18F-FDG PET in Parkinsonism:

Differential Diagnosis and Cognitive Impairment in Parkinson's disease

Running title: 18F-FDG PET in Parkinsonism

Philipp T. Meyer¹, Lars Frings¹,², Gerta Rücker³, and Sabine Hellwig⁴

¹Department of Nuclear Medicine, ²Center for Geriatrics and Gerontology Freiburg,
³Institute for Medical Biometry and Statistics, and ⁴Department of Psychiatry,
Medical Center – University of Freiburg, Faculty of Medicine,
University of Freiburg, Freiburg, Germany

Corresponding Author:
Philipp T. Meyer, MD, PhD
Department of Nuclear Medicine
Medical Center – University of Freiburg
Hugstetter Strasse 55
79106 Freiburg, Germany
Phone: +49-(0)761-270.39160
Fax: +49-(0)761-270.39300
Email: philipp.meyer@uniklinik-freiburg.de
ABSTRACT

Accurate differential diagnosis of parkinsonism is of paramount therapeutic and prognostic importance. In addition, with the development of invasive therapies and novel disease-specific therapies, strategies for patient enrichment in trial populations are of growing importance. Imaging disease-specific patterns of regional glucose metabolism with positron emission tomography and $[^{18}\text{F}]$fluoro-2-deoxy-2-D-glucose ($^{18}\text{F}$-FDG) allows for a highly accurate distinction between Parkinson’s disease (PD) and atypical parkinsonian syndromes (APS) including multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Based on a preliminary meta-analysis of currently available studies with inclusion of multiple disease groups, we estimated the diagnostic sensitivity and specificity for visual PET readings supported by voxel-based statistical analyses for diagnosis of APS to be 91.4% and 90.6%, respectively. Diagnostic specificity of $^{18}\text{F}$-FDG PET for diagnosing MSA, PSP and CBD was consistently shown to be high (>90%), whereas sensitivity was more variable (>75%). It is increasingly acknowledged that cognitive impairment represents a major challenge in PD, with mild cognitive impairment (PD-MCI) being a prodromal stage of PD with dementia (PDD). In line with clinical and neuropsychological studies, recent PET studies demonstrated that posterior cortical dysfunction in non-demented PD patients precedes cognitive decline and the development of PDD by several years. Taken together, current literature underscores the utility of $^{18}\text{F}$-FDG PET for diagnostic evaluation of parkinsonism and its promising role for assessment and risk stratification of cognitive impairment in PD.

Key words: FDG PET; Parkinson’s disease, PD; multiple system atrophy, MSA; progressive supranuclear palsy, PSP; corticobasal degeneration, CBD; mild cognitive impairment, MCI; PD with dementia, PDD.
INTRODUCTION

Molecular neuroimaging using positron emission tomography (PET) allows for a quantitative visualization of functional and molecular processes in vivo. The most commonly used radiotracer is $[^{18}\text{F}]$fluoro-2-deoxy-2-D-glucose ($^{18}\text{F}$-FDG) for the assessment of regional cerebral glucose metabolism as a marker of neuronal function. By the virtue of disclosing disease-specific alterations due to synaptic dysfunction, neuronal degeneration and accompanying compensatory network changes, $^{18}\text{F}$-FDG PET has become an essential part in the diagnostic work-up of patients with neurodegenerative disorders, most notably dementia. Although disease-specific patterns of regional glucose metabolism in patients with parkinsonism are known since the early days of PET imaging (e.g., (1-3)), the valuable role of $^{18}\text{F}$-FDG PET for differential diagnosis of parkinsonism has been increasingly acknowledged only in recent years. This interest was prompted by several promising studies from different research groups worldwide, particularly of the group from the Feinstein Institute (Manhasset, NY) (see Table 1).

Against this background, this clinically oriented review on the use of $^{18}\text{F}$-FDG PET in neurodegenerative parkinsonism provides the clinical practitioner with an update on

I. the clinical demand and rationale for $^{18}\text{F}$-FDG PET imaging in parkinsonism,

II. typical $^{18}\text{F}$-FDG PET patterns and their value for differential diagnosis of parkinsonism (including a preliminary meta-analysis of recent studies), and

III. the promising role of $^{18}\text{F}$-FDG PET for diagnostic assessment and risk stratification in cognitive impairment in Parkinson’s disease (PD), as an outlook.
CLINICAL DEMAND AND RATIONAL FOR $^{18}$F-FDG PET IMAGING IN PARKINSONISM

Parkinson’s Disease

The clinical diagnosis of PD, as the most common neurodegenerative cause of parkinsonism, relies on the presence of the cardinal motor manifestations bradykinesia, resting tremor and rigidity. Clear response to dopaminergic therapy and the presence of either olfactory loss or cardiac sympathetic denervation are supportive criteria (4). Moreover, diagnosis of clinically established PD requires absence of features of atypical parkinsonian syndromes (APS; see below).

The histopathological hallmark of PD is the so-called Lewy-pathology (i.e., alpha-synuclein immunoreactive neuronal inclusions) (5). Intracerebral Lewy-pathology starts at clearly defined induction sites and advances in a topographically predictable sequence affecting brain stem, subcortical nuclei and neocortex (6). Consequently, loss of nigrostriatal dopaminergic projection neurons of the substantia nigra pars compacta (SNpc) (5) is primarily responsible for the development of typical motor symptoms. Cortical spread of Lewy pathology in addition to concomitant, possibly synergistic pathologies (e.g., Alzheimer type pathology) and distant effects via disruption of modulatory projections from noradrenergic, serotonergic, dopaminergic and cholinergic brainstem and basal forebrain nuclei contributes to cognitive decline, ranging from PD with mild cognitive impairment (PD-MCI) to PD with dementia (PDD) (7). Although controversial, clinicians distinguish dementia with Lewy bodies (DLB) from PDD depending on the so-called 1-year-rule (i.e., the diagnosis is PDD if the onset of dementia occurs more than 1 years after the onset of parkinsonism) (8). The continuum of PD, PDD and DLB is often referred to as the spectrum of Lewy body disease (LBD) (9).
Atypical Parkinsonian Syndromes

The APS comprise multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), which are a heterogeneous group of neurodegenerative disorders characterized by levodopa-refractory parkinsonism and distinctive atypical clinical features (10). In case of MSA progressive autonomic failure, parkinsonian, cerebellar and pyramidal features are observed in various combinations. It is classified as parkinsonian subtype (MSA-P) if parkinsonism is the most prominent feature and as cerebellar subtype (MSA-C) if cerebellar ataxia predominates (11). MSA is defined as a primary oligodendroglial alpha-synucleinopathy with consecutive neuronal degeneration (11). MSA pathology most severely affects the substantia nigra, caudate and putamen, cerebellar white matter, pontine and inferior olivary nuclei and the medullary tegmentum (12).

The 4-repeat tauopathies PSP and CBD may be considered to represent different manifestations of a disease spectrum with several common clinical, pathological, genetic and biochemical features (13). In case of PSP, recent Movement Disorder Society clinical diagnostic criteria for PSP (MDS-PSP criteria) propose the four core functional domains ocular motor dysfunction, postural instability, akinesia, and cognitive dysfunction as characteristic clinical manifestations (14). Several clinical PSP presentations have been defined, with the combination of early onset postural instability and falls with vertical ocular motor dysfunction representing the most frequent presentation (so-called Richardson's syndrome, PSP-RS). Of particular relevance for the present context are also PSP presentations with prominent parkinsonism (PSP-P) resembling PD (possibly including tremor and response to levodopa) and a corticobasal syndrome (CBS, see below; PSP-CBS) (14). PSP is histopathologically defined by intracerebral aggregation of the microtubule-associated protein tau, predominantly involving isoforms with four microtubule-binding repeats (4R-tau), in neurofibrillary tangles, oligodendrocytic coils, and, specifically, astrocytic tufts (14). Albeit heterogeneity in the distribution of tau pathology in PSP has to be recognized (reflecting clinical diversity), globus pallidus, subthalamic nucleus and
substantia nigra are consistently the regions being most severely affected, while less tau immunoreactivity is detected in the posterior frontal cortex (15).

Based on autopsy-confirmed cases, four clinical phenotypes associated with pathology of CBD have been proposed (16). The CBS phenotype, as the most frequent, prototypical variant, is characterized by asymmetric presentation of limb rigidity or akinesia, limb dystonia, or myoclonus, oro-buccal or limb apraxia, cortical sensory deficit or alien limb phenomenon (16). Like PSP, CBD may also cause a frontal behavioral syndrome, primary progressive aphasia and even a PSP-like syndrome. CBD is also characterized by widespread deposition of hyperphosphorylated 4-repeat tau in neurons and glia, the latter as astrocytic plaques. Strategic regions severely affected by CBD are superior frontal gyrus, motor cortex and SN (5).

Treatment & Prognosis

Clinicopathological studies suggest that the clinical diagnosis of PD is inaccurate in about 20-25% of patients (17,18). APS are frequently misdiagnosed as PD. Even at advanced stages, when patients present with distinctive clinical features, a relevant fraction of patients with MSA and PSP (about 30%) and, particularly, CBD (up to 74%) receive an incorrect diagnosis (19). The limited accuracy represents a major obstacle for treatment selection and reliable prognostic counselling: For PD, functional reconstitution of the dopaminergic nigrostriatal pathway is essential. Dopaminergic drugs alleviate both, motor and (to some extent) non-motor symptoms and improve quality of life (20). Trials investigating possible neuroprotective agents have supported, although not proven, disease-modifying effects of dopaminergics in PD (21). Given that common side effects (i.e. psychosis, orthostatic hypotension, gastrointestinal disorders) may substantially compromise the clinical condition, reliable treatment-predictive biomarkers and diagnoses are desirable. Moreover, unnecessary treatment costs need to be avoided. For the management of advanced PD (when intractable levodopa-induced motor complications develop) invasive techniques including deep brain stimulation, stereotactic neurosurgery and other ablative treatments, and subcutaneous apomorphine therapy or intraduodenal levodopa infusion
are available (22,23). Experimental therapies have tried to restore striatal dopamine in PD patients by gene-based and cell-based approaches. Aside from ethical considerations and logistic challenges, data concerning the use of human fetal ventral mesencephalic allografts in PD are controversial (for review see (24,25)).

The focus of current drug therapy in APS is still primarily on alleviating disease symptoms, which is often ineffective (10). Available data on interventional therapies in APS is sparse: Small case series highlight the risk of clinical worsening after deep brain stimulation in histologically proven MSA patients and strongly discourage its use (26). In line with this, another case report revealed a rapid postoperative deterioration of a patient diagnosed post mortem as CBD, who received a thalamotomy (27). At present, no effective treatment exists to delay disease progression in APS. In turn, disease-modifying trials with rasagiline and rifampicin in MSA or tideglusib and davunetide in PSP yielded negative results (for review see (10)). Strategies to enhance trial success have been proposed such as enrichment-design for novel disease-specific molecularly targeted therapeutics or identification of preclinical stages of parkinsonism allowing for primary prevention and early disease-modifying trials. Most recently, several immunotherapeutic approaches to modify clearance, aggregation and transport of alpha-synuclein (for review see (28)) and tau (for review see (29)) have been explored.

Survival in PD is distinctly better compared to APS: While some population-based studies did not find higher mortality (e.g., (30), others convincingly demonstrated an increased age-adjusted mortality in PD (e.g., (31)). Higher age at onset, as in APS, is also associated with a higher PD mortality (reviewed in (32)), but median survival was still 10.3 years in a recent population-based cohort with a high average age of 70 years at diagnosis (30). However, development of PDD is associated with a strong increase in mortality (33). In fact, the mean time span between onset of dementia and death appears to be only about 2-4 years (33,34). APS are characterized by the early presence of additional debilitating symptoms and a more rapid progression to death compared to PD (10). According to clinicopathological studies APS share a
comparably short survival of about 7-8 years from symptom onset or less than 3-4 years from typically somewhat delayed clinical diagnosis (reviewed in (32)).

Taken together, accurate diagnosis of the underlying cause of parkinsonism is requested for decisions on treatment strategies (including invasive techniques), inclusion into therapy trials (e.g., enrichment of patient populations for novel therapies), and prognostic statements.

DIFFERENTIAL DIAGNOSIS OF PARKINSONISM

In the opinion of the authors and as practiced by many centers, $^{18}$F-FDG-PET may be used for differential diagnosis of parkinsonism when there is substantial uncertainty regarding the underlying cause of parkinsonism after comprehensive evaluation by a movement disorder specialist and when the result of the examination is expected to alter patient management (e.g., ordering further diagnostic tests, medication and other treatments, patient counselling). This view is strengthened by a larger prospective study supporting Level I American Academy of Neurology Level of Evidence for $^{18}$F-FDG-PET as a test of APS differential diagnosis ((35); see also editorial comment (36)) and the present meta-analysis (see below).

Preceding diagnostic work-up usually includes MRI, which may provide valuable diagnostic findings in secondary parkinsonism (e.g., vascular parkinsonism) and in APS with relatively high specificity but low sensitivity (particularly in early disease stages) (37). In our experience, it is neither necessary nor effective in terms of costs and radiation burden to verify a neurodegenerative cause of parkinsonism by imaging nigrostriatal integrity (e.g., $^{123}$I-FP-CIT SPECT) always beforehand, because an $^{18}$F-FDG PET scan in patients with suspected APS often provides very typical findings that render additional imaging of nigrostriatal integrity dispensable. Concerning the technical aspects of $^{18}$F-FDG PET brain imaging (e.g., patient preparation, data acquisition, image interpretation), we refer to the respective procedure guidelines (38,39).
Disease-specific Patterns of Regional Glucose Metabolism

Disease-specific patterns of altered cerebral glucose metabolism used for differential diagnosis of PD and APS subgroups (e.g., (35, 40-42)) are schematically illustrated in Fig. 1. Furthermore, transaxial $^{18}$F-FDG PET images and outputs of currently used image analysis methods are depicted in Fig. 2:

Scans in PD patients often show no major abnormality at first glance. On closer inspection and especially on voxel-based statistical analyses, PD is characterized by a posterior temporoparietal, occipital and sometimes frontal hypometabolism (especially in PD with cognitive impairment, see below) and relative hypermetabolism of putamen, pallidum, thalamus sensorimotor cortex, pons and cerebellum.

Conversely, MSA patients show a marked hypometabolism of (posterior) putamen, pons and cerebellum, which may be more pronounced in striatum or in pons and cerebellum, depending on the predominant side of degeneration and, thus, clinical presentation (striatonigral/MSA-P and olivopontocerebellar/MSA-C, respectively) (43). Of note, an isolated cerebellar hypometabolism may also occur in other causes of cerebellar degeneration (e.g., paraneoplastic or spinocerebellar ataxia). Group analyses demonstrated also a frontal hypometabolism that may spread to parietal and temporal areas simultaneously with the onset of cognitive impairment (44). The latter finding, however, is less apparent in individual analyses and of little help for differential diagnosis by $^{18}$F-FDG PET.

In case of PSP, regional hypometabolism is consistently noted in medial, dorsal and ventrolateral frontal areas (i.e., anterior cingulate gyrus, supplementary motor area (SMA), precentral gyrus, premotor to posterior prefrontal areas), caudate, thalamus and upper brain stem. These findings have also been confirmed in a recent study with post mortem verification (45). Of note, recently proposed MDS-PSP criteria set a framework to diagnose several PSP predominance types (14), which can be expected to also differ on $^{18}$F-FDG PET. For example,
aforementioned functional domains have been linked to predominant regional hypometabolism of bilateral anterior cingulate gyrus (vertical gaze palsy; (46)), thalamus (repeated unprovoked falls; (47)), midbrain (gait freezing; (48)) and left medial and dorsolateral frontal lobe (non-fluent aphasia; (49)).

Finally, CBD is characterized by a usually highly asymmetric hypometabolism of frontoparietal areas, striatum and thalamus contralateral to the most affected body side. Cortical hypometabolism may be pronounced in parietal cortex and usually extends across the sensorimotor cortex into the cingulate gyrus and premotor to posterior prefrontal areas.

Of note, a CBS may also be caused by several other diseases aside from CBD, e.g. most notably including Alzheimer’s disease and PSP. Consequently, the clinical diagnosis CBD is notoriously inaccurate: Only about 25-50% of patients with a CBS suffer from CBD on post mortem examination, whereas only 25-30% of patients with neuropathologically verified CBD present with a CBS (19,50). Likewise, imaging results in patients with clinically diagnosed PSP and CBD may be very similar. In direct comparison of clinically defined patient groups, PSP patients showed a lower metabolism in midbrain, thalamus and cingulate gyrus, while CBD patients revealed a more pronounced and asymmetric hypometabolism in parietal and sensorimotor cortex and striatum (51-54). According to recent studies with support by post mortem data, parietal involvement and the asymmetry of aforementioned frontoparietal hypometabolism appears to be most characteristic of CBD (45,55). However, asymmetric hypometabolism on 18F-FDG PET may also be encountered in PSP (see example in Fig. 2), with an asymmetric PSP presentation being related to an asymmetric metabolism in motor cortex, cingulate gyrus and thalamus (51). Finally, a recent study suggests that more prominent temporoparietal than frontal hypometabolism points towards an underlying Alzheimer pathology in patients with CBS, as confirmed by amyloid PET and pathology in roughly two thirds of these cases (56).
The aforementioned results were mostly gained from categorical comparisons. However, they fit the results gained from spatial covariance analyses, which were employed to detect abnormal metabolic networks in PD, MSA, PSP and CBD. These disease-related patterns (i.e., PDRP, MSARP, PSPRP, and CBDRP, respectively) (Fig. 3) were demonstrated to be highly reproducible, to correlate with disease severity and duration (albeit to variable extent in PD, MSA and PSP), and to allow for prospective discrimination between cohorts (55,57-59); for a recent review see (60). Furthermore, these patterns were confirmed by several independent groups relying on different patient populations and equipment (e.g., (61-63)). PDRP expression inversely correlates with striatal dopaminergic integrity (as assessed by $^{18}$F-FDOPA PET) (64) and is already significantly increased in the ipsilateral (“presymptomatic”) hemisphere of patients with hemi-parkinsonism (65). Likewise, recent studies demonstrated that PDRP expression is also increased in rapid-eye-movement sleep behavior disorder (66,67), being a significant predictor of phenoconversion to PD or DLB (assessed with perfusion SPECT; (66)). In parallel to respective metabolic changes (i.e., decrease in putamen/pallidum, sensorimotor cortex and cerebellum, increase in precuneus) and symptom improvement, PDRP expression was also found to decline with levodopa administration and deep brain stimulation of the subthalamic nucleus in PD (e.g., (68)). Thus, covariance patterns of cerebral glucose metabolism represent very interesting, observer-independent biomarkers for (early) diagnosis and therapy monitoring.

**Diagnostic Value – Preliminary Meta-Analysis**

Several larger, in part prospective studies investigated the applicability of $^{18}$F-FDG-PET for the differential diagnosis of parkinsonism. Given the paucity of disease-specific treatments in APS subtypes, the distinction PD vs. APS (as an umbrella diagnosis) is of major therapeutic and prognostic relevance. To better characterize the value of $^{18}$F-FDG PET for diagnosis of APS (as target condition, i.e., positive case; opposed to PD) and to compare the analysis methods employed so far, we conducted a preliminary meta-analysis (see Supplement).
Table 1 summarized the results of currently available studies and the resulting meta-analysis. PET image analyses can be divided into two major approaches (see also Fig. 2; for a recent review of image analysis methods see for instance (69)): Five studies (35,40,41,70,71) employed observer-dependent visual reads supported by voxel-bases statistical analyses in comparison to healthy control subjects (done by statistical parametric mapping, SPM, (http://www.fil.ion.ucl.ac.uk/spm/) or Neurostat/3D-SSP (72). Three studies employed observer-independent automated statistical classifications of patients with parkinsonism that used logistic regression based on the expression of metabolic covariance patterns (see above) (42,73) or a relevance vector machine in combination with bootstrap resampling for non-hierarchical multiclass classification (74).

Most studies found a very high accuracy (>90%) of 18F-FDG-PET for the distinction between APS and PD. Fig. 4 gives the summary ROC curves for the two analysis approaches employed. The estimated pooled sensitivity of observer-dependent visual reads supported by voxel-based statistical analyses is significantly higher than the pooled sensitivity of observer-independent automated classifications (91.4% vs. 76.5%; p < 0.01), while the pooled specificity was slightly, though not significantly higher for the automated analyses (94.7% vs. 90.6%; Table 1).

Various factors might influence the diagnostic performance of 18F-FDG PET. However, current studies support the robustness of the method:

Exploring the effect of disease duration on classification accuracy, Eckert et al. (2005) (40) showed that the agreement with the final clinical diagnosis was slightly higher for patients with early-stage PD (disease duration < 5 years) than those with late-stage PD (98% vs. 92%) when using SPM-supported readings, but not for visual readings alone (88% vs. 97%). No difference was observed for the distinction between PD and APS in the studies by Hellwig et al. (2012) (35) and Tripathi et al. (2016) (73) when stratifying by disease duration (area under the ROC curve ≥ 0.93), whereas diagnostic sensitivity was somewhat higher in patients with longer
disease duration (≥ 2 years) compared to those with a shorter disease duration in the study by Tang et al. (2010) (42) (APS: 87% vs. 72%; PD: 88% vs. 77%).

Interestingly, in the latter study diagnostic performance increased with longer clinical follow-up (≥ 2 years), which suggests that the apparent lower performance of imaging classification in patients with short follow-up (< 2 years) is probably caused by initial clinical uncertainty, not incorrect imaging diagnosis (42).

In the study by Hellwig et al. (2012) (35), 11 of 34 LBD patients received the final diagnosis PDD or DLB after follow-up. Exclusion of these patients did not affect the diagnostic performance of 18F-FDG PET (area under the AUC curve: 0.93 vs. 0.94, before and after exclusion of PDD/DLB, respectively).

Given the aforementioned effects of treatment on regional metabolism and metabolic network expression, it may be advisable to scan patients in OFF medication state. However, a study comparing diagnostic performance of the PDRP to distinguish between normal controls and PD patients in OFF and ON states showed no major impact (62), and the effect of medication on regional metabolism in patients with APS in unknown. Studies summarized in Table 1 were done under both conditions without apparent impact.

The notably higher sensitivity of observer-dependent visual reads supported by voxel-based statistical analyses may represent an advantage compared to observer-independent automated analyses. In turn, observer-dependence may be a disadvantage if expertise is limited. However, Eckert et al. (2005) (40) demonstrated that non-expert investigators using SPM-supported reads performed superior (92% accuracy) to experts using visual reads alone (85%), while two experts performed comparable with (91%) and without (92%) using SPM-supported reads in the study by Tripathi et al. (2013) (71). Since Neurostat/3D-SSP does not cover the striatum, SPM might be preferable, especially if reads are performed by non-experts. A limitation of the current automated method based on disease-specific network expression are
the cases classified as “indeterminate parkinsonism”, which accounted for 14% and 19% of patients (42,73). This issue seems to limit sensitivity for early APS (73) and may also become more relevant if patients with severe structural abnormalities or alternative diagnosis are included.

Aside from multiclass relevance vector machine analysis (74), specificity of the PET diagnoses of APS subgroups MSA, PSP and CBD usually exceeded 90% (as requested for a confirmatory test), while sensitivity was 77% - 96% for MSA, 74% - 100% for PSP, and 75% - 91% for CBD (35,40-42,70,71,73). Such subgroup classifications will be important for patient enrichment in future trials with disease- or pathology-specific treatments. However, given the clinical and imaging ambiguity in case of PSP and CBD, it may be advisable to use a combined PSP/CBD tauopathy category for PET readings, which reaches a sensitivity and specificity of 87% and 100% (35).

Finally, a recent study investigated the prognostic value of 18F-FDG PET in parkinsonism. Employing a follow-up up to 6 years (median survival duration: PD, not reached; APS, 4.1 years after PET), risk stratification concerning overall survival yielded by PET was at least as good as that provided by the clinical diagnosis filed 1 year after PET (age-adjusted hazard ratios relative to PD for PET: PSP/CBD 5.2, MSA 5.6; for clinical diagnosis: PSP/CBD 4.5, MSA not significant) (32). This study highlighted for the first time the prognostic relevance of 18F-FDG PET which is of particular importance not only for the patients but also their relatives and caregivers.

OUTLOOK: COGNITIVE IMPAIRMENT IN PARKINSON’S DISEASE

Cognitive Impairment in PD

The onset of cognitive impairment in PD per definition (see above) follows the onset of motor symptoms (8), and the diagnosis of both PDD and PD-MCI require an established PD diagnosis (75,76). Cognitive impairment is frequent in PD, with up to 80% of all patients with PD
developing dementia over the long term (77,78). The putative prodromal stage of PDD, PD-MCI (requiring functional independence in contrast to PDD, where activities of daily living are impaired), is common in non-demented patients with PD (cross-sectional prevalence of 27%; (79)). In a population-based study, 20% of incident PD cases had PD-MCI, and another 20% developed PD-MCI over the 5-year study period; PD-MCI was a major risk factor for PDD, with annual conversion rates of 13% (79), which is similar to the rate of conversion of MCI (without PD) to Alzheimer's dementia (80). However, a significant proportion of PD-MCI patients also reverted to normal cognition in that study (25% over 5 years; (79)).

The spatial distribution of Lewy-related pathology contributes to the type of predominant cognitive deficit in a given patient, and the most affected cognitive domains in PD are executive, visuospatial, attention, and memory functions (76, 81). The diagnosis of PD-MCI requires objective cognitive impairment, at least on a scale of global cognitive abilities (level 1, (76)). However, greater diagnostic certainty and sensitivity is achieved with at least 2 neuropsychological tests probing each of the four cognitive domains mentioned above plus the language domain (level 2, (76)). While the current PD-MCI diagnostic criteria recommend formal neuropsychological testing across a range of cognitive domains, it might be especially efficient to focus on visuospatial abilities or semantic fluency: There is emerging evidence for a dual cognitive syndrome in PD (82, 83), a frontostriatal (FS) syndrome and a posterior cortical syndrome (PCS). These syndromes are presumably independent, but they frequently co-occur. Cognitive deficits of the FS syndrome are typically found in phonemic verbal fluency and other executive functions, like flexibility or planning abilities. By contrast, figure drawing, but also semantic verbal fluency or episodic memory, occur as part of the PCS. Importantly, the risk for developing dementia is not associated with the FS, but significantly increased in the presence of the PCS (83), thereby exhibiting special prognostic value. Whereas disturbance of the dopaminergic transmitter system (due to degeneration of the substantia nigra pars compacta) presumably underlies the FS syndrome, altered cholinergic transmission (due to degeneration of
the Nucleus basalis of Meynert) is primarily associated with the PCS (81). Consistently, a recent meta-analysis provided strongest evidence for efficacy of acetylcholinesterase inhibitors (donepezil, rivastigmine) in the treatment of cognitive (and psychiatric) symptoms in PDD/DLB (84).

Because of the high prevalence and clinical importance of cognitive impairment in PD valid biomarkers for risk stratification are wanted.

**18F-FDG PET Imaging of Cognitive Impairment in PD**

Interestingly, cortical hypometabolism, particularly in posterior temporoparietal and occipital areas, is frequently observed in non-demented PD patients (Figs. 1 and 2). These changes often match the changes seen in PDD and also DLB, thus raising the question if they predict cognitive decline in PD.

Both PDD and DLB are characterized by a widespread lateral frontal and temporoparietal hypometabolism in addition to an occipital hypometabolism which distinguishes PDD and DLB from Alzheimer’s dementia (e.g., (85, 86)). In turn, metabolic differences between PDD and DLB appear to be subtle, if any (87). The widespread involvement of cortical and subcortical areas in LBD was also demonstrated by studies showing an extensive positive correlation between mini-mental status examination and regional glucose metabolism in lateral parietal, occipital, temporal and frontal association cortices, anterior cingulate, precuneus and caudate nucleus across the spectrum of PD to PDD (88, 89).

Consequently, spatial covariance analyses were found to be sensitive enough to identify a PD-related cognitive pattern (PDCP) even in non-demented patients, which is characterized by metabolic decreases in rostral SMA, dorsal premotor area, prefrontal cortex, precuneus and parietal cortex, and increases in cerebellar vermis and dentate nucleus (90). PDCP was demonstrated to be reproducible across institutions and patient populations (minor differences, e.g., regarding caudate nucleus and anterior cingulate, may stem from different tests), to
correlate with executive and memory performance and to be increased in PD-MCI compared to cognitively unimpaired PD patients (90-92). Despite its spatial overlap with the PDRP, PDCP is orthogonal to PDRP and does not correlate with severity of motor impairment (90,93). Expression of the PDCP seems to correlate with nigrostriatal dopaminergic dysfunction of the caudate nucleus (64,94) and with levodopa-induced improvement in verbal learning in a subgroup of PD patients without dementia (95). Thus, assessing PDCP expression may be a valuable tool for objectifying and monitoring cognitive dysfunction in PD. Future studies also need to explore the predictive value of PDCP expression for cognitive decline in PD-MCI in comparison to more specific posterior cortical measures, given the particular prognostic value of the PCS.

Results of several longitudinal studies investigating cognitive decline and regional metabolism in PD have recently become available: In a seminal work, Bohnen et al. (2011) (96) demonstrated that conversion from PD to PDD was heralded by significant hypometabolism in posterior cingulate, occipital cortex (Brodmann area 18/19) and caudate nucleus. Primary visual cortex (Brodmann area 17) hypometabolism was also observed in cognitively stable PD patients. Metabolic decline was widespread in converters on 2-year follow-up PET, involving the association cortices, posterior cingulate, hippocampus and thalamus. Subsequent studies in non-demented PD patients confirmed these results, showing that hypometabolism in bilateral precuneus and lateral posterior temporoparietal and occipital regions at baseline predicted cognitive decline in the following three years (97-99). These findings also agree with earlier cross-sectional studies (e.g., (87,100)).

PET studies in PD patients with MCI support the notion that PD-MCI represents a prodromal stage of PDD, especially in those with posterior cortical hypometabolism: Patients with MCI typically exhibit decreased temporoparietal, occipital, precuneus and frontal metabolism when compared to healthy controls and, to a lesser extent, to PD patients without MCI (88,91,98,101,102). These changes were more pronounced in multi-domain compared to
single-domain MCI (91,102). Of note, recent studies, employing the current diagnostic criteria for PD-MCI, demonstrated that the overall pattern of hypometabolism gradually develops from smaller clusters of mainly parietal and occipital, sometimes frontal hypometabolism in cognitively normal PD, over more widespread parietal, occipital, frontal and, to a lesser extent, (posterior) temporal clusters in PD-MCI to extensive parietal, occipital, frontal and temporal hypometabolism in PDD (88,98,103). Interestingly, hypometabolism on \(^{18}\)F-FDG PET preceded spatially matching atrophic changes on MRI (103). Across the entire group of PD, PD-MCI and PDD patients, regional glucose metabolism correlated with memory and visuospatial functions in posterior temporal and parietal regions and with attentional, executive and language functions also in frontal regions (88,98). Several additional clinical observations also support the strong negative prognostic value of posterior cortical hypometabolism: Recent longitudinal studies demonstrated that visual hallucinations and hyposmia, which all coincided with a marked temporoparietal and occipital hypometabolism in PD (with or without MCI), were associated with an increased conversion to PDD (104,105). Likewise, PD patients with rapid-eye-movement sleep behavior disorder showed lower cognitive performance, a higher likelihood of MCI and posterior cortical hypometabolism compared to PD patient without (106). Finally, the aforementioned long-term follow-up study found that patients with posterior cortical hypometabolism exhibited a twice as high mortality risk than PD patients without such a pattern (32).

Taken together, the nuclear medicine practitioner should be aware of the importance of posterior cortical hypometabolism. Although it is probably premature to propose it as a clinically used predictor of cognitive decline in PD, it may prompt further examinations and special consideration under specific circumstances (e.g., counselling of patients with PD-MCI or before initiating invasive therapies like deep brain stimulation).
CONCLUSION

\(^{18}\text{F}-\text{FDG PET allows for an accurate differentiation between PD and APS, which is of paramount therapeutic and prognostic importance. Furthermore, }^{18}\text{F}-\text{FDG PET provides a highly specific differential diagnosis between the APS subtypes MSA, PSP and CBD. However, given the limited accuracy of the clinical diagnosis as reference standard, future studies with post mortem verification are needed for validation of diagnostic imaging pattern, particularly in tauopathies.}

Current \(^{18}\text{F}-\text{FDG PET studies strongly support the concept that PD-MCI represents a prodromal stage of PDD. These studies underline that posterior cortical hypometabolism in non-demented PD patients is not only a diagnostically useful epiphenomenon but a negative prognostic marker. Future prospective studies are needed to confirm the prognostic value of }^{18}\text{F}-\text{FDG PET.}\)
ABBREVIATIONS

PD, Parkinson’s disease

PD-MCI, PD with mild cognitive impairment

PDD, PD with dementia

DLB, dementia with Lewy bodies

LBD, Lewy body diseases (comprising PD, PD-MCI, PDD and DLB)

MSA, multiple system atrophy

MSA-P, MSA with parkinsonism

MSA-C, MSA with cerebellar symptoms

PSP, progressive supranuclear palsy

CBD, corticobasal degeneration

CBS, corticobasal syndrome

APS, atypical parkinsonian syndrome (comprising MSA, PSP and CBD)

\(^{18}\text{F-FDG, }[^{18}\text{F}]\text{fluoro-2-deoxy-2-D-glucose}\)

PET, positon emission tomography

SPECT, single-photon emission computed tomography

MRI, magnetic resonance tomography

SPM, statistical parametric mapping

ROC, receiver operating characteristics curve

PDRP, PD-related pattern

PDCR, PD-related cognitive pattern

MSARP, MSA-related pattern

PSPRP, PSP-related pattern

CBDRP, CBD-related pattern
REFERENCES


FIGURES & LEGENDS

**FIGURE 1:** Summary and schematic illustration of typical clinical findings and disease-specific metabolic patterns yielded by $^{18}$F-FDG PET in parkinsonism.

Green, regions with relative hypermetabolism; red, regions with hypometabolism; orange, possible metabolic decreases in Parkinson’s disease (PD; especially in patients with cognitive impairment); MSA, multiple system atrophy; PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; shown are lateral (left) and medial (right) views of the brain; please note that hypometabolism in CBD is usually markedly asymmetric with lower metabolism contralateral to the clinically more affected body side; INC, increase; DEC, decrease; for detailed information see text.
FIGURE 2: Typical $^{18}$F-FDG PET findings in individual patients with parkinsonism as depicted by currently used image analysis methods.

Left panel, spatially normalized transaxial $^{18}$F-FDG PET cross-sections at levels of the cerebellum, basal ganglia and dorsal frontoparietal cortex, datasets were threshold for optimal display;

left middle panel, individual results of a voxel-wise statistical analysis with Neurostat/3D-SSP, given are lateral and medial views of the brain, metabolic deficits compared to age-matched normal control subjects are color-coded as Z scores;
right middle panel, individual results of a voxel-wise statistical analysis with statistical parametric mapping (SPM), given are t-maps in comparison to age-matched normal control subjects overlaid onto the SPM MRI template, metabolic decreases (blue color-scale) and increases (hot metal color-scale) were thresholded at a voxel-wise p-level < 0.01 and a cluster extent > 50 voxels.

right panel, Z score values (relative to healthy controls) of metabolic covariance network expression for the PD-related pattern (PDRP), MSA-related pattern (MSARP), PSP-related pattern (PSPRP) and CBD-related pattern (CBDRP); note that the network showing the highest expression (encircled) always matched the reference diagnosis; the expression scores for the PD-related cognitive pattern were 0.7 in the patient with PD Hoehn & Yahr (H&Y) stage II without mild cognitive impairment (MCI) and 2.6 in the patient with PD H&Y IV with MCI, respectively; the authors like to thank Dr. Yilong Ma and Dr. David Eidelberg, Center for Neurosciences, The Feinstein Institute for Medical Research, Manhasset, NY, for providing the analyses of disease-specific metabolic network expression.

For additional abbreviations see Fig. 1.
FIGURE 3: Disease-related metabolic covariance patterns.

A, Parkinson’s disease-related pattern; B, multiple system atrophy-related pattern; C, progressive supranuclear palsy-related pattern; D, corticobasal degeneration-related pattern; metabolic increases and decreases are color-coded in blue and red, respectively; voxel-loadings are z-scored; please note that CBDRP expression is usually markedly asymmetric (i.e., higher contralateral to clinically more affected body side); for detailed information see text.

Figure (modified) from Ko et al. (Journal of Cerebral Blood Flow & Metabolism 2017), Reprint with permission of the journal (SAGE journals).
FIGURE 4: Summary receiver operating characteristics (ROC) curves for the differentiation between Parkinson’s disease and atypical parkinsonian syndromes by $^{18}$F-FDG PET (APS as target condition, i.e., positive case).

The green and red lines represent the summary ROC curves of observer-dependent visual reads supported by voxel-based statistical analyses (methods 1.1 and 1.2 in Table 1; area under the curve 0.96 [95%-confidence interval: 0.94 - 0.98]) and observer-independent automated classifications (methods 2.1 and 2.2 in Table 1; area under the curve 0.94 [0.90 - 0.97]), respectively.
Table 1: Overview and preliminary meta-analysis of available studies on the differential diagnosis of parkinsonism by $^{18}$F-FDG PET including multiple disease groups (the group of APS as target condition, i.e., positive case)

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*p < 0.01; ’95% confidence interval; Med., parkinsonism medication; D, discontinued before PET; C, continued; 1.1, observer-dependent visual analysis supported by statistical parametric mapping; 1.2, observer-dependent visual analysis supported by Neurostat/3D-SSP; 2.1, observer-independent automated classification based on metabolic covariance patterns; 2.2, observer-independent automated classifications based on a relevance vector machine; TP, true-positive for an atypical parkinsonian syndrome (APS; including MSA, PSP and CBD); TN, true-negative for APS; FP, false-positive for APS; FN, false-negative for APS; Sens., sensitivity; Spec., specificity; LR+, positive likelihood ratio; LR−, negative likelihood ratio; Prev., prevalence of APS in study population; PPV, positive predictive values; NPV, negative predictive value; PD, Parkinson’s disease; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; n.a., not applicable; n.d., not defined; misc., miscellaneous.
SUPPLEMENT

Diagnostic Value – Preliminary Meta-Analysis: Methods

In brief: We conducted a careful Medline search (up to May 2017) and consecutive reference survey of retrieved studies to identify all studies that investigated the diagnostic performance of \( ^{18} \text{F-FDG PET} \) for differential diagnosis of parkinsonism in individual patients in a double-blinded manner (i.e., imaging analysis unaware of clinical diagnosis and \textit{vice versa}), included at least 3 diagnostic patient groups (typically PD, MSA and PSP; to reflect clinical reality) and provided sufficient data on individual patients to calculate study-specific and pooled diagnostic measures. Clinical diagnosis after follow-up served as reference standard in these studies. Summary receiver operating characteristics curves and estimates of diagnostic performance were calculated by meta-regression with the R packages “mada” (1) (R package version 0.5.7. https://CRAN.R-project.org/package=mada) and “meta” (2) (http://meta-analysis-with-r.org/) (3) (The R project, https://www.R-project.org/), in which the PET analysis method was used as covariate (i.e., observer-dependent visual reads supported by voxel-based statistical analyses \textit{or} observer-independent automated classifications; see below). This also in part accounts for overlapping patient populations in the studies by Eckert et al. (2005) (4) and Tang et al. (2010) (5), and Tripathi et al. (2013) (6) and Tripathi et al. (2016) (7), who used an observer-dependent visual analysis supported by SPM in the earlier studies and an observer-independent automated classification based on metabolic covariance patterns in the later studies.
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18F-FDG PET in Parkinsonism: Differential Diagnosis and Cognitive Impairment in Parkinson's disease

Philipp T Meyer, Lars Frings, Gerta Rücker and Sabine Hellwig

J Nucl Med.
Published online: September 14, 2017.
Doi: 10.2967/jnumed.116.186403

This article and updated information are available at:
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The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

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