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ORIGINAL ARTICLE

Predictive value of dopamine transporter SPECT imaging with [^{123}I]PE2I in patients with subtle parkinsonian symptoms

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Abstract
Purpose To examine the diagnostic sensitivity and specificity of dopamine transporter SPECT imaging with a highly dopamine transporter selective radioligand. The study included consecutively enrolled, drug-naive patients with an average short history of parkinsonian motor symptoms, referred for diagnostic scanning.

Methods The study group comprised 288 patients naive to antiparkinson treatment who were enrolled as they were admitted for a diagnostic SPECT scan with the radioligand [^{123}I]-*N*-(3-iodoprop-2E-enyl)-2-β-carbomethoxy-3β-(4-methylphenyl)nortropane (^{123}I-PE2I). After the diagnostic scanning, patients were followed clinically with an average follow-up of 19.7 ± 12.5 months.
Results A diagnosis could be clinically settled in 189 patients and among these patients, a dopamine transporter scan had a sensitivity of 88% and a specificity of 91% for discrimination between patients with and without striatal neurodegeneration. In cognitively impaired patients (Mini Mental State Examination <27) the specificity was 75% and the sensitivity 95%. A striatal anterior–posterior ratio (APR) of >2 differentiated between idiopathic Parkinson's disease and atypical parkinsonian syndromes with a specificity of 84% and a sensitivity of 63%.
Conclusion In drug-naive patients with subtle clinical parkinsonian motor symptoms, dopamine transporter scan using ^{123}I-PE21 has a high sensitivity and specificity in distinguishing between patients with and without striatal neurodegeneration. The specificity is lower in patients who are also cognitively impaired. Calculation of the striatal APR can assist in differentiating between idiopathic Parkinson's disease and atypical parkinsonian syndromes.

Keywords Predictive value · Parkinsonism · SPECT · Dopamine transporter

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Introduction

Cerebral SPECT imaging of the dopamine transporter (DAT) is widely acknowledged as a diagnostic tool for

discriminating between clinically well-defined groups of patients with and without striatal neurodegeneration pathology, e.g. idiopathic Parkinson's disease (PD) vs. essential tremor [1] or Lewy body dementia (DLB) vs. Alzheimer's disease (AD) [2]. In the clinical work-up, DAT SPECT imaging can assist the neurologist either in support of an early diagnosis, when symptoms are mild and the medical history is short, or in patients with atypical presentation of clinical symptoms and/or atypical disease progression.

A recent meta-analysis [3] has shown that DAT SPECT is highly specific (about 100%) but moderately sensitive (8–100%) in its ability to discriminate between patients with idiopathic PD in an early phase and healthy people. There are reasons to question if the specificity is always this high and why the sensitivity is apparently so much lower. In particular, patients included in the meta-analysis were already diagnosed with idiopathic PD at the time of the SPECT scan, and this is not the usual situation when DAT SPECT imaging is to serve as a diagnostic tool. This also means that the patients were treated with antiparkinson drugs, and the impact of dopaminergic drug treatment on DAT binding is still disputed [4]. Finally, specificity and sensitivity may vary for the individual diagnoses which means that the specific referral pattern within each study may result in different diagnostic outcomes.

In 2005 DAT SPECT imaging became a part of the diagnostic criteria for DLB [5]. Since then DAT SPECT has increasingly been used as an aid in the differential diagnosis between DLB and AD. However, inclusion of patients with other disorders involving cognitive impairment that also exhibit a more widespread cerebral degeneration (atrophy) is likely to lead to a higher rate of false-positive DAT SPECT scans, which will lead to a lower diagnostic specificity [6].

Reported diagnostic sensitivity varies considerably between studies [3] and we recently suggested that lack of radioligand selectivity for the DAT could potentially account for some of false-negative DAT scan outcomes, since with the widely used DAT radiotracer ^{123}I-FP-CIT a significant fraction of the SPECT signal is attributable to serotonin transporters, in contrast to the radioligand used in this study, [^{123}I]-*N*-(3-iodoprop-2E-enyl)-2-β-carbomethoxy-3β-(4-methylphenyl)nortropane ([^{123}I]PE2I) [7]. The latter is also not affected by selective serotonin reuptake inhibitors [8], as is the case for [^{123}I]FP-CIT binding [9]. [^{123}I]PE2I shows similar test–retest results to the other DAT radioligands available [10, 11].

The purpose of this study was to calculate the sensitivity and specificity of a DAT SPECT scan in a large number of consecutively enrolled, drug-naive patients with a an average short history of parkinsonian motor symptoms referred because of diagnostic uncertainty. We used the highly selective DAT radiotracer [^{123}I]PE2I and clinical follow-up to establish a final clinical diagnosis, as the "gold standard". We also assessed how the presence of cognitive impairment in the patients affected sensitivity and specificity of DAT SPECT imaging.

Methods and materials

Patients and healthy controls

Between January 2003 and March 2008, 288 patients were enrolled in the study. The group prospectively included all patients admitted for a diagnostic DAT SPECT scan at the Department of Neurology Rigshospitalet, Copenhagen. A post-hoc exclusion criterion for calculation of the diagnostic value was a final diagnosis not previously related to DAT SPECT outcome or a final diagnosis with inconclusive DAT SPECT scan results. The department has about 25,000 patient contacts per year of patients with mixed neurological symptoms. At the department there is a specialized memory clinic accounting for about 6,500 of the 25,000 contacts. The department has several specialists in movement disorders, but does not offer a clinic specializing in movement disorders. All patients were referred by a neurologist who suspected a disease involving striatal neurodegeneration. The diagnostic uncertainty in most patients was because of a very short history of discrete parkinsonian motor symptoms, but also in some patients because of very slow progression of symptoms or atypical symptoms.

None of the patients had received treatment for PD prior to the scan, but 21 were taking antidepressive medication (in all patients selective serotonin reuptake inhibitors) on the day of the DAT SPECT scan. Approximately half of the patients were referred from the general department of neurology and half of them from the memory clinic. Immediately prior to or on the day of the SPECT scan patients had a routine neurological examination including Mini Mental State Examination (MMSE), and assessments with the Hoehn and Yahr scale. Core motor features of parkinsonism (bradykinesia, tremor, rigidity and postural stability) were recorded. In the same period, 28 healthy volunteers (16 men, mean age 47.8 years, range 23–71 years) received a DAT SPECT scan. The SPECT scan procedures in the patients and volunteers were identical, and the outcomes have been described previously. The healthy volunteers were also examined neurologically to ensure they were not suffering from any neurological disease [10–12].

The study was performed in accordance with the ethical standards of the Declarations of Helsinki and was approved

by the ethics committee of Copenhagen (protocol number KF 02-150/98, KF 12-009/04, H-B-2008-024).

SPECT scanning

To block thyroidal uptake of free radioiodine, subjects received 200 mg potassium perchloride intravenously 15–20 min before injection of the DAT radioligand [^{123}I]PE2I. Subsequently an average intravenous bolus of [^{123}I]PE2I was given, immediately followed by a constant infusion of [^{123}I]PE2I for 3 h to maintain steady-state [12]. After 2 h of infusion, SPECT imaging was performed with a triple-head IRIX camera (Philips Medical, Cleveland, OH) fitted with low-energy, general all-purpose, parallel-hole collimators (spatial resolution 8.5 mm at 10 cm). The images were reconstructed with a program based on MATLAB 6.5 (Mathworks) using standard filtered back-projection with a low pass fourth-order Butterworth filter at 0.3 Nyquist (= 0.64 cm^{-1}). The SPECT data were reconstructed immediately after the scan and the result of the SPECT scan determined. Reconstruction and region of interest (ROI) manual delineation procedures have both been described previously [10, 11].

The outcome parameter, the nondisplaceable binding potential (BP_{ND}) [13], was calculated at plasma steady state conditions, and is defined as:

$$BP_{ND} = \frac{specifically\ bound\ radioligand}{Nondisplaceable\ radioligand\ in\ brain\ tissue}$$

BP_{ND} data from the healthy volunteers defined whether or not a patient's SPECT scan outcome was normal. A patient with a BP_{ND} below 2 SD of the controls was considered as having an abnormally reduced DAT binding. We chose to include the lowest (right or left side) value rather than the average BP_{ND} so that a large asymmetry would not conceal a unilaterally abnormal SPECT scan. Based on the BP_{ND} values obtained from the striatum, caudate nucleus and putamen, we calculated the striatal side-to-side (STS) asymmetry ratio:

$$STS\ asymmetry\ ratio = \frac{highest\ striatal\ BP_{ND}}{lowest\ striatal\ BP_{ND}}$$

and the anterior–posterior ratio (APR) (in the most affected hemisphere):

$$APR = \frac{caudate\ BP_{ND}}{putamen\ BP_{ND}}$$

For each patient, the BP_{ND} values derived from the 28 healthy volunteers were age-corrected to match the age of the patient (using a striatal 2.8% reduction per decade; data from our own cohort of healthy controls [8, 10, 12]). The age-normalized individual DAT availability was calculated according to:

$$Age-adjusted\ BP_{ND} = \frac{BP_{ND(patient)}}{BP_{ND}(age-adjusted\ normal\ value)} \times 100\%$$

The age-adjusted BP_{ND} was used for comparison of the different diagnostic groups.

Diagnostic evaluations

For each patient, an initial clinical diagnosis was suggested prior to the [^{123}I]PE2I SPECT scan by the referring neurologist. After the SPECT scan the patients were followed clinically by a movement or dementia disorder specialist, and a neurologist gave a diagnosis when a final clinical diagnosis could be settled. For the purposes of this study, the final diagnosis was double-checked in accordance with established criteria [5, 14–20] by two neurologists specializing in neurodegenerative disorders both with more than 15 years of experience (M.K., B.B.A.). The specialists were both blinded to the results of the DAT SPECT scan and their diagnoses were based on history, symptoms and paraclinical data derived from the clinical records. Great care was also taken to remove any notes in the records that addressed the outcome of the DAT scan. In addition, the potential bias that the outcome of the DAT scan may have had on the neurologist in charge of the patient would tend to diminish as time passed and the clinical picture became clearer. Obviously the experts thereby were excluding the DAT SPECT supportive criteria in patients with DLB and idiopathic PD. The final clinical diagnosis was settled between August 2008 and January 2010. According to the final clinical diagnosis, the patients were divided into two groups of disorders, those with or without dopaminergic striatal neurodegeneration.

Statistical analysis

All statistical analyses were performed with Instat 3.1a (GraphPad Software) and graphical presentations were prepared with Prism 5.00v (GraphPad Software). To compare multiple groups with regard to BP_{ND}, STS asymmetry ratio and APR, a Bonferroni-corrected one-way ANOVA Kruskal-Wallis test was used. Comparison between clinical core symptoms and correlation with DAT binding and post-hoc analyses were performed using the unpaired Student's *t*-test. p values <0.05 were considered statistically significant.

Results

Table 1 shows patient demographics at the time of SPECT scanning. The presence of bradykinesia and rigidity was

Table 1 Patient demographics on the day of the DAT SPECT scan. If not otherwise stated, the data are presented as means (range)

Characteristic	Parkinson's disease (n=28)	Atypical parkinsonian syndromes (n=35)	Lewy body dementia (n=54)	Alzheimer's disease (n=17)	Overall (n=189)
Age (years)	64 (42–82)	65 (47–80)	75 (56–85)	71 (53–85)	67 (41–85)
Female gender (n)	12	13	21	3	72
Symptoms prior to scan (months)	26 (4–108)	39 (6–168)	26 (6–108)	33 (12–120)	39 (4–240)[a]
Tremor (%)	61	37	44	41	41
Rigidity (%)	86	80	57	53	59
Bradykinesia (%)	82	91	76	53	72
Postural instability (%)	21	23	30	24	38
More than one core symptom (n)	82	74	63	41	61
Hoehn and Yahr score	1.8 (1–3)	2.4 (1–4)	2.3 (1–5)	2.0 (1–3)	2.2±0.9
MMSE score	25.6 (21–30)	24.3 (15–30)	22 (11–30)	24 (13–29)	25.3±4.8
Follow-up (months)	22.4 (4–67)	19.0 (4–48)	16.0 (4–54)	24.7 (4–41)	19.7 (4–67)

[a] A high duration of symptoms was mainly seen in patients with spinocerebellar ataxia type 3 and idiopathic late-onset cerebellar ataxia.

associated with a significantly lower DAT BP_{ND} (t-test, $p<0.05$), whereas the presence of postural instability and tremor was not (t-test, $p\geq0.2$).

The average follow-up time was 19.7±12.7 months. Table 2 shows the distribution of major diagnostic categories before and after follow-up; diagnostic certainty increased considerably during the follow-up period. A final clinical diagnosis was settled in 224 out of the 288 patients (see the flow chart, Fig. 1). Of these 224 patients, 35 were excluded because they received a final clinical diagnosis that to our knowledge has not previously been related to DAT SPECT outcomes or the results have been inconclusive. The unrelated diagnoses included Creutzfeldt-Jakob disease (n=4), normal pressure hydrocephalus (n=12) and infections or poisoning (alcohol, manganese, medical) in the central nervous system (n=7) or 2), and the inconclusive diagnosis was vascular PD (n=12) [21]. Hence, in these 35 patients the final clinical diagnosis could not be used to determine the anticipated outcome of the initial [^{123}I]PE2I SPECT scan. Patient demographics regarding the overall and main groups of the 189 patients are displayed in Table 1.

Table 2 Initial clinical diagnosis (at the time of referral for the [^{123}I]PE2I scan) and final clinical diagnosis at follow-up. More than 90% of patients had a probable diagnosis at follow-up compared to only 10% at the time of referral

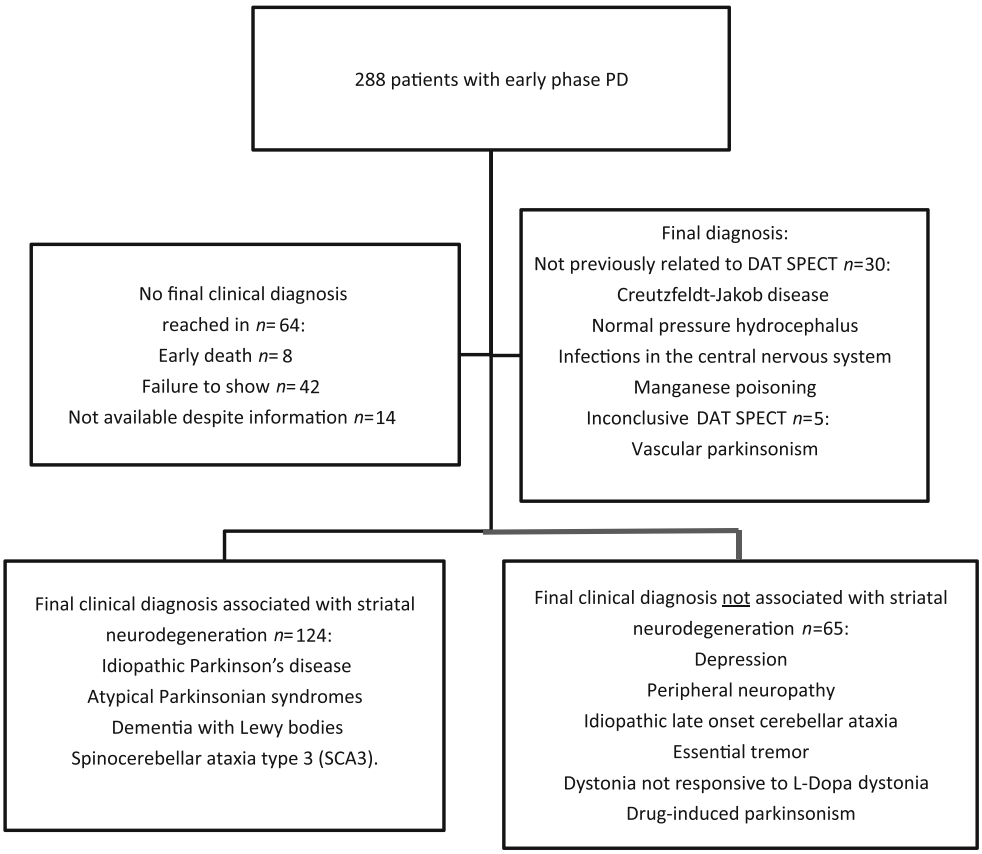
	Initial clinical diagnosis (n)	Final clinical diagnosis (n)
Possible atypical parkinsonian syndrome	39	2
Probable atypical parkinsonian syndrome	3	32
Possible Parkinson's disease	65	5
Probable Parkinson's disease	1	23
Possible Lewy body dementia	45	5
Probable Lewy body dementia	18	49
Possible Alzheimer's disease	6	2
Probable Alzheimer's disease	0	17

In 64 patients no final clinical diagnosis could be settled. Of these 64 patients, 50 (17.5 %) were lost due to death and thereby a short follow-up time (<4 months, n=8) or failure to show up (n=42). In the remaining 14 patients no final clinical diagnosis could be established. Although all relevant clinical data were available, all 14 of these patients had an abnormal DAT SPECT scan. The distribution of final clinical diagnoses not associated with (known) involvement of the nigrostriatal pathway were as follows (possible/probable): depression (1/8), peripheral neuropathy (0/15), idiopathic late-onset cerebellar ataxia (0/11), essential tremor (0/5), dystonia not responsive to L-DOPA (0/5), and drug-induced parkinsonism (0/2). Finally, five patients had genotypically verified spinocerebellar ataxia type 3.

DAT SPECT results

Figure 2a shows the individual striatal age-related percentage DAT BP_{ND} values in individual patients and healthy volunteers. Patients diagnosed with DLB, idiopathic PD, or atypical parkinsonian syndromes (APS) (multisystem atrophy, corticobasal degeneration and progressive supranuclear palsy or spinocerebellar ataxia type 3) had significantly lower BP_{ND} values than healthy controls (ANOVA, $p<0.001$) and also lower than patients with AD (ANOVA, $p<0.001$). In patients diagnosed with depression, AD, peripheral nerve dysfunction, dystonia, essential tremor or idiopathic late-onset cerebellar ataxia, the striatal BP_{ND} values

Fig. 1 Study design



were not significantly different from those in the controls (ANOVA, $p>0.05$).

Sensitivity and specificity

Figure 2b shows the individual striatal BP_{ND} values as a function of age. Of the 189 patients, 65 had a normal DAT SPECT scan and 124 had an abnormal DAT SPECT scan. According to their final clinical diagnosis, patients were grouped into those with and those without striatal neurodegeneration and together with their regional (striatum, caudate, or putamen) BP_{ND}, 2×2 tables were established to calculate sensitivity and specificity. The results using different ROI are shown in Table 3. The striatal ROI generated the highest specificity whereas the sensitivity was the same for the striatum and putamen alone.

Predictive values

Based on the data in Fig. 2b and the 2×2 tables the predictive values were calculated. The overall positive predictive value (PPV) was 95% using the striatum as ROI. This means that in a patient with an abnormally reduced DAT SPECT scan, the referring physician can conclude with a 95% likelihood that the patient is suffering from a movement disorder associated with striatal dopaminergic degeneration. The negative predictive value (NPV) was lower (80%) and was similar for BP_{ND} values measured in the putamen and striatum, whereas normal DAT binding measured in the caudate nucleus had a low NPV. Hence, only every fifth patient with slight or moderate symptoms of parkinsonism with a normal DAT SPECT scan will get a final clinical diagnosis of a movement disorder associated with striatal dopaminergic degeneration.

DAT SPECT in patients with signs of cognitive impairment

In patients with signs of cognitive deterioration (MMSE score <27) DAT SPECT had a sensitivity of 95% and a specificity of 72%, whereas the corresponding values in patients with a score of ≥27 were 99% and 84%. That is, the NPV of a DAT SPECT was lower in cognitively impaired patients.

Intra-image assessments

In 4.4% of patients with a final clinical diagnosis not associated with striatal degeneration, the APR was abnormal (>2 SD of normal controls), whereas only 1.5% had an abnormal STS asymmetry ratio. The corresponding values

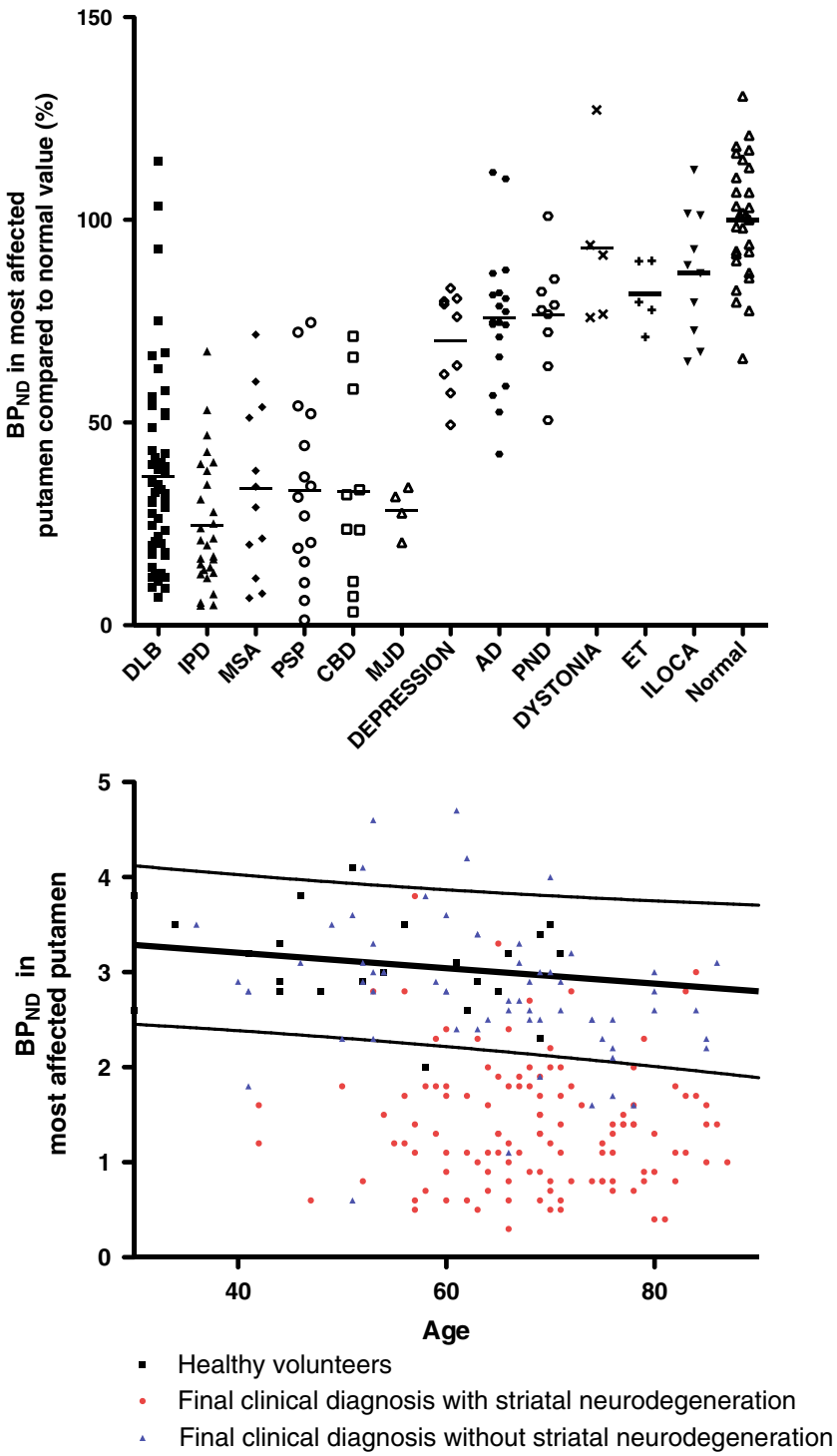


Fig. 2 **a** Distribution of striatal BP_{ND} (lower value of the two sides) according to the different final clinical diagnoses. Patients with DLB, idiopathic PD, multisystem atrophy, progressive supranuclear palsy, corticobasal degeneration and spinocerebellar ataxia type 3 all had a significantly lower striatal BP_{ND} value than the healthy controls (ANOVA, $p<0.01$) and the AD patients (ANOVA, $p<0.01$) (*DLB* Lewy body dementia, *IPD* idiopathic Parkinson's disease, *MSA* multisystem atrophy, *PSP* progressive supranuclear palsy, *CBD* corticobasal degeneration, *MJD* Machado-Joseph disease *SCA3* spinocerebellar ataxia type 3, *AD* Alzheimer's disease, *PND* peripheral nerve disease, *ET* essential tremor, *ILOCA* idiopathic late-onset cerebellar ataxia). **b** Individual striatal BP_{ND} (in the more affected side) as a function of age ($n=189$). The *thicker line* represents the linear regression line calculated on the basis of the healthy volunteers and the *thinner lines* represent ±2 standard deviations (*blue triangles* below the lower thinner line represent false-positive SPECT DAT scans; *red dots* between the thinner lines represent false-negative SPECT DAT scans)

were 54.7% and 59.3% in those with a final clinical diagnosis associated with striatal degeneration. Patients with idiopathic PD had a significantly higher STS asymmetry ratio and APR than patients with DLB ($p<0.001$). Among the APS. only patients with progressive supranuclear palsy had a significantly lower APR than those with idiopathic PD (ANOVA, $p<0.01$) and none had a lower STS asymmetry ratio than those with idiopathic PD. However, the APS patients as a group had a lower APR ratio than those with idiopathic PD ($p<0.001$), whereas their STS asymmetry ratio was only marginally different (Student's *t*-test, $p=0.06$; Fig. 3). An APR cut-off value of 2 allowed patients with an APS to be distinguished from those with idiopathic PD with 63% sensitivity and 84% specificity. If the APR was >2, the odds ratio for idiopathic PD vs. APS was 9.

Table 3 Overall sensitivity, specificity, predictive values and likelihood ratios of DAT SPECT scans between patients with a final clinical diagnosis with and without striatal neurodegeneration using different ROIs. Sensitivity and specificity were calculated using 2×2 tables. Values are percentages

ROI	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Likelihood ratio	
					Positive	Negative
Striatum	87	91	95	80	9.5	0.1
Caudate nucleus	80	85	90	70	5.2	0.2
Putamen	92	83	91	84	5.4	0.1

Discussion

This consecutive longitudinal study is the first to show the predictive value of a DAT SPECT scan in an large unsorted group of patients with diagnostic uncertainty, who were antiparkinson medication-naive and had a mean history of about 3 years of symptoms. The data would be particularly useful for clinicians who employ DAT SPECT as a predictive tool for early diagnosis of striatal neurodegeneration in patients for whom a probable clinical diagnosis and treatment have not yet been determined.

Specificity of DAT SPECT

Most other studies have shown a 100% specificity of DAT SPECT [3]. Our definition of normalcy (2 SD below the average of healthy controls) explains 2.5% of the lower specificity that we found in this study. We showed that in many of the patients with a false abnormal DAT scan, the final diagnosis was AD. In patients with striatal neurodegeneration, symptoms of dementia and depression are quite frequent [22, 23] and accordingly, it can be difficult to distinguish patients with global cerebral neurodegeneration (e.g. AD patients) from those with a dopaminergic striatal neurodegeneration (e.g. DLB patients) [24]. In our patients the sensitivity of a DAT SPECT scan was high in both those with cognitive impairment (MMSE score <27) and in those without cognitive impairment (>95 %), whereas the specificity was lower in those with cognitive impairment (75% vs. 84%) which is comparable to a the findings of a multicentre study [25]. This is also in accordance with earlier reports that AD patients generally have lower (although perhaps not statistically significantly lower) DAT binding than age-matched healthy controls [6] indicating abnormally reduced striatal DAT binding. Interestingly, we found that bradykinesia and rigidity are more likely to be associated with an abnormal DAT SPECT than are tremor and postural instability; this confirms earlier observations in patients with well-defined idiopathic PD [1].

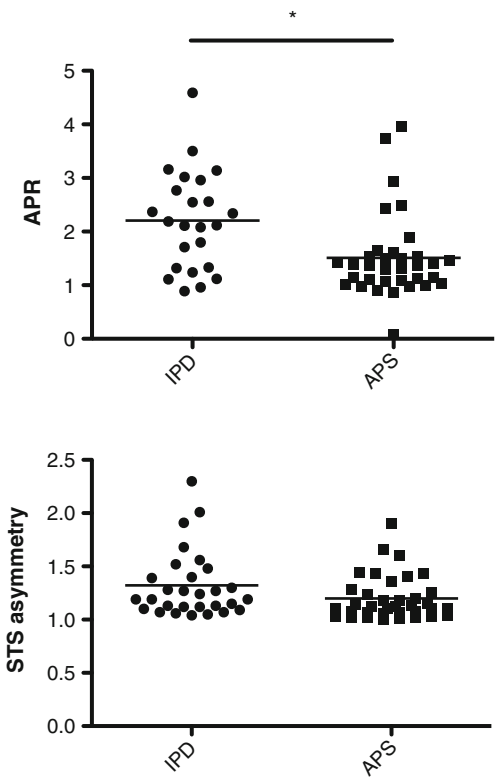


Fig. 3 STS ratio and APR in the patients with idiopathic PD (*IPD*) and those with an APS ($p<0.001$ for APR, $p=0.06$ for STS ratio; Student's *t*-test)

Sensitivity of DAT SPECT

In many recent studies involving DAT SPECT imaging, the phenomenon of 'scans without evidence of dopaminergic deficits' (SWEDD) [26] has been used. Original this was described in a patient with a clinical probable diagnosis that included a long duration of PD symptoms who, despite the probable diagnosis, had a normal DAT scan. SWEDD should therefore not be used in every patient with presumed PD who turns out to have a normal DAT scan. There is debate as to whether SWEDD patients (a) do not have PD, (b) have PD without presynaptic nigrostriatal degeneration, or (c) have nigrostriatal degeneration not detectable with SPECT. All three cases could be reasons for the large distribution in sensitivity found in the studies in the meta-analysis [3]. Newer studies indicate that many patients with a false-normal DAT SPECT scan do have other diagnoses when examined later [27]. In our study, we found very few patients with a false-normal DAT SPECT scan. As can be

seen in Fig. 2a, the majority of these patients had DLB, and this is also reflected in the higher sensitivity found in our patients with MMSE score >27. A similar result was also observed in another multicentre study in 2009 [25] comparing the accuracy of SPECT DAT in patients with and without DLB. Of the 63 patients with DLB, 18 had a normal DAT SPECT scan. The Electronic supplementary material shows how dementia can affect the predictive value of a DAT SPECT scan.

Another reason for the high sensitivity in our study could also be because of the radioligand used for DAT imaging. Previous studies that have assessed the utility of DAT SPECT have used the cocaine derivative [^{123}I]β-CIT [28] and later the more DAT-selective radioisotope [^{123}I]FP-CIT [29]. In theory, the lower selectivity of [^{123}I]FP-CIT would overestimate the DAT BP_{ND} in patients with a high striatal serotonin transporter availability and increase the rate of false-negative scans, thereby lowering sensitivity. This needs to be explored in future studies. In patients with decreased DAT density, [^{123}I]PE2I SPECT BP_{ND} has reproducibility similar to that using [^{123}I]FP-CIT and [^{123}I]β-CIT [10], whereas it has higher reproducibility in subjects with normal binding [11]. However, [^{123}I]PE2I is currently not generally licensed for clinical use.

Idiopathic PD vs. APS

Many previous DAT SPECT studies have failed to differentiate between APS and idiopathic PD [3, 29, 30] on the basis of striatal binding alone, but only rarely have they taken intra-image ratios into account. We found statistically significant differences in the APR between patients with idiopathic PD and all those with APS considered as one group. This result supports the findings of an earlier retrospective study that also found a significantly lower APR between these groups [31]. Using an APR cut-off value of 2 resulted in a sensitivity of 63% and a specificity of 84%, with a nine times higher likelihood of a diagnosis of idiopathic PD than APS. Once again, the referral pattern determines the clinical usefulness of this cut-off value; this can be appreciated in the Electronic supplementary material.

Predictive values of DAT SPECT

The sensitivity and specificity of a DAT SPECT scan do not provide a clinically useful indication of its accuracy since it is the predictive value that is most important to the referring clinician. A proper assessment of the NPV and PPV of a DAT SPECT scan would require a prospective study of a large patient sample in which the patients are consecutively enrolled in order to reflect the prevalence of patients with an abnormal DAT SPECT scan. The overall PPV found in our study (95%) is comparable to that found by Vlaar et al. [29] (PPV 99%), but the NPV was higher (80% vs. 48%). This difference could again be a result of differences in the radioligand employed or of the medication status of the patients, but is most likely a result of differences between the patient populations of the two studies. The Electronic supplementary material shows simulations that reflect how the NPV and PPV changed with the referral pattern. This gives the referring clinician a tool that may assist in interpreting a DAT SPECT result based on their own referral pattern.

Limitations

A limitation of our study is that the final clinical diagnosis was not settled histopathologically, but relied on a combination of follow-up and patient records. Symptoms of striatal neurodegeneration worsen over time (our own data and [32]), and at later stages a clinical diagnosis is not difficult. Clinicopathological studies also suggest that when probable idiopathic PD is diagnosed there is a more than 80% concordance between expert clinical diagnosis and the presence of nigral Lewy bodies [33]. However, even though the clinical criteria are not in 100% concordance with post-mortem findings, a clinical follow-up still predicts how we diagnose the patient about 2 years later. During these years patients with striatal neurodegenerative disorders loose additional dopaminergic neurons, neurons that could be an important target for dopamine-preserving pharmaceuticals [34].

Conclusion

In consecutively enrolled patients who were anti-idiopathic PD medication-naive and who had an average short history of parkinsonism, DAT SPECT with [^{123}I]PE2I had a high sensitivity and specificity for distinguishing between patients with and without striatal neurodegeneration. In patients with cognitive impairment in addition to idiopathic PD motor core symptoms, the specificity was lower.

The NPV and PPV are dependent of the referral pattern, and in this study, both the NPV and PPV were high (80% and 95%) because of the low prevalence of patients with a final clinical diagnosis associated with an abnormal DAT SPECT scan. In centres with more patients with idiopathic PD than with APS, DAT SPECT with the highly selective radioligand [^{123}I]PE2I would have a PPV above 80% in favour of idiopathic PD vs. APS using the APR.

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Conflicts of interest None.

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