Current Neurology and Neuroscience Reports (2019) 19: 56
https://doi.org/10.1007/s11910-019-0966-3

NEUROIMAGING (N. PAVESE, SECTION EDITOR)

Recent Advancement and Clinical Implications of 18FDG-PET in Parkinson's Disease, Atypical Parkinsonisms, and Other Movement Disorders

Cecilia Peralta[1] · Federico Biafore[2] · Tamara Soto Depetris[1] · Maria Bastianello[3]

Published online: 29 June 2019

Abstract

Purpose of Review The molecular imaging field has been very instrumental in identifying the multiple network interactions that compose the human brain. The cerebral glucose metabolism is associated with neural function. 18F-fluoro-deoxyglucose-PET (FDG-PET) studies reflect brain metabolism in a pattern-specific manner. This article reviews FDG-PET studies in Parkinson's disease (PD), atypical parkinsonism (AP), Huntington's disease (HD), and dystonia.

Recent Findings The metabolic pattern of PD, disease progression, non-motor symptoms such as fatigue, depression, apathy, impulse control disorders, and cognitive impairment, and the risk of progression to dementia have been identified with FDG-PET studies. In prodromal PD, the REM sleep behavior disorder-related covariance pattern has been described. In AP, FDG-PET studies have demonstrated to be superior to D2/D3 SPECT in differentiating PD from AP. The metabolic patterns of HD and dystonia have also been described.

Summary FDG-PET studies are an excellent tool to identify patterns of brain metabolism.

Keywords 18FDG-PET studies · Parkinson's disease · Atypical parkinsonisms · Prodromal parkinsonism · Huntington's disease · Dystonia

Introduction

Knowledge of cerebral structure and function in Parkinson's disease (PD) and atypical parkinsonisms (AP) was obtained from animal studies or pathological studies rather than "in vivo" observations of the human brain. However, the understanding of how the brain is composed of highly interconnected networks that link regions involved in motor, cognitive, and behavioral functions (rather than separated regions) was derived of imaging studies. The last decade has been in particular very relevant in advances of the molecular imaging field to explore the living human brain [1••].

The radiotracer [18F]-fluoro-deoxyglucose (FDG) is analogous to glucose and cerebral glucose metabolism is closely associated with local neural integrity and functional state of neurons.

FDG is transported into the neurons by glucose transporter proteins (GLUT) and its uptake increases with synaptic activity and decreases with neural dysfunction. This is especially relevant in neurodegenerative diseases where glucose metabolism is connected with cell death by pathways mediated by glucose-metabolizing enzymes [2].

FDG positron emission tomography (FDG-PET) is a powerful tool to detect and to quantify network abnormalities analyzed by covariance analysis and expressed in a pattern-specific manner, delineating functional brain regions and metabolism in neurodegenerative diseases. Although FDG-PET may be regarded as less specific than biomarkers of brain amyloidosis or tauopathy in detecting the underlying pathophysiology in PD and AP, it has proven to be very instrumental in identifying patterns of brain hypometabolism where

This article is part of the Topical Collection on *Neuroimaging*

✉ Cecilia Peralta
ceciliaperalta@yahoo.com.ar

[1] Department of Neurology, CEMIC University Hospital, Elias Galván 4102, C1431FWO Buenos Aires, Argentina

[2] Department of Biostatistics, School of Science and Technology, National University of San Martín, Campus Miguelete, 25 de Mayo y Francia, Buenos Aires, Argentina

[3] Department of Molecular and Metabolic Imaging, CEMIC University Hospital, Elias Galván, 4102 Buenos Aires, Argentina

neuronal dysfunction may even predate the structural anatomical changes, thus being highly relevant in the daily clinical practice.

In this review, we will focus on how the FDG-PET studies may contribute to the diagnosis, differential diagnosis, and also the assessment of progression of neurodegeneration in PD and AP as well as future directions in research. We will also briefly describe findings in other movement disorders such as Huntington's disease (HD) and dystonia.

PD Metabolic Pattern—Topographically Distributed Networks

Although the primary biochemical pathology of PD is localized into the substantia nigra (SN), lesions of the presynaptic dopaminergic terminal produce widespread abnormalities through topographically distributed networks. These networks are topographically organized and functionally distributed to connect regions such as the nigrostriatal pathway that associates the SN with dorsal striatum, one of the major dopaminergic pathways in the brain which is particularly involved in the production of movement, the mesolimbic pathway that links the ventral tegmental area (VTA) to ventral striatum, involved in the occurrence of impulse control disorders (ICDs) and the mesocortical pathway (VTA with the prefrontal cortex) that regulates executive functions, attention, and cognition [3, 4].

The most important PD-related metabolic pattern, the PD-related spatial covariance pattern (PDRP), has been identified in association with motor symptoms in 1994 by Eidelberg and colleagues. The PDRP has been repeatedly characterized by decreased metabolism in PD patients compared with healthy controls (HC), in parietal association, visual cortex, and lateral premotor and prefrontal association cortices, and by increased metabolism in the pons, bilateral thalamus, pallidum, dorsal putamen, primary motor cortex, and supplementary motor area [5]. However, in the inferior parietal cortex for which HC showed connectivity with posterior putamen, PD patients showed connectivity with anterior putamen. These results suggest the existence of possible compensatory alterations or remapping in PD that increase the role of the anterior putamen, in agreement with the posterior putamen's earlier and greater dopaminergic dysfunction in PD [6, 7].

The clinical correlates of the PDRP have also been extensively investigated. It was observed that PDRP expression correlated positively with UPDRS scores, akinetic-rigid motor symptoms, and disease duration [8].

Following this imaging-clinical correlation, Granert et al. built a topological map based on regional patterns of the cerebral metabolic rate of glucose measured with FDG-PET to localize single subjects' disease status according to "PD-typical" and Alzheimer's disease, "AD-typical," pattern expression in patients with PD, Parkinson's disease dementia, dementia with Lewy bodies (DLB), amnestic mild cognitive impairment, and AD.

The patterns obtained were related to the severity of clinical symptoms. In view of these strong correlations between metabolic and clinical measurements (cognitive vs motor pattern), the authors propose that FDG-PET imaging may even more significantly correlate with the clinical symptoms than with an underlying pathology [9•].

However, the time at which these abnormalities appear is not entirely clear, as it is their relationship to indices of disease progression. To clarify this issue, 15 early-stage PD patients underwent multitracer PET imaging at baseline, 24, and 48 months, scanned with FDG to assess the expression of the PDRP and cognitive metabolic covariance pattern (PDCP) and with [18F]-fluoropropyl βCIT (FP-CIT) to quantify longitudinal changes in caudate and putamen dopamine transporter (DAT) binding.

The study observed that disease progression was associated with increasing metabolism in the subthalamic nucleus (STN) and internal globus pallidus, as well as in the dorsal pons and primary motor cortex, with declining metabolism in the prefrontal and inferior parietal regions. PDRP expression was elevated at baseline and increased progressively over time as well as PDCP activity and correlated negatively with the uptake of striatal DAT binding and increases in motor ratings [10].

Further, the PDRP pattern has also been validated in primate models of PD with experimental parkinsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exposure, where similar network abnormalities have been observed, which remained stable over 3 months [11].

The network-level abnormalities reflect the release of the basal ganglia from nigral inhibition and the distribution of the α-synuclein pathogenesis. Functionally, there is an overactivation of the putamen, which increases the inhibitory afferents to the lateral pallidum producing increased metabolism and reduction in inhibitory afferents to the STN. The excitatory projections to the medial pallidum (MGP) increase, resulting in increased MGP metabolism, and the inhibitory projections from the MGP to the ventral thalamus also increase, resulting in increased metabolism in these thalamic structures [5, 12, 13].

Moreover, the activity of the PDRP was also modulated by dopaminergic replacement therapy, deep brain stimulation (DBS), and STN gene therapy.

STN-DBS inhibits the PDRP producing elevations in parietal and occipital glucose metabolism and reductions in caudate, putamen, cerebellum, and frontal cortex glucose metabolism. Clinically, there is a correlation of improving rigidity

and within imaging an increment in glucose metabolism in the parietal lobe to the degree of PDRP modulation [14•].

A network modulation was also observed with levodopa therapy associated with significant metabolic reductions in the putamen/globus pallidus, sensorimotor cortex, and cerebellar vermis, as well as increases in the precuneus, correlating also with clinical improvements [15].

In a blinded surgical trial of gene therapy for PD, the rate of PDRP progression measured over 1 year was consistently reduced while it was not affected by placebo treatment, highlighting that PDRP can also be considered a reliable biomarker of treatment response [16].

The PDRP is not related to tremor reflecting the distinct pathophysiological pathways of bradykinesia/rigidity and tremor. A different metabolic model, the PD tremor-related pattern (PDTR), was identified in tremor-dominant PD patients before and after thalamic DBS [17].

The PDTR was characterized by covarying increases in the cerebellum/dentate nucleus and primary motor cortex and to a lesser extent the caudate and putamen. The PDTR expression scores were correlated with tremor, but not to bradykinesia/rigidity scores.

The pathophysiology of parkinsonian tremor is thought to be characterized by a different metabolic network involving primarily the cerebello-thalamo-cortical pathways, distinct from that of akinesia and rigidity which is related to the loss of nigral dopaminergic projections to the putamen.

This observation is further supported by the fact that the parkinsonian tremor is not linearly responsive to dopaminergic therapy.

The effect of treatment on this network has also been evaluated. The PDTR was modulated by DBS of the ventral intermediate (Vim) thalamic nucleus; although STN-DBS reduced activity of both PDTR and PDRP, PDTR was better modulated by Vim DBS than by STN-DBS [17].

Another well-characterized network in PD is the default mode network (DMN). The DMN describes resting brain function, when the brain is not engaged in a task.

In HC, the resting state (RS) network was topographically similar to the DMN with relative metabolic increases in the posterior cingulate, medial prefrontal cortex, precuneus, and lateral parietal association regions.

A RS network resembling the DMN has also been identified in FDG-PET studies in early PD patients. The expression of the RS network measured at rest and during motor execution and motor sequence learning in PD and HC showed that the NL1-PC1, a major normal metabolic RS network, was less activated during task performance compared to the rest condition. In advanced PD, this task-related "deactivation" of the RS network was not evident and it was increasingly replaced by a pathological network, the PDRP [18].

Can Metabolic Network Activity Be Imaged in Prodromal PD?

Idiopathic REM sleep behavior disorder (iRBD) is regarded as one of the strongest predictors of PD. In view of the need to find reliable neuroimaging markers to predict the onset of parkinsonism in the prodromal phase of PD, several imaging studies have been performed in iRBD patients.

FDG-PET studies in iRBD identified a RBD-related covariance pattern (RBDRP) and also the expression of the PDRP [19, 20].

In one of the studies, Wu et al. identified the RBDRP in 21 patients with RBD and examined its evolution in 21 age-matched patients with hemi-PD (Hoehn and Yahr 1) and 16 patients with moderate PD (Hoehn and Yahr 2–3) to assess the correlations between the RBDRP and PDRP networks [20]. The authors found that the covariance pattern was characterized by relative increases in sensorimotor, superior frontal, cingulate, thalamic, pontine, and cerebellar metabolism associated with decreases in occipital, midbrain, and superior temporal metabolism showing that the RBDRP constitutes a unique metabolic network in RBD patients that reflects the neuronal circuits linking the brainstem, thalamus, cerebellum, and the cortex. The expression levels of this network have been found to be abnormally elevated in the clinically unaffected hemisphere of early PD patients and in preclinical subjects with RBD and in the hemi-PD patients although slightly lower than in patients with iRBD. The RBDRP expression decreased significantly in the moderate parkinsonian patients, suggesting that the network expression has a potential as a marker for phenoconversion, although it is not yet entirely clear which components were promoting neurodegeneration or which were compensatory.

In another study, Holtbernd and colleagues evaluated 2 groups of iRBD patients and HC. One group underwent RS metabolic brain imaging with FDG-PET. The second group of 17 patients, who received RS brain perfusion imaging with ethylcysteinate dimer SPECT, were followed up for 4.6 ± 2.5 years by investigators blinded to the imaging results.

The PDRP expression was elevated in both groups of subjects with RBD. The study concluded that network abnormalities in subjects with iRBD were associated with a greater likelihood of phenoconversion to a progressive neurodegenerative syndrome and that phenoconversion to multiple system atrophy (MSA) was more likely in individuals with lower PDRP expression at baseline compared to patients who converted to PD/DLB, suggesting that this network may be able to predict which disorder a patient with iRBD may develop. However, more validation studies are needed before these observations can be used to predict phenoconversion in iRBD patients [19].

Cognitive Impairment in PD

Degeneration of cholinergic and dopaminergic pathways are the most important components of cognitive dysfunction in PD, although its occurrence may be influenced by many other neurotransmitter system alterations [21].

FDG-PET studies have also been used to explore the metabolic functional correlates of PD with cognitive impairment. Network studies have revealed a consistent metabolic pattern associated with cognitive decline in non-demented PD patients characterized by hypometabolism in frontal and parietal regions and hypermetabolism in the cerebellar dentate nucleus, the PDCP, basically a fronto-parietal network, which is related to executive and memory dysfunction [22, 23].

The level expression of the PDCP correlated with executive and memory performance, but not with motor scores, and its expression was significantly higher in PD patients with mild cognitive impairment than in cognitively intact patients.

There is a great need for reliable biomarkers to identify PD patients with cognitive impairment who may progress to dementia during the course of the disease. It is well known that advanced age, longer disease duration, worse motor and non-motor impairments, visual-spatial and memory deficits, or multidomain mild cognitive impairment are the most reliable risk factors for developing PD dementia [24].

However, no biomarker has been able to solidly predict at a patient level, those patients who will convert to dementia.

FDG-PET studies have shown in cross-sectional and longitudinal studies that progressive cortical hypometabolism of the parietal and occipital regions characterize the transition from normal cognition to dementia in PD [25, 26]. In addition, a study combining FDG-PET with structural imaging concluded that hypometabolism predates atrophy in these brain regions [27].

A recently published study showed that FDG-PET with statistical parametric mapping detected patterns of hypometabolism that predicted the risk of a patient with PD to progress to dementia by 4 years [28••]. In this study, 54 PD patients received an extensive motor and cognitive assessment and a single-subject FDG-PET evaluation at baseline. The FDG-PET was evaluated by 2 expert raters to identify a "typical PD pattern" (29 patients) or an "atypical pattern" (DLB, AD, corticobasal syndrome (CBS), and frontotemporal dementia (FTD), 25 patients). At 4-year follow-up, 13 patients, all showing "atypical pattern" at baseline, progressed to PD dementia. The DLB- and AD-like patterns were the best predictor for incident dementia (sensitivity 85%, specificity 88%), independently from cognitive baseline classification, suggesting that FDG-PET at the single-subject level might help in identifying PD patients at risk of developing dementia.

Non-motor Symptoms in PD

Distinct patterns of metabolic abnormalities have been identified in relation with the development of non-motor symptoms (NMS). Compared to HC, patients with and without ICDs showed a moderately quite similar connectivity pattern involving bilateral temporal lobes. However, patients with ICDs showed a diffuse connectivity in bilateral posterior temporal lobes and right fronto-parietal lobes including the orbitofrontal area. In patients with ICDs, right middle and inferior temporal gyri exhibit decreased connectivity with the left caudate and a trend for increased connectivity with the right inferior fronto-orbital cortex. These findings led the authors to hypothesize that this temporo-limbic disconnection disrupts the integration of information about the reward, contributing to the addictive process [29].

The neural basis of apathy encompasses the prefrontal cortex, limbic regions, and the basal ganglia. In apathetic PD patients, it was observed, according to a study of 45 patients with PD who were neither depressed nor demented, positive correlations between the apathy score and cerebral metabolism in the right inferior and middle frontal gyrus, right cuneus, and right anterior insula and negative correlations with the cerebellar metabolism in the semilunar lobules bilaterally within the posterior lobe.

Interestingly, it was observed that the metabolism in the bilateral posterior lobe of the cerebellum inversely correlated with apathy scores due to strong anatomic connections between the cerebellum and the prefrontal cortices via thalamus. These results indicate that the frontal, temporal, and cerebellar areas, known to be involved in reward, emotion, and cognition, are also involved in apathy in PD patients without dementia or depression [30].

In another study that enrolled 26 nondemented PD subjects and 12 HC who underwent FDG-PET magnetic resonance imaging (MRI) and a complete neuropsychological battery, PD subjects presented significant reductions in executive/attention function, memory/verbal learning, speed of thinking, and significantly increased depression, anxiety, and apathy scores compared with HC. Depressive symptoms correlated with increased amygdala metabolism; anxiety scores correlated with decreased caudate metabolism and apathy scores correlated with increased metabolism in the anterior cingulate and orbitofrontal lobe and decreased metabolism in the temporoparietal association cortex, showing that emotional dysfunction in PD is associated with distinct patterns of cerebral metabolic changes [31].

Fatigue is a common NMS in PD manifesting as a sensation of lack of energy. To identify the neural substrates of fatigue in PD, 23 PD patients with fatigue underwent FDG-PET scan and the metabolic activities were compared to those without fatigue using statistical parametric mapping analysis. The PD group exhibited a correlation between higher level of

fatigue and metabolic changes in cortical regions associated with the salience (right insular region) and default (bilateral posterior cingulate cortex) networks, suggesting that fatigue may be the expression of metabolic abnormality interactions between brain regions linked to the salience network and other neural networks [32].

Atypical Parkinsonism

The differential diagnosis of parkinsonian disorders can be challenging, especially early in the disease course. FDG-PET studies have been used to identify patterns of brain metabolism in PD and also in the more common differential diagnosis of AP such as progressive supranuclear palsy (PSP), MSA, and corticobasal degeneration (CBD).

FDG-PET-related patterns have been repeatedly demonstrated in AP. In MSA, a pattern characterized by hypometabolism in the putamen and cerebellum has been described [33], in PSP a pattern consisting of hypometabolism in the prefrontal cortex, frontal eye fields, caudate nuclei, medial thalamus, and upper brainstem [34], and in CBD a pattern reflecting hypometabolism of the cortex and basal ganglia of one hemisphere and the contralateral cerebellum to the side with akinetic-rigid parkinsonism and apraxia [35]. The hypometabolism is typically found in the motor and premotor cortices, but may also involve the prefrontal or posterior parietal and lateral temporal cortex, and the cingulate gyrus. The heterogeneity of metabolic patterns found in CBS is most likely due to the variety of different pathologies that can present as CBS which include CBD, PSP, AD, FTD, and a mix of these conditions.

As opposed to PD, where the metabolic pattern in the basal ganglia is basically spared or increased, in AP, the metabolic pattern is reduced, as it was previously described in MSA, PSP, and CBD [36]. Table 1 gives an overview of network abnormalities in PD, AP, and other movement disorders.

FDG-PET studies performed at the time of initial referral of patients with parkinsonism demonstrated that they accurately predicted the clinical diagnosis of patients made at follow-up, according to a study of 135 parkinsonian patients. The results of visual assessments and computer-assisted interpretation were compared with 2-year follow-up clinical evaluations made by independent movement disorder specialists who were blinded to the original PET findings. It was found that blinded computer assessment agreed with clinical diagnosis in 92.4% of all subjects (97.7% early PD, 96% MSA, 85% PSP, 90.1% CBD, 86.5% HC). Concordance of visual inspection with clinical diagnosis was achieved in 85.4% of the patients [37].

In routine clinical practice, the FDG-PET scan of a patient can be assessed visually and the metabolic pattern identified, thus orientating the clinician in the diagnostic possibilities particularly in early stages of the disease. The European Association of Nuclear Medicine procedural guidelines [38] and also the latest criteria for PSP diagnosis by the Movement Disorders Society support the use of FDG-PET to differentiate between PD and AP [39•].

Although dopamine D2/D3 receptor (D2R)-SPECT was recommended by international guidelines to separate AP from PD [40], a recent meta-analysis suggested that the diagnostic accuracy of D2R-SPECT was low and did not discriminate between AP subgroups, since normal postsynaptic D2R availability did not preclude an AP [41].

Therefore, Hellwig at al. compared FDG-PET and [1,2,3 I]iodobenzamide (IBZM)-SPECT for the differentiation between PD and AP. PET scans were interpreted in 2 consecutive levels: in the first level, the readers classified each scan as indicative of PD or AP. In a second level, the AP-positive scans were categorized as being indicative of MSA, PSP, or CBD. After a follow-up of 12 months, a movement disorders specialist blinded for the FDG-PET established whether the clinical diagnosis accorded or not with the FDG-PET pattern diagnosis [42].

The study showed that the area under the receiver operating characteristic curve for differentiating between PD and AP with FDG-PET was 0.94, significantly larger than for IBZM-SPECT (0.74), while it did not significantly differ among AP subgroups, suggesting that FDG-PET is superior to IBZM-SPECT in differentiating PD from AP. FDG-PET reliably differentiates AP subgroups and this finding may better guide the clinical routine examinations of parkinsonian patients.

Other Movement Disorders

FDG-PET in HD

The FDG-PET studies in symptomatic HD patients have shown glucose hypometabolism in the striatum and the cortex which correlated respectively with motor and cognitive dysfunction [43–45]. This pattern of glucose hypometabolism was also observed in premanifest HD gene carriers [46]. Further, a bilateral increase in thalamic, occipital, and cerebellar glucose metabolism has also been identified as a typical pattern of HD [47].

In a study to evaluate functional brain network associated with the progression of preclinical HD, 12 premanifest HD mutation carriers received FDG-PET at baseline and at 1.5, 4, and 7 years. The subjects were also scanned with [^{11}C]-raclopride PET to measure decline in D_2 receptor binding. In these subjects, it was observed a linear increase over 7 years in network activity, characterized by progressive decline in glucose metabolism in striatum, thalamus, insula, and posterior cingulate gyrus and in the prefrontal and occipital cortex

Table 1 Common FDG-PET findings in Parkinson's disease, atypical parkinsonism, Huntington's disease, and dystonia

Network/ disorder	Glucose metabolic pattern
Parkinson's disease	
PDRP	↑ Pons, bilateral thalamus, pallidum, dorsal putamen, primary motor cortex, and supplementary motor area
	↓ Parietal, visual, lateral premotor, and prefrontal association cortex
PDTR	↑ Cerebellar dentate nucleus, primary motor cortex, caudate, and putamen
PDCP	↑ Cerebellar dentate nucleus
	↓ Frontal and parietal regions
RBDRP	↑ Sensorimotor, superior frontal, cingulate cortex, thalamic, pons, and cerebellar
	↓ Occipital, midbrain, and superior temporal region
Atypical parkinsonism	
MSA	↓ Putamen and cerebellum
PSP	↓ Prefrontal cortex, frontal eye fields, caudate, medial thalamus, and upper brainstem
CBD	↓ Cortex and basal ganglia of one hemisphere and contralateral cerebellum to the side of parkinsonism and apraxia
Huntington's disease	
HD/carriers	↓ Striatum and cortex
	↑ Thalamic, occipital, and cerebellum
Dystonia	
DYT1	↑ Basal ganglia, cerebellum, and supplementary motor area
DYT6	↓ Putamen and cerebellum, thalamus
DYT11	↑ Inferior pons and posterior thalamus

↑ = increase, ↓ = decrease

associated with progressive increase in the cerebellum, pons, hippocampus, and orbitofrontal cortex, accompanied by a linear decline in D2 striatal density. This finding emphasizes that the metabolic network imaging provides a sensitive measure of disease progression in premanifest HD, helping in patient selection for disease-modifying clinical trials [48].

Dystonia

Different studies have shown that the role of abnormalities within the basal ganglia circuitry may not be the only factor associated with dystonia. More recent evidence suggests that dystonia may occur as a consequence of involvement of both basal ganglia-thalamo-cortical and cerebello-thalamo-cortical pathways [49, 50].

In generalized as well as in focal dystonia, common FDG-PET findings have been observed in basal ganglia and associated outflow pathways to sensorimotor cortex and to other regions involved with motor control and responses, which may be associated with an abnormal sensorimotor integration that facilitates the occurrence of dystonia. Recent findings suggest that dystonia is a dynamic disorder related to abnormal cell function due to complex brain network abnormalities [50, 51•].

In patients with DYT1 dystonia, a pattern of increased regional metabolic activity involving the basal ganglia, cerebellum, and supplementary motor cortex was identified [52], while in DYT6 dystonia, opposite patterns of tracer uptake in the putamen were observed [53] and in DYT11 myoclonus dystonia, it was described an increased metabolism in the inferior pons and in the posterior thalamus [54], showing that different types of dystonia may be associated with different FDG-PET patterns.

Future Directions in Research

The computational and mathematical fields are taking place in the medical sciences. In this regard, computerized classifiers are being increasingly used in PD and AP. In the past years, studies have used classifiers or machine learning approaches to analyze FDG-PET studies.

A recently published study evaluated the potential utility of the PDRP as a biomarker for clinical trials of early-stage PD using FDG-PET and two machine learning approaches (scaled subprofile model (SSM) and NPAIRS with canonical variates analysis) in 17 HC and 23 PD patients. The study concluded that both classifiers were able to discriminate HC from PD, correlated with Hoehn and Yahr stage and UPDRS scores with high similarities of metabolic patterns [55•].

Very interestingly, a future area of research is dedicated to overcome one of the limitations of PET studies, the low spatial

resolution. The recent integration of PET and MRI in a single hybrid scanner would help in this issue since MRI provides high-resolution information on brain anatomy, volumetry, structural, and functional connectivity and brain perfusion, which can be used to improve spatial resolution of data acquired with PET. In the field of movement disorders, the current state of knowledge is still limited; however, combining metabolic and functional connectivity data may provide a fundamental tool to understand the pathophysiology of these disorders which are due to complex interactions between multiple networks [56].

Conclusion

The network analysis of FDG-PET may provide adequate biomarkers for diagnosis and differential diagnosis in PD and AP, thus being of diagnostic and predictive value, easily accessible in daily clinical practice, and widely available.

FDG-PET imaging can be used to establish a metabolic pattern in neurodegenerative diseases. The association with underlying pathologies will require either neuropathological confirmation or the use of additional imaging methods, for example, markers of TAU or amyloid.

Compliance with Ethical Standards

Conflict of Interest Cecilia Peralta, Federico Biafore, Tamara Soto, and Maria Bastianello each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Strafella AP, Bohnen NI, Perlmutter JS, Eidelberg D, Pavese N, Van Eimeren T, et al. Molecular imaging to track Parkinson's disease and atypical parkinsonisms: new imaging frontiers. Mov Disord. 2017;32(2):181–92. **The authors provide an overview of molecular imaging advances in PD and AP, how these approaches help to their understanding and revise exciting new tracer developments.**
2. Mergenthaler P, Lindauer U, Dienel GA, Meisel A. Sugar for the brain: the role of glucose in physiological and pathological brain function. Trends Neurosci. 2013;36(10):587–97.
3. Ikemoto S. Brain reward circuitry beyond the mesolimbic dopamine system: a neurobiological theory. Neurosci Biobehav Rev. 2010;35(2):129–50.
4. Jellinger KA. Post mortem studies in Parkinson's disease—is it possible to detect brain areas for specific symptoms? J Neural Transm Suppl. 1999;56:1–29.
5. Eidelberg D, Moeller JR, Dhawan V, Spetsieris P, Takikawa S, Ishikawa T, et al. The metabolic topography of parkinsonism. J Cereb Blood Flow Metab. 1994;14(5):783–801.
6. Helmich RC, Derikx LC, Bakker M, Scheeringa R, Bloem BR, Toni I. Spatial remapping of cortico-striatal connectivity in Parkinson's disease. Cereb Cortex. 2010;20(5):1175–86.
7. Brooks DJ, Pavese N. Imaging biomarkers in Parkinson's disease. Prog Neurobiol. 2011;95(4):614–28.
8. Holtbernd F, Ma Y, Peng S, Schwartz F, Timmermann L, Kracht L, et al. Dopaminergic correlates of metabolic network activity in Parkinson's disease. Hum Brain Mapp. 2015;36:3575–85.
9.• Granert O, Drzezga AE, Boecker H, Perneczky R, Kurz A, Götz J, et al. Metabolic topology of neurodegenerative disorders: influence of cognitive and motor deficits. J Nucl Med. 2015;56(12):1916–21. **The study describes the important correlations between FDG-PET metabolic pattern and clinical measurements (cognitive AD-typical vs motor PD-typical pattern)**.
10. Huang C, Tang C, Feigin A, Lesser M, Ma Y, Pourfar M, et al. Changes in network activity with the progression of Parkinson's disease. Brain. 2007;130(**Pt 7**:1834–46.
11. Ma Y, Johnston TH, Peng S, Zuo C, Koprich JB, Fox SH, et al. Reproducibility of a parkinsonism-related metabolic brain network in non-human primates: a descriptive pilot study with FDG PET. Mov Disord. 2015;30(9):1283–8.
12. Surmeier DJ, Obeso JA, Halliday GM. Selective neuronal vulnerability in Parkinson disease. Nat Rev Neurosci. 2017;18(2):101–13.
13. Su PC, Ma Y, Fukuda M, Mentis MJ, Tseng HM, Yen RF, et al. Metabolic changes following subthalamotomy for advanced Parkinson's disease. Ann Neurol. 2001;50(4):514–20.
14.• Cao C, Zhang H, Li D, Zhan S, Zhang J, Zhang X, et al. Modified fluorodeoxyglucose metabolism in motor circuitry by subthalamic deep brain stimulation. Stereotact Funct Neurosurg. 2017;95(2):93–101. **The paper provides insight in the modulation of the motor circuitry of PD patients by STN-DBS using FDG-PET and the correlations between glucose metabolism and clinical symptoms.**
15. Asanuma K, Tang C, Ma Y, Dhawan V, Mattis P, Edwards C, et al. Network modulation in the treatment of Parkinson's disease. Brain. 2006;129(**Pt 10**:2667–78.
16. Ko JH, Feigin A, Mattis PJ, Tang CC, Ma Y, Dhawan V, et al. Network modulation following sham surgery in Parkinson's disease. J Clin Invest. 2014;124(8):3656–66.
17. Mure H, Hirano S, Tang CC, Isaias IU, Antonini A, Ma Y, et al. Parkinson's disease tremor-related metabolic network: characterization, progression, and treatment effects. Neuroimage. 2011;54(2):1244–53.
18. Spetsieris PG, Ko JH, Tang CC, Nazem A, Sako W, Peng S, et al. Metabolic resting-state brain networks in health and disease. Proc Natl Acad Sci U S A. 2015;112(8):2563–8.
19. Holtbernd F, Gagnon JF, Postuma RB, Ma Y, Tang CC, Feigin A, et al. Abnormal metabolic network activity in REM sleep behavior disorder. Neurology. 2014;82:620–7.
20. Wu P, Yu H, Peng S, Dauvilliers Y, Wang J, Ge J, et al. Consistent abnormalities in metabolic network activity in idiopathic rapid eye movement sleep behaviour disorder. Brain. 2014;137:3122–8.
21. Ztaou S, Amalric M. Contribution of cholinergic interneurons to striatal pathophysiology in Parkinson's disease. Neurochem Int. 2019;126:1–10.
22. Huang C, Mattis P, Tang C, Perrine K, Carbon M, Eidelberg D. Metabolic brain networks associated with cognitive function in Parkinson's disease. Neuroimage. 2007;34(2):714–23.
23. Williams-Gray CH, Evans JR, Goris A, Foltynie T, Ban M, Robbins TW, et al. The distinct cognitive syndromes of Parkinson's disease:

5 year follow-up of the CamPaIGN cohort. Brain. 2009;132(**Pt 11**: 2958–69.
24. Litvan I, Goldman JG, Tröster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord. 2012;27(3):349–56.
25. Liepelt I, Reimold M, Maetzler W, Godau J, Reischl G, Gaenslen A, et al. Cortical hypometabolism assessed by a metabolic ratio in Parkinson's disease primarily reflects cognitive deterioration-[18F]FDG-PET. Mov Disord. 2009;24(10):1504–11.
26. Garcia-Garcia D, Clavero P, Gasca Salas C, Lamet I, Arbizu J, Gonzalez-Redondo R, et al. Posterior parietooccipital hypometabolism may differentiate mild cognitive impairment from dementia in Parkinson's disease. Eur J Nucl Med Mol Imaging. 2012;39(11):1767–77.
27. González-Redondo R, García-García D, Clavero P, Gasca-Salas C, García-Eulate R, Zubieta JL, et al. Grey matter hypometabolism and atrophy in Parkinson's disease with cognitive impairment: a two-step process. Brain. 2014;137(**Pt 8**:2356–67.
28.•• Pilotto A, Premi E, Paola Caminiti S, Presotto L, Turrone R, Alberici A, et al. Single-subject SPM FDG-PET patterns predict risk of dementia progression in Parkinson disease. Neurology. 2018;90(12):e1029–37. **The study evaluates FDG-PET imaging as a possible single-subject marker of progression to dementia in PD. At 4-year follow-up, all patients showing atypical brain metabolic patterns at baseline progressed to PD dementia. The DLB- and AD-like SPM patterns were the best predictor for incident dementia with a sensitivity of 85% and a specificity of 88%.**
29. Verger A, Klesse E, Chawki MB, Witjas T, Azulay JP, Eusebio A, et al. Brain PET substrate of impulse control disorders in Parkinson's disease: a metabolic connectivity study. Hum Brain Mapp. 2018;39(8):3178–86.
30. Robert G, Le Jeune F, Lozachmeur C, Drapier S, Dondaine T, Péron J, et al. Apathy in patients with Parkinson disease without dementia or depression: a PET study. Neurology. 2012;79(11):1155–60.
31. Huang C, Ravdin LD, Nirenberg MJ, Piboolnurak P, Severt L, Maniscalco JS, et al. Neuroimaging markers of motor and nonmotor features of Parkinson's disease: an 18f fluorodeoxyglucose positron emission computed tomography study. Dement Geriatr Cogn Disord. 2013;35(3–4):183–96.
32. Cho SS, Aminian K, Li C, Lang AE, Houle S, Strafella AP. Fatigue in Parkinson's disease: the contribution of cerebral metabolic changes. Hum Brain Mapp. 2017;38(1):283–92.
33. Eckert T, Tang C, Ma Y, Brown N, Lin T, Frucht S, et al. Abnormal metabolic networks in atypical parkinsonism. Mov Disord. 2008;23(5):727–33.
34. Zalewski N, Botha H, Whitwell JL, Lowe V, Dickson DW, Josephs KA. FDG-PET in pathologically confirmed spontaneous 4R-tauopathy variants. J Neurol. 2014;261(4):710–6.
35. Juh R, Pae CU, Kim TS, Lee CU, Choe B, Suh T. Cerebral glucose metabolism in corticobasal degeneration comparison with progressive supranuclear palsy using statistical mapping analysis. Neurosci Lett. 2005;383(1–2):22–7.
36. Sarikaya I. PET imaging in neurology: Alzheimer's and Parkinson's diseases. Nucl Med Commun. 2015;36(8):775–81.
37. Eckert T, Barnes A, Dhawan V, Frucht S, Gordon MF, Feigin AS, et al. FDG PET in the differential diagnosis of parkinsonian disorders. Neuroimage. 2005;26(3):912–21.
38. Walker Z, Gandolfo F, Orini S, Garibotto V, Agosta F, Arbizu J, et al. Clinical utility of FDG PET in Parkinson's disease and atypical parkinsonism associated with dementia. Eur J Nucl Med Mol Imaging. 2018;45(9):1534–45.
39.• Hoglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. Mov Disord. 2017;32(6):853–64. **This is a consensus-based revision of the clinical diagnostic criteria for PSP. New criteria consistent of four functional domains as clinical predictors of PSP, combinations of clinical features stratified by degrees of diagnostic certainty, clinical clues, and imaging findings as supportive features are discussed.**
40. Van Laere K, Varrone A, Brooj J. EANM procedure guidelines for brain neurotransmission SPECT/PET using dopamine D2 receptor ligands, version 2. Eur J Nucl Med Mol Imaging. 2010;37:434–42.
41. Vlaar AM, van Kroonenburgh MJ, Kessels AG, Weber WE. Meta-analysis of the literature on diagnostic accuracy of SPECT in parkinsonian syndromes. BMC Neurol. 2007;7:27.
42. Hellwig S, Amtage F, Kreft A, Buchert R, Winz OH, Vach W, et al. [^{18}F]FDG-PET is superior to [^{123}I]IBZM-SPECT for the differential diagnosis of parkinsonism. Neurology. 2012;79(13):1314–22.
43. Young AB, Penney JB, Starosta-Rubinstein S, Markel DS, Berent S, Giordani B, et al. PET scan investigations of Huntington's disease: cerebral metabolic correlates of neurological features and functional decline. Ann Neurol. 1986;20(3):296–303.
44. Kuwert T, Lange HW, Langen KJ, Herzog H, Aulich A, Feinendegen LE. Cortical and subcortical glucose consumption measured by PET in patients with Huntington's disease. Brain. 1990;113(**Pt 5**:1405–23.
45. Antonini A, Leenders KL, Spiegel R, Meier D, Vontobel P, Weigell-Weber M, et al. Striatal glucose metabolism and dopamine D2 receptor binding in asymptomatic gene carriers and patients with Huntington's disease. Brain. 1996;119(Pt 6):2085–95.
46. Ciarmiello A, Cannella M, Lastoria S, Simonelli M, Frati L, Rubinsztein DC, et al. Brain white-matter volume loss and glucose hypometabolism precede the clinical symptoms of Huntington's disease. J Nucl Med. 2006;47:215–22.
47. Feigin A, Tang C, Ma Y, Mattis P, Zgaljardic D, Guttman M, et al. Thalamic metabolism and symptom onset in preclinical Huntington's disease. Brain. 2007;130:2858–67.
48. Tang CC, Feigin A, Ma Y, Habeck C, Paulsen JS, Leenders KL, et al. Metabolic network as a progression biomarker of premanifest Huntington's disease. J Clin Invest. 2013;123(9):4076–88.
49. Neychev VK, Gross R, Lehéricy S, Hess EJ, Jinnah HA. The functional neuroanatomy of dystonia. Neurobiol Dis. 2011;42(2):185–201.
50. Lehéricy S, Tijssen MAJ, Vidailhet M, Kaji R, Meunier S. The anatomical basis of dystonia: current view using neuroimaging. Mov Disord. 2013;28(7):944–57.
51.• Kaji R, Bhatia K, Graybiel AM. Pathogenesis of dystonia: is it of cerebellar or basal ganglia origin? J Neurol Neurosurg Psychiatry. 2018;89(5):488–92. **The paper reviews current evidence on a new functional interaction between the cerebellum and basal ganglia in the pathogenesis of dystonia; highlighting it is now regarded as a 'network' disorder including the cerebellum.**
52. Trost M, Carbon M, Edwards C, Ma Y, Raymond D, Mentis MJ, et al. Primary dystonia: is abnormal functional brain architecture linked to genotype? Ann Neurol. 2002;52(6):853–6.
53. Carbon M, Eidelberg D. Abnormal structure-function relationships in hereditary dystonia. Neuroscience. 2009;164(1):220–9.
54. Carbon M, Raymond D, Ozelius L, Saunders-Pullman R, Frucht S, Dhawan V, et al. Metabolic changes in DYT11 myoclonus-dystonia. Neurology. 2013;80(4):385–91.
55.• Matthews DC, Lerman H, Lukic A, Andrews RD, Mirelman A, Wernick MN, et al. FDG PET Parkinson's disease-related pattern as a biomarker for clinical trials in early stage disease. Neuroimage Clin. 2018;20:572–9. **The authors present evidence on how FDG-PET using two classifiers can discriminate HC from PD observing very similar metabolic patters, consistent with the PDRP. They propose that FDG-PET and multivariate classification can provide an objective biomarker of disease stage with the potential to detect treatment effects on PD progression.**

56. Tondo G, Esposito M, Dervenoulas G, Wilson H, Politis M, Pagano G. Hybrid PET-MRI applications in movement disorders. Int Rev Neurobiol. 2019;144:211–57.