Published in "European Journal of Nuclear Medicine and Molecular Imaging 43(3): 509–516, 2016"
which should be cited to refer to this work.

Distinct spatiotemporal patterns for disease duration and stage in Parkinson's disease

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Abstract
Purpose To assess correlations between the degree of dopaminergic depletion measured using single-photon emission computed tomography (SPECT) and different clinical parameters of disease progression in Parkinson's disease (PD).
Methods This retrospective study included 970 consecutive patients undergoing ^{123}I-ioflupane SPECT scans in our institution between 2003 and 2013, from which we selected a study population of 411 patients according to their clinical diagnosis: 301 patients with PD (69.4±11.0 years, of age, 163 men) and 110 patients with nondegenerative conditions included as controls (72.7±8.0 years of age, 55 men). Comprehensive and operator-independent data analysis included spatial normalization into standard space, estimation of the mean uptake values in the striatum (caudate nucleus + putamen) and voxel-wise correlation between SPECT signal intensity and disease stage as well as disease duration in order to investigate the spatiotemporal pattern of the dopaminergic nigrostriatal degeneration. To compensate for potential interactions between disease stage and disease duration, one parameter was used as nonexplanatory coregressor for the other.
Results Increasing disease stage was associated with an exponential decrease in ^{123}I-ioflupane uptake (R^2=0.1501) particularly in the head of the ipsilateral caudate nucleus (p<0.0001), whereas increasing disease duration was associated with a linear decrease in ^{123}I-ioflupane uptake (p<0.0001; R^2=0.1532) particularly in the contralateral anterior putamen (p<0.0001).

Keypoints • Disease stage and disease duration have different spatiotemporal patterns of dopaminergic depletion in PD.
• ^{123}I-Ioflupane uptake in the striatum decreases exponentially with disease stages.
• Disease stage correlates particularly with uptake in the head of the caudate nucleus with ipsilateral predominance.
• ^{123}I-ioflupane uptake in the striatum decreases linearly with disease duration.
• Disease duration correlates particularly with uptake in the anterior putamen with contralateral predominance.
• The operator-independent spatial normalization of ^{123}I-ioflupane SPECT scans provides a reference database for research and clinical studies based on a large sample of 411 patients.

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Conclusion We observed two distinct spatiotemporal patterns of posterior to anterior dopaminergic depletion associated with disease stage and disease duration in patients with PD. The developed operator-independent reference database of 411 ^{123}I-ioflupane SPECT scans can be used for clinical and research applications.

Keywords Parkinson's disease · ^{123}I-ioflupane SPECT · Voxel-wise analysis · Disease duration · Disease stage

Introduction

Over the last two decades, ^{123}I-ioflupane SPECT has become a routinely used tool for the diagnosis of Parkinson's disease (PD). It has proved particularly useful in distinguishing PD and other degenerative forms of parkinsonism from nondegenerative movement disorders such as essential tremor, dystonia, drug-induced parkinsonism and many others [1–6]. It may also serve as a powerful instrument for the in vivo clinical investigation of the pathophysiological mechanisms underlying this neurodegenerative disorder. The technique involves a radioactive ligand (^{123}I-ioflupane) of the presynaptic dopamine transporter (DAT), which has been shown to reflect degeneration of the dopaminergic nigrostriatal pathway in PD [3, 7, 8]. More recently, several investigations have assessed a potential link between ^{123}I-ioflupane SPECT data and progression of PD, and have shown a negative correlation between striatal ^{123}I-ioflupane uptake and disease stage [3, 7, 9–11]. However, most of these studies included a relatively limited number of patients (16 PD vs. 10 controls [7], 41 PD [9], 32 PD vs. 24 controls [10], 19 PD [11], 103 PD [3]) and analysed manually defined regions of interest (ROI).

Our present study included a unique cohort of 301 PD and 110 control patients identified from among 970 consecutive patients scanned using the same SPECT apparatus and following the same acquisition protocol in our institution between 2003 and 2013. We conducted an operator-independent voxel-wise analysis in order to evaluate the correlation between striatal uptake of ^{123}I-ioflupane and disease duration and disease stage in patients with PD at a high spatial resolution.

Materials and methods

Participants

The local ethics committee approved this retrospective study, which included 970 patients who had consecutively undergone a brain ^{123}I-ioflupane SPECT scan in our institution between October 2003 and September 2013. From this cohort, we identified 411 patients who met the following criteria: (1) a visually assessed brain ^{123}I-ioflupane SPECT scan, (2) extensive neurological testing and follow-up, (3) a well-established diagnosis of PD (patient group) or a neurological disorder known to spare the nigrostriatal dopaminergic system (control group), and (4) the absence of structural abnormalities on brain MRI.

In the PD group, the diagnosis was established by a trained movement disorders specialist following the UK Parkinson's Disease Society Brain Bank criteria. Criteria included the presence of bradykinesia associated with at least one of the following three criteria: 4–6 Hz resting tremor, rigidity or postural instability. Supportive features included, among others, unilateral onset, progressive course, an excellent and sustained response to levodopa or typical levodopa-induced dyskinesia. Of note, patients exhibiting atypical features suggesting another form of degenerative parkinsonism, such as multiple system atrophy, progressive supranuclear palsy or corticobasal degeneration, or secondary parkinsonism such as vascular parkinsonism or normal pressure hydrocephalus were all excluded. Importantly, while ^{123}I-ioflupane SPECT data were not used to establish a specific diagnosis of PD, an abnormal scan was required to confirm degenerative parkinsonism. Accordingly, in the PD group,^{123}I-ioflupane SPECT typically showed an asymmetrical reduction in striatal uptake more marked in the putamen than in the caudate nucleus. PD patients were staged according to the Hoehn and Yahr (H&Y) classification, from mild and unilateral (stage 1) to advanced and bilateral disease stages (stages 4 and 5) [12]. The control group included patients who had had a ^{123} I-ioflupane SPECT scan to assess an unusual tremor, unclear parkinsonism or other movement disorder of uncertain origin, and whose scan turned out to be normal. This control group therefore included patients with essential tremor, drug-induced parkinsonism, psychogenic parkinsonism and various conditions known to be associated with an unaltered nigrostriatal pathway.

Demographic and clinical data

The control group comprised 110 patients (age 72.7± 8.0 years, 55 men). The patient group comprised 301 PD patients stratified as follows: H&Y stage 1 (43 patients), H&Y stage 2 (142 patients), H&Y stage 3 (83 patients), H&Y stage 4 (19 patients) and H&Y stage 5 (13 patients; Table 1). As expected, there were significant differences between adjacent groups regarding age except between group H&Y stage 3 and 4 (p=0.471) and between H&Y stage 4 and 5 (p=0.965). Statistical analysis did not reveal any significant differences among the groups in terms of gender.

Table 1 Demographic and clinical characteristics

	Control group	Hoehn and Yahr stage				
		1	2	3	4	5
Sex (m/f)	55/55	18/25 (n.s. vs. control)	85/58 (n.s. vs. stage 1)	42/41 (n.s. vs. stage 2)	9/10 (n.s. vs. stage 3)	9/4 (n.s. vs. stage 4)
Age (years)	72.7±8.0	62.3±11.3 ($p<0.01$ vs. control)	67.8±10.9 ($p<0.05$ vs. stage 1)	73.5±8.9 ($p<0.001$ vs. stage 2)	75.2±10.2 (n.s. vs. stage 3)	75±9.5 (n.s. vs. stage 4)
Disease duration (years)	–	2.1±2.3	3.8±5.0	5.1±4.4	5.3±4.7	7.1±6.0

n.s. not significant

SPECT image acquisition

After blocking thyroid uptake with either Lugol solution or sodium perchlorate, about 185 MBq of ^{123}I-FP-CIT was administered intravenously. SPECT images were acquired 4 h after injection on a triple-head gamma camera (Toshiba Medical Systems, Tokyo, Japan) and fan-beam, low-energy, high-resolution collimators. Images were acquired in steps of 6° over 360° and a 128×128 matrix. Patients were positioned using a head holder to minimize head motion. Images were corrected for scatter using a triple-energy window method and for photon attenuation using a 0.15/cm uniform coefficient. Dopaminergic agents were not discontinued. All images were reconstructed using Toshiba GMS software version 5 with the same reconstruction algorithms and parameters. More details have been provided by Garibotto et al. [13].

MR image acquisition

MR imaging was performed over a period of 10 years as part of routine clinical work-up. This explains the variable MR protocol, but all patients had at least T2 imaging, fluid attenuation inversion recovery imaging and diffusion-weighted imaging or diffusion tensor imaging to rule out structural brain lesions. Moreover, white matter lesions were assessed according to the Fazekas scale [14]. A group of 103 patients had an additional high-resolution Magnetization Prepared Rapid Gradient Echo (MPRAGE) 3D T1 brain magnetic resonance scan as part of clinical routine using a 3.0-T MR system (Magnetom Trio; Siemens, Erlangen Germany) with the following parameters 256×256 matrix, 176 sections, 1×1×1 mm, TE=2.3 ms, TR=2.300 ms.

Statistical analysis

Statistical analyses were performed with GraphPad Prism (version 6.0, www.graphpad.com) and FSL (FMRIB Software Library, version 5.0, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki).

Image postprocessing

In a first step, we created a ^{123}I-ioflupane-specific template based on 103 patients who had both a ^{123}I-ioflupane SPECT and a 3D T1 MPRAGE MRI scan. Each individual brain ^{123}I-ioflupane scan was linearly registered to the same patient 3D T1 data using FLIRT (FMRIB's linear image registration tool, part of FSL) [15, 16] and 6° of motion. Additionally, the 3D T1 data from individual patients were nonlinearly registered to the Montreal neurological institute (MNI) standard space by running FNIRT (part of FSL). This nonlinear transformation matrix was then applied to the individual ^{123}I-ioflupane scans. Finally, a ^{123}I-ioflupane-specific template was generated by merging and averaging all ^{123}I-ioflupane images (using fslmerge and fslmeants, parts of FSL). In summary, this procedure created a nonlinear spatial normalization of the ^{123}I-ioflupane scan into standard space using the information from the 3D T1 high-resolution MRI imaging in individual patients. Similar procedures have been used successfully in previous investigations [17, 18].

In a second step, all individual ^{123}I-ioflupane SPECT scans were spatially normalized to this ^{123}I-ioflupane SPECT template. In addition to the spatial normalization, the ^{123}I-ioflupane SPECT scans were also intensity normalized by subtracting the average signal in the occipital region as reference region to each individual ^{123}I-ioflupane data by using fslmaths (part of FSL). The resulting images were then divided by the average signal of the occipital region as described by Garibotto et al. [13]. The occipital region mask was manually created using fslview (part of FSL) on the MNI152_T1_2mm_brain template.

To take into account the asymmetrical nature of PD, using fslswapdim we flipped images in patients with predominantly left-sided clinical symptoms to have the clinical predominance of the disease on the same side, so that the right side of the images corresponded to the

clinically less affected body side and the left side to the more affected body side in all subjects including controls. This was done after spatial normalization.

Analysis of mean ^{123}I-ioflupane uptake

The mean ^{123}I-ioflupane uptake values were calculated using a mask of the striatum. This striatal mask was created using the Harvard Oxford subcortical atlas (included in FSL) by combining the regions of the left and right putamen and caudate nucleus using fslmaths. The patients were grouped according to disease stage (defined as the H&Y stage at the time of image acquisition) and disease duration according to the time elapsed between the appearance of the first PD symptom and image acquisition and as described below (Table 2). The mean ^{123}I-ioflupane uptakes in the striatal mask were calculated for each group as well as for controls using fslmeants. Linear and nonlinear regression was applied to the mean values (exponential one-decay linear regression). Note that the control values were not taken into account by the software for the operations described above.

Voxel-wise analysis of ^{123}I-ioflupane uptake

Voxel-wise analysis was performed by permutation testing (n=5,000) using the randomise function (part of FSL) and Threshold-Free Cluster Enhancement (TFCE) error considering multiple comparison corrected p values <0.05 corrected as significant [19]. The analysis was run for both disease stage according to the H&Y stage and disease duration in years since the first identified PD symptom, investigating positive and negative linear correlations. Note that for the correlation with disease duration, disease stage was used as a nonexplanatory coregressor to compensate for a potentially confounding effect of disease duration. The analysis was done similarly for disease stage. Moreover, age and gender were used as coregressors to compensate for potential effects of age and gender. To assess the laterality of these results, we compared the voxel values in the striatum between the ipsilateral (right) side and the contralateral (left) side for disease stage and disease duration using unpaired t tests. In order not to bias the results, the statistical analysis did not include the control group.

Results

Analysis of mean ^{123}I-ioflupane uptake

Evolution of the average ^{123}I-ioflupane uptake showed a posterior to anterior progression of the dopaminergic depletion in the striatum, particularly the putamen, related to disease stage (Fig. 1, top) and duration (Fig. 1, bottom), but with two distinct patterns. We found an exponential decrease in ^{123}I-ioflupane uptakes with progressive disease stage (R^2=0.1509). Conversely, the ^{123}I-ioflupane uptakes decreased linearly with progressive disease duration (p<0.0001; R^2=0.1532).

Voxel-wise analysis of ^{123}I-ioflupane uptake

The voxel-wise analysis revealed two different spatiotemporal patterns of ^{123}I-ioflupane uptake with increasing disease duration and disease stage. Increasing disease duration correlated with decreased uptake particularly in the anterior part of the putamen with a contralateral predominance (p<0.0001). Conversely, increasing disease stage was correlated with decreased ^{123}I-ioflupane uptake particularly in the head of the caudate nucleus with an ipsilateral predominance (p<0.0001). The voxel-wise analyses of disease duration and disease stage were performed using the other parameter as coregressor in order to exclude potentially confounding interactions between these two factors (Fig. 2).

Discussion

We developed an operator-independent database of ^{123}I-ioflupane scans for research and clinical studies based on a large sample of 301 consecutive PD patients and 110 controls who underwent extensive neurological evaluation and follow-up. Using this reference database, we demonstrated two

Table 2 Patient grouping

Disease duration			Disease stage		
Duration (years)	Group	No. of patients	H&Y stage	Group	No. of patients
0–1	1	99	1	1	43
1.25–2	2	61	2	2	143
2.5–5	3	62	3	3	83
6–9	4	42	4	4	19
>10	5	37	5	5	13

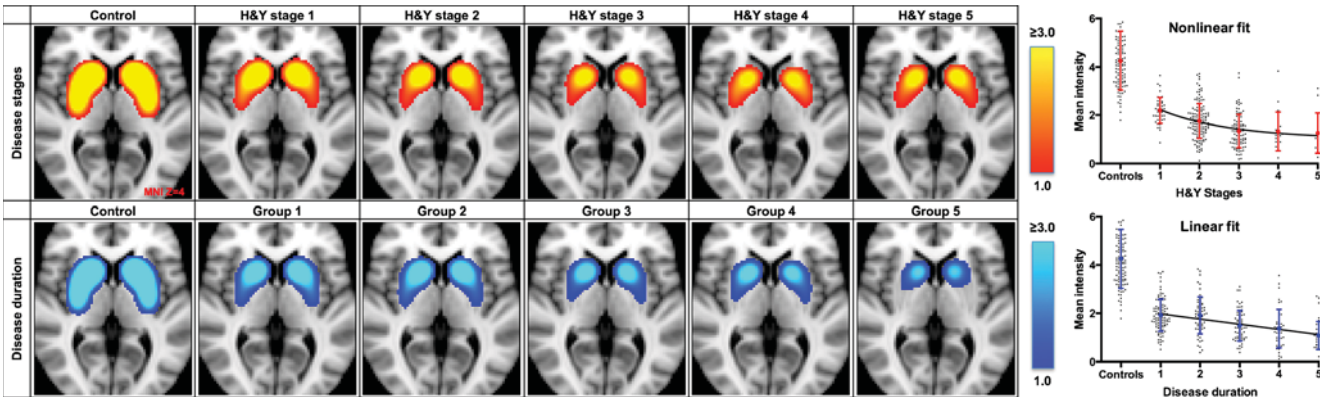

Fig. 1 Mean ^{123}I-ioflupane uptake as a function of increasing Hoehn and Yahr disease stage (*top*) and increasing disease duration (*bottom*) superimposed on the Montreal Neurological Institute (MNI) standard space (T1 2-mm brain transverse section, z=4). *Top* The normalized intensities range from 1 (low intensity, *red*) to 3 (high intensity. *yellow*). ^{123}I-Ioflupane uptake decreases exponentially (R^2=0.1501) with increasing Hoehn and Yahr stage. *Bottom* The normalized intensities range from 1 (*dark blue*) to 3 (*light blue*). ^{123}I-Ioflupane uptake decreases linearly with disease duration (p<0.0001, R^2=0.1532; *group 1* short disease duration, *group 5* long disease duration)

distinct spatiotemporal patterns of dopaminergic depletion in PD. Overall, both disease duration and disease stage were associated with progressive dopaminergic depletion in the striatum, particularly the putamen, with a posterior to anterior gradient, in accordance with the findings of many previous studies. Interestingly, we found that increasing disease stage was associated with an exponential dopaminergic depletion particularly in the ipsilateral head of the caudate nucleus, while increasing disease duration was associated with linear dopaminergic depletion particularly in the contralateral anterior putamen.

Disease stage

During the past two decades, several molecular imaging studies have assessed the link between progression of PD and degeneration of the nigrostriatal dopaminergic system [3, 7, 9–11]. Most have observed a correlation between disease

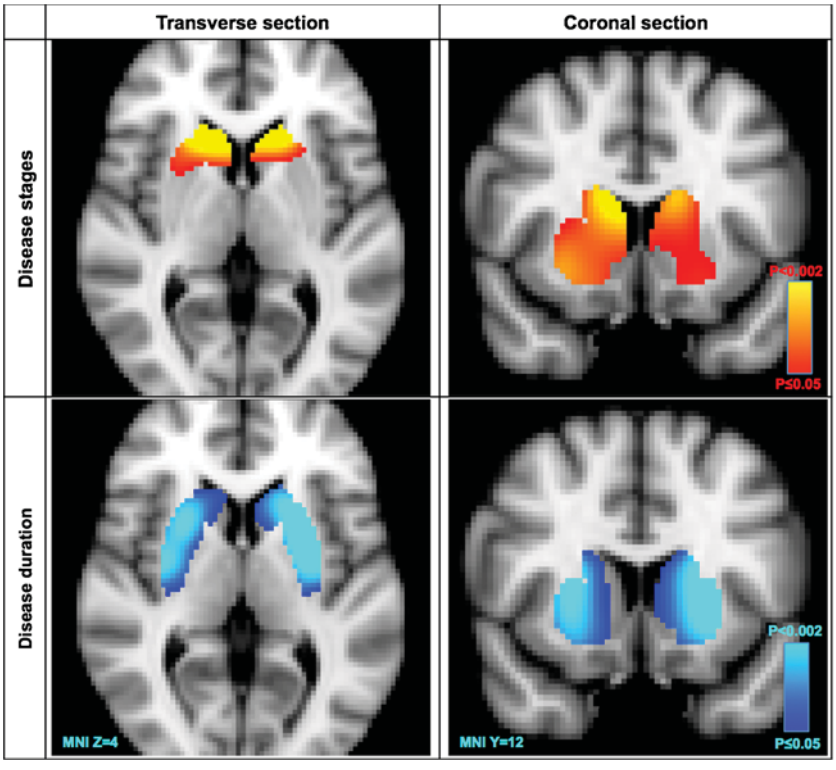

Fig. 2 Correlations corresponding to Hoehn and Yahr stage (*red*) and disease duration (*blue*) superimposed on the Montreal Neurological Institute (MNI) standard space (T1 2-mm brain transverse section, z=4, and coronal section, y=12)

stage and deterioration of the signal obtained by in vivo neuroimaging assessment of the dopaminergic system either with ^{18}F-Dopa PET or with SPECT [3, 9, 10, 20–22], yet a few studies have failed to confirm this correlation [23, 24]. Overall, in our study, we definitely observed a clear posterior to anterior progression of dopaminergic depletion with increasing disease stage, in agreement with the findings of previous investigations [3, 25, 26]. Interestingly, Benamer et al. assessed 41 PD patients with Hoehn and Yahr stages I to IV and found a linear decrease in mean striatal uptake with increasing disease stage based on a ROI approach in a cross-sectional design [9]. Our results, obtained in a much larger cohort of 301 PD patients and an operator-independent voxel-wise analysis, in contrast demonstrated an exponential decrease in striatal uptake. This difference might be related to different scales for rating disease stage. Indeed, while Benamer et al. [9] used the Unified Parkinson's Disease Rating Score (UPDRS), we used the H&Y staging system, which is far less sensitive to the effects of levodopa and other antiparkinsonian medications.

The exponential decrease in striatal uptake with progressive disease stage indicates a faster dopaminergic depletion in early than in more advanced disease stages, following a steady percentage of neuronal loss or a variable absolute value of loss, more marked in the early phase of the condition. It is noteworthy that the few neuropathological investigations that have addressed this issue have indicated that the neuronal loss occurring in the PD substantia nigra pars compacta seems to follow a nonlinear exponential profile, as in our study, whereby neuronal loss within the nigrostriatal system is massive during the first few years after disease initiation and far less pronounced afterwards [27, 28]. The large variability in the data presented in Fig. 1b, d reflects the substantial interindividual variability of PD, as discussed by Benamer et al. [9].

In the majority of the investigations discussed above ROI analysis was used, and this, because of poor spatial resolution, may have biased the results. As a novel finding, the operator-independent voxel-wise analysis applied in this large cohort was able to show that uptake in the head of the caudate nucleus appears to be correlated with disease stage. This unexpected yet robust finding suggests that the anterior striatum is also the site of an intense and active degenerative process that takes place in more advanced stages of the disease, whereas the posterior striatum sustains massive neurodegeneration earlier in the disease course, as supported by the nonlinear decrease in the reduction of ^{123}I-ioflupane uptake. In addition, at later stages, there might be a floor effect whereby ligand uptake is so low that a further reduction may no longer be captured. This finding is clinically meaningful as the caudate nucleus is essentially involved in the associative loop of the basal ganglia circuitry, and may well play an important role in late cognitive features of PD, including executive dysfunction that is found in the vast majority of patients, apathy, memory loss, cognitive decline and, eventually, overt dementia.

Disease duration

In contrast to disease stage, few previous studies have investigated the correlation between striatal uptake and disease duration. Overall, increasing disease duration was again associated with a posterior to anterior decrease in striatal ^{123}I-ioflupane striatal uptake. In a longitudinal ROI-based study in 32 PD patients and 24 controls, Marek et al. found a linear decrease in striatal ^{123}I-β-CIT uptake [10]. Our operator-independent analysis reproduced this linear decrease in dopaminergic depletion in PD patients with increasing disease duration. As an additional finding, voxel-wise correlation analysis showed that the anterior part of the putamen was progressively impaired with increasing disease duration, which, as discussed in the previous section, can also be interpreted as a later step in the nigrostriatal degenerative process, whereby as structures become more affected with disease progression following a caudorostral gradient, the precommissural striatum undergoes rapid and severe degeneration later than the postcommissural striatum where the degenerative process has already slowed down.

Laterality

While it is commonly accepted that there is a good correlation between the body side more affected by parkinsonism and a more marked contralateral decrease in striatal uptake, some previous investigations have shown partially conflicting results regarding the laterality of the dopaminergic depletion [4, 7, 9, 11]. In the current study, we disentangled the interaction of disease stage and duration. We were able to demonstrate that increasing disease stage was correlated with a predominantly ipsilateral dopaminergic depletion particularly in the head of the caudate nucleus, while increasing disease duration was correlated with predominantly contralateral dopaminergic depletion particularly in the anterior putamen. This complex interaction between disease stage and duration, which was not compensated for in the investigations discussed above, might explain the partially conflicting results among the previous studies.

Strengths and limitations

The major strength of this study is the large sample size of 301 consecutive PD patients and 110 controls who were all scanned in the same institution using the same protocol and machine. Moreover, all postprocessing steps were operator-independent, resulting in a reference database for clinical and research applications. In order to compensate for

potentially confounding effects between disease duration and disease stage, we used the other parameter as a nonexplanatory coregressor, i.e. analysing duration and controlling for stage, and vice versa. Additionally, we used gender and age as additional coregressor to compensate for the well-known dopaminergic depletion linked to ageing [22, 24, 29, 30].

We used the H&Y scale [12] to assess disease stage. This scale was established in 1967 in a very large cohort of PD patients who were followed over 15 years at a time when no effective treatment for PD was available. Thus, the H&Y scale reflects the natural course of PD independently of any therapeutic intervention. This five-stage scale is easy to use and is therefore considered by many movement disorder experts a robust scale to follow disease progression, especially in later stages of the condition. On the other hand, the UPDRS [31] was developed as a comprehensive instrument for the evaluation of impairment and disability at a certain time point so that outcomes among different clinical trials or any therapeutic interventions could be directly compared. The UPDRS is highly sensitive to dopaminergic treatments and levodopa-responsive symptoms are particularly weighted. Consequently, as the vast majority of our patients were chronically treated with antiparkinsonian medications, and because an off-medication UPDRS score was not available at the time of the scan, we decided to rely on the H&Y staging system as a measure of disease progression as it better reflects the long-term stage of the disease and is less influenced by current medication. It is noteworthy, however, that there is as yet no ideal, validated and medication-insensitive clinical scale specifically dedicated to the measurement of disease progression in PD.

A limitation of the current investigation was its retrospective nature and the fact that patients were included from a clinical setting with a nonstandardized clinical work-up. The variable exposure to symptomatic medication in this clinical study might have been another potential bias. However, several studies have shown that standard antiparkinsonian treatment does not significantly affect the data obtained by ^{123}I-ioflupane SPECT [32–34]. A previous multicentre study assessed 139 healthy controls [35] and another related study from the same multicentre database assessed 122 healthy controls focusing notably on ageing and gender differences [36]. In contrast to these studies, our database includes controls and patients, and provides a voxel-wise rather than a region-based analysis.

Finally, we believe that the findings of this study may be clinically useful and may help clarify some problematic situations at the bedside, for example discrepancies between the patient's perception of symptoms and the SPECT data, development of PD-related cognitive decline versus cognitive symptoms as side effects of medication or even perhaps distinguishing between the various degenerative forms of parkinsonism.

Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was waived by the local ethics committee (retrospective analysis of imaging data acquired during clinical work-up).

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