	Inf	<.001	
Right striatum (putamen)	28	2	−5	7.71	<.001	
Left striatum (putamen)	26	−4	0	7.52	<.001	
Midbrain ventral	0	−12	−10	7.2	<.001	
Pons	−8	−26	−22	5	<.001	
Decreases in MSA-P vs PD						
Ventral midbrain	10	−12	−8	4.56	.001	.001
Dorsal midbrain	6	−28	−15	4.43	.001	
Dorsal pons	4	−28	−25	4.15	.001	
Decreases in MSA-P vs controls						
Ventral midbrain	2	−10	−10	7.27	<.001	.001
Right striatum (putamen)	24	−6	0	7.16	<.001	
Right striatum (caudate)	10	20	10	6.82	<.001	
Left striatum (putamen)	−20	−2	2	6.74	<.001	
Left striatum (caudate)	−6	22	−2	6.59	<.001	
Pons	0	−26	−25	4.45	.001	
Decreases in PD vs controls						
Right striatum (putamen)	28	2	2	6.86	<.001	.001
Left striatum (putamen)	−26	−4	0	6.32	<.001	
Right striatum (caudate)	8	20	4	5.76	<.001	
Left striatum (caudate)	12	20	−2	4.8	.01	

Abbreviations: [^{123}I]β-CIT V_3'', specific-to-nondisplaceable equilibrium partition coefficient values on iodine I 123–labeled 2β-carbomethoxy-3β-(4-iodophenyl)tropane single-photon emission tomography; Inf, infinity; MSA-P, multiple-system atrophy (Parkinson variant); PD, Parkinson disease; PSP, progressive supranuclear palsy; SPM, statistical parametric mapping.

*MNI (Montreal Neurological Institute) coordinates have been transformed to Talairach coordinates by the software package mni2tal.m (http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml).

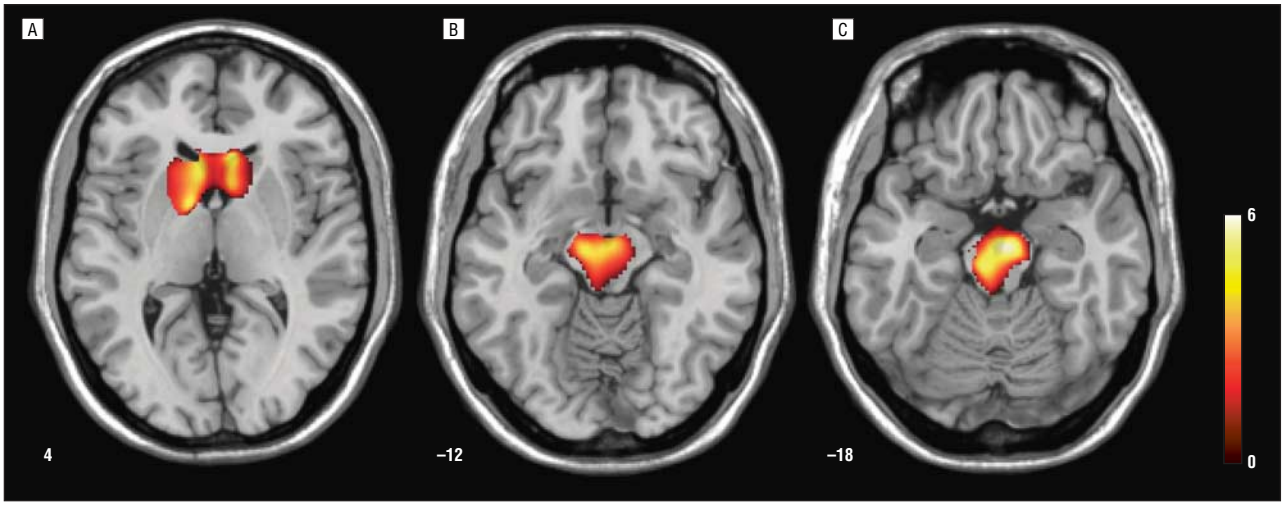

Figure 2. Statistical parametric mapping transverse maximum intensity projection maps rendered onto a stereotactically normalized magnetic resonance image, showing areas of significant decreases in specific-to-nondisplaceable equilibrium partition coefficient (V3′′) values on iodine I 123–labeled 2β-carbomethoxy-3β-(4-iodophenyl)tropane ([^{123}I]β-CIT) single-photon emission tomography in the caudate (A), midbrain (B), and pons (C) in progressive supranuclear palsy compared with Parkinson disease. Numbers in A, B, and C correspond to the z coordinate in Talairach space.

Table 4. Diagnostic Classification Based on Midbrain Mean [^{123}I]β-CIT V_3'' Values Using a Cutoff Level of 2.3*

Clinical Classification (No.)	Predicted by Changes of Midbrain [^{123}I]β-CIT V_3'' Uptake, No. (%)	
	PD	APD
PD (17)	**16** (**94.1**)	1 (5.9)
APD (29)	3 (10.3)	**26** (**89.7**)
PSP (14)	2 (14.3)	**12** (**85.7**)
MSA-P (15)	1 (6.7)	**14** (**93.3**)

Abbreviations: APD, atypical parkinsonian disorders; [^{123}I]β-CIT V_3'', specific-to-nondisplaceable equilibrium partition coefficient values on iodine I 123–labeled 2β-carbomethoxy-3β-(4-iodophenyl)tropane single-photon emission computed tomography; MSA-P, multiple-system atrophy (Parkinson variant); PD, Parkinson disease; PSP, progressive supranuclear palsy.

*Classification of patients' midbrain [^{123}I]β-CIT uptake based on a cutoff level of 2.3 with respect to their clinical diagnosis was calculated by stepwise logistic regression analysis followed by receiver operating characteristic analysis. Rows represent the clinical diagnosis, and columns, the diagnosis predicted by midbrain [^{123}I]β-CIT V_3'' values. Boldface indicates corrected diagnosis.

by [^{123}I]β-CIT SPECT,[8,30-33] the reduced [^{123}I]β-CIT uptake detected in the midbrain and pontine areas of the PSP group likely corresponds to a more widespread decline of monoaminergic neurotransmitter systems when compared with PD. This would be in line with reported neuropathologic findings in patients with PSP, showing neuronal loss or neurofibrillary tangles or both in brainstem areas containing DAT-, SERT-, or noradrenergic transporter–bearing neurons, such as the substantia nigra, locus ceruleus, and raphe nuclei.[19,36-40]

In our study, the precision of the assignment of signal alterations to anatomic structures was limited by the spatial resolution of a conventional dual-headed SPECT camera, together with partial volume effects that affect quantification of signals in structures smaller than twice the full-width half-maximum resolution of the scanner used. This nonlinear effect leads to an underestimation of the radioactivity concentration in small objects.[41-43] In the present study, the caudate and the reported areas within the brainstem are likely to be affected in subjects with relatively high tracer uptake, resulting in an underestimated [^{123}Iβ]-CIT signal of those brain regions. On the other hand, spillover effects occur from areas with higher [^{123}I]β-CIT uptake into adjacent brain areas, as is the case between the caudate and anterior putamen, leading to an overestimation of the [^{123}I]β-CIT uptake in the caudate of subjects with high putaminal signal. Although treatment with dopaminergic and serotonergic drugs can potentially affect [^{123}I]β-CIT binding, differences in drug treatment are unlikely to explain the observed differences in brain [^{123}I]β-CIT uptake between groups in this study. None of the patients was taking selective serotonin reuptake inhibitors at the time of the imaging study, and while all patients with PD and most of the patients with APD were taking levodopa or dopamine agonists or both, effects on DAT binding of those drugs may be neglected, according to recent studies.[44-46] Although the patient groups were matched for age and disease duration, motor disability as assessed by the Unified Parkinson's Disease Rating Scale was more severe in MSA-P and PSP than PD, reflecting differences in the natural course of these disorders. In the absence of postmortem verification,[47] we cannot exclude misdiagnosis in some of the clinically diagnosed patients. However, clinical diagnoses were based on stringent criteria[18-20] and all patients were followed up clinically for at least 2 years after having completed the imaging study, without change in diagnosis, thus making the clinical diagnosis of the patients very reliable.[2,3]

CONCLUSIONS

The results of the present study support the potential of DAT imaging using SPECT as a differential diagnostic tool to distinguish between PD and APDs such as PSP and MSA-P when voxelwise analysis is applied. Using striatal [^{123}I]β-CIT V_3'' values, we did not observe any overlap between controls and the patients with parkinsonian disorders. Using a cutoff midbrain [^{123}I]β-CIT V_3'' value of 2.3, we were able to correctly classify 91.3% of patients with APD and PD (42 of all 46 patients with parkinsonism). Similar to previous neuroimaging studies,[23,27,48-51] we were not able to differentiate between PSP and MSA-P; however, our data suggest that quantification of midbrain DAT signal may enhance the diagnostic yield of [^{123}I]β-CIT SPECT in patients with parkinsonism.

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Correspondence: Klaus Seppi, MD, Department of Neurology, Medical University Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria (klaus.seppi@uibk.ac.at).
Author Contributions: Drs Seppi and Scherfler contributed equally to this study, had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Seppi, Scherfler, Schocke, Goebel, Wenning, and Poewe. *Acquisition of data:* Seppi, Scherfler, Donnemiller, Virgolini, Schocke, Boesch, and Brenneis. *Analysis and interpretation of data:* Seppi, Scherfler, Donnemiller, Schocke, Goebel, Mair, and Poewe. *Drafting of the manuscript:* Seppi, Scherfler, and Poewe. *Critical revision of the manuscript for important intellectual content*: Scherfler, Donnemiller, Virgolini, Schocke, Goebel, Mair, Boesch, Brenneis, Wenning, and Poewe. *Statistical analysis:* Seppi, Scherfler, Goebel, and Brenneis. *Administrative, technical, and material support:* Donnemiller, Schocke, Mair, Boesch, and Poewe. *Study supervision:* Seppi, Scherfler, Virgolini, Wenning, and Poewe.
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