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Review Article

Nuclear imaging in Parkinson's disease: The past, the present, and the future

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ABSTRACT

The current review analyzed Parkinson's disease-related (PD) literature published from 1817 to 2021 and specifically concentrated on imaging-related works published from the 1960s to 2021. We analyzed the history of PD-related imaging development, its current condition, and pointed out some understudied aspects to be investigated in the future. The present review is specifically concentrated on nuclear imaging techniques. The available imaging armamentarium for PD investigation is very broad, variable, and diversified and includes structural, diffusion-weighted and diffusion tensor, resting-state, and task-based functional MRI, proton magnetic resonance spectroscopy, transcranial B-mode sonography, single-photon emission CT (SPECT), and positron emission tomography (PET). Specifically, PET is a reliable tool for quantifying nigrostriatal functions, glucose metabolism, amyloid, tau, and α-synuclein molecular imaging, as well as neuroinflammation. Besides ^{18}F-DOPA and ^{18}F-FDG, PET and SPECT use various other radiopharmaceuticals. Also, some studies have demonstrated that myocardial ^{123}I-MIBG scintigraphy can be useful for the early differential diagnosis of patients with PD from other atypical PD. However, in addition to further perfecting of differential diagnosis imaging tools, some aspects of etiology (PD genetics), pathology (the pons and medulla), pathophysiology (neuroinflammation), and early diagnosis of PD remain understudied. The currently available set of neuroimaging tools can provide adequate imaging data for early diagnosis, differential diagnosis, progression assessment, and treatment assessment of PD. To adjust this armamentarium to routine clinical needs, there is an urgent need for the generally accepted protocol for PD-related imaging investigations. Closer cooperation and data exchange between radiologists and pathologists are desirable.

So slight and nearly imperceptible are the first inroads of this malady, and so extremely slow is its progress, that it rarely happens, that the patient can form any recollection of the precise period of its commencement.

James Parkinson, 1817, [1].

Tremor is not always the first symptom.

Oppenheim H. Textbook of Nervous Diseases, 1911. [2]

1. Introduction

The current review analyzed Parkinson's disease-related (PD) literature published from 1817 to 2021 and specifically concentrated on imaging-related works published from the 1960s to 2021. The present review is specifically concentrated on nuclear imaging techniques.

1.1. Search strategy

The literature search was performed on the Medline/PubMed, SCOPUS, and ScienceDirect databases using the following disease-specific keywords: "Parkinson," "Lewy," "multiple system atrophy," "corticobasal degeneration," "progressive supranuclear palsy" + one of the modality-specific keywords: "positron emission tomography," "single-photon emission computed tomography" (with appropriate PET and SPECT acronyms), as well as ^{18}F-FDG, ^{18}F-DOPA, other radiotracers, and "proton spectroscopy." While "magnetic resonance imaging," (MRI) was not the main keyword, some MRI-specific publications were also

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included in the study to demonstrate how PET, SPECT, and MRI can reinforce each other. The literature search was not restricted to articles written in English; foreign language articles were also considered if the clear translations could be obtained. The search was concentrated on the articles being published since 1980 and up-to-date. The earlier publications, starting from 1817, were used for brief description of the pre-imaging and early-imaging periods of the Parkinson-related research activities. The abstracts were screened for relevance with animal studies as an exclusion criterion. The described neuroimaging modalities were identified and representative examples were selected, with a focus on major publications of human studies over the past 40 years. The final list of selected studies represents a wide range of neuroimaging studies of PD and PD-related disorders and some autopsy-involved publications that reinforced or questioned the imaging findings. The most pertinent articles were then read and discussed.

2. The past

Since Parkinson's disease (PD) was described in 1817 as "shaking palsy", the precise knowledge of its pathology was developing very slowly. The first scientifically sound post-mortem examinations of the brain of PD patients were performed only in the 1860s [3,4] and the disease was connected to the substantia nigra only in the 1910s [5,6]. Neuroimaging was applied to PD only in the 1960s. Attempts for stereotaxic surgical treatment of PD patients played a stimulating role in this innovation but X-ray angiographic findings mainly described cerebral atrophy thus confirming the fact already known since the 1860s [7,8]. In the 1970s, CT was introduced as a new imaging tool for PD assessment. Alas, plain X-ray CT of the 1970s was able to detect brain atrophy around the lateral ventricles and the third ventricle or general cortical atrophy and ventricular enlargement thus again confirming the facts known for a hundred years [9,10].

Only in the 1980s, the PD neuroimaging armamentarium became complex and included CT, MRI, and positron emission tomography (PET). The pioneering MRI findings were not very impressive and detected "a narrowing of the signal from the pars compacta of the substantia nigra" or "slightly decreased signal intensity of the putamen" in addition to already well-known cerebral atrophy and ventricular enlargement [11–14]. As for PET, the initially used ^{18}F-2-deoxy-2-fluoro-D-glucose (^{18}F-FDG), while widely used in clinical oncology, appeared to be not an ideal tracer for PD cases and FDG/PET did not provide sound new results at this time [15]. Yet, an introduction of PET was a welcome attempt to add pathophysiological functional imaging method to MRI and CT anatomical imaging techniques. Already in 1983, Garnett et al. suggested ^{18}F-6-fluorodopa (L-3,4-dihydroxy-6-18F-fluorophenylalanine; ^{18}F-DOPA) as a proper radionuclide to study PD [16,17]. That is why, in 1992, Eidelberg suggested reinforcing PET with the single-photon emission CT (SPECT) and to add or replace ^{18}F-FDG with ^{18}F-DOPA as an important tracer for studying the dopaminergic system that is more specific for PD cases [18] (Fig. 1).

Indeed, regarding the molecular imaging of the PD-impaired dopaminergic system, SPECT and PET tracers target the presynaptic membrane dopamine transporters, the presynaptic intraneuronal vesicular transporter system, the vesicular Dopamine Storage System, and the postsynaptic dopamine receptors. Initially, ^{18}F-DOPA was considered to reflect the physiological abundance of L-DOPA (levodopa), and several studies of PD that implemented ^{18}F-DOPA PET demonstrated the usefulness of the method for detecting the fate of nigrostriatal dopamine neurons, frontal, midbrain and striatal dopaminergic function, and other elements useful for PD diagnosis and assessment [19–21]. Currently, it is understood that F-dopa PET reflects the ability of the terminals to decarboxylate exogenous L-DOPA. Within the neurons, ^{18}F-DOPA is converted to fluorodopamine by DOPA decarboxylase and stored in the presynaptic vesicles, thus reflecting the integrity of the presynaptic dopaminergic neurons. That is why the newly introduced transcranial ultrasound investigation of PD also was based on the assessment of ^{18}F-DOPA-uptake [22,23].

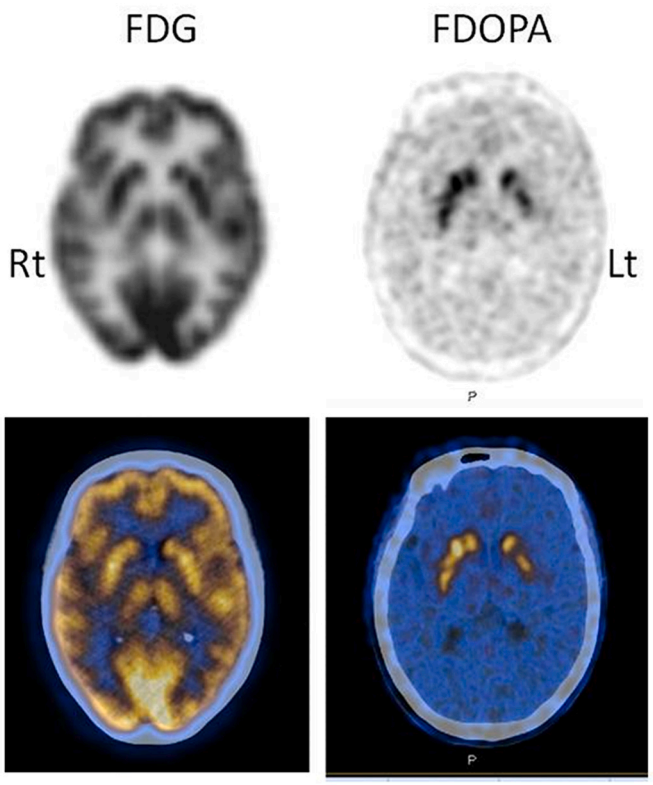

Fig. 1. A 61-year old female with known neurosarcoidosis was referred to ^{18}F-DOPA PET-CT scan because of her complaints on right leg rigidity and postural tremor. Parkinson's disease was suggested. ^{18}F-FDG brain PET-CT was performed during whole body ^{18}F-FDG scan to evaluate the sarcoidosis disease activity. For the brain, ^{18}F-FDG image was normal but ^{18}F-DOPA image showed reduced F-DOPA uptake in the left posterior putamen compatible with the patient's complaints and with early Parkinson's disease.

Despite these promising results, neuroimaging in general, and nuclear imaging in particular, were not counted as important tools for the diagnosis and assessment of PD. Already in the 2000s, the emerging publications and guidelines did not recommend MRI for diagnosis of PD [24,25] or, at least, limited its usefulness to differential diagnosis between PD and other parkinsonian syndromes or types of atrophy [24,26]. FDG/PET was rejected, the role of SPECT was limited to differential diagnosis between PD and other tremor disorders, ^{18}F-DOPA PET was ignored, and ultrasonography was not recommended at all [24–26]. Such an approach to neuroimaging was summarized in 2013 as "imaging plays a limited role in diagnosis" of PD [27].

This "limited role in diagnosis" verdict was predictable. The absolute majority of the imaging studies being performed from the 1970s to the 2000s investigated patients with already established diagnoses of PD. It seemed that the imaging techniques can confirm the diagnosis rather than establish the diagnosis. In difficult cases, neuroimaging could be used to distinguish PD from other akinetic rigid syndromes but such role was understood as "limited". Secondly, from the 1860s to the 1990s, researchers had collected and analyzed an impressive amount of data obtained during autopsies. The post-mortem investigation of PD started with gross pathology and plain histology and ended with cytology, cytoarchitectonic analysis, quantitative analysis, and immunohistochemical procedures that permitted investigation of cytoarchitecture, chemoarchitecture, fiber connections, and various projections of the involved areas of the PD brain in detail. Neuroimaging, as a set of in vivo techniques, just confirmed most of these data. For example, in 2008, Politis et al. used ^{18}F-DOPA PET and ^{11}C-raclopride PET to demonstrate an impairment of hypothalamic function in PD [28]. Such impairment

was established for parkinsonism in 1953 [29]. Neuroimaging attempts in the field of PD were appreciated but they were not valued as a real breakthrough achievement. But neuroradiologists did not give up.

3. The present

The imaging for PD survived because of a very obvious fact: the accuracy of clinical diagnosis remained insufficient and was highly dependent on the level of expertise, the experience of the clinician, and duration of follow-up. Certain neurologic conditions mimic PD, making it difficult to diagnose in its early stages. (Fig. 2). The meta-analysis paper published in 2016 examined the diagnostic accuracy of clinical diagnosis of PD reported in the last 25 years [30]. The best diagnostic results arrived from movement disorders experts, but still misdiagnosis was about 20%. The authors concluded that imaging and other biomarkers are urgently needed to improve clinical diagnosis [30]. Neuroimaging biomarkers (PET, SPECT, MRI) were proposed as important tools for the differential diagnosis and prognosis for PD cases [31].

Secondly, neuroimaging presented an investigative option that postmortem analysis could not offer: a longitudinal study of PD patients. Such ^{18}F-DOPA PET study was published in 2011 and demonstrated that besides the degeneration of nigrostriatal dopamine neurons, while the fastest annual declines of ^{18}F-DOPA influx was occurring in putamen (8.1%), locus coeruleus (7.8%), and globus pallidus interna (7.7%), such a decline can be also traced in caudate and hypothalamus [32].

David Eidelberg promoted the use of neuroimaging for PD since 1992 [18]. Twenty years after that, he edited a comprehensive manual on "Imaging in Parkinson's Disease" that was published in 2012 [33] and a new era began for PD imaging. The manual explained that PET and SPECT, dopamine transporter (DAT) SPECT, in particular, can provide dopaminergic imaging and investigate the cerebral glucose metabolism in PD, while MRI provides traditional, volumetric, and voxel-based morphometry through its structural, diffusion-weighted, diffusion tensor, resting BOLD, and task-based functional modalities. It was demonstrated that the PD-specific imaging techniques can investigate tremor, atypical parkinsonian syndromes, accompanying neuroinflammation, cognitive dysfunction, and PD progression and assess the outcomes of pharmacologic treatment, surgical interventions, and cell-based therapies [33]. In 2014, contrary to previous negativism [24–27], PET was accepted as an important investigative tool for PD [34]. While MRI fails to diagnose PD because morphological alterations in the brain are usually detectable only at advanced stages, PET can catch the early stages of the disease and be useful in the differential diagnosis of PD with parkinsonian syndromes and essential tremor [35].

The first question was: How reliable is ^{18}F-DOPA PET in the diagnosis of PD? In 2016, it was established that ^{18}F-DOPA PET has high accuracy with a sensitivity of 95% and specificity of 100% [36]. (Figs. 3 and 4). The etiology of PD is based on a degenerative process affecting the substantia nigra pars compacta that reflects on the dopaminergic

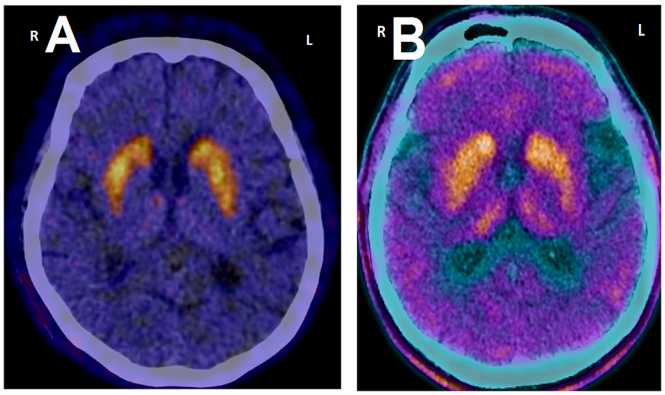

Fig. 3. A. ^{18}F-DOPA axial PET-CT slice at the level of the striatum demonstrating bilateral homogenous symmetrical uptake of the tracer in the caudate and the putamen area consistent with a normal distribution of dopaminergic neurons.
B. ^{18}F-DOPA axial PET-CT slice at the level of the striatum demonstrating asymmetrical reduced uptake of the tracer especially at the putamen area more pronounced in the left side consistent with reduced dopaminergic neurons compatible with Parkinson's disease.

neurons in the striatum and, specifically, in dorsal-caudal putamen. Therefore, the subsequent question was: How early can ^{18}F-DOPA be used to demonstrate this dopaminergic deficit?

3.1. Nuclear imaging and an early PD diagnostics

To that moment, Oppenheim's observation of 1911 that "tremor is not always the first symptom" had been developed to the whole concept of a prodromal or preclinical stage of PD. This stage consisted of the following subsequent steps: idiopathic rapid eye movement (REM) sleep behavior disorder (RBD or IRBD) → depression → constipation → anxiety → hyposmia → onset of motor symptoms [37,38]. Of them, IRBD attracted the main attention being the first prodromal condition that may appear a decade prior to motor symptoms. During IRBD, the physiological atonia during REM sleep is absent or greatly diminished and the dream-enacting behavior is associated with nightmares. It was well documented that the majority of patients with IRBD will progress to PD, dementia with Lewy bodies, and, less frequently, multiple system atrophy within a decade [37–41]. Already in 2000, it was reported that PET can detect the decreased striatal dopaminergic innervation in IRBD cases [42]. In a recent prospective case-control PET study, the authors assessed patients with IRBD and no clinical evidence of parkinsonism and cognitive impairment, and healthy controls. Neuroinflammation was assessed with ^{11}C-PK11195 PET tracer and the dopaminergic function in the putamen and caudate with ^{18}F-DOPA PET. It appeared to be possible to detect neuroinflammation of the substantia nigra and

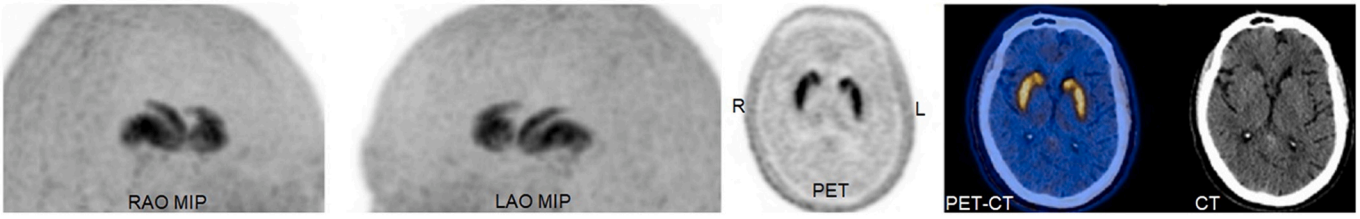

Fig. 2. A 76-year old patient with bipolar disorder who has been treated with Lithium for decades began to develop symptoms of rigidity and an altered gait, namely symptoms compatible with a diagnosis of Parkinsonism. The Lithium levels were within the therapeutic range. The pictures present normal ^{18}F-DOPA PET-CT scan and the patient was diagnosed having Lithium induced Parkinsonism. The images show uniform uptake within the bilateral caudate and putamen in a pattern of normal physiological uptake. Maximum Intensity Projections (MIP) images show ^{18}F-DOPA normal striatal "rabbit-shaped" uptake pattern. Medication-induced Parkinsonism occurs frequently in patients using antipsychotic medication.
The Lithium dosage was reduced gradually and within a few months all neurological symptoms subsided completely. (RAO = right anterior oblique, LAO = left anterior oblique).

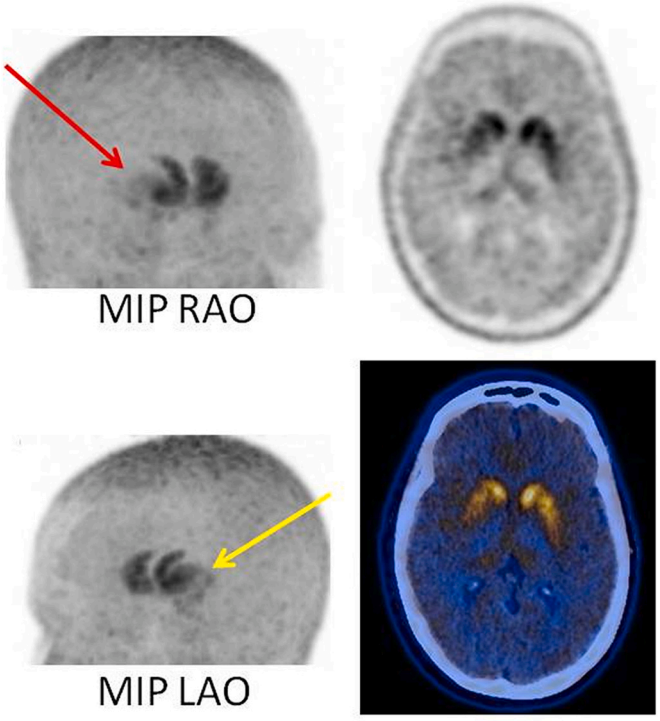

Fig. 4. A 52 year old female suffering from anosmia and REM sleep behavior disorder for many years was referred to ^{18}F-DOPA axial PET-CT because of newly appeared tremor in her left hand and general fatigue. Brain MRI was normal. ^{18}F-DOPA PET-CT demonstrated a reduced uptake in both posterior putamens being more pronounced on the right side compatible with the patient's symptom suggesting PD. MIP images clearly showed the reduced F-DOPA in the posterior putamen on the right side (red arrow), less so in the left putamen (yellow arrow). (RAO = right anterior oblique, LAO = left anterior oblique). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

reduced ^{18}F-DOPA uptake in the left and right putamens in patients with IRBD [43]. Findings from prospective studies of patients with IRBD showed a 41% risk of progression to PD or dementia with Lewy bodies within 5 years of IRBD diagnosis and up to 91% by 14 years [37,39,44]. Therefore, it became obvious that ^{18}F-DOPA PET may detect early onset of PD a decade prior to motor symptoms.

This finding led to a conclusion that ^{18}F-DOPA PET may be used for monitoring and evaluating the disease progression, dopamine receptor mapping, and evaluation of levodopa-induced dyskinesias that may occur during chronic PD treatment with L-DOPA [45–47]. For assessing the progression rate, it was suggested to combine ^{18}F-DOPA PET with ^{11}C-PE2I PET for more precise results [48]. In recent publications about the role of ^{18}F-DOPA for movement disorders, it was claimed to be the best diagnostic tool for PD and other movement disorders [35,48]. Yet, the main function of ^{18}F-DOPA PET is still seen by various authors to be a tool for differential diagnosis between PD and Parkinson "plus" syndromes, dementia with Lewy bodies, essential tremor, psychogenic, post-neuroleptic or vascular parkinsonisms, dopa-responsive dystonia, atypical parkinsonian disorders, and Alzheimer's disease [31,33,35,49–51]. This opinion is only partially correct. If ^{18}F-DOPA PET was reinforced by ^{123}I-Ioflupane SPECT, PD can be differentiated from psychogenic, vascular, or post-neuroleptic parkinsonism that demonstrate normal readings for ^{18}F-DOPA PET uptake [52–54] as well as from dopa-responsive dystonia that demonstrates no longitudinal changes in ^{18}F-DOPA PET uptake [55,56]. At the same time, this radiotracer cannot differentiate PD and Parkinson "plus" syndromes [51,57]. For dementia with Lewy bodies with its symmetrical reduction of radiotracer uptake, ^{123}I-Ioflupane SPECT and ^{18}F-FDG PET-involved investigations may be more important than ^{18}F-DOPA PET [58]. The summary for nuclear imaging in early PD diagnostics is presented in Table 1.

3.2. Nuclear imaging and PD differential diagnosis

While differential diagnosis between PD and Alzheimer's disease, essential tremor, and dementia with Lewy bodies is relatively simple, there are certain conditions, namely, progressive supranuclear palsy (PSP), multiple system sclerosis (MSA), and corticobasal syndrome (CBS) that require an additional effort to distinguish them from PD. PSP was studied with MRI and both ^{18}F-DOPA and ^{18}F-FDG PET for a long time with and without connection with PD [59–62]. ^{99}mTc-ECD SPECT was also applied for this purpose [63]. In summary, even early PD cases can be differentiated from PSP. Specifically for ^{18}F-DOPA PET, PD cases present an asymmetrical loss of putaminal ^{18}F-DOPA with relative preservation of the caudate earlier on in the disease while PSP cases demonstrate a diffuse and symmetrical decrease in striatal ^{18}F-DOPA including the caudate nucleus. The imaging assessment of MSA is more difficult. It also was studied with MRI and ^{18}F-DOPA, ^{11}C(*R*)-PK11195, and ^{18}F-FDG PET [64–67]. The difficulty arrived because in MSA cases ^{18}F-DOPA uptake is reduced bilaterally and cannot be differentiated from late-stage PD. In this case, it was recommended to use ^{18}F-FDG PET but the best MSA/PD differential diagnosis results were obtained from the usage of sympathetic cardiac ^{123}I-Metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy or SPECT [50]. CBS is, perhaps, the most difficult disorder to diagnose and to distinguish from PD. SPECT, ^{18}F-DOPA PET, and ^{18}F-FDG PET were tried to assess or at least detect nigrostriatal dysfunction in CBS [68–70]. Alas, how it was observed already in 2019, none of the currently available tau-PET ligands is clinically applicable and in numerous CBS cases, the correct diagnosis is established post-mortem by pathological examination [71]. Most recent ^{18}F-FDG PET-involved studies of CBS demonstrated a significant progress in our understanding and assessment of amyloid status, speech and language impairment, ideomotor apraxia, and imitation apraxia in CBS cases [72–74]. These studies permitted to differentiate classical CBS from fulminant CBS and CBS due to Alzheimer's disease from other pathologies [74,75]. Yet, PD vs. CBS issue still remains unclear.

Another approach to the differential diagnosis problem suggests that DAT SPECT may be a tool of choice in cases of "mild, incomplete, or uncertain parkinsonism" [76]. (Fig. 5). DAT is located presynaptically on dopamine neurons serving as a marker for certain dopamine-related neurological diseases. However, while (99 m)Tc-TRODAT-1 DAT SPECT provides a reliable alternative to ^{18}F-FDOPA PET in the evaluation of PD cases, its usefulness for differential diagnostic purposes was recently questioned. It was demonstrated that DAT SPECT provides "low discrimination between PD with bilateral motor symptoms and PSP" [77] and cannot differentiate MSA from PD, PSP, and dementia with Lewy bodies [78]. In addition, the cost-effectiveness of the clinical use of

Table 1
The summary for nuclear imaging in early PD diagnostics. Abbreviation: IRBD - idiopathic rapid eye movement (REM) sleep behavior disorder.

Complaint/condition	Radiotracer/imaging tool	[ref]
IRBD	^{11}C-dihydrotetrabenazine PET	[42]
	^{11}C-PK11195 PET, ^{18}F-DOPA PET	[31,43,95,103]
	^{11}C-donepezil PET, ^{123}I-MIBG SPECT	[95,123]
	^{11}C-MeNER PET	[103]
	^{123}I-FP-CIT SPECT, ^{18}F-FDG-PET	[110,125]
Depression	^{123}I-FP-CIT SPECT, DAT PET	[90,110,121]
Constipation	^{18}F-DOPA PET	[99]
	^{11}C-donepezil PET	[122]
	DAT-SPECT imaging with DaTscan™	[124]
Anxiety	^{123}I-FP-CIT SPECT, DAT PET	[90,110,121]
Hyposmia	^{123}I-FP-CIT DAT-SPECT, ^{18}F-FDG-PET	[125,126]
Onset of motor symptoms	All of the above but mainly ^{18}F-DOPA PET	

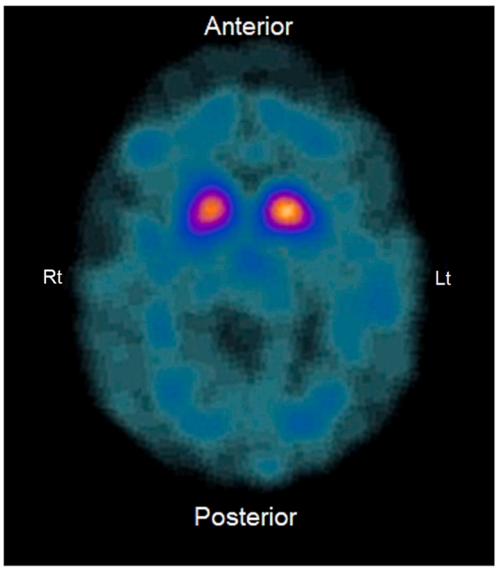

Fig. 5. Dopamine Transporter (DAT) abnormal SPECT scan: the bilateral loss of putaminal uptake with reduced uptake of the right caudate nucleus in comparison to the left side. This kind of image is compatible with Hoehn and Yahr stage 2–3 Parkinson's disease severity.

DAT-SPECT is not certain [45].

4. The future

4.1. PD genetics

In addition to further perfecting of differential diagnosis imaging tools, some aspects of etiology, pathology/pathophysiology, and early diagnosis of PD remain understudied. For etiology, there are several gene mutations that are linked to PD. It is difficult to distinguish idiopathic PD from familial PD clinically. There are about 70 different genes that can mutate and trigger early-onset parkinsonism [79]. ^{18}F-DOPA PET was tried for PD genetic studies since 2004 [80]. For some specific examples, it is not entirely clear how PRKN gene (AR-JP, PARK2, Parkin, PDJ) mutations cause PD by disrupting normal cell activities such as the supply and release of synaptic vesicles, particularly those that contain dopamine. As PRKN is normally abundant in the brain, its loss could lead to the impairment or death of nerve cells, including those that produce dopamine and this loss of dopamine-producing nerve cells is ^{18}F-DOPA PET-detectable [81]. Mutations in the PRKN gene may also disrupt the regulation of mitochondria and/or cause ubiquitin ligase disorder. Researchers speculate that mitochondrial dysfunction in dopamine-producing nerve cells may play an important role in causing the signs and symptoms of PD [79,81,82] and neuroimaging may add some valuable data for this discussion.

Mutations in LRRK2 gene (PARK8) are associated both with the juvenile form of PD, which appears before age 20 and with a late-onset form that begins after age 50 [83]. Having a first-degree or any relative with PD is counted as the main risk factor for PD development [84]. ^{18}F-DOPA PET can be used to detect dopaminergic deficit even in asymptomatic relative carrying the gene mutation LRRK2 [85]. It is claimed that ^{18}F-DOPA PET is a useful tool delineating differences between familial and idiopathic PD since the ^{18}F-DOPA deficit in familial PD is more symmetric bilaterally and can be seen even in asymptomatic family members [85–87]. The genetics of PD is a fast-growing area in PD studies and undoubtedly neuroimaging will contribute to it.

4.2. PD pathology

Within the area of PD pathology, imaging of the pons and medulla is extremely understudied. Already in the 19th century, numerous pathologists, being ignorant about the role of the substantia nigra in PD, detected changes in the pons and medulla of PD patients that were described as "softening of the pons and medulla" at that time and pronounced these parts of the brainstem "the seat of the disease" for PD [4,88–90]. All the above-cited neuroimaging research reports and reviews describe various PD-specific changes in the substantia nigra, in general, and the substantia nigra pars compacta, in particular, ventrolateral thalamic areas and the thalamus in general, ventral tegmental area, hypothalamus, putamen, internal pallidum, the caudate nucleus, the striatum, insula, amygdala, and up to the motor cortex, but the pons and medulla are overlooked with an exception of rarely mentioned locus coeruleus of the pons.

For MRI studies, it was explained that the investigation of the brainstem with MRI "has been hampered for years due to this brain structure's physiological and anatomical characteristics" and "remains a challenge" [91,92]. For PET, being concentrated on dopaminergic function throughout the brain, the researchers investigated the above-mentioned midbrain structures, the basal ganglia, and areas above them but did not pay scrupulous attention to the areas below the midbrain even though the reduced influx of ^{18}F-DOPA was detected in the dorsal pontine regions already in 1999 [19]. It sounds amazing, but the pioneering findings of the pathologists of the 19th century were fully confirmed in the 21st century. Investigating the brains of PD patients in various stages of the disease, the pathologists established that the PD-related changes start in the intermediate reticular zone of the medulla with further ascending to the great raphe nucleus (the pons), gigantocellular reticular nucleus, and locus coeruleus of the pons, and only after that, they affect the midbrain with the dopaminergic substantia nigra, the basal forebrain, amygdala, thalamus, hypothalamus, and, finally, cerebral allo- and neocortex [93–96]. The 19th century observation that the brainstem is "the seat of the disease" for PD was reconfirmed in 2002 [97]. From 2002 to 2004, Braak and his associates had developed staging of PD brain pathology and clearly indicated that the presymptomatic stages of PD are connected with the medulla oblongata and olfactory bulb [98–100].

For neuroimaging modalities, ^{11}C-WAY 100635 PET study detected involvement of the midbrain raphe nucleus in PD and established that this involvement correlates with severity of PD tremor [101]. This finding was confirmed by the SPECT study that used ^{123}I-FP-CIT as a marker suitable for both dopamine and serotonin transporter availability assessment [102]. This research also indicated a connection between the severities of resting tremor in early drug-naïve PD patients and the brainstem raphe nuclei involvement in PD processes. Another SPECT study with the same ^{123}I-FP-CIT marker detected that PD patients had lower tracer uptake in the striatum and ventral midbrain but higher uptake in the thalamus and raphe nuclei than controls [103]. The authors concluded that PD patients may have upregulation of brain serotonin transporter function at the early phase of the disease.

Specifically for MRI, a T1-weighted MRI study detected the significant white and grey matter volume reduction in the brain stem, between the pons and the medulla oblongata in PD cases [104]. Another PD-related MRI study implemented diffusion-weighted imaging approach-track density imaging (TDI) and the results demonstrated significant increases in track density from the lower medulla to the diencephalon and striatum with involvement of the locus coeruleus and pedunculopontine nucleus in the pons [80]. The neurochemical profiles of the pons, putamen, and substantia nigra of PD patients were quantified by 7 T (T) proton magnetic resonance spectroscopy [105]. The authors found that γ-Aminobutyric acid (GABA) concentrations in the pons and putamen were significantly higher in patients than in controls. The GABA elevation was more significant in the pons (64%) than in the putamen (32%). In 2018, ultrahigh-field (UHF) MRI scanning was suggested for in-depth investigation of different brainstem-based circuitries that may have a connection with the development of PD [92]. Finally, already in 2020, it was demonstrated that T1-weighted MRI can

distinguish between various atypical parkinsonian syndromes by measuring the volume of the medulla, pons, superior cerebellar peduncle, and midbrain that is different in CBS, MSA, and PSP cases [106]. A multimodality imaging case-control study of 2018 indicated the involvement of the brainstem in IRBD pathology as well and detected decreased neuromelanin-sensitive MRI locus coeruleus:pons ratio [107]. The authors concluded that that α-synuclein pathology in PD initially targets peripheral autonomic nerves and then spreads rostrally to the brainstem. It was also suggested to use the pons to midbrain area ratio as a reliable MR-marker to assess PD but no subsequent studies followed [108]. To summarize, we have these ten PD-related neuroimaging studies of the pons and medulla in addition to hundreds of studies dedicated to midbrain structures, the basal ganglia, and areas above them. Such misbalance is somewhat strange and, most probably, neuroradiologists will investigate the PD-affected brainstem in more detail in the future for the purposes of early diagnostics of PD.

4.3. PD pathophysiology

For PD pathophysiology, neuroinflammation remains a challenge. It is important to note that besides PD itself, neuroinflammation exists also in other Parkinsonian diseases such as the above-mentioned MSA, PSP, CBS, and PD-related IRBD and it is PET-detectable [43,109,110]. For PET, ^{18}F-DOPA uptake may also be seen in inflammatory tissue in general or benign brain tumors [111]. Additional imaging studies in this area are very desirable for inflammation monitoring and selecting suitable therapeutic drugs that can modulate neuroinflammation [110]. Braak et al. suggested that etiology of idiopathic PD may be "subject to neuroinvasion by an unknown pathogen," probably viral [112–114]. If this hypothesis will become an established fact, the phenomenon of PD-related inflammation will become more understandable. In such a case, the inflammation-detection-related imaging techniques will become very important.

4.4. PD early diagnosis

For early diagnosis of PD, while IRBD was explored in-depth and the latest PET study found that the dopaminergic and noradrenergic neurotransmitter systems degenerate in parallel in the IRBD phenotype of prodromal PD [115], the second prodromal PD condition, constipation, was completely overlooked. Meanwhile, constipation is the second strongest risk factor associated with later PD diagnosis after having a family history of PD or tremor [84]. Pathological α-synuclein deposition is present throughout the gastrointestinal tract up to 20 years preceding the diagnosis of PD and constipation prevalence tends to increase with disease progression [116]. While a common and somewhat subjective feeling, constipation is very difficult to assess and this is not a neuroimaging task. But for nuclear imaging in general, if ^{18}F-DOPA PET/CT whole-body scans are analyzed, the greatest ^{18}F-DOPA activity can be seen not in the brain but the liver, pancreas, other exocrine glands, elements of the gastrointestinal tract, and the urinary system [111]. The colonic ^{11}C-donepezil uptake is decreased in IRBD cases [107]. About 80% of PD patients, including de novo PD patients, exhibit prolonged colonic transit time and perhaps PET imaging will provide some important findings in this area of PD studies in the future. Returning to the hypothesis of neuroinvasion by an unknown pathogen, its authors suggested that the stomach may be a route to the pathogenic invasion in question because "early sites of Lewy pathology are the olfactory bulb and enteric plexus of the stomach" [113]. Again, if this hypothesis will become an established fact, than PD-related neuroimaging will be reinforced by the gastrointestinal tract-related imaging.

4.5. The α-synuclein dilemma

Lewy bodies, their association with PD, and their presence in substantia nigra were described already in the 1910s [117,118]. For the next hundred years, this subject had remained a solely histologic diagnostic issue that was stimulated by introduction of an advanced silver-staining technique for α-synuclein in immunoreactive Lewy bodies [119]. Currently, cerebrospinal fluid, saliva, and blood α-synuclein levels, high-resolution ion-mobility mass spectrometry, and photomicrographs obtained from skin or colon biopsies and postmortem brain tissue samples permit to assess Lewy bodies, Lewy neuritis, and α-synuclein concentrations and deposition peculiarities quite accurately [120,121]. The question may arise of why nuclear imaging should be added to this armamentarium? We already know that PD, Parkinson's disease dementia, dementia with Lewy bodies, and MSA are α-synucleinopathies while CBS and PSP are tauopathies.

This question received several answers. First, while α-synuclein aggregates appear in the body much earlier than the motor symptoms reveal themselves, it was suggested that α-synuclein-specific imaging may help in the early diagnosis of prodromal PD [116,122]. Such approach raises the cost-effectiveness issue because contrary to β-amyloid-specific imaging (^{11}C-PIB and several ^{18}F-labeled tracers) and tau imaging (^{18}F-AV-1451, ^{18}F-T808, ^{18}F-THK523, ^{18}F-THK5105, ^{18}F-THK5351, and less effective ^{11}C-PBB3) no suitable tracers were yet developed for α-synuclein [122,123]. Secondly, when such tracers are developed, they may be used for evaluation of the degree, location, progression of PD, and to monitor the effectiveness of treatment [122]. The cost-effectiveness issue will remain because progression of PD and therapeutic effectiveness has been successfully monitored by several already existing methods. The authors of the current review see the effectiveness of the future α-synuclein imaging not in its clinical application but rather in further investigation of PD pathology. Two hypotheses exist: either α-synuclein aggregates trigger neuroinflammation that leads to neurodegeneration, or rather neurodegeneration appears first and neuroinflammation is an aftereffect of it [124–127]. Further progress in α-synuclein nuclear imaging may clarify the matter.

Waiting for a proper α-synuclein-specific radiotracer, an attempt was made to assess the involvement of α-synuclein in PD pathological process indirectly by checking the condition of autonomic nerve terminals in prodromal stages of PD using ^{11}C-donepezil, ^{123}I-MIBG, and ^{18}F-DOPA PET [107]. The pathological changes in the peripheral autonomic nervous system were detected, but this PET study was not reinforced with biopsy results and the involvement of α-synuclein remained unclear.

4.6. The PD-imaging protocol

Summarizing all the above-said, the currently available imaging armamentarium for PD investigation is very broad, variable, and diversified and includes structural, diffusion-weighted and diffusion tensor, resting-state, and task-based functional MRI, proton magnetic resonance spectroscopy, transcranial B-mode sonography, SPECT, and PET. Already in 2014, Politis indicated a dozen of MRI techniques and about a hundred various radiotracers that were used for investigation of PD [45]. Not all of them are needed, suitable, and practicable for a routine clinical practice. There are three main clinical tasks in PD cases: early diagnosis, differential diagnosis, and longitudinal treatment monitoring; and the imaging modalities are to be selected accordingly. Specifically, PET is a reliable tool for quantifying nigrostriatal functions, glucose metabolism, amyloid, tau and α-synuclein molecular imaging, as well as neuroinflammation [128]. Besides ^{18}F-DOPA and ^{18}F-FDG, PET and SPECT use various other radiopharmaceuticals. Also, some studies have demonstrated that myocardial ^{123}I-MIBG scintigraphy can be useful for the early differential diagnosis of patients with PD from other atypical PD [50,107,129].

While impressive, such variability of tools was questioned from practicability and clinical usefulness viewpoints. Suitable for in-depth scientific research purposes, advanced imaging PD-related techniques were assessed as time-consuming, unsuitable for routine clinical work, and an opinion was expressed that "no neuroimaging modalities are

specifically recommended for routine use in clinical practice" [45,118]. Thus, the above-mentioned [24–27] negativism toward PD-related imaging partially remained. It is not surprising because no generally accepted PD-imaging protocol currently exists. To answer this urgent need, Nicastro et al. suggested the clinical work-up in the evaluation of a subject with parkinsonism [128]. The authors selected four imaging tools: ^{18}F-DOPA PET, ^{18}F-FDG PET, ^{123}I-MIBG scintigraphy, and D2 PET. Of them, ^{18}F-DOPA PET may help to separate degenerative and non-degenerative conditions as the first step of the imaging investigation. After that, ^{18}F-FDG PET and ^{123}I-MIBG scintigraphy will help to separate PD cases from CBS, MSA, and PSP cases because ^{18}F-FDG will be normal in PD and pathological in CBS, MSA, and PSP, while ^{123}I-MIBG will be pathological in PD and normal in the other conditions. D2 PET was selected to investigate the function of D2 postsynaptic receptor. This tool uses ^{11}C-raclopride, which usually shows normal or increased uptake in unmedicated PD patients [130]. When D2 PET is applied, the uptake readings will be normal in PD and CBS and pathological in MSA and PSP [131,132]. If the altered extrastriatal serotonergic transmission is suspected in early PD, ^{123}I-FP-CIT SPECT images may be analyzed [133]. Such clinical work-up suggestion is a welcome step in the right direction and, most probably, the full protocol for neuroimaging investigation of PD and of differential diagnosis of PD-suspicious cases will appear in the nearest future. DAT SPECT may be included in this protocol given the latest works introducing the improvement of the method [134–136]. Recently it was suggested that DAT SPECT could be reinforced with an artificial neural network approach and "functional dopamine transporter volume" as a new quantitative index to evaluate the 3D volume of functional DATs and with automated image-based classification system for striatal DAT uptake [137–139]. In general, PET and SPECT scans are evaluated either by qualitative method based on a visual assessment of a radiotracer uptake in the region of interest or by semi-quantitative interpretation that permit to establish indexes and ratios of the uptake between various zones within the region of interest (for example, Caudate-putamen index, CPI) [140]. It is expected that such quantitative index approach will be further developed in the future.

Another currently acute and will-be-developed in future topic deals with COVID-19-related brain damages and neurological complications. ^{18}F-FDG PET was used to investigate post-COVID parkinsonism and cortical hypo-metabolism as well as hyper-metabolism in the brainstem, mesial temporal lobes, and basal ganglia were detected [141]. Another study with ^{18}F-FDG PET established that COVID-hyposmia and PD-hyposmia are of different origin and with different parts of the brain being affected [142].

While the differential diagnosis protocol is more or less clear, the early diagnosis protocol is not at all clear. The earlier-mentioned Braak staging of PD brain pathology [98–100] is well-known among the neuroradiologists. In the review paper dedicated to PD-related neuroimaging, Weingarten et al. mentioned that this staging assumes the earliest stages of PD to be detected in the medulla in the dorsal motor nucleus of the vagus, the olfactory cortex, enteric nervous system, and some other areas of the peripheral nervous system [143]. It brings us again to serotonin-specific ^{123}I-FP-CIT SPECT and other modalities beyond well-established dopamine-specific imaging that are to be further explored. Non-dopamine lesions in PD were described in detail [144,145], but the described imaging armamentarium was relatively limited and included functional MRI (fMRI), ^{123}I-meta-iodobenzylguanidine (MIBG), ^{11}C-WAY 100635 PET, and ^{18}F-FDG PET in addition to the above-mentioned ^{123}I-FP-CIT SPECT. Yet, the emerging literature on PD imaging is still dopamine-concentrated that prevents a design of the early diagnosis protocol.

In connection with the early diagnosis of PD, the closer cooperation between neuropathologists and neuroradiologists is very desirable. In addition to the above-mentioned Braak six-grade pathological staging of PD, the glossopharyngeal and vagal areas, immunoreactive astrocytes in the forebrain, lesions in dorsal horn layer I, parasympathetic and sympathetic pre- and postganglionic neurons, the medulla oblongata, pontine tegmentum, and olfactory bulb/anterior olfactory nucleus involvement in the PD development were most scrupulously studied by pathologists [146–149]. Pathologists also detected neuroinflammation of the substantia nigra and changes in the left and right putamens in patients with IRBD [150]. But, how Del Tredici and Braak lamented already in 2020, while the pathological staging for PD exists in general, cell loss and synapse loss are not staged yet [151]. This is a clear invitation to cooperation between neuropathologists and neuroradiologists.

5. Conclusion

Currently available set of neuroimaging tools, that includes various types of MRI, proton magnetic resonance spectroscopy, SPECT, PET, and scintigraphy, can provide adequate imaging data for early diagnosis, differential diagnosis, progression assessment, and treatment assessment of PD. To adjust this armamentarium to routine clinical needs, there is an urgent need for the generally accepted protocol for PD-related imaging investigations. Closer cooperation and data exchange between radiologists and pathologists is desirable.

Disclosure of conflicts of interest

The authors declare no conflict of interest.

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