Functional brain imaging in the differential diagnosis of Parkinson's disease

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The accurate diagnosis of idiopathic Parkinson’s disease (IPD) is not only important for deciding on treatment strategies and providing a prognosis, but also crucial for studies designed to investigate the aetiology and pathogenesis of parkinsonian disorders. Over recent decades, improvements in the characterisation of the parkinsonian syndromes have led to improvements in clinical diagnostic accuracy; however, clinical criteria alone are not always sufficient to distinguish between IPD and other parkinsonian syndromes, particularly in the early stages of disease and in atypical presentations. Therefore, in addition to the development and implementation of diagnostic clinical assessments, there is a need for available objective markers to aid the physician in the differential diagnosis of IPD. Functional neuroimaging holds the promise of improved diagnosis and allows assessment in early disease. In this review, the use of PET and single photon emission CT in the differential diagnosis of IPD are discussed.

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The diagnosis of idiopathic Parkinson’s disease (IPD) is straightforward in most cases, according to UK Parkinson’s Disease Society Brain Bank criteria. Diagnosis depends on the presence of two or more cardinal motor features such as rest tremor, bradykinesia, or rigidity. However, a common dilemma for doctors assessing patients in movement-disorder clinics, is that the main features of IPD are shared, at least in part, by several other disorders. The more common differential diagnoses of IPD include essential tremor, vascular parkinsonism, drug induced parkinsonism, progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal ganglionic degeneration, dementia with Lewy bodies, and Alzheimer’s disease. To add further to the diagnostic confusion, some, if not all, of the above disorders can have a mild to moderate response to dopaminergic drugs. The prognosis and management of each disorder differs significantly from IPD, and to a greater or lesser extent from each other. Thus, the ability to reach a firm diagnosis and distinguish between different parkinsonian entities is of clinical importance. In addition to differentiating between the above-mentioned disease types, there is a need to diagnose IPD; although later in the course of IPD the distinction is clear, the clinical demarcation between IPD and normality can be less clear early in a patient’s history, particularly if treatment response is unknown.

In a clinical pathology study, diagnostic accuracy for IPD was around 75%; 25% of patients diagnosed with IPD had PSP, MSA, Alzheimer’s disease, or basal ganglia vascular disease on post mortem. More recently, a similar investigation by the same researchers found a high diagnostic accuracy for IPD (90%), suggesting that clinicians are becoming more adept at interpreting atypical clinical features. In the more recent study, MSA accounted for most false positives; whereas in the previous study, PSP was most likely to be clinically mistaken for IPD. However, the suggested 90% diagnostic accuracy for IPD almost certainly represents a best-case scenario. All of the patients studied had died, and the physicians making a prospective clinical diagnosis therefore had the benefit of witnessing end-stage disease.

Along with the need for a high accuracy in diagnosing IPD, which in part depends on the ability to separate IPD from atypical parkinsonism, there is a need to separate atypical parkinsonism into disease types (PSP, MSA, corticobasal ganglionic degeneration, dementia with Lewy bodies, Alzheimer’s disease, and vascular parkinsonism). The diagnostic accuracy for these specific disease entities around death is higher than for IPD; however, there is less diagnostic accuracy earlier in disease. Indeed, in a recent community based study by Nath and colleagues, the diagnostic accuracy for PSP was only about 60%. However, with the publication of clinical diagnostic criteria for MSA, PSP, corticobasal ganglionic degeneration, and dementia with Lewy bodies this situation should improve. Nevertheless, even with the best possible diagnostic criteria, the number of false positive and false negative diagnoses is likely to remain significant, especially in the early stages of disease, where the clinical features that discriminate the atypical disorders may be mild or absent. Therefore, in addition to the development and implementation of diagnostic clinical assessments, there is a need for available objective markers to aid the physician in the diagnosis of IPD.

Various objective measures have been suggested in the differential diagnosis of IPD, including a range of olfactory, electrophysiological, autonomic and neuropsychological tests. However, the most developed area in terms of providing an objective assessment is neuroimaging. Multiple imaging methods assessing nigrostriatal dopaminergic dysfunction, regional brain metabolic disturbance, localised...
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volumetric change, and changes in receptor availability, have been developed over the past few decades.

Before turning to the various imaging types in detail and considering how these may be used to differentiate IPD from atypical parkinsonian disorders, it is useful to briefly consider the underlying pathology of the various diseases that make up the list of differential diagnosis of IPD. The main pathology of the early stages of IPD is the loss of the dopaminergic neurons that project from the substantia nigra pars compacta in the midbrain to the striatal complex (putamen and caudate nucleus) in the forebrain. In this tract—the nigrostriatal pathway—the neuronal cell bodies are located in the substantia nigra pars compacta with the dopamine releasing terminal projections ending in the striatum. Hence, an imaging method with sensitivity to show degeneration of the nigrostriatal pathway, either cell-body loss in the midbrain or terminal loss in the striatum, will, in theory, identify abnormal striatal innervation. Patients with essential tremor, vascular parkinsonism, drug-induced parkinsonism, and Alzheimer’s disease—disorders that do not typically cause nigrostriatal degeneration—will also have normal striatal innervation. Thus, imaging techniques that distinguish normal from abnormal nigrostriatal innervation help to rule out IPD, but normal dopamine terminal imaging does not differentiate between normality, essential tremor, vascular parkinsonism, drug-induced parkinsonism, and Alzheimer’s disease. By contrast, PSP, MSA, corticobasal ganglionic degeneration, and dementia with Lewy bodies (with akinetic rigid features)—disorders that like IPD share nigrostriatal degeneration as a common pathological feature—will all have abnormalities in nigrostriatal imaging. Although abnormal striatal imaging will differentiate IPD, PSP, MSA, corticobasal ganglionic degeneration, and dementia with Lewy bodies from normality, the use of neuroimaging to distinguish these disorders from each other is more complex.

A wide range of neuroimaging methods is currently available. Functional imaging techniques like PET and single-photon emission CT (SPECT) can be used with various radioactive tracers (radioligands) to provide quantitative assessment of regional blood flow, glucose metabolism, and brain pharmacology and the assessment of both resting brain function and task-related cerebral activation patterns in health and in different pathological disorders. The use of these imaging methods in the differential diagnosis of IPD will be considered in detail.

PET in the differential diagnosis of IPD

The imaging technique with the highest resolution and power to differentiate between normal and abnormal nigrostriatal innervation is three-dimensional PET. Although less widely available and more costly than SPECT and MRI, the greater sensitivity of three-dimensional PET makes this imaging method the gold standard.

PET provides a measure of the in vivo binding and metabolism of compounds that have been tagged with short-lived positron emitting isotopes. In this process, a biological compound is chemically combined with a radioisotope such as carbon-11 or fluorine-18 produced in a cyclotron. These radiolabelled biological compounds emit positrons, which produce pairs of gamma rays that are detected by the PET scanner. By measurement of the amount and origin of radiation emitted, a quantitative three-dimensional image of tracer distribution can be generated. With the use of appropriate mathematical models, it is possible to quantify the degree of specific radioactive emission from a given brain region and relate this to the state of the biologically tagged compound; the degree of binding or metabolism of the biologically active compound is dependent on the condition of the underlying tissue.

Dopaminergic neurons offer three sites to which biological compounds tagged with positron emitting isotopes can bind: the dopamine transporter, which is found on the plasma membrane of the dopamine terminal and is responsible for the reuptake of dopamine from the synaptic cleft; the vesicular monoamine transporter 2, which is located on the vesicular membrane and allows the packaging of terminal dopamine into synaptic vesicles; and the enzyme aromatic-amino-acid decarboxylase, which is mainly inside the synaptic terminal and enables transformation of dopa to dopamine.

**F-dopa PET**

The uptake of the radiotracer **F-dopa** is dependent upon all of the above mechanisms. **F-dopa** PET was first described as a marker of presynaptic dopamine terminals in 1983. Since then there have been over 100 descriptions of the use of this tracer in IPD. This tracer is a marker of the accumulation and metabolism of levodopa (tagged with **F**) in the putamen and caudate nucleus over the time course of the scan, where the rate of accumulation of **F-dopa** in the striatum is dependent upon the integrity of the terminal plexus. Research in animal models and post-mortem studies have shown that **F-dopa** uptake relates to both nigrostriatal cell loss and striatal concentrations of dopamine. Therefore, in a patient with IPD, less accumulation of the tracer is qualitatively seen in the putamen and loss of terminal innervation is proved (figure 1).

By use of a mathematical model, the absolute specific uptake of the tracer can be quantified (as an influx constant) and the absolute and percentage difference from normality can be determined. Previous cross sectional studies in IPD have shown a negative correlation between putamen **F-dopa** uptake and motor Unified Parkinson’s Disease Rating Scale (UPDRS) scores.

Several studies have reported that by the time patients with IPD present clinically, they have lost up to 50% of normal **F-dopa** uptake from the primarily affected caudal putamen. Studies with two-dimensional PET have shown that the **F-dopa** PET has an 85% sensitivity to early IPD, although there is an overlap between normal and abnormal putaminal uptake values. In three dimensional PET, however, there is a clear difference between normal and abnormal putaminal uptake, particularly when absolute values in the caudal putamen, the initial locus of putamen pathology in IPD, are compared. The difference between normal and abnormal striatal **F-dopa** uptake can be further...
proved by investigation of the asymmetry in uptake between the left and right putamen. Asymmetry is not seen in healthy individuals, whereas in patients with IPD one putamen is typically affected to a greater extent than the other, reflecting the higher degree of terminal loss in the primarily affected putamen (figure 1). A further method to improve the differentiation between normality and IPD is to compare the degree of change in the putamen with that in the caudate nucleus. In healthy controls, the ratio of caudal putamen to caudate nucleus 18F-dopa uptake is about 1, whereas in early IPD this ratio is around 0.6, with substantial decrease in uptake in the caudal putamen (50%) compared with the decrease seen in the caudate nucleus (10%). However, although the separation between normal and abnormal nigrostriatal uptake values is complete with 3D 18F-dopa PET; data providing positive and negative predictive values have not been published. In a recent study investigating the disease-modifying effect of the dopamine agonist ropinirole in early IPD (REAL PET study), 11% of previously untreated patients with clinically classified IPD with symptoms duration of 2 years or less had entirely normal 18F-dopa imaging. This level of discordance between early clinical diagnosis and 18F-dopa PET imaging was also seen in another study of similarly early cases of IPD (unpublished), and in a recent 123I-beta-CIT SPECT investigation. In the REAL PET study, all patients with normal baseline imaging continued to have normal imaging 2 years later, suggesting that the baseline scan was "correct", although to confirm that these patients do indeed have normal nigrostriatal tracts and that the 18F-dopa PET imaging was "correct", post-mortem data would be required. A further investigation into their clinical diagnosis is underway. As mentioned above, patients with essential tremor or vascular parkinsonism would also be expected to have normal 18F-dopa striatal binding.

Although the ability to demonstrate reductions in 18F-dopa uptake in the putamen can help in the diagnosis of IPD, the differentiation of IPD from PSP, MSA, or corticobasal ganglionic degeneration, or the distinction of these last three diseases from each other, is more difficult. The different pattern of nigrostriatal loss in IPD compared with atypical parkinsonism may be helpful. As described by Fearnley and Lees, the pattern of pathological change across the nigra in IPD is highly conserved and commences in the lateral ventral tier. Change in this nigral region will produce early caudal putamen terminal loss whereas, in PSP and MSA, nigral cell-body change is more extensive and nigral projections to the caudate nucleus become involved earlier in the course of disease. The pathological difference in the degree of caudate nucleus involvement can be identified in vivo with 18F-dopa PET. Several studies with this technique have shown that in patients with PSP, MSA, and corticobasal ganglionic degeneration, mean 18F-dopa uptake in the posterior putamen is decreased to concentrations similar to those of patients with IPD with similar disease duration, but caudate nucleus uptake is more affected (figure 2). However, although the power of 18F-dopa PET to
In addition to the assessment of striatal terminal aromatic-amino-acid decarboxylase activity, PET radiotracers have been developed that bind to either the dopamine transporter (\(^{11}\text{C}\)-nomifensine, \(^{11}\text{C}\)-CFT, \(^{18}\text{F}\)-CFT and \(^{11}\text{C}\)-RTI-32 PET)\(^{57-62}\) or the vesicular monoamine transporter 2 (\(^{11}\text{C}\)-dihydrotetrabenazine PET).\(^{63-66}\) These tracers, which also provide a measure of presynaptic dopamine terminal integrity, show similar findings in IPD to those seen with \(^{18}\text{F}\)-dopa PET, and provide a sensitive means of discriminating patients with early IPD from healthy people (figure 3). However, in an attempt to maintain normal synaptic dopamine concentrations in IPD, striatal compensatory responses occur which include upregulation of aromatic-amino-acid decarboxylase and downregulation of the dopamine transporter, and this can be shown with PET.\(^{25}\) As with \(^{18}\text{F}\)-dopa PET findings in MSA and IPD, patients with MSA have reduced binding of \(^{11}\text{C}\)-nomifensine in the putamen which is similar to the decrease in IPD.\(^{41}\) Also, as seen with \(^{11}\text{F}\)-dopa PET, caudate binding of \(^{11}\text{C}\)-nomifensine is significantly lower in MSA than in IPD of similar locomotor disability, although once again the discriminating power is not high.\(^{11}\)

Assessment of presynaptic dopamine terminal integrity within the putamen only partly differentiates between IPD and atypical parkinsonism. Therefore, in order to better differentiate between typical and atypical disease, radiotracers have been investigated that assess other indices of striatal receptors and function.

Dopamine D2 receptors

One difference in striatal pathology, shown by post-mortem investigation, between IPD and atypical parkinsonism is the loss of striatal D2 receptors. In both PSP and MSA, in contrast to IPD, there is a significant loss of putaminal D2-receptor availability.\(^{46-71}\) In PSP and MSA this represents GABAergic spiny interneuron loss rather than functional change. Consequently, by investigating the availability of the D2 receptor in vivo, in IPD compared with MSA and PSP, investigators have shown it is possible to differentiate these disorders. Leenders and colleagues\(^{72}\) first reported normal striatal uptake of \(^{11}\text{C}\)-raclopride, a marker of the D2 receptor, in untreated patients with IPD. Subsequently, several studies with \(^{11}\text{C}\)-raclopride have shown that putaminal D2 availability is normal or mildly upregulated (10–20%) in untreated IPD, presumably as a compensatory response to the decrease in presynaptic dopamine.\(^{72-75}\) Where both \(^{18}\text{F}\)-dopa and \(^{11}\text{C}\)-raclopride have been used in patients with IPD who have not received treatment, an inverse correlation between the binding of the two tracers has been found.\(^{33}\) In treated or longstanding IPD, D2 binding either normalises (if previously increased) or is only mildly reduced.\(^{75,76}\) This lack of change in D2 availability in IPD is in contrast to the situation in PSP and MSA, where a significant reduction in D2 radiotracer binding is seen,\(^{56,77}\) and a 100% separation between IPD and MSA was achieved by use of putaminal \(^{11}\text{C}\)-raclopride binding.\(^{58}\) Despite the ability of D2 receptor binding to separate IPD from PSP and MSA, decreased binding will be seen in both the latter two disorders, and therefore D2 imaging alone will not separate these two from each other.

\(^{18}\text{F}\)-deoxyglucose

In addition to changes in striatal pharmacology (receptor, transporter, or enzyme status) PET can be used to quantify resting concentrations of regional cerebral metabolic rate using radiolabelled glucose or oxygen. By use of the radiotracers \(^{18}\text{F}\)-deoxyglucose and oxygen-15 it can be seen that in early IPD striatal metabolic activity is increased in the lentiform nucleus contralateral to the affected limb.\(^{78,79}\) Indeed, Eidelberg and colleagues\(^{80}\) have shown with principal component analysis a pattern of raised lentiform nucleus and reduced premotor metabolism in IPD, the degree of which relates to motor severity. In advanced IPD, in contrast to early IPD, decreased caudate nucleus and cortical metabolic activity have been reported,\(^{81,82}\) and in bilaterally affected IPD more diffuse hypometabolism may be seen, with decreased cortical glucose metabolism correlating with psychometric performance.\(^{83}\) Moreover, in IPD with frank dementia, as with Alzheimer’s disease, there is hypometabolism in posterior parietal and associated temporal areas.\(^{84}\) However, in contrast to Alzheimer’s disease, in IPD dementia occipital hypometabolism is seen, which may in part explain the greater degree of visual hallucination in this form of dementia.\(^{85}\) In contrast to early IPD, where striatal metabolism is either normal or increased, in PSP and MSA striatal metabolic activity is low\(^{86,87,88}\) (figure 4).
In a recent study by Antonini and colleagues, all eight patients with MSA were discriminated from healthy people and those with IPD by comparing striatal \(^{18}\text{F}\)-deoxyglucose metabolism, although other studies suggest that the discriminating power of \(^{18}\text{F}\)-deoxyglucose is much lower than this. In PSP, in addition to widespread striatal and cortical hypometabolism, there is particularly diminished glucose utilisation in the frontal cortex—(figure 4)—this may then offer a PET imaging mechanism by which PSP and MSA can be divided. In contrast to advanced IPD, PSP, and MSA—in which cortical hypometabolism is largely symmetrical—in corticobasal ganglionic degeneration, cortical hypometabolism is more asymmetric and particularly targets the parietal cortex, again offering a potential PET method by which corticobasal ganglionic degeneration can be differentiated from the other atypical forms.

**SPECT in the differential diagnosis of IPD**

In terms of radioactive brain imaging, the most readily available is SPECT, because it uses radioisotopes with a long half-life and does not require an on-site cyclotron. With regard to SPECT imaging and the differential diagnosis of IPD, many of the general issues are similar to those encountered with the use of PET and are therefore discussed in the PET section.

The site on the dopamine terminal targeted in most SPECT studies of the differential diagnosis of IPD is the dopamine transporter, and the most commonly used radiotracer is \(^{123}\text{I}\)-beta-CIT. Imaging the dopamine transporter, with either SPECT or PET techniques, assumes that the density of the dopamine transporter per dopamine neuron remains constant and therefore the degree of transporter binding within the putamen and caudate nucleus reflects the integrity of the dopamine terminal plexus. In IPD, the transporter is probably downregulated in an attempt to maintain synaptic dopamine concentrations, and chronic dopaminergic treatments may modify dopamine transporter expression and consequently, ligand uptake.\(^{19,20}\) The predictive power of \(^{123}\text{I}\)-beta-CIT SPECT in discriminating normal from abnormal striatal signal binding is high, and transporter binding correlates with off-medication UPDRS scores.\(^{21,22}\) Indeed, this ability to differentiate normal from abnormal striatal innervation has been used to differentiate IPD from essential tremor and vascular parkinsonism, disorders that, as with \(^{18}\text{F}\)-dopa PET, show normal tracer binding.\(^{23,24}\)

Although the ability to discriminate normal from abnormal striatal terminal integrity is as high with \(^{123}\text{I}\)-beta-CIT SPECT, the ability to differentiate between the atypical forms is low. Again, as with \(^{18}\text{F}\)-dopa PET, in IPD there is a putamen/caudate ratio bias, with more than 50% loss in \(^{123}\text{I}\)-beta-CIT SPECT binding in the putamen by the time of disease presentation. In contrast to IPD, the atypical parkinsonian diseases cause a greater degree of change in the caudate nucleus, particularly in MSA, but this, as for the PET techniques, is only poorly differentiating.\(^{25,26}\)

Many new compounds targeting the dopamine transporter have recently been developed. The fluoropropyl derivative of \(^{123}\text{I}\)-beta-CIT, \(^{123}\text{I}\)-beta-FP-FE, has faster kinetics than beta-CIT and is quick to reach equilibrium.\(^{27}\) These characteristics have the advantage that \(^{123}\text{I}\)-FP-FE SPECT correlates with clinical motor scores in IPD and has a high discriminating power to differentiate early IPD from essential tremor or normality.\(^{28-30}\) Also, as for \(^{123}\text{I}\)-beta-CIT, \(^{123}\text{I}\)-FP-FE SPECT is likely to only poorly differentiate typical IPD from atypical forms.

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<th>Dopamine transporter radioligands</th>
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<td><strong>PET</strong></td>
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<tr>
<td>(^{11}\text{C})-cocaine</td>
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<td>(^{11}\text{C}) or (^{18}\text{F})–beta-CFT (2-beta-carbomethoxy-3beta-[4-fluorophenyl]tropane)</td>
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<td>(^{11}\text{C})-RTI-32 (methyl [1R-2-exo-3-exo]-8-methyl-3-[4-methylphenyl]-8-azabicyclo[3.2.1]octane-2-carboxylate)</td>
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<td><strong>SPECT</strong></td>
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<tr>
<td>(^{123}\text{I})-beta-CIT (carbomethoxy-3-[4-iodophenyl]tropane)</td>
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<tr>
<td>(^{99}\text{mTc})-TRODAT</td>
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<tr>
<td>(^{99}\text{mTc})-technepine</td>
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<td><strong>Both</strong></td>
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<td>(^{123}\text{I})-FP-CIT (N-omega-fluoropropyl-2 beta-carbomethoxy-3 beta-[4-iodophenyl]nortropane; (^{18}\text{F}) for PET, (^{123}\text{I}) for SPECT)</td>
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<td>(^{11}\text{C})-FP-CIT (alto for PET, (^{11}\text{C}) for SPECT)</td>
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<td>(^{123}\text{I})-FP-FE (N-omega-fluoropropyl-2 beta-carbomethoxy-3 beta-[4-iodophenyl]nortropane; (^{18}\text{F}) for PET, (^{123}\text{I}) for SPECT)</td>
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<td>(^{11}\text{C})-FE (N-[2-fluoroethyl]-2beta-carbomethoxy-3beta-[4-iodophenyl]tropane; (^{11}\text{C}) for PET, (^{123}\text{I}) for SPECT)</td>
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<td>(^{123}\text{I})-FE (N-[3-iodoprop-2-enyl]-2beta-carbomethoxy-3beta-[4-methyl (phenyl) nortropane; (^{11}\text{C}) for PET, (^{123}\text{I}) for SPECT)</td>
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Another compound PE21 (labelled with either 11C or 123I) has been recently suggested as suitable for both PET and SPECT use, and may have the advantage of very good selectivity for dopamine transporters.103,104 Some dopamine transporters tracers can be used with either PET or SPECT cameras, and some can be used with both (panel).105

As with PET imaging, assessment of striatal D2 receptor binding is possible with SPECT, the radiotracer 123I-lodoazide.106-107 By use of 123I-lodoazide SPECT D2 binding has been reported to be increased in early PD.108 In contrast, as seen with PET, D2 binding is decreased in MSA,109 and therefore 123I-lodoazide SPECT can be used to differentiate IPD from atypical disease. Studies have suggested a strategy of imaging presynaptic and postsynaptic dopaminergic sites by using a double scan technique (dopamine transporter ligand and 123I-lodoazide) for better discrimination between IPD and parkinsonism. Whereas a DAT scan is useful for the differentiation of parkinsonism from normality, SD2 SPECT is useful in further differentiating MSA from IPD and possibly PSP.110

Conclusion
Although the diagnosis of IPD and other parkinsonian syndromes is essentially a clinical assessment, the role of functional neuroimaging such as PET and SPECT is becoming increasingly important both from the perspective of an early and accurate diagnosis, and as an in vivo method to answer questions about the basic pathophysiology of these diseases.

Authors’ contributions
Both authors contributed equally to the data search, writing of the review, and preparation of the figures and panel.

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We have no conflicts of interest.

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