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SYSTEMATIC REVIEW

Role of [^{18}F]-FDG PET in patients with atypical parkinsonism associated with dementia

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Abstract

Purpose The present review aims to discuss indications for the use of [^{18}F]-FDG PET in patients with APS associated with dementia as emerged in the EANM/EAN joint recommendations for its use in dementia. New lines of evidence emerged after the EANM/EAN consensus have here been systematically reviewed.

Methods We searched in the databases PubMed, PMC, Google Scholar, Medline using as text "positron emission tomography—PET", "PET/CT", "MR" and "Parkinsonian Syndromes", "Atypical Parkinsonism", "progressive supranuclear palsy", "cortico-basal syndrome", "dementia with Lewy Bodies". We selected only PET studies or multimodal imaging studies including the use of [^{18}F]-FDG PET.

Results Atypical parkinsonian syndromes (APS) associated with dementia are complex clinical scenarios including progressive supranuclear palsy (PSP), corticobasal syndrome/degeneration (CBS/CBD) and dementia with Lewy bodies (DLB). The clinical diagnosis of these diseases is often challenging and has relevant repercussions for patients' management and prognosis. A systematic review of the articles published between December 2015 and December 2019 (so after the deadline of the literature search at the time of the EAN/EANM recommendations) was carried out. A total of further 18 papers met our inclusion criteria.

Conclusion Although available studies in patients with APS and dementia suffer from methodological limitations, the expert consensus emerged from the EANM/EAN recommendations was in favor of its use for specific clinical questions in these group of patients. Studies in a larger number of patients published after the publication of the joint recommendations have further supported the use of ^{18}F-FDG PET in patients with APS associated with dementia.

Keywords Brain [^{18}f]-FDG PET · Atypical parkinsonian syndromes · Neurodegenerative parkinsonism · Dementia

Introduction

[^{18}F]-FDG PET has a long-standing role in the diagnostic work-up of the main forms of dementia. In particular, it has been extensively used to differentiate between neurodegenerative dementia and other causes of cognitive impairment as well as for the differential diagnosis within neurodegenerative dementia [1]. [^{18}F]-FDG is considered a marker of neurodegeneration as its in vivo uptake is strongly correlated with cerebral synaptic density and activity [2]. For this reason, the hypometabolic patterns highlighted by [^{18}F]-FDG PET provide information on the extent and localization of neuronal dysfunction and thus on the endophenotype of neuronal injury. Accordingly, [^{18}F]-FDG PET plays its major role in the early diagnosis of mild cognitive impairment (MCI) due to AD in the differential diagnosis between dementing disorders and to differentiate within atypical parkinsonian syndromes (APS) [1]. The clinical role of [^{18}F]-FDG PET has been quoted in clinical, neuroimaging-oriented and procedural guidelines, but, until very recently, specific evidence-based recommendations on the use of [^{18}F]-FDG PET in neurodegenerative were still lacking [1, 3–5]. In 2018 the European Association of Nuclear Medicine (EANM) and the European Academy of Neurology (EAN) jointly published recommendations

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for the use of brain [^{18}F]-FDG PET in neurodegenerative cognitive impairment and Dementia (from now on EANM/EAN recommendations) [1]. This initiative aimed to better guide clinicians on the use of this tool and included a set of 21 clinical questions that were addressed on the basis of literature evidence and expert consensus. Several of these questions were specifically assessing the role of [^{18}F]-FDG PET to support the diagnosis of patients with suspected APS associated with dementia [1, 6, 7], a complex clinical scenario with repercussion for patients' prognosis and management. In fact, neurodegenerative parkinsonian syndromes are a group of movement disorders associated with other symptoms possibly including cognitive impairment and characterized by significantly different prognoses and response to L-DOPA treatment [7]. From the neuropathological point of view, neurodegenerative parkinsonian disorders can be classified in α-synucleinopathies (PD with and without cognitive impairment/dementia, dementia with DLB and multiple system atrophy—MSA) and tauopathies (CBD and PSP) [7, 8]. APS, also known as Parkinson-plus syndromes include PSP, CBD and DLB. Despite an increasing interest on the use of [^{18}F]-FDG PET in the settings of APS, several studies published prior to the EANM/EAN recommendations were characterized by methodological limitations including lack of critical outcomes, inadequate gold standard and absence of head-to-head comparison with other methods. Recent studies published after the publication of the joint recommendations have provided further robust lines of evidence on the use of [^{18}F]-FDG PET in patients with APS associated with dementia. The present review aims to summarize and comment on the evidence-based indications for the use of [^{18}F]-FDG PET in patients with APS associated with dementia as well as the expert opinion emerged from the EANM/EAN joint recommendations in this clinical settings. New lines of evidence emerged after the EANM/EAN consensus have also been systematically reviewed and commented. In fact, the EANM/EAN consensus was based on a systematic literature search as for November 2015 and a number of studies based on proper methodology have been made available after this deadline.

Search strategies

We searched (last update on December 2019) in the databases PubMed (https://www.ncbi.nlm.nih.gov) PMC, Google Scholar, Medline using both as text and as MeSH (Medical Subject Headings) terms the following: "positron emission tomography—PET", "PET/CT", "PET/MRI", "MR" and "Parkinsonian Syndromes", 'Atypical Parkinsonism", "progressive supranuclear palsy", "cortico-basal syndrome", "dementia with Lewy Bodies". Articles investing the role of [^{18}F]-FDG PET in Parkinson's disease with dementia were not included unless specifically aiming to assess the accuracy of PET in the differential diagnosis with respect to atypical parkinsonian syndromes associated with dementia. Similarly, articles specifically discussing the role in multiple system atrophy (MSA), another neurodegenerative atypical parkinsonian syndrome, were not selected. As a matter of fact, MSA very rarely affects cognition and the aim of the present review is to address the role of [^{18}F]-FDG PET in atypical parkinsonian syndromes associated with dementia.

No language restriction was applied to the research, but reviewed articles were limited to the English language. Among all the retrieved articles, we selected only studies and case series presenting [^{18}F]-FDG PET studies or multimodal imaging studies including the use of [^{18}F]-FDG PET. All the studies already included and commented in the EANM/EAN recommendations were reviewed. A systematic review of the articles published between December 2015 and December 2019 (so after the deadline of the literature search at the time of the EAN/EANM recommendations) was in particular carried out and here reported. A total of 18 papers met our inclusion criteria and were selected [9–26]. Characteristics of the selected studies are summarized in Table 1.

Role of [^{18}F]-FDG PET for the differential diagnosis between idiopathic PD and APS associated with dementia

Both subjects with PD and APS show an early reduction in presynaptic dopaminergic function as testified by dopamine transporter (DAT) SPECT and [^{18}F]-DOPA PET [27, 28]. Accordingly, although a differential pattern of reduced uptake has been described at the group level, a real distinction between PD and APS cannot be reliably made by means of DAT SPECT or [^{18}F]-DOPA PET [29]. Disease-specific patterns of regional glucose metabolism in patients with parkinsonism are well documented [6]. However, the valuable capability of [^{18}F]-FDG PET for the accurate differentiation between PD and APS has been unanimously accepted only in recent years [30]. In a meta-analysis, Meyer et al. well described the different [^{18}F]-FDG patterns in PD and APS [31]. PD is characterized by a posterior temporoparietal, occipital hypometabolism with a relative hypermetabolism (or at least preserved metabolism) of the putamen, pallidium, thalamus sensorimotor cortex, pons, and cerebellum [32]. This preserved metabolism in the basal ganglia is a robust way to distinguish between PD and DLB on one side and the other APS on the other [30]. In fact, the majority of APS namely PSP and CBD (as well as MSA which is generally not associated with cognitive impairment) are characterized by reduced uptake in the basal ganglia and

Table 1 Studies evaluating the role of FDG PET in patients with atypical parkinsonian syndromes associated with dementia from December 2015 to December 2019

References	Study type	Patients' characteristics	Aims	Methods	Results
Gjerum et al. [9]	Retrospective	35 DLB patients, 36 AD patients, and 23 healthy controls	To differentiate DLB with and without amyloid beta pathology (Aβ±)	Rating according to a visual CIS scale based on specific reading criteria	DLB patients had a significantly higher visual CIS score compared to AD patients and controls. A specific cutoff visual CIS score was able to significantly differentiate DLB Aβ- patients from DLB Aβ + patients
Imai et al. [10]	Retrospective	45 AD patients, 18 DLB patients, and 142 CTR	To assess the topology with global and nodal parameters in AD, DLB and CTR	Graph-theoretical method to generate the network topology in AD patients, DLB patients, and CTR individuals	The whole metabolic network was preserved in CTR while diffusely decreased connection was found in AD and partially but more deeply decreased connection was observed in DLB. The metabolic topology revealed that the right posterior cingulate and the left transverse temporal gyrus were significantly different between AD and DLB
Gupta et al. [11]	Retrospective	72 demented patients with a "posterior" clinical syndrome	To study the imaging patterns of PCA and DLB on FDG PET able to identify areas of overlap and differences and to develop a prediction model to assist in diagnosis using univariate and multivariate analyses	All patients underwent FDG PET/CT of the brain and dopamine transporter imaging with SPECT scan on separate days. The patients were divided into PCA with normal TRODAT uptake ($n=34$) and DLB with abnormal TRODAT uptake ($n=38$). The FDG PET/CT uptake patterns were recorded and areas of significant hypometabolism by z score analysis were considered as abnormal. Receiver operator characteristics (ROC) curve analysis was used to determine cutoff z scores and binary logistic regression analysis was used to determine the odds ratio of being in the predicted groups	Significantly hypometabolism in parietotemporooccipital association cortices and cingulate cortices in PCA patients. DLB patients showed significantly reduced uptake in the visual cortex. No significant difference was found between z score of occipital association cortex which showed hypometabolism in both groups. The cutoff z score values derived from the ROC curve: parietal association (cutoff 3, sensitivity65.6%, specificity 68.7%), temporal association (cutoff 2, sensitivity 78%, specificity 75%) and posterior cingulate (cutoff 0.5, sensitivity 93.7%, specificity 40.6%). Odds ratio (with 95% confidence interval) for being in the PCA group as derived from univariate logistic regression was 3.66 (1.30–10.32), 10.71 (3.36–34.13) and 7.85 (1.57–39.17). The cutoff z score of primary visual cortex as derived from ROC curve was zero with sensitivity of 87.5%, specificity of 71.9%, and the odds ratio for being the in the DLB group was 24.7 with 95% confidence interval of 5.99–101.85
Beretta et al. [12]	Retrospective	Sixty patients were diagnosed as DLB ($n=35$) and AD ($n=25$) dementia according with the standard research diagnostic criteria	To assess the relationship between brain metabolic dysfunction and visuospatial deficits, in DLB and AD	Patients underwent FDG PET and an extended neuropsychological evaluation, including MMSE, language, memory, executive functions and visuospatial abilities tests. The MMSE scoring. Offline voxel-wise correlation analysis between NPS scores and FDG-PET brain metabolism was then performed, correcting for MMSE, sex and disease duration	Both groups presented reduced visuospatial performances. In DLB, worse performance at tests total score, i.e., more severe visuospatial impairment, correlated with brain occipital hypometabolism (i.e., lateral occipital cortex, calcarine cortex, fusiform and lingual gyri). In AD, worse performance at NPS total score correlated with brain hypometabolism in the right parietal cortex (i.e., superior and inferior parietal cortex and angular gyrus)

Table 1 (continued)

References	Study type	Patients' characteristics	Aims	Methods	Results
Sala et al. [13]	Retrospective	Large cohort of DLB patients ($N=72$)	To assess the relationship between brain metabolic dysfunction and visuospatial deficits, in DLB and AD	To evaluate large-scale resting-state networks' integrity and their interactions	Both local and long-distance metabolic connectivity alterations, affecting the posterior cortical networks as well as the limbic and attention networks were highlighted (widespread derangement of the brain connectome). Patients with the lowest visual and attention cognitive scores showed the most severe connectivity derangement in regions of the primary visual network. Network-level alterations were differentially associated with the core clinical manifestations, namely, hallucinations with more severe metabolic dysfunction of the attention and visual networks, and RBD with alterations of connectivity of attention and subcortical networks
Pillai et al. [14]	Retrospective	49 patients evaluated at one tertiary memory clinic (suspected) AD, DLB, FTD based on accepted clinical criteria	To assess the value of previously known FDG-PET occipital cortex hypometabolism, and cingulate island sign biomarkers of DLB against a novel amygdala signature	FDG-PET regional metabolism was delineated by automatic segmentation as well as manual tracing of amygdala and posterior cingulate volumes of interest. Mean normalized values calculated for regional FDG-PET signatures of DLB: occipital cortex hypometabolism and preservation of posterior cingulate and amygdala metabolism relative to whole brain metabolism were evaluated	Significant overlap between DLB and AD patients (occipital, parietal, temporal and frontal hypometabolism) and between DLB and FTD (frontal hypometabolism and the posterior cingulate sign) were identified. Right amygdala ($p=0.028$) and right posterior cingulate ($p=0.035$) mean normalized regional metabolism levels were preserved in DLB compared to AD. Among subjects at less advanced stages of dementia, relative preservation of regional metabolism was notable across both left ($p=0.006$) and right ($p=0.020$) amygdala
Caminiti et al. [15]	Retrospective	$N=72$ patients with heterogeneous clinical classification at entry (mild cognitive impairment, atypical parkinsonisms, possible DLB, probable DLB, and other dementias) and an established diagnosis of DLB at a later follow-up	To provide an extensive validation of the FDG-PET metabolic signatures in supporting DLB diagnosis near the first clinical assessment, which is characterized by high diagnostic uncertainty, at the single-subject level	Generation of patterns of FDG-PET hypometabolism in single cases using a validated voxel-wise analysis ($p<0.05$, FWE-corrected)	The single-subject FDG-PET hypometabolism pattern, showing temporoparietal and occipital involvement, was highly consistent across DLB cases. Clinical classification at entry produced several misclassifications with an agreement of only 61.1% with the diagnostic reference. On the contrary, FDG-PET hypometabolism maps alone accurately predicted diagnosis of DLB at follow-up (88.9%)
Zhou et al. [16]	Retrospective	22 AD patients, 18 PDD patients, 22 DLB patients and 22 CTR subjects	To study the difference of brain networks in various dementia subtypes	Graph theory methods to investigate altered whole-brain intrinsic glucose metabolic functional networks	The three dementia groups, compared to CTR group, the small-world characteristics were lost. Additionally, compared with HC group, the clustering coefficients of three dementia groups were higher; the characteristic path lengths were longer. In terms of local efficiency and global efficiency, it was at the lowest level in DLB group

Table 1 (continued)

References	Study type	Patients' characteristics	Aims	Methods	Results
Nedelska et al. [17]	Retrospective	Clinically probable DLB patients ($n=19$), age-matched patients with probable Alzheimer's disease dementia (AD; $n=19$) and matched controls ($n=76$)	To measure perfusion cingulate island sign ratio on arterial spin labeling MRI (ASL-CISr), and its associations with FDG-CISr, uptake on tau-PET and clinical severity in DLB	Patients and CTR underwent MRI with three-dimensional pseudo-continuous arterial spin labeling, 18F-FDG-PET and 18F-AV-1451 tau PET. Patterns of cortical perfusion and metabolism were derived from quantitative maps using statistical parametric mapping	DLB patients showed hypoperfusion on ASL-MRI in precuneus, cuneus and posterior parietooccipital cortices, compared to controls, and relatively spared posterior cingulate gyrus, similar to pattern of hypometabolism on FDG-PET. DLB patients had higher ASL-CISr and FDG-CISr than AD patients ($p<0.001$). ASL-CISr correlated with FDG-CISr in DLB patients ($r=0.67$; $p=0.002$). Accuracy of distinguishing DLB from AD patients was 0.80 for ASL-CISr and 0.91 for FDG-CISr. Lower ASL-CISr was moderately associated with a higher composite medial temporal AV-1451 uptake ($r=-0.50$; $p=0.03$) in DLB. Lower perfusion in precuneus and cuneus was associated with worse global clinical scores
Hamed et al. [18]	Retrospective	35 consecutive patients with a clinical diagnosis of probable, possible, or definite DLB as defined by the latest DLB Consortium Report	To determine whether occipital and cingulate hypometabolism is being underreported or missed on FDG PET-CT in patients with DLB	ROIs consisting of glucose hypometabolism in frontal, parietal, temporal, occipital, and cingulate areas were tabulated and charted separately by the authors from the reports. A blinded nuclear medicine physician read the images independently and marked ROI's separately. A Cohen's Kappa coefficient statistic was calculated	25.71% and 17.14% of patients reported occipital and cingulate hypometabolism, respectively. Independent reads demonstrated significant disagreement with the proportion of occipital and cingulate hypometabolism being reported on initial reads: 91.43% and 85.71%, respectively. Cohen's Kappa statistic determinations demonstrated significant agreement only with parietal hypometabolism ($p<0.05$)
Whitwell et al. [19]	Retrospective	Sixteen clinically diagnosed PCA and 13 probable DLB subjects	To determine whether patterns of hypometabolism or the cingulate island sign differed between PCA and DLB	Regional hypometabolism was assessed compared with a control cohort ($n=29$) using voxel-and region-level analyses in statistical parametric mapping. A ratio of metabolism in the posterior cingulate to precuneus plus cuneus was calculated to assess the cingulate island sign. In addition, the 18F-FDG PET scans were visually assessed to determine whether the cingulate island sign was present in each subject	PCA and DLB showed overlapping patterns of hypometabolism involving the lateral occipital lobe, lingual gyrus, cuneus, precuneus, posterior cingulate, inferior parietal lobe, supramarginal gyrus, striatum, and thalamus. However, DLB showed greater hypometabolism in the medial occipital lobe, orbitofrontal cortex, anterior temporal lobe, and caudate nucleus than PCA, and PCA showed more asymmetric patterns of hypometabolism than DLB. The cingulate island sign was present in both DLB and PCA, although it was more asymmetric in PCA

Table 1 (continued)

References	Study type	Patients' characteristics	Aims	Methods	Results
Caminiti et al. [20]	Retrospective	42 dementia with Lewy bodies patients, as compared to 42 CTR	To gain an overview of brain systems affected by neurodegeneration, we characterized the [18F]FDG-PET metabolic connectivity	Whole-brain and anatomically driven analyses, targeting cholinergic and dopaminergic pathways, and the α-synuclein spreading	Decreases in local metabolic connectivity within occipital cortex, thalamus, and cerebellum, and increases within frontal, temporal, parietal, and basal ganglia regions. There were also long-range disconnections among these brain regions, all supporting a disruption of the functional hierarchy characterizing the normal brain. The anatomically driven analysis revealed alterations within brain structures early affected by α-synuclein pathology, supporting Braak's early pathological staging in dementia with Lewy bodies. The dopaminergic striato-cortical pathway was severely affected, as well as the cholinergic networks, with an extensive decrease in connectivity in Ch1-Ch2, Ch5-Ch6 networks, and the lateral Ch4 capsular network significantly towards the occipital cortex
Dodich et al. [21]	Retrospective	70 patients fulfilling current criteria for CBS ($n=33$) or PSPs ($n=37$)	To assess the clinical-metabolic correlates of language impairment in a large sample of patients clinically diagnosed as corticobasal syndrome (CBS) and progressive supranuclear palsy syndrome (PSPs)	All subjects underwent clinical-neuropsychological and FDG-PET assessments at the time of diagnosis. The whole patient's cohort was grouped into three subgroups according to the language characteristics, i.e., (a) nfv-PPA; (b) subtle language impairments, LANG-; (c) no language deficits, NOL-. FDG-PET data were analyzed using an optimized voxel-based SPM method at the single-subject and group levels to evaluate specific hypometabolic patterns and regional dysfunctional FDG-PET commonalities in subgroups	FDG-PET results in individuals with a nfv-PPA diagnosis were consistent with the typical nfv-PPA pattern of hypometabolism (i.e., left fronto-insular and superior medial frontal cortex involvement), both in CBS and PSPs. The LANG-CBS and LANG-PSPs subjects had different FDG-PET hypometabolic patterns involving, respectively, parietal and frontal regions. As expected, NOL-CBS and NOL-PSPs showed a predominant right hemisphere involvement, with selective functional metabolic signatures typical of the two syndromes
Beyer et al. [22]	Retrospective	117 demented patients submitted to FDG PET for differential diagnosis of dementia. Patients were followed clinically for a minimum of one year and their final clinical diagnosis was recorded	To evaluate the strengths and limitations of standalone FDG-PET for the identification of Tau-positive atypical parkinsonian syndromes (T + APS)	FDG-PET was rated visually (positive/negative) and categorized as high, moderate or low likelihood of T + APS and other neurodegenerative disorders. Positive and negative predictive values (PPV/NPV) of FDG-PET readings for the different subgroups relative to their final clinical diagnosis was then calculated	PPV was excellent when FDG-PET indicated a high likelihood of T + APS in combination with low to moderate likelihood of another neurodegenerative disorder. PPV was distinctly lower when FDG-PET indicated only a moderate likelihood of T + APS or when there was deemed equal likelihood of other neurodegenerative disorder. NPV of FDG-PET with a low likelihood for T + APS was high

Table 1 (continued)

References	Study type	Patients' characteristics	Aims	Methods	Results
Brajkovic et al. [23]	Retrospective	72 patients with parkinsonism (age 34–80 years) referred to our center by movement disorder specialists	To assess the utility of FDG-PET imaging in differential diagnosis of Parkinsonism in clinical practice	FDG-PET diagnosis was obtained by visual assessment of individual scans combined with voxel-based statistical parametric mapping analysis. FDG-PET diagnosis assigned at the time of imaging was compared with the final clinical diagnosis made by the movement disorder specialists after ≥ 2 years follow-up	FDG-PET findings were consistent with IPD in 27, MSA in 18, PSP in 19 and CBS in 2 patients. The final clinical diagnosis was IPD in 29, MSA in 20, PSP in 21 and CBS in 2 patients. Concordance between the FDG-PET and clinical diagnoses was 92% in the overall sample (IPD 93%, MSA 90%, PSP 91% and CBS 100%). The diagnostic accuracy of FDG-PET was 93% for IPD and 97% for PSP
Smith et al. [24]	Retrospective	8 patients with CBS, 17 controls, 31 patients with AD, and 11 patients with PSP from the Swedish BioFINDER study	To study the usefulness of 18F-AV-1451 PET in patients with CBS (FDG PET and MRI were used for comparison)	Patients underwent clinical assessment, 18F-AV-1451 PET, MRI, and quantification of β-amyloid pathology. A subset of participants also underwent 18F-FDG-PET	^{18}F-AV-1451 was able to distinguish between patients with AD dementia and PSP. Cortical atrophy measured with MRI and decreased 18F-fluorodeoxyglucose uptake were more widespread than 18F-AV-1451 uptake and probably represent earlier, yet less specific, markers of CBS. Cortical AV-1451 uptake did not correlate with cortical thickness or glucose hypometabolism
Pardini et al. [25]	Retrospective	29 patients with a diagnosis of CBS who underwent FDG-PET scan and postmortem neuropathologic examination	To evaluate brain FDG PET differences among patients with a clinical diagnosis of corticobasal syndrome (CBS) and distinct underling primary pathologies	Patients were divided into subgroups on the basis of primary pathologic diagnosis: CBS-CBD (14 patients), CBS-Alzheimer disease (CBS-AD) (10 patients), and CBS-progressive supranuclear palsy (CBS-PSP) (5 patients). Thirteen age-matched healthy patients who underwent FDG-PET were the control group (HC). FDG-PET scans were compared between the subgroups and the CTR using SPM	Compared to CTR, the patients with CBS presented significant hypometabolism in frontoparietal regions, including the perirolandic area, basal ganglia, and thalamus of the clinically more affected hemisphere. Patients with CBS-CBD showed a similar pattern with a more marked, bilateral involvement of the basal ganglia. Patients with CBS-AD presented with posterior, asymmetric hypometabolism, including the lateral parietal and temporal lobes and the posterior cingulate. Finally, patients with CBS-PSP disclosed a more anterior hypometabolic pattern, including the medial frontal regions and the anterior cingulate. A conjunction analysis revealed that the primary motor cortex was the only common area of hypometabolism in all groups, irrespective of pathologic diagnosis

Table 1 (continued)

References	Study type	Patients' characteristics	Aims	Methods	Results
Morbelli et al. [26]	Retrospective	171 DLB patients belonging to the imaging repository of the European DLB Consortium	To identify brain regions whose metabolic impairment contributes to dementia with Lewy bodies (DLB) clinical core features expression and to assess the influence of severity of global cognitive impairment on the DLB hypometabolic pattern	Principal component analysis was applied to identify brain regions relevant to the local data variance. A linear regression model was applied to generate core-feature-specific patterns controlling for the main confounding variables (Mini-Mental State Examination [MMSE], age, education, gender, and center). Regression analysis to the locally normalized intensities was performed to generate an MMSE-sensitive map	Regions of more preserved metabolism are relatively consistent across the variegate DLB spectrum. By contrast, core features were associated with more prominent hypometabolism in specific regions, reflecting the possibility of a close clinical imaging correlation. MMSE positively covaried with metabolism in the left superior frontal gyrus, bilateral-parietal cortex, and left precuneus, and negatively with metabolism in the insula, medial frontal gyrus, hippocampus in the left hemisphere, and right cerebellum

AD Alzheimer's disease; *DLB* dementia with Lewy bodies; *CBS/CBD* corticobasal syndrome/corticobasal degeneration; *PSP* progressive supranuclear palsy; CIS cingulate island sign; *CTR* controls; *PCA* posterior cortical atrophy; *RBD*, REM sleep behavior disorders; *FTD*, fronto-temporal dementia; *nfv-PPA* non-fluent variant of primary progressive aphasia

in other subcortical structures [30]. Hellwig et al. prospectively investigated the diagnostic value of [^{18}F]-FDG PET and post-synaptic dopaminergic imaging with SPECT (D2 SPECT) in differentiating between Lewy body diseases (PD/DLB) and APS [30]. The diagnostic value of [^{18}F]-FDG PET to differentiate within APS subgroups was also addressed in the same study. They recruited and examined 95 patients with both [^{18}F]-FDG PET and D2 SPECT. The area under the receiver operating characteristic curve for discrimination between APS and LBD was significantly larger for [^{18}F]-FDG PET (0.94) than for [^{123}I]IBZM-SPECT (0.74). Sensitivity/specificity of [^{18}F]-FDG PET for diagnosing APS was 86%/91%, respectively. Sensitivity/specificity of [^{18}F]-FDG PET in identifying APS subgroups was 74%/95% for PSP, and 75%/92% for CBD. Authors concluded that the diagnostic accuracy of [^{18}F]-FDG PET for discriminating LBD from APS is considerably higher than for ^{123}I-IBZM-SPECT and that [^{18}F]-FDG PET reliably differentiates APS subgroups with high specificity [30]. A similar approach was followed in an autoptic study by Tang et al. who developed an automated image-based classification procedure to differentiate individual patients with idiopathic PD, MSA, and PSP [33, 34]. These authors demonstrated that by applying a two-step classification, the vast majority of patients examined with [^{18}F]-FDG PET for this differential diagnosis falls into one of these two categories (PD or APS) and then [^{18}F]-FDG PET has high specificity in distinguishing within APS and could help in selecting treatment for early-stage patients [30, 33].

Accordingly, the EANM/EAN recommendations supported the use of [^{18}F]-FDG for the differential diagnosis between PD and APS due to the existence of a typical metabolic pattern of hypometabolism in PDD and in APS (in particular in PSP which predominantly affects the frontal, thalamic, striatal and midbrain regions; see below paragraph on PSP). Of note, several studies on the value of [^{18}F]-FDG in patients with APS associated with dementia were carried out supporting the visual analysis with automated voxel-based methods [35, 36]. The importance of this approach was also underlined in the EANM/EANM recommendations [37]. In fact, sensitivity between visual and automatic analysis might be similar but accuracy of visual analysis is affected by reader's experience and the automatic assessment generally improves specificity [38]. This is particularly relevant in patients with suspected neurodegenerative parkinsonian syndromes as subcortical structures have to be inspected. These structures are closer to the median line and the presence of asymmetry can thus be less easily spotted through visual analysis [39]. Representative examples of [^{18}F]-FDG PET patterns in patients with PD and APS are reported in Fig. 1. Further

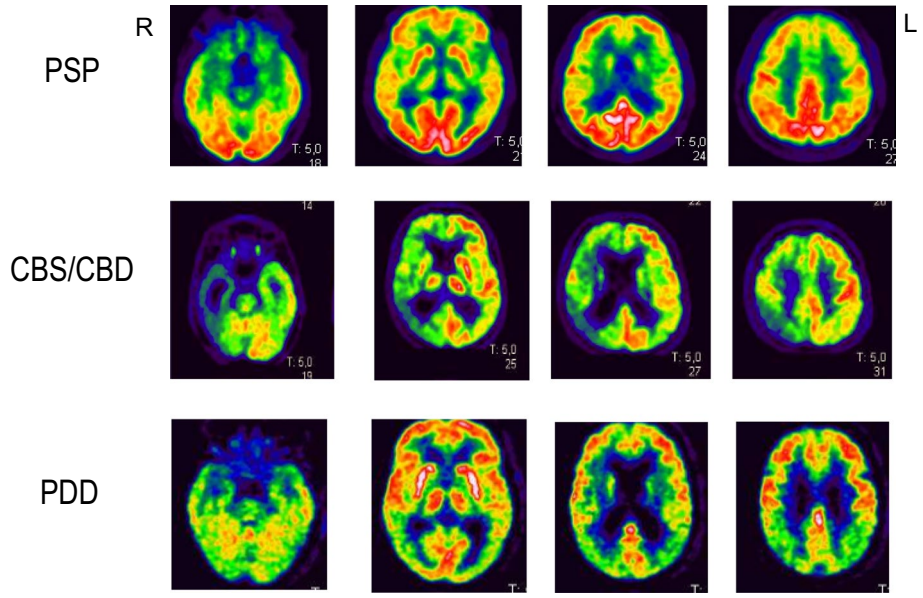

Fig. 1 Representative examples of ^{18}F-FDG PET hypometabolism pattern in patients with progressive supranuclear palsy (PSP), corticobasal syndrome/corticobasal degeneration (CBS/CBD) and Parkinson's disease associated with dementia (PDD). In PSP, the hypometabolic pattern predominantly affects anterior cingulate, frontal-lateral cortex, striatum, the thalamus, and midbrain regions. In this case, the hypometabolism is mild and affects both hemispheres (upper panel). In CBS/CBD, the most frequent ^{18}F-FDG PET features reported in patients with CBS is the presence of asymmetric hypometabolism in the parietal and frontal cortex, in the thalamus and ganglia of the contralateral hemispheres with respect to the most clinically affected body side. In this case marked hypometabolism affects the right hemisphere (middle panel). In patients with PDD the hypometabolic pattern includes temporoparietal and occipital cortex with spared metabolism or even relative hypermetabolism in the basal ganglia (clearly telling apart the brain metabolic profile of PDD with respect to atypical parkinsonian syndromes). As in this case (lower panel), many patients with PDD are also characterized by the cingulate island sign (hypometabolism in the precuneus with relatively spared metabolism in posterior cingulate). In fact PD, PDD and dementia with Lewy bodies (DLB) are probably two opposite sides of the same spectrum of disease (at the moment clinically differentiated only on the basis of the timeframe of onset of cognitive and motor symptoms)

details on hypometabolic patterns in different APS and main references are reported in Table 2.

Role of [^{18}F]-FDG PET in patients with PSP

PSP is a neurodegenerative disease defined by intra-cerebral aggregation of the microtubule-associated protein tau and belongs to the spectrum of frontotemporal degeneration. Clinically, it is characterized by the presence of different combinations of motor, gait, cognitive and behavioral features.

Based on combinations of clinical manifestations, different subtypes have been identified: Richardson's syndrome (PSP-RS, the most frequent phenotype), PSP-parkinsonism (PSP-P), PSP with progressive gait freezing (PSP-PGF), PSP with predominant frontal presentation (PSP-F), PSP with a predominant speech/language disorder (PSP-SL), and PSP with predominant corticobasal syndrome (PSP–CBS) [40].

Early clinical diagnosis of PSP is challenging but essential for an accurate definition of prognosis for appropriate patients' management as well as for the possible allocation to interventional clinical trials of new potentially effective disease-modifying agents.

The differential diagnosis between PSP and iPD is particularly complex for several reasons. First, there is often an overlap between the clinical presentation of PSP and PD [6]. This occurs especially in the case of PSP-P in which features of Parkinson's disease, such as asymmetrical tremor, bradykinesia and rigidity, overlap with the clinical presentation of PSP [6].

Moreover, in PSP patients a possible initial misleading positive response to Levodopa treatment can be present. Finally, one of the most typical features of PSP, the impairment in conjugate ocular movements with vertical supranuclear gaze palsy frequently occurs late in the course of the disease, only allowing a retrospective diagnosis [6, 41]. The [^{18}F]-FDG PET PSP-related pattern has been repeatedly demonstrated. It predominantly affects anterior cingulate, frontal lateral cortex, striatum, the thalamus, and midbrain regions [6, 29]. In different studies, 18F-FDG PET demonstrated specificity, sensitivity and overall accuracy to be 52.9–75%, 80–100%, 67.6–83.9%, respectively, with an AUC of 0.80 [6, 42, 43]. In the above-mentioned study, Tang et al. used a voxel-based spatial

Table 2 Expected patterns of hypometabolism in atypical neurodegenerative Parkinsonian syndromes associated with dementia

Atypical parkinsonian syndrome	Expected pattern	Main references
Dementia with Lewy bodies	Lateral temporal and posterior parietal hypometabolism with a prominent involment of lateral and mesial occipital hypometabolism, associated with so-called posterior cingulate island sign (hypometabolism of precuneus with relatively spared posterior cingulate metabolism)	[7, 13–20, 26, 33, 34, 42, 63, 70, 71]
Progressive supranuclear palsy	Hypometabolism in anterior cingulate, frontal-lateral cortex, striatum, thalamus and midbrain regions	[6, 21–23, 33, 34, 39, 41, 42, 59]
Corticobasal syndrome/degeneration	Markedly asymmetric hypometabolism in the parietal and frontal cortex (usually involving the motor and premotor cortices), in the thalamus and in the basal ganglia	[6, 25, 50–54, 60, 62, 66]

covariance mapping applied to 18F-FDG PET images to identify specific disease-related metabolic patterns in patients with neurodegenerative disorders. As mentioned, a multiple-pattern imaging technique to calculate the probability of patients with Parkinsonism of having PD, PSP or MSA was developed and it was demonstrated that just a few number of scans are characterized by an indeterminate pattern [32]. However, in the proposed two-step classification, the sensitivity of the [^{18}F]-FDG PET for the specific identification of PSP from other APS was moderate, with a range between 73 and 88%, while specificity and PPV were, respectively, 90–94% and 85–96% [6, 30, 32].

It should be noted, however, that when trying to discriminate within APS, the most complex scenario from clinical and imaging point of view is represented by the differential diagnosis between PSP and CBD with a wide range of sensitivity reported in the published studies (73–88%) [25, 30]. As already mentioned, the EANM–EAN consensus recommendation supported the use of [^{18}F]-FDG PET for the differential diagnosis between PSP and PD given the well-documented definition of a typical and recognizable metabolic pattern of hypometabolism in these two clinical entities [6]. This conclusion is also consistent with the diagnostic criteria for PSP recently proposed by the Movement Disorder Society [39].

Role of [^{18}F]-FDG PET in patients with CBS/CBD

Cortical basal syndrome is a neurological syndrome characterized by dystonia, rigidity, akinesia, myoclonus, tremor and poor response to levodopa. Typically, it is characterized by marked asymmetry, including limb apraxia and the alien limb phenomenon. Other symptoms include speech and language impairment and cognitive decline with frontal features [44–46]. CBS was once considered to reliably predict the presence of an underlying CBD. More recently autoptic studies have revealed a wide range of potential substrates for CBS including not only CBD but also AD, PSP, DLB, frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP) and prion disease. In particular, autoptic series have demonstrated that AD is the underlying etiology in approximately 25% of patients and corticobasal pathology is found only in about 50% of all clinically diagnosed patients [47–51]. Accordingly, the term CBS now describes a clinical phenotype which has been shown to have a heterogeneous underlying pathology. Patients with CBS due to AD (CBS-AD) tend to show greater episodic memory loss and visuospatial deficits, whereas CBS patients due to FTLD pathology (CBS-FTLD) show more behavioral changes, executive dysfunction, non-fluent aphasia and orobuccal apraxia [50, 52–54]. Moreover CBS-AD generally have a significantly longer disease duration, a more marked memory and visuospatial impairment, dressing apraxia, myoclonus and hemisensory neglect compared to CBS-CBD. Conversely, CBS-CBD cases are expected to show more marked rigidity compared to CBS-AD. However, despite these expected different clinical features, specificity and sensitivity of clinical diagnosis of CBS/CBD are remarkably low and a neuroimaging tool has been proposed to improve accuracy of clinical diagnosis. Patterns of asymmetric frontoparietal brain atrophy at structural MRI and hypometabolism at [^{18}F]-FDG PET have been associated with both CBS and in particular by CBD pathology [55, 56]. In particular, an autoptic study carried out by Whitwell et al. demonstrated that focal patterns of atrophy on MRI could be useful to help predict underlying pathology in CBS [53]. In fact in 24 patients with CBS who had undergone MRI during life and came to autopsy, they highlighted that all CBS pathologic groups have gray matter loss in premotor cortices, supplemental motor area, and insula on imaging. However, CBS–FTLD showed significantly greater loss in prefrontal cortex than the other groups, whereas CBS–AD showed significantly greater loss in temporoparietal lobe than the other groups. The focus of loss was similar in CBS–CBD

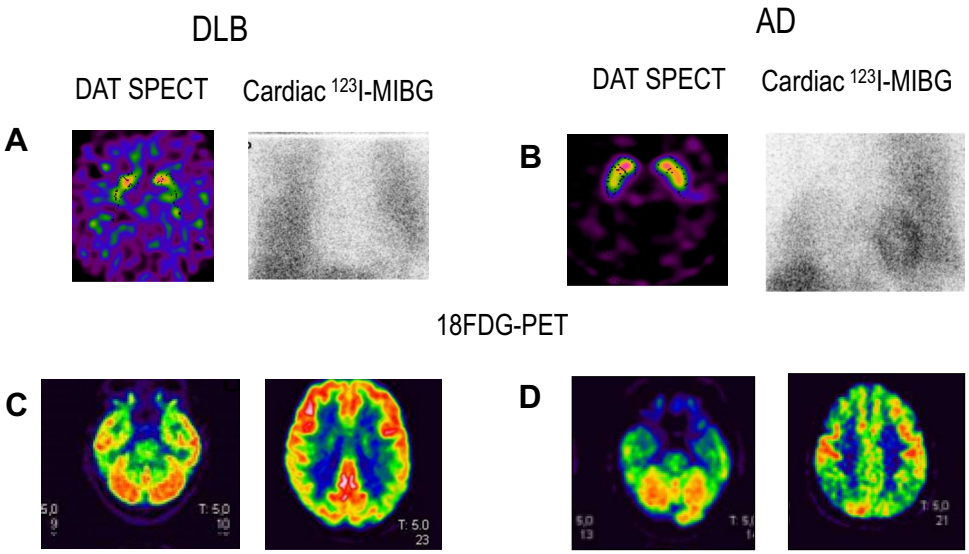

Fig. 2 Molecular imaging biomarkers in patients with dementia with Lewy bodies (DLB) with respect to Alzheimer's disease (AD) patients. DAT SPECT and ^{123}I-MIBG ardiac imaging are both characterized by reduced tracer uptake in DLB patients (**a**) while normal findings are expected in patients with AD (**b**). Both DAT SPECT and ^{123}I-MIBG ardiac imaging area classified as indicative biomarkers according to the revised Mckeith riteria for the diagnosis of DLB [54]. ^{18}F-FDG PET is a supportive biomarker in DLB patients. It typically shows lateral temporal and posterior parietal hypometabolism with a prominent involvement of lateral and mesial occipital hypometabolism, associated with the so-called posterior cingulate (PCC) island sign (CIS) corresponding to the presence of hypometabolism in the precuneus with a relatively spared metabolism in PCC (C). Metabolism at medial temporal lobes level (MTL) is also relatively spared with respect to AD patients showing the same level of cognitive impairment. AD patients are characterized by temporoparietal hypometabolism with more prominent reduction in MTL metabolism and hypometabolism involving both precuneus and PCC

and CBS–PSP, although more severe in CBS–CBD [53]. However, while both structural MRI and [^{18}F]-FDG PET are considered markers of neurodegeneration, it is well-known that in neurodegenerative diseases, synaptic degeneration precedes neuronal death for a substantial period of time [56]. According, the presence of features of CBS–CBD and of other pathological substrates of CBS should be earlier evident on [^{18}F]-FDG PET than on structural MRI [57]. The most frequent [^{18}F]-FDG PET features reported in patients with CBS is the presence of asymmetric hypometabolism in the parietal and frontal cortex, in the thalamus and in the ganglia contralateral to the most clinically affected body side [6]. The role of [^{18}F]-FDG PET in predicting underlying pathology in patients with CBS has been extensively discussed in the EAN/EANM joint recommendations. Several studies carried out with proper methodology and including critical outcomes were revised by the panelists [30, 58–67]. Given the different possible pathological substrates of CBS, a critical feature that can be also assessed in vivo is the presence/absence of amyloid pathology. Accordingly, some authors used amyloid PET as a reference standard for clinical diagnosis and tested the ability of [^{18}F]-FDG PET to predict AD pathology in CBS patients [60, 61]. Sensitivity ranged from 91 to 95%, specificity from 58 to 75% and accuracy from 73 to 82% [6]. [^{18}F]-FDG PET demonstrated a higher sensitivity (about 90%) to predict amyloid positive status with respect to MRI [60, 61]. In particular, the combination of the CBD-specific clinical criteria with 18F-FDG PET produced the best global discrimination of patients with amyloid positive compared to CBD amyloid negative. Similarly, splitting CBS patients into frontal or temporoparietal clinical variants helped to predict the likelihood of underlying AD at single patient level [60]. This evidence is consistent with previous studies showing that [^{18}F]-FDG PET is useful in differentiating AD from FTLD [1].

The accuracy of the differential diagnosis between CBD and idiopathic Parkinson's disease (PD) or other atypical parkinsonisms was also addressed in previous studies and comments in the EAN/EANM recommendations [6]. In the differential diagnosis between CBS and other atypical parkinsonisms, [^{18}F]-FDG PET showed moderate-to-good sensitivity (81–91%) and very good specificity (91–100%) [30, 58–67]. However, Cordato et al. reported similar hypometabolic patterns in autopsy-confirmed CBD and PSP and other studies showed moderate sensitivity (76–79%) and heterogeneous specificity (69–92%) only for the differentiation between CBD and PSP [62]. Accordingly, the expert panel considered as "fair" the formal evidence supporting the clinical use of [^{18}F]-FDG PET in identifying the underlying neuropathology in CBS patients and supported the clinical use of [^{18}F]-FDG PET in this clinical setting [6]. After the

publication of the EANM/EAN consensus, an autoptic study evaluating the capability of [^{18}F]-FDG PET to predict (or at least to orient toward underlying pathology in CBS patients) was published by Pardini et al. [25]. They demonstrated that patients with CBS, different underling pathologies are associated with different patterns of hypometabolism. In particular thanks to a voxel-based approach, they highlighted a specific difference also between CBS–CBD and CBS–PSP by showing that patients with CBS–PSP have a more anterior hypometabolic pattern, including the medial frontal regions and the anterior cingulate [25]. Finally, in the same study a conjunction analysis revealed that the primary motor cortex is the only common area of hypometabolism in all groups, irrespective of pathologic diagnosis. This region thus reflects the presence of corticobasal syndrome but is not further useful for the differential diagnosis. In the next future, other direct or indirect biomarkers of pathological proteins depositions including TAU and amyloid PET can be used as gold standard to refine clinical and imaging criteria to predict underlying pathology in patients with CBS [68, 69].

Role of [^{18}F]-FDG PET in patients with possible or probable DLB

DLB is a dementing disorders characterized by the combination of attention fluctuations, visual hallucinations, REM sleep behavior disorder (RBD), and parkinsonism. Clinically, distinguishing DLB from other neurodegenerative diseases, in particular from AD, represents a diagnostic challenge and has relevant repercussion for patients' management and treatment [70].

The revised 2017 diagnostic criteria for DLB defined clinical features and diagnostic biomarkers and provide guidance about optimal methods to establish and interpret DLB biomarkers [70]. In particular, three indicative biomarkers have been identified, including reduced dopamine transporter uptake in basal ganglia as demonstrated by SPECT or PET, reduced uptake on ^{123}I-metaiodobenzylguanidine myocardial scintigraphy (MIBG), and polysomnographic confirmation of REM sleep without atonia [70].

DAT SPECT in particular has a long-standing role to support the differential diagnosis between DLB and AD which are characterized by reduced and normal uptake, respectively [70, 71]. However, it has been demonstrated that around 10% of DLB patients' area is characterized by a negative DAT SPECT at symptoms onset (becoming positive later on in the course of the disease) [72, 73]. This peculiar behavior was demonstrated to be due to more a predominantly limbic and neocortical LBD pathology load at presentation with only moderate neuronal loss in the substantia nigra [74]. The pattern of hypometabolism, as assessed by [^{18}F]-FDG PET and EEG slowing down were listed, by McKeith as supportive biomarkers helping the diagnostic evaluation but still lacking clearly confirmed diagnostic specificity[70]. Representative examples of molecular imaging findings in patients with DLB with respect to patients with AD are reported in Fig. 2.

The typical [^{18}F]-FDG PET pattern in patients with DLB is characterized by lateral temporal and posterior parietal hypometabolism with a prominent involvement of lateral and mesial occipital hypometabolism, associated with the so-called posterior cingulate (PCC) island sign (CIS) [7]. The CIS corresponds to the presence of hypometabolism in the precuneus with a relatively spared metabolism in PCC [75]. Hypometabolism in the dorsolateral frontal cortex (DLFC) can also be present in later stages [8, 75–77].

Previous studies have addressed the role of [^{18}F]-FDG PET to support the differential diagnosis between AD and DLB and found a 70–92% sensitivity range, 74–100% specificity range and 72–96% accuracy range [6, 7]. Studies reporting only hypometabolic patterns disclosed a partially overlapping profile in AD and DLB, except for a marked hypometabolism in the visual cortex in DLB and relative preservation of metabolism in the posterior cingulate cortex. The systematic revision of the literature performed within the EANM/EAN recommendations ranked as good the level of evidence for the use of [^{18}F]-FDG PET between DLB and AD patients [7]. Autoptic studies are also available [78]. These studies have confirmed the accuracy of the described hypometabolic pattern [78]. Other studies have also demonstrated higher accuracy of [^{18}F]-FDG PET with respect to MRI (which differentiates between AD and DLB thanks to less prominent atrophy in the medial temporal lobe in DLB patients with respect to AD) [78–80]. For all these reasons the expert opinion that emerged from the EAN/EANM recommendations supported the use of [^{18}F]-FDG PET for discriminating DLB and AD [7]. Very recently, after the publication of the recommendations, larger databases of DLB patients have been made available and further lines of evidence have supported the use of [^{18}F]-FDG PET in this settings. In a study carried out by the European DLB consortium on 171 DLB patients examined with [^{18}F]-FDG PET, brain regions whose metabolic impairment contributes to DLB clinical core features expression were specifically investigated [65]. Thanks to a principal component analysis (PCA) approach, Morbelli et al. demonstrated that the presence of parkinsonism and visual hallucinations negatively covaries with bilateral parietal cortex, precuneus, and anterior cingulate metabolism and with bilateral dorsolateral-frontal cortex, posterior cingulate, and parietal metabolism respectively [26]. By contrast, the presence of rapid eye movement sleep behavior disorders (RBD) was associated with hypometabolism in bilateral parietooccipital cortex, precuneus, and ventrolateral-frontal metabolism and cognitive fluctuations was associated with reduced occipital

metabolism. In the same study the influence of severity of global cognitive impairment on the DLB hypometabolic pattern (as measured with MMSE) was also investigated and it was demonstrated that the expression of the CIS is influenced by disease severity [26]. In fact this sign was less clearly evident in presence of a more marked MMSE reduction [26]. These findings nicely fit with another study in a relatively large population of DLB patients carried out by Caminiti et al. [15]. This latter study provided an extensive validation for [^{18}F]-FDG PET metabolic signatures by supporting DLB diagnosis close to first clinical assessment at single-subject level and by showing high power of the [^{18}F]-FDG hypometabolic signature in predicting the final clinical diagnosis. [^{18}F]-FDG PET allowed a 50% increase in accuracy compared to the first clinical assessment alone and allowing a high discriminative power, distinguishing DLB from AD [15].

Conclusion

In conclusion, a large body of literature has suggested that [^{18}F]-FDG PET can provide advances in the clinical evaluation, differential diagnosis and understanding of the endophenotype of atypical parkinsonian syndromes associated with dementia. Although the complete validation of its use in the clinical setting can be further supported by prospective studies including critical outcome in large group of patients, the huge experience on [^{18}F]-FDG already available for neurodegenerative dementia can be easily translated in the setting of parkinsonian syndromes assisting neurologists in these complex clinical scenarios.

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Compliance with ethical standards

Conflict of interest SM received speaker honoraria from General Electric and Eli-Lilly. The other authors declare no conflict of interest.

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