Parkinsonism and Related Disorders 59 (2019) 93–100

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

What a neurologist should know about PET and SPECT functional imaging for parkinsonism: A practical perspective

Stéphane Thobois[a,b,c,*], Stéphane Prange[a,b], Christian Scheiber[d], Emmanuel Broussolle[a,b,c]

[a] Univ Lyon, Institut des Sciences Cognitives Marc Jeannerod, CNRS, UMR 5229, F-69675, Bron, France
[b] Hospices Civils de Lyon, Hôpital Neurologique Pierre Wertheimer, Service de Neurologie C, Centre Expert Parkinson, Lyon, France
[c] Univ Lyon, Faculté de Médecine et de Maïeutique Lyon Sud Charles Mérieux, F-69921, Oullins, France
[d] Hospices Civils de Lyon, Hôpital Neurologique Pierre Wertheimer, Service de Médecine Nucléaire, Lyon, France

ABSTRACT

The diagnosis of a parkinsonian syndrome based on clinical criteria remains sometimes difficult, especially at disease onset. Brain or heart molecular imaging techniques (SPECT or PET) can provide a major help to improve and speed up diagnosis, influencing treatment strategies. Presynaptic dopaminergic imaging using either [^{18}F]-Dopa PET or ^{123}I -2β-Carbomethoxy-3β-(4-Iodophenyl)- N-(3-Fluoropropyl) Nortropane ([^{123}I]-Ioflupane)SPECT demonstrates or rules out the presence of a dopaminergic degenerative process. This allows to distinguish Parkinson's disease, Parkinson "plus" syndromes and dementia with Lewy bodies (reduced radiotracers binding) from essential tremor, psychogenic, post-neuroleptic or vascular parkinsonisms, dopa-responsive dystonia and Alzheimer's disease (normal radiotracers binding). For differential diagnosis between Parkinson's disease and Parkinson "plus" syndromes, brain molecular imaging with [^{18}F]-Fluorodeoxyglucose ([^{18}F]-FDG) PET or ^{99m}Tc-HMPAO SPECT can provide useful information, whereas [^{18}F]-Dopa PET or [^{123}I]-Ioflupane does not separate these entities. Finally, sympathetic cardiac [^{123}I]-Metaiodobenzylguanidine ([^{123}I]-MIBG) scintigraphy or SPECT can help distinguishing Parkinson's disease and dementia with Lew bodies (decreased binding) from multiple system atrophy and progressive supranuclear palsy (normal binding). New radiotracers notably those targeting the pathological process itself such as Tau aggregates are under development and may provide interesting informations to delineate the different Parkinson "plus" syndromes.

1. Introduction

The diagnosis of Parkinson's disease (PD), parkinsonian syndromes and many movement disorders relies mostly on clinical criteria. Such criteria and red flags are regularly updated in order to improve diagnosis accuracy but this one may remain challenging. This is notably the case for PD, progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD) or dementia with Lewy bodies (DLB) [1–5]. Vascular, post neuroleptic or psychogenic parkinsonisms or atypical tremor may as well be difficult to distinguish from PD. Thus, despite efforts made by experts in the field to define detailed clinical criteria, the accuracy of clinical diagnosis remains insufficient and highly dependent on the level of expertise, experience of the clinician and duration of follow-up [6]. A recent meta-analysis showed that diagnosis accuracy for parkinsonism based on experts statement was of 79.6% for early diagnosis and 83.9% later, whereas non experts neurologists provide a good diagnosis in only 73.8% [6]. Diagnosis correctness clearly improves after 3.6 years of disease evolution [6]. The anatomopathological confirmation, very rarely available, remains the gold standard for diagnosis and reveals 25% errors in the diagnosis of PD provided by general neurologists [7]. In another clinicopathological series 26% of possible PD and 82% of probable PD had their diagnosis confirmed by neuropathology [8]. This last study also showed that the agreement between clinical and pathological diagnosis was much better beyond 5 years of disease evolution, which, again stresses the importance of follow-up duration (53% before 5 years disease evolution versus 85% after 5 years). For MSA and PSP clinicopathological studies have shown 30% diagnosis errors and up to 74% for CBD [9]. The sensitivity of the clinical diagnosis of PD, MSA and PSP were respectively of 89.2%, 64.3% and 52.9% while the specificity was of 57.8% for PD, 99% for MSA and 100% for PSP [7]. In movement disorder units the sensitivity of the clinical diagnosis of PD, MSA and PSP were respectively of 91.1%, 88.2% and 84.2%, showing the importance of clinical expertise [10]. Nevertheless, tools that improve diagnosis accuracy are mandatory because providing the right diagnosis as early as possible has important consequences in terms of prognosis and treatment choice [11]. As such, brain or heart molecular imaging using single photon emission computed tomography (SPECT) and positron emission tomography (PET), in combination with morphological brain imaging using MRI serve as powerful tools to investigate

* Corresponding author. Hospices Civils de Lyon, Hôpital Neurologique Pierre Wertheimer, Service de Neurologie C, Centre Expert Parkinson, F-69677, Bron, France.

E-mail address: stephane.thobois@chu-lyon.fr (S. Thobois).

https://doi.org/10.1016/j.parkreldis.2018.08.016
Received 5 July 2018; Received in revised form 23 August 2018; Accepted 24 August 2018
1353-8020/

parkinsonian syndromes [12]. The aim of the present review is to give an overview on the role of available SPECT and PET molecular imaging tools in routine clinical practice nowadays and in the future.

2. SPECT and PET functional imaging tools for neurologists in routine clinical practice

2.1. Dopaminergic system imaging

Several SPECT or PET radiotracers are available for the clinicians. They assess the presynaptic dopaminergic innervation and confirm or not the presence of a dopaminergic degenerative process. The most commonly used is the [^{123}I]-Ioflupane SPECT or DATscan* that measures the dopamine transporter (DAT) availability. Many other DAT radiotracers exist but are not routinely accessible and will not be detailed here. Using PET, [^{18}F]-Dopa is frequently used and measures the dopa-decarboxylase activity, which is another way to determine the integrity of presynaptic dopaminergic terminals [13]. In PD, the typical feature, notably early in the disease course, is an asymmetrical reduction of striatal binding with a rostrocaudal gradient and relative preservation of the caudate nucleus in comparison to the putamen [14]. Postsynaptic dopaminergic radiotracers such as [^{123}I]IBZM SPECT or [^{11}C]-Raclopride PET also exist but are not used in routine practice.

A recent clinicopathological study in PD suggested that [^{123}I]-Ioflupane SPECT reflects DAT functioning rather than the number of dopaminergic neurons but others studies found a relationship between the uptake of this tracer and nigral dopaminergic neuronal density [15,16]. Furthermore, even if striatal [^{123}I]-Ioflupane uptake is well correlated with disease duration and severity on a population basis, important discrepancies often exist between the degree of reduction of tracer uptake and the severity of motor symptoms on an individual basis [15,17]. In other words, one can see patients with major DAT tracer uptake reduction but minor motor symptoms or the opposite. This could, at least partly, be explained by the fact that [^{123}I]-Ioflupane SPECT or other DAT radiotracers, because of a compensatory down-regulation of DAT functioning, could overexpress the actual dopaminergic degeneration [18]. On the contrary a compensatory overactivity of dopa-decarboxylase could minimize [^{18}F]-Dopa sensitivity to the degenerative process. This has to be theoretically taken into account but, in routine practice, both [^{18}F]-Dopa PET and [^{123}I]-Ioflupane SPECT provide close information on the presence or absence of a dopaminergic nigrostriatal degeneration.

For [^{123}I]-Ioflupane SPECT there are some drug interactions that can affect the binding, but, this is, most of the time, a minor issue. More precisely all drugs that block the DAT must be stopped 1–2 weeks before DAT imaging, otherwise a complete drop in tracer binding will be observed (false positive) [19,20]. This concerns for example cocaine, methylphenidate, amphetamine or modafinil. Most antidepressant drugs, but also memantine and amantadine, have a minor effect on DAT tracer binding ($<$ 15%) notably because [^{123}I]-Ioflupane is not fully selective for DAT and also labels serotonin transporter, which can be affected by concomitant intake of most antidepressant drugs. However this effect is limited and will not dramatically change the results, which allows to perform [^{123}I]-Ioflupane SPECT while patients still take these drugs [19,20]. Furthermore this is not an issue when visual assessment is performed but should be considered when performing semi-quantitative analysis. On the other hand, dopaminergic treatments can be maintained.

Analysis of [^{123}I]-Ioflupane SPECT or [^{18}F]-Dopa PET is still frequently performed using simple visual inspection but many centers, nowadays, rather use semi-quantitative assessment in comparison with age-matched normal values, which is superior and advisable when the visual read is inconclusive. Both methods have excellent sensitivity (95–97%) and specificity (97–100%), meaning few false negatives and positives [21–23].

2.2. Metabolic activity and brain perfusion imaging

[^{18}F]-Fluorodeoxyglucose ([^{18}F]-FDG) PET measures cerebral glucose metabolism, which reflects synaptic and neuronal activity [12]. [^{18}F]-FDG PET sensitivity is above 75% and its specificity above 90% in differential diagnosis between PD and atypical parkinsonisms [24,25]. As [^{18}F]-FDG PET is not available everywhere, variations of cerebral blood flow with SPECT and ^{99m}Tc-HMPAO can also provide useful information on local brain dysfunction [26]. Both tools are useful to distinguish PD from Parkinson “plus” syndromes but it is noteworthy that SPECT has much lower spatial resolution and global accuracy as compared with PET.

2.3. Sympathetic myocardiac innervation imaging

[^{123}I]-Metaiodobenzylguanidine ([^{123}I]-MIBG) scintigraphy or SPECT provides information about peripheral sympathetic myocardial innervation and reveals the presence or absence of post-ganglionic sympathetic denervation that can help differentiating PD/DLB (decreased cardiac binding) from MSA and PSP (normal binding). [^{123}I]-MIBG scintigraphy or SPECT has a sensitivity comprised between 81 and 88% but below 70% at early stages of the disease, while its specificity is comprised between 77 and 89% [27–37].

3. Indications and limits of functional imaging in routine clinical practice

Neurologists are facing several important issues when seeing for the first time a patient with a suspicion of parkinsonian syndrome, falling into two main categories.

3.1. Is there a dopaminergic degeneration?

The presence or absence of presynaptic dopaminergic denervation is a key marker to decipher degenerative parkinsonian syndrome including PD, PSP, MSA, CBD and DLB from differential diagnoses without any dopaminergic degeneration.

3.1.1. Atypical tremor versus presynaptic parkinsonism

This encompasses notably non parkinsonian tremor such as essential tremor that may sometimes have an unusual presentation (asymmetrical, doubt on a rest component, doubt on rigidity). In that situation [^{123}I]-Ioflupane SPECT is normal in more than 99% of the cases and subjects with normal [^{123}I]-Ioflupane SPECT never become parkinsonian (Fig. 1). On the contrary patients with abnormal [^{123}I]-Ioflupane SPECT but a clinical presentation not typical of PD will, in 65% of the cases, evolve to PD [38–40]. As mentioned previously, the specificity to rule out essential or non parkinsonian tremor is very high comprised between 97 and 100% [19,21]. Therefore [^{123}I]-Ioflupane SPECT is an excellent tool to distinguish tremor from presynaptic parkinsonism whatever its subtype (PD, PSP, MSA …) and can correct clinically overdiagnosed PD [1–5,39–42].

3.1.2. Presynaptic versus non presynaptic parkinsonism

Non presynaptic parkinsonian syndromes designate psychogenic, post-neuroleptic and vascular (except those due to subtantia nigra or striatal stroke) parkinsonisms as well as idiopathic normal pressure hydrocephalus. Clinical presentation may be misleading and, sometimes, patients exhibit symptoms both related to neurodegenerative and non degenerative processes (for example, PD patients with a worsening of symptoms due to neuroleptics). The distinction between non presynaptic and presynaptic parkinsonian syndromes is of great importance to avoid prescription of useless and potentially deleterious antiparkinsonian drugs. This is, for instance, the case for psychotic patients exhibiting post-neuroleptic parkinsonism, for whom a dopaminergic treatment may lead to psychiatric side effects.

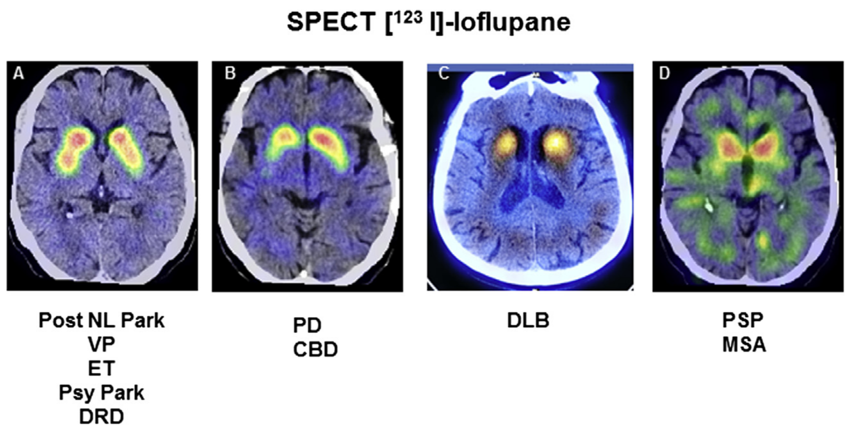

Fig. 1. SPECT [^{123}I]-Ioflupane assessing presynaptic dopaminergic innervation in parkinsonian syndromes. A: Normal striatal radiotracer binding in post-neuroleptic parkinsonism (Post NL Park), vascular parkinsonism (VP), essential tremor (ET) and psychogenic parkinsonism (Psy Park); B: bilateral and asymmetrical reduction of striatal binding with rostrocaudal gradient in Parkinson's disease (PD) and corticobasal degeneration (CBD); C: bilateral reduction of striatal binding in dementia with Lewy bodies (DLB); D: bilateral reduction of striatal binding in progressive supranuclear palsy (PSP) and multiple system atrophy (MSA).

Patients with psychogenic or post-neuroleptic parkinsonism have a normal [^{123}I]-Ioflupane SPECT or [^{18}F]-Dopa PET [43–47] (Fig. 1). In drug-induced parkinsonism the presence of a reduced [^{123}I]-Ioflupane binding is the only predictor of a risk of parkinsonian symptoms progression and levodopa response, which is in favor of an underlying degenerative process [48]. The combined use of functional imaging and electrophysiology could further improve differential diagnosis between psychogenic and non psychogenic parkinsonism [43].

Vascular parkinsonism due to leucoaraiosis is characterized by a normal or a mild homogenous reduction of striatal [^{123}I]-Ioflupane SPECT or [^{18}F]-Dopa PET uptake [49,50] (Fig. 1). On the contrary, parkinsonism induced by substantia nigra or striatum strokes are associated with a major ipsilateral reduction of [^{123}I]-Ioflupane uptake.

Idiopathic normal pressure hydrocephalus may sometimes associate parkinsonian signs to the classical triad. The few dopaminergic radiotracers studies having analyzed patients with idiopathic normal pressure hydrocephalus found, for some of them, no presynaptic dopaminergic denervation but decreased dopaminergic receptor availability [51], while others revealed a reduction of dopaminergic tracers uptake in less than half of the cases [52].

3.1.3. PD versus doparesponsive dystonia

Doparesponsive dystonia (DRD) and young onset PD may be difficult to distinguish clinically at disease onset. However, contrary to PD, DRD does not progress and [^{123}I]-Ioflupane SPECT or [^{18}F]-Dopa PET are normal in DRD [53].

3.1.4. DLB versus Alzheimer disease

Contrary to Alzheimer's disease, [^{123}I]-Ioflupane SPECT or [^{18}F]-Dopa PET are abnormal in DLB [54–56]. [^{123}I]-Ioflupane SPECT sensitivity and specificity to diagnose or rule out DLB in clinically and autopsy diagnosed cases are 78–87% and 90–94% [54–57].

3.1.5. The SWEDD issue

Patients suspected of PD but without abnormalities on [^{123}I]-Ioflupane SPECT or [^{18}F]-Dopa PET correspond to the so-called “Scan without evidence of dopaminergic degeneration” or SWEDD. This entity remains highly debated and some authors propose its complete abandon while others consider it as a particular but poorly understood entity [58]. It is very unlikely that SWEDD are due to a lack of sensitivity to detect dopaminergic denervation at early stage of PD as these functional imaging methods can detect dopaminergic denervation even before any clinical manifestations (and predict phenoconversion) and, obviously, more easily when motor symptoms start, which corresponds to a reduction of at least 60% dopaminergic innervation [59]. SWEDD represent a small percentage of patients suspected of PD or other degenerative parkinsonian syndromes. This percentage is variable and comprised between 1 and 2% and 15% [60–62]. Furthermore the risk of conversion to PD at 5 years follow-up is mild and has been evaluated at 12.5% in a recent study [63]. These patients do not disclose the progression of dopaminergic lesions and motor signs usually seen in PD [41,64]. The most likely explanation is that SWEDD represent alternative diagnosis such as dystonic tremor, atypical tremor or non presynaptic parkinsonism (psychogenic, post-neuroleptic …). Errors in [^{123}I]-Ioflupane SPECT interpretation may also explain some cases of SWEDD. Indeed, in a recent study, only 0.2% of [^{123}I]-Ioflupane SPECT were finally considered as normal in patients suspected of PD after reinterpretation versus 2.4% in first instance [65].

3.2. Parkinson's disease or Parkinson “plus” syndrome?

3.2.1. Interest of presynaptic dopaminergic radiotracers

Convergent evidence has demonstrated that, at an individual level, [^{123}I]-Ioflupane SPECT or [^{18}F]-Dopa PET do not allow to differentiate PD and Parkinson “plus” syndromes [66–69]. (Fig. 1). At the level of a population of patients, dopaminergic denervation is, however, more important and goes faster in Parkinson “plus” syndromes than in PD, and lesions are more homogeneous and less asymmetrical within the striatum in PSP and MSA compared to CBD and PD [70–72]. In addition, a relative preservation of dopaminergic terminals is observed in MSA with cerebellar features (MSAc) as well as a greater dopaminergic denervation in the caudate nucleus in PSP compared to MSAc and PD on the one hand and in MSA with predominant parkinsonism (MSAp) compared to MSAc on the other hand [73,74]. However these elements are not suitable to provide individual differential diagnosis in routine clinical practice. Furthermore, the anticipated greater asymmetry of dopaminergic degeneration in PD compared to MSA was not confirmed in autopsy-proven cases [69].

3.2.2. Interest of post-synaptic dopaminergic radiotracers

Because of the extension of the degenerative process to post-synaptic dopaminergic receptors it is expected that post-synaptic dopaminergic radiotracers such as [^{123}I]IBZM SPECT or [^{11}C]-Raclopride PET could help differentiating PD from Parkinson “plus” syndromes. Some studies have indeed shown a decrease of these radiotracers binding in the striatum in MSA and PSP compared to PD but the important impact of chronic dopaminergic drugs on dopaminergic receptors can, per se, affect their uptake [66,75–78]. More precisely, dopamine agonists and levodopa can induce an internalization of D1 and D2 dopaminergic receptors and, in turn, a decrease of dopaminergic postsynaptic radiotracers even in PD [77,78]. Thus these tools may be useful in untreated patients but not reliable in chronically treated patients, which represents the most common situation. Furthermore, these radiotracers are not available in many nuclear medicine centers. A comparison of sensitivity and specificity of [^{123}I]IBZM SPECT and diffusion weighted MRI has, in addition, clearly shown a superiority of the MRI to differentiate patients with MSAp and PD.

3.2.3. Interest of studying brain metabolism and brain perfusion

The use of perfusion SPECT allows correct discrimination between PD and Parkinson "plus" syndromes in 67% of the cases versus 58% for [^{123}I]-Ioflupane SPECT but the combination of both approaches leads to a much better diagnosis accuracy comprised between 82.4% and 86.1% [79,80]. ^{99m}Tc-HMPAO SPECT shows a bilateral fronto-parietal and thalamus hypoperfusion in CBD compared to PD [81]. In MSA compared to PD some studies showed surprisingly that the only difference between PD and MSA consisted in an occipital hypoperfusion in PD [82]. In PSP brain hypoperfusion is noted in the anterior cingulate and medial frontal cortex [83].

Another more interesting brain molecular imaging tool to achieve a good delineation between PD and Parkinson "plus" syndromes is the study of cerebral glucose metabolism using [^{18}F]-FDG PET. Several studies have shown that its sensitivity is above 75% and its specificity above 90% leading to diagnosis accuracy greater than 90% [24,25,84,85]. More precisely PSP is characterized by frontal lobe, caudate and mesencephalon hypometabolism, while MSA is characterized by cerebellum, pons and putamen hypometabolism, CBD by lateralized fronto-parietal, thalamic and striatum hypometabolism and PD by relatively spared metabolism in the putamen, sensorimotor cortex and cerebellum [24,25,84–86] (Fig. 2). In DLB, hypometabolism of the lateral occipital cortex is highly sensitive (93%) while the relative preservation of the mid to posterior cingulate gyrus is very specific (100%) [84,85,87]. However it has to be noted that the preservation of posterior cingulate cortex relative to the precuneus tends to disappear with disease progression in DLB [88]. For DLB diagnosis [^{18}F]-FDG PET appears better than blood flow measure using ^{99m}Tc-HMPAO SPECT [89]. Finally, a recent report found a hypometabolism in caudate nucleus and putamen and preserved cortical metabolism in idiopathic normal pressure hydrocephalus [90].

3.2.4. Interest of studying sympathetic innervation

[^{123}I]-MIBG scintigraphy or SPECT reveals the presence of postganglionic sympathetic myocardial denervation in PD as measured by a reduced heart/mediastinum uptake ratio, whereas this ratio is normal in MSA and PSP patients [27–37] (Fig. 3). Meta-analyses have shown a sensitivity of 82–88% and a specificity of 77–89%. In addition, there is a good correlation between MIBG scintigraphy or SPECT finding and the loss of subtantia nigra neuromelanin hypersignal in PD [91]. [^{123}I] MIBG scintigraphy or SPECT may also be useful to differentiate PD and vascular parkinsonism [92]. Furthermore, [^{123}I]MIBG scintigraphy or SPECT has now been acknowledged to better differentiate DLB form other dementia in comparison to [^{123}I]-Ioflupane SPECT that may be positive even in some forms of frontotemporal dementia [93]. It has however to be acknowledged that [^{123}I]MIBG scintigraphy or SPECT may be abnormal in up to 30% of MSA patients [28,29] and normal at disease onset in PD [94,95].

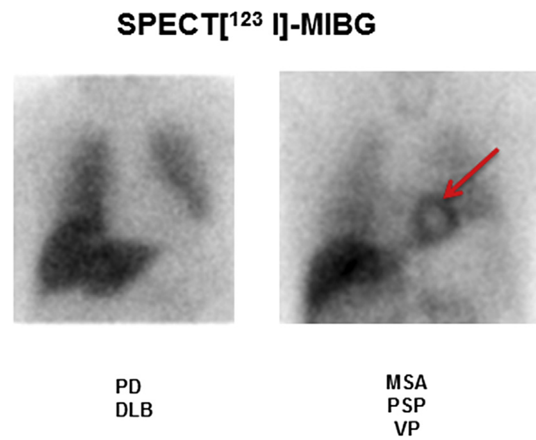

Fig. 3. SPECT [^{123}I]-MIBG measuring postganglionic sympathetic innervation in parkinsonian syndromes. A: reduced heart/mediastinum uptake ratio in Parkinson's disease (PD) and dementia with Lewy bodies (DLB); B: normal heart/mediastinum uptake ratio in multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and vascular parkinsonism (VP).

3.3. Interest of future radiotracers

Involvement of Tau protein in Alzheimer's disease, CBD and PSP explains the reason why recent attempts are made to develop PET Tau radiotracers. Several Tau ligands are under development notably the [^{18}F]-AV1451 for PET. Increased Tau deposits in basal ganglia and mesencephalon in PSP vs AD and controls and increased Tau deposits in temporal cortex in AD vs PSP and controls have been demonstrated using [^{18}F]-AV1451 PET [96]. Compared to PD and controls, [^{18}F]-Flortaucipir discloses an increased binding in globus pallidus, midbrain, subthalamic nucleus (STN) and dentate nucleus in PSP patients [97]. The abnormalities of Tau tracer binding observed in subcortical regions in PSP compared to PD are not correlated to motor and cognitive manifestations severity and not associated with increased cortical Tau binding [98,99]. Furthermore age also induces Tau deposits, which has to be taken into account [99].

In CBD, using two different Tau tracer, the [^{18}F]-THK5351 and the [^{18}F]-AV1451, an asymmetrical increase of binding has been observed in the globus pallidus, and pre and postcentral gyrus as well as in the pyramidal tract [98,100]. The different topography of [^{18}F]-AV1451 increased binding may help differentiating PSP from CBD and AD [99].

These results seem promising but they are still preliminary and some controversies exist. Indeed a recent study did not find any difference of [^{18}F]-AV1451 binding between PSP, PD and controls suggesting that this tracer may be more appropriate to detect paired helical filaments found in AD than straight Tau filaments observed in PSP

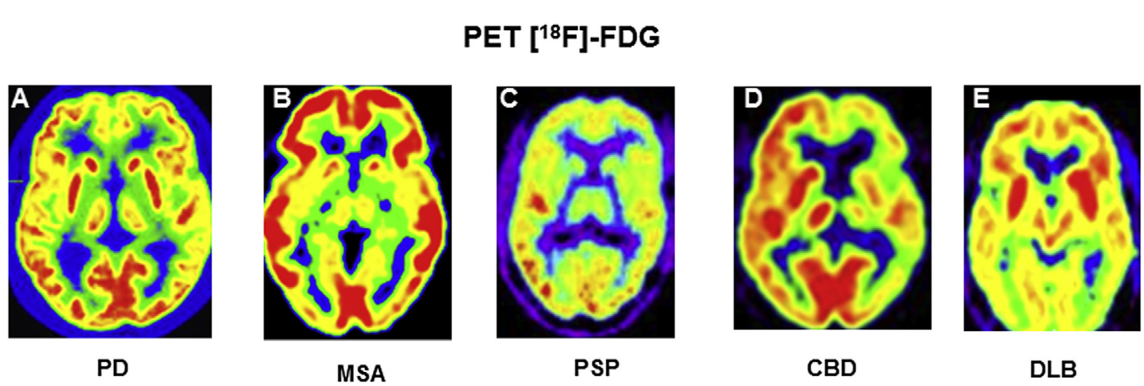

Fig. 2. PET [^{18} F]-FDG assessing brain glucose metabolism in degenerative parkinsonian syndromes. A: bilateral striatal hypermetabolism in Parkinson's disease (PD); B: bilateral striatal hypometabolism in multiple system atrophy (MSA); C: bilateral frontal hypometabolism in progressive supranuclear palsy (PSP); D: asymmetrical frontoparietal hypometabolism in corticobasal degeneration (CBD); E: bilateral occipital hypometabolism in dementia with Lewy bodies (DLB).

Table 1
SPECT and PET findings in routine clinical practice.

Disease	[^{123}I]-Ioflupane SPECT Dopaminergic innervation	[^{18}F]-FDG PET Brain metabolism	[^{123} I]-MIBG cardiac SPECT Sympathetic innervation
PD	Asymmetrical striatal reduction of binding with rostro-caudal gradient	Relative putamen, sensorimotor cortex and cerebellum hypermetabolism	Reduction of heart/ mediastinum ratio binding
Non presynaptic parkinsonism (VP, postNL, psychogenic, NPH) ET and DRD	Normal Sometimes slightly reduced in VP	NPH: hypometabolism in caudate nucleus and putamen and preserved cortical metabolism VP: Hypometabolism depending on the topography of vascular lesions ET, postNLand psychogenic Park: normal	Normal
MSA	Homogeneous and less asymmetrical (unconstant) reduction of binding within the striatum in MSA vs PD and CBD. Greater abnormalities in MSAp versus MSAc	Cerebellum, pons and putamen hypometabolism	Normal in the majority of cases but abnormal in 30% of the cases
PSP	Homogeneous and less asymmetrical reduction of radiotracer uptake in the striatum in PSP vs PD and CBD. Greater abnormalities in PSP versus MSAc and PD	Frontal lobe, caudate and mesencephalon hypometabolism	Normal
CBD	Asymmetrical striatal reduction of radiotracer uptake	Lateralized fronto-parietal, thalamic and striatal hypometabolism	Normal
DLB	Symetrical striatal reduction of radiotracer uptake	Lateral occipital cortex hypometabolism and relative preservation of the mid to posterior cingulate gyrus metabolism	Reduction of heart/ mediastinum ratio binding

Abbreviations: PD: Parkinson's disease; VP: vascular parkinsonism; postNL: post neuroleptic parkinsonism; NPH: normal pressure hydrocephalus; ET: essential tremor; DRD: doparesponsive dystonia; MSA: multiple system atrophy; PSP: progressive supranuclear palsy; CBD: cortico-basal degeneration; DLB: dementia with Lewy Body; SPECT: single photon emision computed tomography; PET: positron emission tomography.

[101]. Furthermore Tau pathology is also frequently observed using [^{18}F]-AV1451 in cognitively impaired PD and DLB patients independently of amyloid burden, which sheds shadow on the specificity of this tracer and its capacity to distinguish PD from PSP or CBD [102]. In addition, there are some methodological issues that will need to be sorted out before using these radiotracers in routine. This concerns in particular off-target binding (including neuromelanin, melanin, blood components, MAO …) and the binding of some Tau radiotracers (PBB3) to α-synuclein [103,104]. Finally a recent study combining [^{18}F]-AV1451 PET and [^{11}C]-Pittsburgh compound B (PIB) to measure amyloid deposits revealed that Tau deposit was not independent but related to β-amyloid status [105]. Overall, although interesting, these new radiotracers will need further analysis before being used in routine.

4. Cost-effectiveness and impact on care of functional imaging

Several studies have addressed the issue of the impact of [^{123}I]-Ioflupane SPECT on diagnosis and care and the cost-effectiveness of this technique. It has been shown that such tool can impact treatment strategy (initiation or withdrawal of dopamine replacement therapy) in 15–35% of the cases and improve the diagnosis or modify the follow-up of patients in 21% of the cases [38,40]. Therefore it is likely to be financially advantageous in clinically uncertain cases. In some rare situations it can even be helpful to perform a second [^{123}I]-Ioflupane SPECT as repeating such exam can help providing a diagnosis in 87.5% of patients with unconclusive diagnosis at baseline [106]. Nevertheless reimbursement level, scanner location, radiopharmaceutical costs, access and cost of clinical evaluation by expert neurologists and consequences of treatment choice are major factors that can differently affect, depending on the country and health system, the interest and cost-effectiveness of [^{123}I]-Ioflupane SPECT [107,108]. Importantly, the decision to prescribe or not a [^{123}I]-Ioflupane SPECT must only be taken after careful clinical investigation, as, whatever the stage of the disease, the accuracy of the diagnosis provided by [^{123}I]-Ioflupane SPECT and clinical expertise are very close [109,110].

A summary of the most important findings obtained with usual PET and SPECT radioradiotracers is provided in Table 1.

5. Conclusion

PET and SPECT molecular imaging using radiotracers allowing the characterization of presynaptic dopaminergic innervation, brain metabolism or perfusion and peripheral sympathetic innervation provide very useful information in routine clinical practice to confirm or rule out clinically evoked diagnosis and to classify the different subtypes of parkinsonisms. Their use has to be limited to patients with challenging diagnosis, only after careful clinical examination and, usually, in combination with morphological imaging (MRI). It is of major importance that the acquisition and analysis of these examinations follow strict procedural guidelines in order to guarantee reliable informations [111,112]. In the future, new radiotracers will allow to study the pathological process itself (Tau or amyloid deposits) but methodological issues still exist and will have to be sorted out. The use of brain or heart molecular imaging techniques notably those permitting very early (even premotor) diagnosis will undoubtedly become of greater importance when disease modifying strategies will emerge.

Disclosures

ST reports grants from Fondation pour la Recherche Medicale, France Parkinson, Fondation Neurodis; personal fees from UCB, Medtronic, Teva, Novartis, Aguettant; non-financial support from Zambon and Abbvie outside the submitted work.

SP reports grants from Fondation pour la Recherche Medicale and France Parkinson.

CS has nothing to disclose.

EB reports grants from Medtronic, personal fees from Abbvie, UCB, and Aguettant.

References

[1] R.B. Postuma, D. Berg, M. Stern, W. Poewe, C.W. Olanow, W. Oertel, J. Obeso, K. Marek, I. Litvan, A.E. Lang, G. Halliday, C.G. Goetz, T. Gasser, B. Dubois, P. Chan, B.R. Bloem, C.H. Adler, G. Deuschl, MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (12) (2015 Oct) 1591–1601.

[2] G.U. Höglinger, G. Respondek, M. Stamelou, C. Kurz, K.A. Josephs, A.E. Lang, B. Mollenhauer, U. Müller, C. Nilsson, J.L. Whitwell, T. Arzberger, E. Englund, E. Gelpi, A. Giese, D.J. Irwin, W.G. Meissner, A. Pantelyat, A. Rajput, J.C. van Swieten, C. Troakes, A. Antonini, K.P. Bhatia, Y. Bordelon, Y. Compta, J.C. Corvol, C. Colosimo, D.W. Dickson, R. Dodel, L. Ferguson, M. Grossman, J. Kassubek, F. Krismer, J. Levin, S. Lorenzl, H.R. Morris, P. Nestor, W.H. Oertel, W. Poewe, G. Rabinovici, J.B. Rowe, G.D. Schellenberg, K. Seppi, T. van Eimeren, G.K. Wenning, A.L. Boxer, L.I. Golbe, I. Litvan, Movement Disorder Society-endorsed PSP Study Group. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria, Mov. Disord. 32 (6) (2017 Jun) 853–864.

[3] S. Gilman, G.K. Wenning, P.A. Low, D.J. Brooks, C.J. Mathias, J.Q. Trojanowski,

N.W. Wood, C. Colosimo, A. Dürr, C.J. Fowler, H. Kaufmann, T. Klockgether, A. Lees, W. Poewe, N. Quinn, T. Revesz, D. Robertson, P. Sandroni, K. Seppi, M. Vidailhet, Second consensus statement on the diagnosis of multiple system atrophy, Neurology 71 (9) (2008 Aug 26) 670–676.
[4] M.J. Armstrong, I. Litvan, A.E. Lang, T.H. Bak, K.P. Bhatia, B. Borroni, A.L. Boxer, D.W. Dickson, M. Grossman, M. Hallett, K.A. Josephs, A. Kertesz, S.E. Lee, B.L. Miller, S.G. Reich, D.E. Riley, E. Tolosa, A.I. Tröster, M. Vidailhet, W.J. Weiner, Criteria for the diagnosis of corticobasal degeneration, Neurology 80 (5) (2013 Jan 29) 496–503.
[5] I.G. McKeith, B.F. Boeve, D.W. Dickson, G. Halliday, J.P. Taylor, D. Weintraub, D. Aarsland, J. Galvin, J. Attems, C.G. Ballard, A. Bayston, T.G. Beach, F. Blanc, N. Bohnen, L. Bonanni, J. Bras, P. Brundin, D. Burn, A. Chen-Plotkin, J.E. Duda, O. El-Agnaf, H. Feldman, T.J. Ferman, D. Ffytche, H. Fujishiro, D. Galasko, J.G. Goldman, S.N. Gomperts, N.R. Graff-Radford, L.S. Honig, A. Iranzo, K. Kantarci, D. Kaufer, W. Kukull, V.M.Y. Lee, J.B. Leverenz, S. Lewis, C. Lippa, A. Lunde, M. Masellis, E. Masliah, P. McLean, B. Mollenhauer, T.J. Montine, E. Moreno, E. Mori, M. Murray, J.T. O'Brien, S. Orimo, R.B. Postuma, S. Ramaswamy, O.A. Ross, D.P. Salmon, A. Singleton, A. Taylor, A. Thomas, P. Tiraboschi, J.B. Toledo, J.Q. Trojanowski, D. Tsuang, Z. Walker, M. Yamada, K. Kosaka, Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium, Neurology 89 (1) (2017 Jul 4) 88–100.
[6] G. Rizzo, M. Copetti, S. Arcuti, D. Martino, A. Fontana, G. Logroscino, Accuracy of clinical diagnosis of Parkinson disease: a systematic review and meta-analysis, Neurology 86 (6) (2016 Feb 9) 566–576.
[7] J. Joutsa, M. Gardberg, M. Röyttä, V. Kaasinen, Diagnostic accuracy of parkinsonism syndromes by general neurologists, Park. Relat. Disord. 20 (8) (2014 Aug) 840–844.
[8] C.H. Adler, T.G. Beach, J.G. Hentz, H.A. Shill, J.N. Caviness, E. Driver-Dunckley, M.N. Sabbagh, L.I. Sue, S.A. Jacobson, C.M. Belden, B.N. Dugger, Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study, Neurology 83 (5) (2014 Jul 29) 406–412.
[9] H. Ling, S.S. O'Sullivan, J.L. Holton, T. Revesz, L.A. Massey, D.R. Williams, D.C. Paviour, A.J. Lees, Does corticobasal degeneration exist? A clinicopathological re-evaluation, Brain 133 (Pt 7) (2010 Jul) 2045–2057.
[10] A.J. Hughes, S.E. Daniel, L. Kilford, A.J. Lees, Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases, J. Neurol. Neurosurg. Psychiatry 55 (3) (1992 Mar) 181–184.
[11] S.S. O'Sullivan, D.R. Williams, D.A. Gallagher, L.A. Massey, L. Silveira-Moriyama, A.J. Lees, Nonmotor symptoms as presenting complaints in Parkinson's disease: a clinicopathological study, Mov. Disord. 23 (1) (2008 Jan) 101–106.
[12] S. Prange, M. Hermier, T. Danaila, C. Laurencin, S. Thobois, Imagerie cérébrale dans les syndromes parkinsoniens, Presse Med. 46 (2 Pt 1) (2017 Mar) 202–209.
[13] J.E. Arena, A.J. Stoessl, Optimizing diagnosis in Parkinson's disease: radionuclide imaging, Park. Relat. Disord. 22 (Suppl 1) (2016 Jan) S47–S51.
[14] R.B. Innis, J.P. Seibyl, B.E. Scanley, M. Laruelle, A. Abi-Dargham, E. Wallace, R.M. Baldwin, Y. Zea-Ponce, S. Zoghbi, S. Wang, Single photon emission computed tomographic imaging demonstrates loss of striatal dopaminetransporters in Parkinson disease, Proc. Natl. Acad. Sci. U. S. A. 90 (24) (1993 Dec 15) 11965–11969.
[15] L. Saari, K. Kivinen, M. Gardberg, J. Joutsa, T. Noponen, V. Kaasinen, Dopamine transporter imaging does not predict the number of nigral neurons in Parkinson disease, Neurology 88 (15) (2017 Apr 11) 1461–1467.
[16] S.J. Colloby, S. McParland, J.T. O'Brien, J. Attems, Neuropathological correlates of dopaminergic imaging in Alzheimer's disease and Lewy body dementias, Brain 135 (Pt 9) (2012 Sep) 2798–2808.
[17] S.J. Colloby, E.D. Williams, D.J. Burn, J.J. Lloyd, I.G. McKeith, J.T. O'Brien, Progression of dopaminergic degeneration in dementia with Lewy bodies and Parkinson's disease with and without dementia assessed using 123I-FP-CIT SPECT, Eur. J. Nucl. Med. Mol. Imag. 32 (10) (2005 Oct) 1176–1185.
[18] M.J. Ribeiro, M. Vidailhet, C. Loc'h, C. Dupel, J.P. Nguyen, M. Ponchant, F. Dollé, M. Peschanski, P. Hantraye, P. Cesaro, Y. Samson, P. Remy, Dopaminergic function and dopamine transporter binding assessed with positron emission tomography in Parkinson disease, Arch. Neurol. 59 (4) (2002 Apr) 580–586.
[19] G. Kägi, K.P. Bhatia, E. Tolosa, The role of DAT-SPECT in movement disorders, J. Neurol. Neurosurg. Psychiatry 81 (1) (2010 Jan) 5–12.
[20] J. Booij, P. Kemp, Dopamine transporter imaging with [(123)I]FP-CIT SPECT: potential effects of drugs, Eur. J. Nucl. Med. Mol. Imag. 35 (2) (2008 Feb) 424–438.
[21] S. Ottaviani, M. Tinazzi, I. Pasquin, W. Nothdurfter, G. Tomelleri, E. Fincati, G. Nordera, G. Moretto, A. Fiaschi, N. Smania, P. Giorgetti, A. Antonini, Comparative analysis of visual and semi-quantitative assessment of striatal [123I] FP-CIT-SPET binding in Parkinson's disease, Neurol. Sci. 27 (6) (2006 Dec) 397–401.
[22] T.S. Benamer, J. Patterson, D.G. Grosset, J. Booij, K. de Bruin, E. van Royen, J.D. Speelman, M.H. Horstink, H.J. Sips, R.A. Dierckx, J. Versijpt, D. Decoo, C. Van Der Linden, D.M. Hadley, M. Doder, A.J. Lees, D.C. Costa, S. Gacinovic, W.H. Oertel, O. Pogarell, H. Hoeffken, K. Joseph, K. Tatsch, J. Schwarz, V. Ries, Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [123I]-FP-CIT study group, Mov. Disord. 15 (3) (2000 May) 503–510.
[23] L. Tossici-Bolt, J.C. Dickson, T. Sera, J. Booij, S. Asenbaun-Nan, M.C. Bagnara, T.V. Borght, C. Jonsson, R. de Nijs, S. Hesse, P.M. Koulibaly, U.O. Akdemir, M. Koole, K. Tatsch, A. Varrone, [123I]FP-CIT ENC-DAT normal database: the impact of the reconstruction and quantification methods, EJNMMI Phys 4 (1) (2017 Dec) 8.
[24] S. Hellwig, F. Amtage, A. Kreft, R. Buchert, O.H. Winz, W. Vach, T.S. Spehl, M. Rijntjes, B. Hellwig, C. Weiller, C. Winkler, W.A. Weber, O. Tüscher, P.T. Meyer, [^{18}F]FDG-PET is superior to [^{123}I]IBZM-SPECT for the differential diagnosis of parkinsonism, Neurology 79 (13) (2012 Sep 25) 1314–1322.
[25] T. Eckert, A. Barnes, V. Dhawan, S. Frucht, M.F. Gordon, A.S. Feigin, D. Eidelberg, FDG PET in the differential diagnosis of parkinsonian disorders, Neuroimage 26 (3) (2005 Jul 1) 912–921.
[26] T. Eckert, K. Van Laere, C. Tang, D.E. Lewis, C. Edwards, P. Santens, D. Eidelberg, Quantification of Parkinson's disease-related network expression with ECD SPECT, Eur. J. Nucl. Med. Mol. Imag. 34 (4) (2007 Apr) 496–501.
[27] F. Novellino, G. Arabia, A. Bagnato, G.L. Cascini, M. Salsone, G. Nicoletti, D. Messina, M. Morelli, S. Paglionico, L. Giofrè, A. Restuccia, G. Torchia, F. Condino, A. Quattrone, Combined use of DAT-SPECT and cardiac MIBG scintigraphy in mixed tremors, Mov. Disord. 24 (15) (2009 Nov 15) 2242–2248.
[28] H. Nagayama, M. Hamamoto, M. Ueda, J. Nagashima, Y. Katayama, Reliability of MIBG myocardial scintigraphy in the diagnosis of Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 76 (2) (2005 Feb) 249–251.
[29] H. Nagayama, M. Ueda, M. Yamazaki, Y. Nishiyama, M. Hamamoto, Y. Katayama, Abnormal cardiac [(123)I]-meta-iodobenzylguanidine uptake in multiple system atrophy, Mov. Disord. 25 (11) (2010 Aug 15) 1744–1747.
[30] K. Ishibashi, Y. Saito, S. Murayama, K. Kanemaru, K. Oda, K. Ishiwata, H. Mizusawa, K. Ishii, Validation of cardiac (123)I-MIBG scintigraphy in patients with Parkinson's disease who were diagnosed with dopamine PET, Eur. J. Nucl. Med. Mol. Imag. 37 (1) (2010 Jan) 3–11.
[31] A. Kikuchi, T. Baba, T. Hasegawa, N. Sugeno, M. Konno, A. Takeda, Differentiating Parkinson's disease from multiple system atrophy by [123I] meta-iodobenzylguanidine myocardial scintigraphy and olfactory test, Park. Relat. Disord. 17 (9) (2011 Nov) 698–700.
[32] S. Orimo, M. Suzuki, A. Inaba, H. Mizusawa, 123I-MIBG myocardial scintigraphy for differentiating Parkinson's disease from other neurodegenerative parkinsonism: a systematic review and meta-analysis, Park. Relat. Disord. 18 (5) (2012 Jun) 494–500.
[33] G. Treglia, E. Cason, Meta-analysis on MIBG scintigraphy in differential diagnosis between Parkinson's disease and neurodegenerative parkinsonism, Park. Relat. Disord. 18 (6) (2012 Jul) 805.
[34] S. Behnke, D. Hellwig, J. Bürmann, A. Runkel, G. Farmakis, C.M. Kirsch, K. Fassbender, G. Becker, U. Dillmann, J. Spiegel, Evaluation of transcranial sonographic findings and MIBG cardiac scintigraphy in the diagnosis of idiopathic Parkinson's disease, Park. Relat. Disord. 19 (11) (2013 Nov) 995–999.
[35] H. Odagiri, T. Baba, Y. Nishio, O. Iizuka, M. Matsuda, K. Inoue, A. Kikuchi, T. Hasegawa, M. Aoki, A. Takeda, Y. Taki, E. Mori, On the utility of MIBG SPECT/CT in evaluating cardiac sympathetic dysfunction in lewy body diseases, PLoS One 11 (4) (2016 Apr 7) e0152746.
[36] Y. Niimi, S. Ito, K. Murate, S. Hirota, C. Hikichi, T. Ishikawa, T. Maeda, R. Nagao, S. Shima, Y. Mizutani, A. Ueda, T. Mutoh, Usefulness of combining 123I-FP-CIT-SPECT striatal asymmetry index and cardiac 123I-metaiodobenzylguanidine scintigraphy examinations for diagnosis of parkinsonisms, J. Neurol. Sci. 377 (2017 Jun 15) 174–178.
[37] N. Uyama, H. Otsuka, T. Shinya, Y. Otomi, M. Harada, W. Sako, Y. Izumi, R. Kaji, Y. Watanabe, S. Takashi, Y. Kunikane, The utility of the combination of a SPECT study with [123I]-FP-CIT of dopamine transporters and [123I]-MIBG myocardial scintigraphy in differentiating Parkinson disease from other degenerative parkinsonian syndromes, Nucl. Med. Commun. 38 (6) (2017 Jun) 487–492.
[38] A.M. Catafau, E. Tolosa, DaTSCAN Clinically Uncertain Parkinsonian Syndromes Study Group, Impact of dopamine transporter SPECT using 123I-Ioflupane on diagnosis and management of patients with clinically uncertain Parkinsonian syndromes, Mov. Disord. 19 (10) (2004 Oct) 1175–1182.
[39] R. Ceravolo, A. Antonini, D. Volterrani, C. Rossi, L. Kiferle, D. Frosini, C. Lucetti, I.U. Isaias, R. Benti, L. Murri, U. Bonuccelli, Predictive value of nigrostriatal dysfunction in isolated tremor: a clinical and SPECT study, Mov. Disord. 23 (14) (2008 Oct 30) 2049–2054.
[40] A. Antonini, P. Berto, S. Lopatriello, F. Tamma, L. Annemans, M. Chambers, Cost-effectiveness of 123I-FP-CIT SPECT in the differential diagnosis of essential tremor and Parkinson's disease in Italy, Mov. Disord. 23 (15) (2008 Nov 15) 2202–2209.
[41] V.L. Marshall, C.B. Reininger, M. Marquardt, J. Patterson, D.M. Hadley, W.H. Oertel, H.T. Benamer, P. Kemp, D. Burn, E. Tolosa, J. Kulisevsky, L. Cunha, D. Costa, J. Booij, K. Tatsch, K.R. Chaudhuri, G. Ulm, O. Pogarell, H. Höffken, A. Gerstner, D.G. Grosset, Parkinson's disease is overdiagnosed clinically at baseline in diagnostically uncertain cases: a 3-year European multicenter study with repeat [123I]FP-CIT SPECT, Mov. Disord. 24 (4) (2009 Mar 15) 500–508.
[42] N. Bajaj, R.A. Hauser, I.D. Grachev, Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with (123I) ioflupane in diagnosis of parkinsonian syndromes, J. Neurol. Neurosurg. Psychiatry 84 (11) (2013 Nov) 1288–1295.
[43] S. Benaderette, P. Zanotti Fregonara, E. Apartis, C. Nguyen, J.M. Trocello, P. Remy, J.Y. Devaux, S. Askienazy, M. Vidailhet, Psychogenic parkinsonism: a combination of clinical, electrophysiological, and [(123)I]-FP-CIT SPECT scan explorations improves diagnostic accuracy, Mov. Disord. 21 (3) (2006 Mar) 310–317.
[44] M. Lorberboym, T.A. Treves, E. Melamed, Y. Lampl, M. Hellmann, R. Djaldetti, [123I]-FP/CIT SPECT imaging for distinguishing drug-induced parkinsonism from Parkinson's disease, Mov. Disord. 21 (4) (2006 Apr) 510–514.
[45] M. Tinazzi, A. Antonini, T. Bovi, I. Pasquin, M. Steinmayr, G. Moretto, A. Fiaschi, S. Ottaviani, Clinical and [123I]FP-CIT SPET imaging follow-up in patients with drug-induced parkinsonism, J. Neurol. 256 (6) (2009 Jun) 910–915.
[46] A.C. Felicio, C. Godeiro-Junior, T.S. Moriyama, M.C. Shih, M.Q. Hoexter, V. Borges, S.M. Silva, C. Aguiar Pde, L.A. Andrade, R.A. Bressan, H.B. Ferraz,

Degenerative parkinsonism in patients with psychogenic parkinsonism: a dopamine transporter imaging study, Clin. Neurol. Neurosurg. 112 (4) (2010 May) 282–285.

[47] J. Yomtoob, K. Koloms, D. Bega, DAT-SPECT imaging in cases of drug-induced parkinsonism in a specialty movement disorders practice, Park. Relat. Disord. pii: S1353–8020 (18) (2018 May 5) 30221–30229, https://doi.org/10.1016/j.parkreldis.2018.04.037 (Epub ahead of print).

[48] M. Tinazzi, F. Morgante, A. Matinella, T. Bovi, A. Cannas, P. Solla, F. Marrosu, A. Nicoletti, M. Zappia, A. Luca, A. Di Stefano, L. Morgante, C. Pacchetti, B. Minafra, M. Sciarretta, C. Dallocchio, S. Rossi, M. Ulivelli, R. Ceravolo, D. Frosini, A. Cipriani, C. Barbui, Imaging of the dopamine transporter predicts pattern of disease progression and response to levodopa in patients with schizophrenia and parkinsonism: a 2-year follow-up multicenter study, Schizophr. Res. 152 (2–3) (2014 Feb) 344–349.

[49] W. Gerschlager, G. Bencsits, W. Pirker, B.R. Bloem, S. Asenbaum, D. Prayer, J.C. Zijlmans, M. Hoffmann, T. Brücke, [^{123}I]beta-CIT SPECT distinguishes vascular parkinsonism from Parkinson's disease, Mov. Disord. 17 (3) (2002 May) 518–523.

[50] S. Benítez-Rivero, V.A. Marín-Oyaga, D. García-Solís, I. Huertas-Fernández, F.J. García-Gómez, S. Jesús, M.T. Cáceres, F. Carrillo, A.M. Ortiz, M. Carballo, P. Mir, Clinical features and ^{123}I-FP-CIT SPECT imaging in vascular parkinsonism and Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 84 (2) (2013 Feb) 122–129.

[51] Y. Ouchi, T. Nakayama, T. Kanno, E. Yoshikawa, T. Shinke, T. Torizuka, In vivo presynaptic and postsynaptic striatal dopamine functions in idiopathic normal pressure hydrocephalus, J. Cerebr. Blood Flow Metabol. 27 (4) (2007 Apr) 803–810.

[52] M. Broggi, V. Redaelli, G. Tringali, F. Restelli, L. Romito, S. Schiavolin, F. Tagliavini, G. Broggi, Normal pressure hydrocephalus and parkinsonism: preliminary data on neurosurgical and neurological treatment, World Neurosurg 90 (2016 Jun) 348–356.

[53] M. Naumann, W. Pirker, K. Reiners, K. Lange, G. Becker, T. Brücke, [^{123}I]beta-CIT single-photon emission tomography in DOPA-responsive dystonia, Mov. Disord. 12 (3) (1997 May) 448–451.

[54] D.C. Costa, Z. Walker, R.W. Walker, F.R. Fontes, Dementia with Lewy bodies versus Alzheimer's disease: role of dopamine transporter imaging, Mov. Disord. 18 (Suppl 7) (2003 Oct) S34–S38.

[55] I. McKeith, J. O'Brien, Z. Walker, K. Tatsch, J. Booij, J. Darcourt, A. Padovani, R. Giubbini, U. Bonuccelli, D. Volterrani, C. Holmes, P. Kemp, N. Tabet, I. Meyer, C. Reininger, DLB Study Group, Sensitivity and specificity of dopamine transporter imaging with ^{123}I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study, Lancet Neurol. 6 (4) (2007 Apr) 305–313.

[56] A.J. Thomas, J. Attems, S.J. Colloby, J.T. O'Brien, I. McKeith, R. Walker, L. Lee, D. Burn, D.J. Lett, Z. Walker, Autopsy validation of ^{123}I-FP-CIT dopaminergic neuroimaging for the diagnosis of DLB, Neurology 88 (3) (2017 Jan 17) 276–283.

[57] N. Papathanasiou, P. Rondogianni, P. Chroni, M. Themistocleous, E. Boviatsis, X. Pedeli, D. Sakas, I. Datseris, Interobserver variability, and visual and quantitative parameters of (123)I-FP-CIT SPECT(DaTSCAN) studies, Ann. Nucl. Med. 26 (3) (2012 Apr) 234–240.

[58] R. Erro, S.A. Schneider, M. Stamelou, N.P. Quinn, K.P. Bhatia, What do patients with scans without evidence of dopaminergic deficit (SWEDD) have? New evidence and continuing controversies, J. Neurol. Neurosurg. Psychiatry 87 (3) (2016 Mar) 319–323.

[59] A. Iranzo, J. Santamaría, F. Valldeoriola, M. Serradell, M. Salamero, C. Gaig, A. Niñerola-Baizán, R. Sánchez-Valle, A. Lladó, R. De Marzi, A. Stefani, K. Seppi, J. Pavia, B. Högl, W. Poewe, E. Tolosa, F. Lomeña, Dopamine transporter imaging deficit predicts early transition to synucleinopathy in idiopathic rapid eye movement sleep behavior disorder, Ann. Neurol. 82 (3) (2017 Sep) 419–428.

[60] N. Nicastro, P.R. Burkhard, V. Garibotto, Scan without evidence of dopaminergic deficit (SWEDD) in degenerative parkinsonism and dementia with Lewy bodies: a prospective study, J. Neurol. Sci. 385 (2018 Feb 15) 17–21.

[61] S. Fahn, D. Oakes, I. Shoulson, K. Kieburtz, A. Rudolph, A. Lang, C.W. Olanow, C. Tanner, K. Marek, Parkinson Study Group, Levodopa and the progression of Parkinson's disease, N. Engl. J. Med. 351 (24) (2004 Dec 9) 2498–2508.

[62] Parkinson Study Group, Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression, J. Am. Med. Assoc. 287 (13) (2002 Apr 3) 1653–1661.

[63] A. Batla, R. Erro, M. Stamelou, S.A. Schneider, P. Schwingenschuh, C. Ganos, K.P. Bhatia, Patients with scans without evidence of dopaminergic deficit: a long-term follow-up study, Mov. Disord. 29 (14) (2014 Dec) 1820–1825.

[64] K. Marek, J. Seibyl, S. Eberly, D. Oakes, I. Shoulson, A.E. Lang, C. Hyson, D. Jennings, Parkinson Study Group PRECEPT Investigators, Longitudinal follow-up of SWEDD subjects in the PRECEPT Study, Neurology 82 (20) (2014 May 20) 1791–1797.

[65] N. Nicastro, V. Garibotto, S. Badoud, P.R. Burkhard, Scan without evidence of dopaminergic deficit: a 10-year retrospective study, Park. Relat. Disord. 31 (2016 Oct) 53–58.

[66] Y.J. Kim, M. Ichise, J.R. Ballinger, D. Vines, S.S. Erami, T. Tatschida, A.E. Lang, Combination of dopamine transporter and D2 receptor SPECT in the diagnostic evaluation of PD, MSA, and PSP, Mov. Disord. 17 (2) (2002 Mar) 303–312.

[67] M. Plotkin, H. Amthauer, S. Klaffke, A. Kühn, L. Lüdemann, G. Arnold, K.D. Wernecke, A. Kupsch, R. Felix, S. Venz, Combined ^{123}I-FP-CIT and ^{123}I-IBZM SPECT for the diagnosis of parkinsonian syndromes: study on 72 patients, J. Neural. Transm. 112 (5) (2005 May) 677–692.

[68] C. Scherfler, K. Seppi, E. Donnemiller, G. Goebel, C. Brenneis, I. Virgolini, G.K. Wenning, W. Poewe, Voxel-wise analysis of [^{123}I]beta-CIT SPECT differentiates the Parkinson variant of multiple system atrophy from idiopathic Parkinson's disease, Brain 128 (Pt 7) (2005 Jul) 1605–1612.

[69] L.D. Perju-Dumbrava, G.G. Kovacs, S. Pirker, K. Jellinger, M. Hoffmann, S. Asenbaum, W. Pirker, Dopamine transporter imaging in autopsy-confirmed Parkinson's disease and multiple system atrophy, Mov. Disord. 27 (1) (2012 Jan) 65–71.

[70] R. Cilia, C. Rossi, D. Frosini, D. Volterrani, C. Siri, C. Pagni, R. Benti, G. Pezzoli, U. Bonuccelli, A. Antonini, R. Ceravolo, Dopamine transporter SPECT imaging in corticobasal syndrome, PLoS One 6 (5) (2011 May 2) e18301.

[71] A. Antonini, R. Benti, R. De Notaris, S. Tesei, A. Zecchinelli, G. Sacilotto, N. Meucci, M. Canesi, C. Mariani, G. Pezzoli, P. Gerundini, 123I-Ioflupane/SPECT binding to striatal dopamine transporter (DAT) uptake in patients with Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy, Neurol. Sci. 24 (3) (2003 Oct) 149–150.

[72] M. Oh, J.S. Kim, J.Y. Kim, K.H. Shin, S.H. Park, H.O. Kim, D.H. Moon, S.J. Oh, S.J. Chung, C.S. Lee, Subregional patterns of preferential striatal dopamine transporter loss differ in Parkinson disease, progressive supranuclear palsy, and multiple-system atrophy, J. Nucl. Med. 53 (3) (2012 Mar) 399–406.

[73] W. Pirker, S. Asenbaum, G. Bencsits, D. Prayer, W. Gerschlager, L. Deecke, T. Brücke, [123I]beta-CIT SPECT in multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration, Mov. Disord. 15 (6) (2000 Nov) 1158–1167.

[74] M. Joling, C. Vriend, O.A. van den Heuvel, P.G.H.M. Raijmakers, P.A. Jones, H.W. Berendse, J. Booij, Analysis of extrastriatal 123I-FP-CIT binding contributes to the differential diagnosis of parkinsonian diseases, J. Nucl. Med. 58 (7) (2017 Jul) 1117–1123.

[75] K. Seppi, M.F. Schocke, E. Donnemiller, R. Esterhammer, C. Kremser, C. Scherfler, A. Diem, W. Jaschke, G.K. Wenning, W. Poewe, Comparison of diffusion-weighted imaging and [^{123}I]IBZM-SPECT for the differentiation of patients with the Parkinson variant of multiple system atrophy from those with Parkinson's disease, Mov. Disord. 19 (12) (2004 Dec) 1438–1445.

[76] A.M. Vlaar, T. de Nijs, A.G. Kessels, F.W. Vreeling, A. Winogrodzka, W.H. Mess, S.C. Tromp, M.J. van Kroonenburgh, W.E. Weber, Diagnostic value of 123I-ioflupane and 123I-iodobenzamide SPECT scans in 248 patients with parkinsonian syndromes, Eur. Neurol. 59 (5) (2008) 258–266.

[77] S. Thobois, F. Vingerhoets, V. Fraix, J. Xie-Brustolin, H. Mollion, N. Costes, P. Mertens, A.L. Benabid, P. Pollak, E. Broussolle, Role of dopaminergic treatment in dopamine receptor down-regulation in advanced Parkinson disease: a positron emission tomographic study, Arch. Neurol. 61 (11) (2004 Nov) 1705–1709.

[78] M. Politis, H. Wilson, K. Wu, D.J. Brooks, P. Piccini, Chronic exposure to dopamine agonists affects the integrity of striatal D2 receptors in Parkinson's patients, Neuroimage Clin 16 (2017 Aug 24) 455–460.

[79] K. Van Laere, C. Casteels, L. De Ceuninck, B. Vanbilloen, A. Maes, L. Mortelmans, W. Vandenberghe, A. Verbruggen, R. Dom, Dual-tracer dopamine transporter and perfusion SPECT in differential diagnosis of parkinsonism using template-based discriminant analysis, J. Nucl. Med. 47 (3) (2006 Mar) 384–392.

[80] S. Takaya, N. Sawamoto, T. Okada, G. Okubo, S. Nishida, K. Togashi, H. Fukuyama, R. Takahashi, Differential diagnosis of parkinsonian syndromes using dopamine transporter and perfusion SPECT, Park. Relat. Disord. 47 (2018 Feb) 15–21.

[81] H.S. Markus, A.J. Lees, G. Lennox, C.D. Marsden, D.C. Costa, Patterns of regional cerebral blood flow in corticobasal degeneration studied using HMPAO SPECT; comparison with Parkinson's disease and normal controls, Mov. Disord. 10 (2) (1995 Mar) 179–187.

[82] I.U. Song, I. Yoo, Y.A. Chung, J. Jeong, The value of brain perfusion SPECT for differentiation between mildly symptomatic idiopathic Parkinson's disease and the Parkinson variant of multiple system atrophy, Nucl. Med. Commun. 36 (10) (2015 Oct) 1049–1054.

[83] A. Varrone, M. Pagani, E. Salvatore, D. Salmaso, V. Sansone, M. Amboni, F. Nobili, G. De Michele, A. Filla, P. Barone, S. Pappatà, M. Salvatore, Identification by [99mTc]ECD SPECT of anterior cingulate hypoperfusion in progressive supranuclear palsy, in comparison with Parkinson's disease, Eur. J. Nucl. Med. Mol. Imag. 34 (7) (2007 Jul) 1071–1081.

[84] Z. Walker, F. Gandolfo, S. Orini, V. Garibotto, F. Agosta, J. Arbizu, F. Bouwman, A. Drzezga, P. Nestor, M. Boccardi, D. Altomare, C. Festari, F. Nobili, EANM-EAN Task Force for the recommendation of FDG PET for Dementing Neurodegenerative Disorders. Clinical utility of FDG PET in Parkinson's disease and atypical parkinsonism associated with dementia, Eur. J. Nucl. Med. Mol. Imag. 45 (9) (2018 Jul) 1534–1545.

[85] F. Nobili, J. Arbizu, F. Bouwman, A. Drzezga, F. Agosta, P. Nestor, Z. Walker, M. Boccardi, EANM-EAN task force for the prescription of FDG-PET for dementing neurodegenerative disorders. European association of nuclear medicine and european academy of neurology recommendations for the use of brain 18 F-fluorodeoxyglucose positron emission tomography in neurodegenerative cognitive impairment and dementia: delphi consensus, Eur. J. Neurol. (2018 Jun 22), https://doi.org/10.1111/ene.13728 (Epub ahead of print).

[86] P.T. Meyer, L. Frings, G. Rücker, S. Hellwig, 18F-FDG PET in parkinsonism: differential diagnosis and evaluation of cognitive impairment, J. Nucl. Med. 58 (12) (2017 Dec) 1888–1898.

[87] S.M. Lim, A. Katsifis, V.L. Villemagne, R. Best, G. Jones, M. Saling, J. Bradshaw, J. Merory, M. Woodward, M. Hopwood, C.C. Rowe, The 18F-FDG PET cingulate island sign and comparison to 123I-beta-CIT SPECT for diagnosis of dementia with Lewy bodies, J. Nucl. Med. 50 (10) (2009 Oct) 1638–1645.

[88] T. Iizuka, R. Iizuka, M. Kameyama, Cingulate island sign temporally changes in dementia with Lewy bodies, Sci. Rep. 7 (1) (2017 Nov 7) 14745.

[89] J.T. O'Brien, M.J. Firbank, C. Davison, N. Barnett, C. Bamford, C. Donaldson,

K. Olsen, K. Herholz, D. Williams, J. Lloyd, 18F-FDG PET and perfusion SPECT in the diagnosis of Alzheimer and Lewy body dementias, J. Nucl. Med. 55 (12) (2014 Dec) 1959–1965.

[90] R.A. Townley, H. Botha, J. Graff-Radford, B.F. Boeve, R.C. Petersen, M.L. Senjem, D.S. Knopman, V. Lowe, C.R. Jack Jr., D.T. Jones, 18F-FDG PET-CT pattern in idiopathic normal pressure hydrocephalus, Neuroimage Clin 18 (2018 Feb 28) 897–902.

[91] F. Miyoshi, T. Ogawa, S.I. Kitao, M. Kitayama, Y. Shinohara, M. Takasugi, S. Fujii, T. Kaminou, Evaluation of Parkinson disease and Alzheimer disease with the use of neuromelanin MR imaging and (123)I-metaiodobenzylguanidine scintigraphy, AJNR Am J Neuroradiol 34 (11) (2013 Nov-Dec) 2113–2118.

[92] J. Navarro-Otano, C. Gaig, A. Muxi, F. Lomeña, Y. Compta, M.T. Buongiorno, M.J. Martí, E. Tolosa, F. Valldeoriola, 123I-MIBG cardiac uptake, smell identification and 123I-FP-CIT SPECT in the differential diagnosis between vascular parkinsonism and Parkinson's disease, Park. Relat. Disord. 20 (2) (2014 Feb) 192–197.

[93] P. Tiraboschi, A. Corso, U.P. Guerra, F. Nobili, A. Piccardo, M.L. Calcagni, D. Volterrani, D. Cecchin, M. Tettamanti, L. Antelmi, S. Vidale, L. Sacco, M. Merello, S. Stefanini, A. Micheli, P. Vai, S. Capitanio, S.V. Gabanelli, R. Riva, P. Pinto, A.M. Biffi, C. Muscio, SCILLA Working Group, (123) I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane single photon emission computed tomography and (123) I-metaiodobenzylguanidine myocardial scintigraphy in differentiating dementia with lewy bodies from other dementias: a comparative study, Ann. Neurol. 80 (3) (2016 Sep) 368–378.

[94] M. Südmeyer, C. Antke, T. Zizek, M. Beu, S. Nikolaus, L. Wojtecki, A. Schnitzler, H.W. Müller, Diagnostic accuracy of combined FP-CIT, IBZM, and MIBG scintigraphy in the differential diagnosis of degenerative parkinsonism: a multidimensional statistical approach, J. Nucl. Med. 52 (5) (2011 May) 733–740.

[95] J.S. Kim, H.E. Park, I.S. Park, Y.S. Oh, D.W. Ryu, I.U. Song, Y.A. Jung, I.R. Yoo, H.S. Choi, P.H. Lee, K.S. Lee, Normal 'heart' in Parkinson's disease: is this a distinct clinical phenotype? Eur. J. Neurol. 24 (2) (2017 Feb) 349–356.

[96] J.L. Whitwell, V.J. Lowe, N. Tosakulwong, S.D. Weigand, M.L. Senjem, C.G. Schwarz, A.J. Spychalla, R.C. Petersen, C.R. Jack Jr., K.A. Josephs, [18 F]AV-1451 tau positron emission tomography in progressive supranuclear palsy, Mov. Disord. 32 (1) (2017 Jan) 124–133.

[97] D.R. Schonhaut, C.T. McMillan, S. Spina, B.C. Dickerson, A. Siderowf, M.D. Devous Sr., R. Tsai, J. Winer, D.S. Russell, I. Litvan, E.D. Roberson, W.W. Seeley, L.T. Grinberg, J.H. Kramer, B.L. Miller, P. Pressman, I. Nasrallah, S.L. Baker, S.N. Gomperts, K.A. Johnson, M. Grossman, W.J. Jagust, A.L. Boxer, G.D. Rabinovici, 18 F-flortaucipir tau positron emission tomography distinguishes established progressive supranuclear palsy from controls and Parkinson disease: a multicenter study, Ann. Neurol. 82 (4) (2017 Oct) 622–634.

[98] R. Smith, M. Schain, C. Nilsson, O. Strandberg, T. Olsson, D. Hägerström, J. Jögi, E. Borroni, M. Schöll, M. Honer, O. Hansson, Increased basal ganglia binding of 18 F-AV-1451 in patients with progressive supranuclear palsy, Mov. Disord. 32 (1) (2017 Jan) 108–114.

[99] H. Cho, J.Y. Choi, M.S. Hwang, S.H. Lee, Y.H. Ryu, M.S. Lee, C.H. Lyoo, Subcortical 18 F-AV-1451 binding patterns in progressive supranuclear palsy, Mov. Disord. 32 (1) (2017 Jan) 134–140.

[100] A. Kikuchi, N. Okamura, T. Hasegawa, R. Harada, S. Watanuki, Y. Funaki, K. Hiraoka, T. Baba, N. Sugeno, R. Oshima, S. Yoshida, J. Kobayashi, M. Ezura, M. Kobayashi, O. Tano, S. Mugikura, R. Iwata, A. Ishiki, K. Furukawa, H. Arai, S. Furumoto, M. Tashiro, K. Yanai, Y. Kudo, A. Takeda, M. Aoki, In vivo visualization of tau deposits in corticobasal syndrome by 18F-THK5351 PET, Neurology 87 (22) (2016 Nov 29) 2309–2316.

[101] S. Coakeley, S.S. Cho, Y. Koshimori, P. Rusjan, M. Harris, C. Ghadery, J. Kim, A.E. Lang, A. Wilson, S. Houle, A.P. Strafella, Positron emission tomography imaging of tau pathology in progressive supranuclear palsy, J. Cerebr. Blood Flow Metabol. 37 (9) (2017 Sep) 3150–3160.

[102] S.N. Gomperts, J.J. Locascio, S.J. Makaretz, A. Schultz, C. Caso, N. Vasdev, R. Sperling, J.H. Growdon, B.C. Dickerson, K. Johnson, Tau positron emission tomographic imaging in the lewy body diseases, JAMA Neurol 73 (11) (2016 Nov 1) 1334–1341.

[103] M. Marquié, E.E. Verwer, A.C. Meltzer, S.J.W. Kim, C. Agüero, J. Gonzalez, S.J. Makaretz, M. Siao Tick Chong, P. Ramanan, A.C. Amaral, M.D. Normandin, C.R. Vanderburg, S.N. Gomperts, K.A. Johnson, M.P. Frosch, T. Gómez-Isla, Lessons learned about [F-18]-AV-1451 off-target binding from an autopsy-confirmed Parkinson's case, Acta Neuropathol Commun 5 (1) (2017 Oct 19) 75.

[104] A. Perez-Soriano, J.E. Arena, K. Dinelle, Q. Miao, J. McKenzie, N. Neilson, A. Puschmann, P. Schaffer, H. Shinotoh, J. Smith-Forrester, E. Shahinfard, N. Vafai, D. Wile, Z. Wszolek, M. Higuchi, V. Sossi, A.J. Stoessl, PBB3 imaging in Parkinsonian disorders: evidence for binding to tau and other proteins, Mov. Disord. 32 (7) (2017 Jul) 1016–1024.

[105] J.R. Winer, A. Maass, P. Pressman, J. Stiver, D.R. Schonhaut, S.L. Baker, J. Kramer, G.D. Rabinovici, W.J. Jagust, Associations between tau, β-amyloid, and cognition in Parkinson disease, JAMA Neurol 75 (2) (2018 Feb 1) 227–235, https://doi.org/10.1001/jamaneurol.2017.3713.

[106] E. Tolosa, T.V. Borght, E. Moreno, DaTSCAN Clinically Uncertain Parkinsonian Syndromes Study Group. Accuracy of DaTSCAN (123I-Ioflupane) SPECT in diagnosis of patients with clinically uncertain parkinsonism: 2-year follow-up of an open-label study, Mov. Disord. 22 (16) (2007 Dec) 2346–2351.

[107] M.F. Covington, N.A. McMillan, P.H. Kuo, Impact of reimbursement cuts on the sustainability and accessibility of dopamine transporter imaging, J. Am. Coll. Radiol. 13 (9) (2016 Sep) 1039–1043.

[108] A.J. Stoessl, Radionuclide scanning to diagnose Parkinson disease: is it cost-effective? Nat. Clin. Pract. Neurol. 5 (1) (2009 Jan) 10–11.

[109] R.C. Dodel, H. Höffken, J.C. Möller, B. Bornschein, T. Klockgether, T. Behr, W.H. Oertel, U. Siebert, Dopamine transporter imaging and SPECT in diagnostic work-up of Parkinson's disease: a decision-analytic approach, Mov. Disord. 18 (Suppl 7) (2003 Oct) S52–S62.

[110] R. De la Fuente-Fernández, Role of DaTSCAN and clinical diagnosis in Parkinson disease, Neurology 78 (10) (2012 Mar 6) 696–701.

[111] J. Darcourt, J. Booij, K. Tatsch, A. Varrone, T. Vander Borght, O.L. Kapucu, K. Någren, F. Nobili, Z. Walker, K. Van Laere, EANM procedure guidelines for brain neurotransmission SPECT using (123)I-labelled dopamine transporter ligands, version 2, Eur. J. Nucl. Med. Mol. Imag. 37 (2) (2010 Feb) 443–450.

[112] K. Van Laere, A. Varrone, J. Booij, T. Vander Borght, F. Nobili, O.L. Kapucu, Z. Walker, K. Någren, K. Tatsch, J. Darcourt, EANM procedure guidelines for brain neurotransmission SPECT/PET using dopamine D2 receptor ligands, version 2, Eur. J. Nucl. Med. Mol. Imag. 37 (2) (2010 Feb) 434–442.