Review Article
PET, SPECT, and MRI imaging for evaluation of Parkinson's disease

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Abstract: This review assesses the primary neuroimaging techniques used to evaluate Parkinson's disease (PD) - a neurological condition characterized by gradual dopamine-producing nerve cell degeneration. The neuroimaging techniques explored include positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI). These modalities offer varying degrees of insights into PD pathophysiology, diagnostic accuracy, specificity by way of exclusion of other Parkinsonian syndromes, and monitoring of disease progression. Neuroimaging is thus crucial for diagnosing and managing PD, with integrated multimodal approaches and novel techniques further enhancing early detection and treatment evaluation.

Keywords: Parkinson's disease (PD), diagnosis, evaluation, positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI)

Introduction

Parkinsonism is a broad classification of neurological movement disorders. The most prevalent form of parkinsonism is Parkinson's Disease (PD) [1]. PD is known to affect 1 to 2 individuals per 1000. The worldwide prevalence of PD is estimated to be 1% of individuals older than 60 years of age. Notably, 5-10% of these patients have a genetic predisposition to PD [2]. PD is characterized as a chronic, progressive neurodegenerative disorder predominantly driven by the degeneration of dopaminergic cells within the substantia nigra and the abnormal accumulation of alpha-synuclein protein aggregates (i.e., Lewy bodies) [3, 4]. The resulting decline of dopamine in the nigrostriatal pathway gives rise to the hallmark manifestations of PD, including bradykinesia, muscle stiffness, resting tremor, and impaired balance and coordination. PD is also often accompanied by an array of non-motor symptoms, including depression, apathy, postural hypotension, cognitive impairment, and sleep disorders [5].

This prevalence and debilitating symptomology highlight the importance of early interventions to slow disease progression. Early intervention in PD is critical for optimizing patient management. Initiating treatment in early phases targets dopaminergic and non-dopaminergic systems before extensive neuronal loss occurs, which can slow progression of both motor and non-motor symptoms [6, 7] (**Figure 1**). Current disease management strategies for PD address dopamine deficiency by aiming to replenish dopamine levels or mimic similar activity in the central nervous system (CNS) [8]. The cornerstone of PD pharmacotherapy is levodopa, a blood-brain-barrier-soluble dopamine precursor, typically combined with carbidopa, a peripheral dopamine decarboxylase inhibitor. Accompanying therapies, including dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, and monoamine oxidase B (MAO-B) inhibitors, are used for symptom management and to bolster levodopa's effects [9, 10]. For instance, early use of MAO-B inhibitors like rasagiline and early initiation of levodopa therapy has shown to slow functional decline and provide symptomatic relief in PD patients [11, 12]. Regarding surgical intervention, deep brain stimulation (DBS) of the subthalamic nucleus is a valuable treatment option for more severe motor symptoms [13]. From a neuroplasticity perspective, early intervention by way of physical exercise and cognitive training enhances compensatory mechanisms and improves functional outcomes in PD [14, 15].

The early diagnosis of PD remains a significant challenge, as it is primarily contingent on clinical criteria, including motor symptoms, which often manifest at a relatively advanced stage with irreversible neuronal degeneration [9]. Furthermore, the clinical presentation of PD can overlap with other Parkinsonian disorders, such as Lewy body dementia and multiple system atrophy (MSA), leading to diagnostic uncertainties, particularly in the earlier stages of the disease [16]. If PD is misdiagnosed as another Parkinsonian disorder, interventions implemented may be ineffective [17]. Consequently, there is a need for objective and reliable biomarkers to facilitate early and accu-
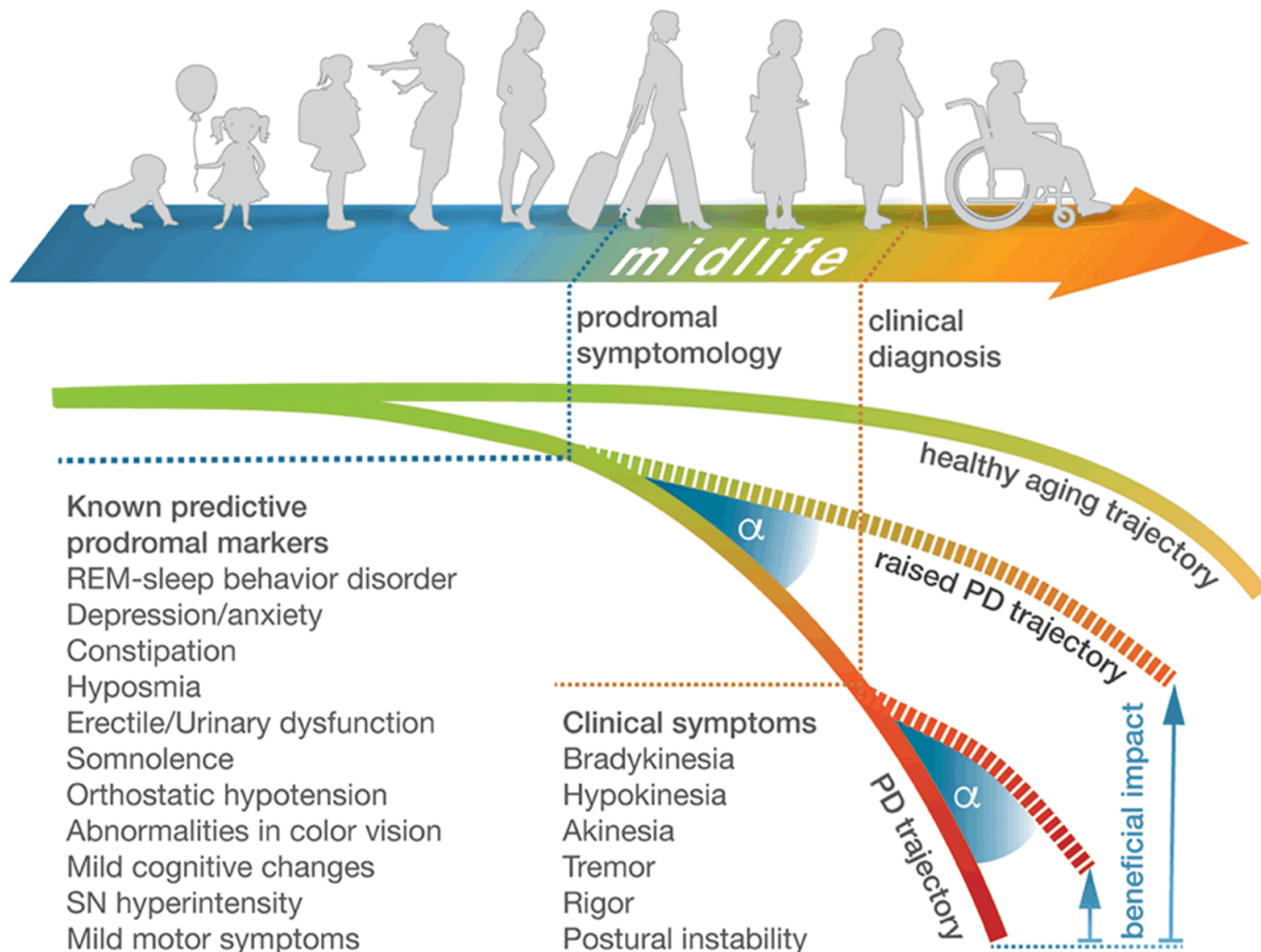
Figure 1. The progression of Parkinson's disease (PD) from its prodromal to clinical stages is depicted in this diagram, illustrating the typical development of the disease across an individual's lifespan - from early childhood through to old age. The upper curve in the diagram represents the trajectory of normal brain health, while the lower curve depicts the divergence observed in those who eventually develop PD. Motor symptoms, which are the defining characteristics of PD, typically appear during the later stages of the disease. However, these motor symptoms are often preceded by a prodromal phase, which may manifest several years, or even decades, earlier during middle age. This prodromal phase is characterized by a range of symptoms that are less specific to PD and exhibit significant variability in terms of their onset, timing, and presentation among different individuals. Reproduced from Kilzheimer A, Hentrich T, Burkhardt S, Schulze-Hentrich JM. The challenge and opportunity to diagnose Parkinson's disease in midlife. Frontiers in Neurology. 2019 Dec 17;10:484578. © 2019, with permission under Creative Commons Attribution 4.0International Public License (https://creativecommons.org/licenses/by/4.0/legalcode) [9].

rate diagnosis, monitor disease progression, and predict therapeutic responses to treatment (e.g., pharmacotherapy and deep brain stimulation (DBS) therapy) [18-20]. Current neuroimaging techniques used for the diagnosis and management of PD provide invaluable insights into the underlying structural and molecular alterations. This review provides an in-depth overview of the main neuroimaging modalities employed in PD such as single-photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI). In addition, we will investigate emerging techniques that could be useful for advancing our understanding of the disease and facilitating personalized treatment strategies.

A brief overview on the pathophysiology of PD

PD is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc). This neurodegeneration results in a reduction in dopamine, disrupting the nigrostriatal pathway, which is critical for motor control [21]. The result of this disruption leads to various motor symptoms, which include rigidity, tremors, postural instability, and bradykinesia. The nigrostriatal pathway, a critical basal ganglia circuitry component, normally facilitates smooth, coordinated movements through balanced dopamine release. In PD, the gradual loss of SNc neurons leads to striatal

dopamine depletion, disturbing the equilibrium of neurotransmitter signaling within the basal ganglia. This disruption extends beyond the dopaminergic system, affecting cholinergic, serotonergic, and noradrenergic pathways [21]. Similarly, PD can extend its pathological reach to multiple brain regions beyond the substantia nigra [22]. A significant indicator of PD is olfactory dysfunction, characterized by the aberrant overexpression of tyrosine hydroxylase-positive (dopaminergic) cells within the olfactory bulb [23, 24]. Post-mortem studies have documented the presence of α-synuclein-containing Lewy bodies in various hypothalamic nuclei [25, 26]. These proteinaceous inclusions not only cause structural abnormalities but also disrupt neuronal function, contributing to non-motor symptoms, including autonomic dysfunction, sleep disturbances, and altered energy metabolism [27]. Both olfactory impairment and hypothalamic Lewy body distribution serve as potential biomarkers in PD, where the former often precedes motor symptoms by years, offering early diagnostic potential, while the latter correlates with disease progression, providing valuable insight into the extent of neurodegeneration [22, 28].

The differential pattern of neurodegeneration in PD versus other Parkinsonian syndromes has significant implications for diagnosis, treatment, and prognosis. In PD, the relative preservation of postsynaptic receptors explains the good initial response to dopamine replacement therapies. Conversely, the poor response to such therapies in atypical Parkinsonian syndromes reflects the loss of both pre- and postsynaptic elements [29]. Non-motor symptoms in PD, such as sleep irregularities, depression, anxiety, and cognitive impairment reflect the involvement of non-dopaminergic systems. The deterioration of norepinephrine-producing neurons in the locus coeruleus, serotonin-secreting neurons in the raphe nuclei, and acetylcholine-releasing neurons in the nucleus basalis of Meynert contribute to these diverse symptoms [30]. Additionally, alpha-synuclein pathology related to the enteric system may explain gastrointestinal symptoms and has led to hypotheses attempting to understand the pathophysiology of PD outside of the CNS [31]. Recent research has also shown evidence of neuroinflammation in the pathogenesis of PD. Activated microglia and astrocytes release pro-inflammatory cytokines, potentially exacerbating neuronal damage [32-35]. Molecular and structural imaging techniques leverage specific targets and structures associated with the pathophysiology of PD and can assist in the evaluation of PD.

Molecular imaging for evaluation of PD

Molecular imaging techniques such as SPECT and PET have the potential to identify and characterize pathophysiology, monitor disease progression, and differentiate PD from other Parkinsonian syndromes. The dopamine transporter (DAT), located on presynaptic membranes of striatal dopaminergic neurons, is crucial for dopamine reuptake and signaling termination [36]. In PD, DAT levels decrease markedly due to dopaminergic neuron loss, serving as a key biomarker for presynaptic dysfunction. SPECT and PET using radiotracers like [123I]-ioflupane (DaTscan) can visualize and quantify DAT reductions. These imaging techniques provide an assessment of dopaminergic system integrity, allowing discrimination of PD from other movement disorders such as essential tremor or other parkinsonisms [37]. On the postsynaptic side, dopamine receptors, particularly the D2 subtype, mediate dopamine's effects in the striatum. In PD, reduced dopamine release leads to chronic under-stimulation of D2 receptors, contributing significantly to motor symptoms. The brain attempts to compensate by upregulating D2 receptor expression, especially in early disease stages. This compensatory mechanism partially explains the delayed onset of motor symptoms, which typically appear after a 60-80% loss of striatal dopamine [38]. Despite significant presynaptic neuronal loss, postsynaptic D2 receptors often remain relatively intact in PD, particularly in early to mid-stages. This preservation of D2 receptors distinguishes PD from atypical parkinsonian syndromes, which often involve both pre- and postsynaptic degeneration, like multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) [39]. PET imaging with D2 receptor-binding radiotracers such as [11C]-raclopride or [18F]-fallypride can assess striatal D2 receptor availability. In PD, these scans typically show preserved or upregulated D2 receptor density, contrasting with the substantial loss of both presynaptic neurons and postsynaptic receptors in MSA or PSP [39].

Role of SPECT in PD

SPECT is an important molecular imaging modality used for the evaluation of PD. It provides 3D images of functional processes in the body through the detection of gamma waves produced by the injection of radiotracers to uncover pathophysiological changes associated with PD [38, 40]. SPECT has been instrumental in elucidating the molecular pathophysiology of Parkinsonian disorders with dopamine transporter radiotracers since its European Medicines Agency (EMA) approval in 2000 and Food and Drug Administration (FDA) approval in 2011 [38]. Two radiotracers that are typically used with SPECT for imaging DAT are [99mTc]TRODAT-1 and [123I]ioflupane. These radiotracers have unique characteristics and applications that allow the differentiation of PD from other similar conditions. Although both are tropane derivatives, [99mTc]TRODAT-1 has a shorter half-life compared to [123I]ioflupane (6 hr vs 13 hr), is commercially more available, and is less expensive [41, 42]. SPECT is valuable in aiding physicians from differentiating PD from essential tremors. In one study, Song et al., aimed to differentiate essential tremor from PD by analyzing cerebral blood flow through SPECT imaging. The investigators utilized Tc-99m hexamethylpropyleneamine oxime (HMPAO) for the SPECT imaging. Song et al., determined that PD patients who

were tremor-dominant displayed significant hypoperfusion in the thalamus and lentiform nucleus when compared to the group with essential tremor patients [43]. Additionally, the researchers performed a SPECT study to identify changes in cerebral blood flow in various brain regions, in which they found additional hypoperfusion of the cerebellum in ET patients and the frontal lobe, parietal lobe, occipital lobe, and cerebellum in TPD patients. It should be noted that these findings were consistent with other published literature on other imaging modalities [44, 45]. Song et al. state that they noticed cerebellar dysfunction was observed in both groups, but the main distinguisher was the hypoperfusion trend.

[99mTc]TRODAT-1 SPECT: [99mTc]TRODAT-1, a tropane derivative, has been intentionally developed to study neurodegenerative diseases like PD [46]. As a tropane derivative, it binds to DAT on presynaptic neurons in the striatum [47]. Initial rodent and monkey animal studies found [99mTc]TRODAT-1 valuable for studying dopaminergic denervation in PD models [48, 49], leading researchers to evaluate its applications in clinical settings. Later, human studies including 78 PD patients and 40 healthy controls demonstrated [99mTc]TRODAT-1 SPECT to exhibit high sensitivity and specificity in detecting reductions in dopamine transporter levels among patients with PD. Given its broad accessibility, [99mTc]TRODAT-1 SPECT was proposed to be a valuable diagnostic tool for patients with PD [50, 51]. Moreover, [99mTc]TRODAT-1's selective localization and high uptake binding to the dopamine transporter in the striatum, where dopaminergic neuronal loss occurs, make it an ideal radiotracer to localize the pathophysiological changes incurred in PD. Additionally, [99mTc]TRODAT-1 imaging has identified trends over the disease course distinguishing PD from MSA, with lower striatal [99mTc]TRODAT-1 binding in MSA than PD [50, 52].

[123I]ioflupane SPECT: [123I]ioflupane, a radioligand with a high affinity for DAT proteins, has been extensively studied for its clinical utility in diagnosing PD [53]. Similar to [99mTc]TRODAT-1, [123I]ioflupane is a tropane derivative that attaches to DAT [54]. A meta-analysis of 20 research studies evaluated the efficacy of [123I]ioflupane SPECT imaging in diagnosing Parkinsonian syndromes, including PD [53]. The analysis revealed that [123I]ioflupane SPECT imaging could accurately differentiate PD from essential tremor with a specificity of 97% to 100% in early PD, highlighting the potential value of SPECT imaging in early diagnosis [52]. However, it is important to note that while [123I]ioflupane SPECT imaging can distinguish essential tremor from PD, it is less able to differentiate between PD, dementia with Lewy bodies, dementia from PD, multiple system atrophy (MSA), or progressive supranuclear palsy [55-57].

Role of PET in PD

PET utilizes radiotracers to identify molecular pathophysiology associated with disease [38, 40]. It allows non-inva-

sive quantification of biochemical processes by utilizing those radiolabeled probes that bind to specific molecular targets, which are imaged to discern their spatial accumulation [31]. As the radioisotopes decay, they emit positrons that rapidly annihilate with nearby electrons, producing pairs of gamma rays emitted in opposing directions. PET scanner detectors capture these coincident gamma rays. Through reconstruction algorithms, the scanner generates three-dimensional tomographic images that quantitatively reflect the spatial distribution and concentration of the radiotracer within the body [58]. PET images are often registered with CT or MR images to improve structural localization. In the context of PD, PET has been instrumental in elucidating PD's in vivo molecular pathophysiology and advancing diagnostic capabilities. Specifically, PET has enabled researchers and clinicians to characterize the stability and function of the nigrostriatal dopaminergic system, which is critical to the disease pathogenesis [59, 60]. 2-deoxy-2-[18F]fluoro-D-glucose ([18F]FDG) has been an important radiotracer in differentiating PD from other Parkinsonian syndromes [38]. More recently, other PET tracers, particularly [18F]-6-L-fluoro-dihydroxyphenylalanine ([18F]FDOPA), have also been introduced for diagnostic purposes.

[18F]FDG PET: [18F]FDG PET is the most widely utilized PET modality in the field of neurodegenerative diseases, including PD [40]. The radiopharmaceutical [18F]FDG is a radiolabeled glucose analog, where the positron-emitting radioactive isotope fluorine-18 replaces the hydroxyl group at the C-2 position of a glucose molecule. This structural similarity to glucose allows [18F]FDG to be taken up by metabolically active neurons through glucose transporters, primarily GLUT1 and GLUT3 [61]. Once inside the cell, [18F]FDG is phosphorylated by hexokinase to [18F]FDG-6-phosphate and cannot be further metabolized in the glycolytic pathway. This trapping mechanism enables the quantification of regional cerebral glucose metabolism, which serves as a surrogate marker for neuronal activity and synaptic function [62]. The uptake and distribution of [18F]FDG in the brain closely mirror the pattern of glucose utilization, reflecting the metabolic demands of different brain regions. With neurodegenerative pathophysiology, [18F]FDG PET can reveal characteristic patterns of hypometabolism or hypermetabolism that correspond to the underlying neuropathological changes [10].

In PD, [18F]FDG PET has revealed characteristic patterns of hypometabolism in various brain regions, including the posterior temporoparietal, occipital, and frontal cortices [63]. These metabolic abnormalities likely reflect the disruption of functional connectivity within neural networks associated with motor, cognitive, and visual processing [64]. Longitudinal studies have shown that these metabolic alterations progress over time, correlating with symptomatic onset and disease progression. Huang et al. (2007) followed 15 non-demented PD patients longitudinally, identifying a progressive decline in glucose metabolism in various brain regions. They identified a cognitive
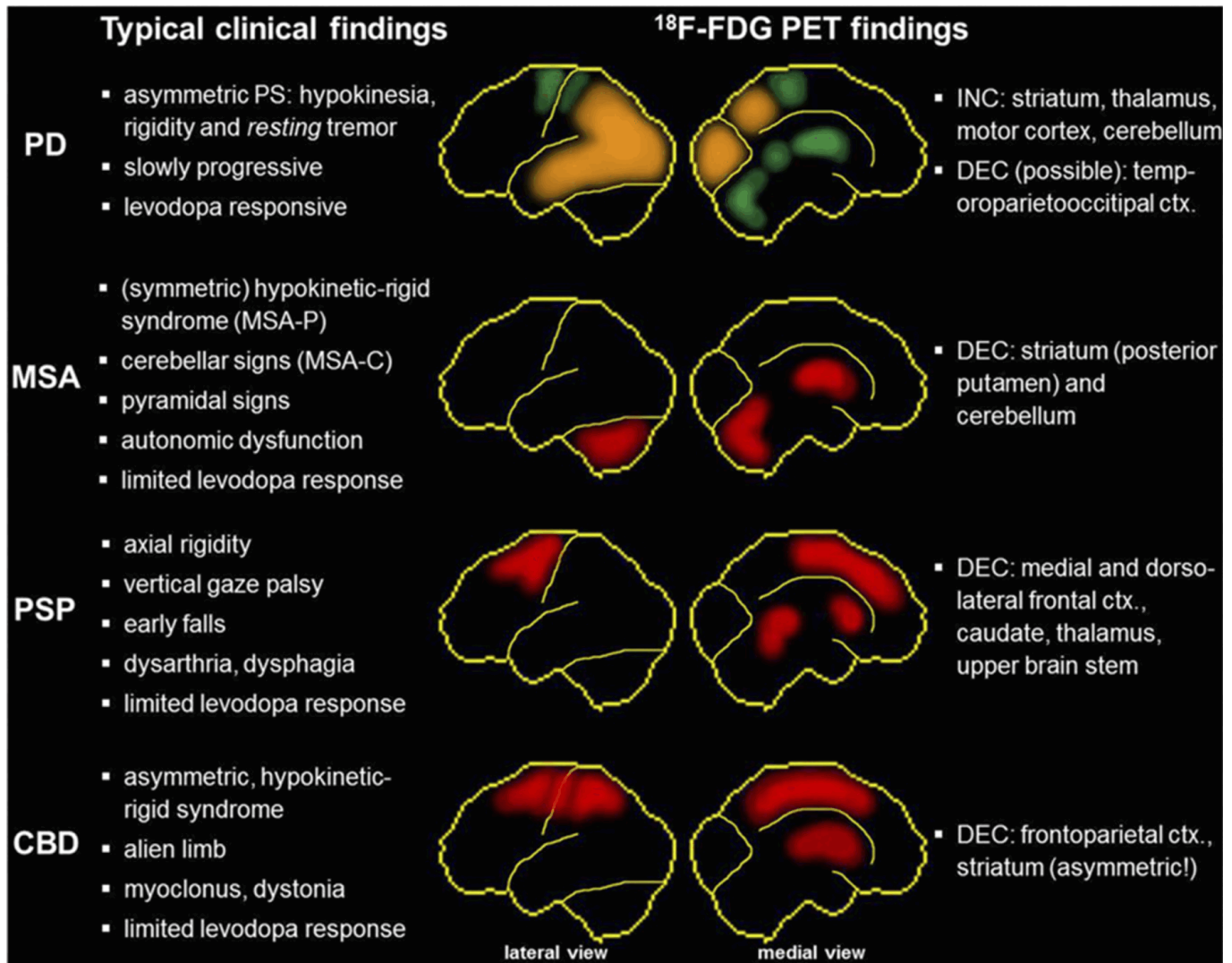
Figure 2. The distinctive clinical features and disease-specific metabolic patterns in Parkinsonian disorders, as identified through [18F] FDG PET imaging, are illustrated here. The lateral (left) and medial (right) views of the brain display regions of relative hypermetabolism (green), hypometabolism (red), and potential metabolic decreases (orange) commonly observed in Parkinson's Disease (PD), particularly among patients experiencing cognitive deficits. In cases of corticobasal degeneration (CBD), hypometabolism is notably asymmetric, with a reduction in metabolic activity on the side of the brain opposite to the most clinically affected body side. Additionally, multiple system atrophy (MSA) subtypes, including those with predominant parkinsonian (MSA-P) and cerebellar (MSA-C) features, present distinct metabolic alteration patterns. Abbreviations: ctx, cortex; DEC, decrease; INC, increase; PS, parkinsonian syndrome. This research was originally published in JNM. Meyer PT, Frings L, Rücker G, Hellwig S. 18F-FDG PET in parkinsonism: differential diagnosis and evaluation of cognitive impairment. Journal of Nuclear Medicine. 2017 Dec 1;58(12):1888-98. © SNMMI [10].

profile specific to PD (PD-related cognitive pattern or PDCP) distinguished by diminished metabolic activity in the anterior supplementary motor area (pre-SMA), precuneus, dorsal premotor cortex, inferior parietal lobule, and left prefrontal region. Concurrently, they observed relative increases in metabolism in the cerebellar vermis and dentate nuclei. The degree of PDCP expression exhibited a significant correlation with individuals' performance on assessments of memory and executive function [65].

Teune et al. (2010) compared 20 PD patients to other neurodegenerative disorders and 18 healthy controls, finding that PD was associated with relatively decreased metabolic activity in contralateral parietooccipital and frontal regions [66]. Borghammer et al. (2010) used high-resolution PET imaging to investigate metabolic changes in small subcortical structures in 21 PD patients and 11 age-matched controls. They observed significant relative hypermetabolism in the external pallidum (GPe) suggesting hypermetabolism in the internal pallidum, thalamic subnuclei, and putamen. They also noted widespread cortical hypometabolism consistent with previous reports in PD patients [67].

A key strength of [18F]FDG PET in PD is its ability to differentiate the disease from other forms of parkinsonism (**Figure 2**) [63]. Hellwig et al. (2012) demonstrated that [18F]FDG PET had superior diagnostic accuracy compared to [123I]IBZM-SPECT in distinguishing between Lewy body diseases (LBD, primarily PD) and atypical parkinsonian

syndromes (APS) in 95 patients with clinically suspected APS. [18F]FDG PET showed a sensitivity of 86% and specificity of 91% for diagnosing APS, with a significantly larger area under the receiver operating characteristic (AUC-ROC) curve (0.94) than [123I]IBZM-SPECT (0.74) for discriminating between APS and LBD. Moreover, [18F]FDG PET reliably differentiated between APS subgroups (multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration) with high sensitivity and specificity [68].

[18F]FDG PET can also differentiate PD from Alzheimer's disease (AD). PD patients exhibit significant hypometabolism in the bilateral inferior parietal lobule, left caudate nucleus, and left inferior frontal gyrus compared to healthy controls [69]. In contrast, AD is characterized by hypometabolism in the posterior cingulate cortex, precuneus, and temporoparietal regions, while frontotemporal dementia (FTD) shows hypometabolism in the frontal and anterior temporal lobes [70]. This differential diagnostic capability is particularly valuable when clinical presentation alone may be ambiguous or concurrent.

[18F]FDG PET has also become an effective tool for investigating the cognitive and neuropsychiatric aspects of PD. Distinct metabolic patterns were found in PD patients with cognitive deficiencies, depression, and apathy. In PD patients with cognitive deficiencies, hypometabolism has been observed in the posterior cingulate cortex, precuneus, and temporo-parietal association areas [71]. Depression in PD has been accompanied by reduced metabolism in the prefrontal cortex, anterior cingulate cortex, and caudate nucleus [72]. Apathy has been linked to hypometabolism in the medial frontal cortex, anterior cingulate cortex, and striatum [73, 74]. These findings suggest the potential of [18F]FDG PET as a biomarker for monitoring these non-motor symptoms and evaluating the efficacy of targeted interventions.

For instance, Garcia-Garcia et al. (2012) studied 68 PD patients (19 with dementia, 28 with mild cognitive impairment [MCI], and 21 with normal cognition) and 20 control subjects using [18F]FDG PET [75]. The study revealed that PD patients with mild cognitive impairment (MCI) demonstrated reduced FDG uptake primarily in the frontal lobe and, to a lesser degree, in parietal regions when compared to cognitively intact patients. In contrast, PD patients with dementia exhibited decreased metabolism in the parietal, occipital, and temporal lobes, with a less pronounced reduction in the frontal lobe compared to those with MCI. Scores on the Mini-Mental State Examination displayed a positive correlation with metabolic activity in multiple cerebral lobes, while distinct cognitive functions were linked to metabolism in specific brain areas [75].

Robert et al. (2012) used [18F]FDG PET to examine the metabolic bases of apathy in 45 non-depressed, non-demented PD patients [76]. They found that apathy scores positively correlated with cerebral metabolism in the right inferior frontal gyrus, right cuneus, right anterior insula, and right middle frontal gyrus. Negative correlations were observed between apathy scores and cerebellar metabolism in the bilateral semilunar lobules of the posterior lobe. Importantly, apathy scores were negatively correlated with cognitive function and correlated positively with the 'retardation' subscore of the Montgomery-Åsberg Depression Rating Scale, but not with motor symptom severity or levodopa dosage. These findings suggest that apathy in PD is associated with metabolic and structural changes in brain regions involved in reward, emotion, and cognition, even in the absence of clinical depression or dementia [77]. While [18F]FDG PET has been extensively studied in PD, it is important to note that metabolic alterations are not entirely specific to the disease and can also be observed in clinical settings with other neurodegenerative conditions [78].

D2/3-binding radiotracers and PET: Several D2/3-binding radiotracers for PET have been developed and routinely used in research settings to image the dopaminergic system [50]. These radiotracers bind specifically to D2/3 receptors, which are primarily located in the striatum and are involved in the regulation of motor function, reward, and cognitive processes [79]. In PD, D2/3 receptor imaging provides information about compensatory mechanisms in response to dopaminergic neuron loss and can monitor treatment response [37, 80]. D2/3 receptor imaging has also been used to study the pathophysiology and treatment of schizophrenia, where increased striatal dopaminergic signaling is thought to underlie positive symptoms, and addiction, where dysregulated dopaminergic signaling in the reward system contributes to compulsive drug-seeking behavior [81, 82].

[18F]FDOPA PET: [18F]FDOPA PET is a highly specific molecular imaging technique that directly assesses the integrity of the nigrostriatal dopaminergic system, a key pathological hallmark of PD. By quantifying the uptake and metabolism of the radiolabeled dopamine precursor [18F]FDOPA in the striatum, clinicians can evaluate the presynaptic dopaminergic function and the degree of neuronal degeneration in the substantia nigra [59]. A comprehensive meta-analysis by Kaasinen and Vahlberg (2017) examined 142 studies involving 3,758 PD patients and 2,046 healthy controls [83]. Results indicate that [18F]FDOPA PET demonstrated exceptional sensitivity and specificity in differentiating PD patients from controls, with a pooled sensitivity of 96.5% and specificity of 94.3% [83]. The study also revealed that [18F]FDOPA uptake in the putamen showed the largest difference between PD patients and controls, with an effect size of -2.52 (95% CI: -2.70 to -2.34), highlighting the putamen as a key region in PD diagnosis [83].

In addition to its diagnostic utility, [18F]FDOPA PET has been extensively employed in monitoring disease progression and evaluating the efficacy of therapeutic interventions targeting the dopaminergic system. A seminal

longitudinal study by Nandhagopal et al. (2009) used [18F] FDOPA PET to track disease progression in PD patients over four years [84]. The researchers followed 78 PD patients and found an annual decline of 5.5% in caudate [18F]FDOPA uptake and 6.3% in putamen uptake. Interestingly, they observed that the rate of decline was not linear, with faster progression in earlier stages of the disease [84]. The role of [18F]FDOPA PET in assessing the effects of deep brain stimulation (DBS) has been a subject of significant interest. A study by Hilker et al. (2003) evaluated 6 PD patients undergoing bilateral subthalamic nucleus DBS [85]. [18F]FDOPA PET was used to test the effects of DBS on dopaminergic function. The researchers found that while DBS significantly improved motor symptoms (reducing the UPDRS motor score by 55.5%), it did not alter striatal [18F]FDOPA uptake. This finding suggested that the clinical benefits of DBS are not mediated through direct effects on dopamine synthesis or storage but rather through modulation of basal ganglia circuitry.

[18F]FDOPA PET has demonstrated exceptional sensitivity and specificity in detecting early dopaminergic deficits, even before the onset of overt motor symptoms, potentially enabling earlier diagnosis and intervention [86]. One study aimed to determine the clinical efficacy of [18F] FDOPA and DAT-SPECT imaging in 11 patients who presented with clinically uncertain Parkinsonian syndrome; the researchers concluded that [18F]FDOPA may have more subtle visual changes, meaning that DAT-SPECT imaging was rated abnormal compared to [18F]FDOPA [87]. This result would necessitate stricter and more uniform criteria of interpretation of the scans. Research indicates that specific patterns of striatal dopamine depletion, such as selective dopamine depletion in the sensorimotor striatum, are associated with distinct clinical phenotypes, such as tremor-dominant or akinetic-rigid subtypes, and a higher risk of levodopa-induced dyskinesia. These results emphasize the possibility of [18F]FDOPA PET as a biomarker for disease subtyping and personalized treatment approaches [88, 89].

While PD research and clinical practice are significantly valuable, widespread implementation of [18F]FDOPA PET faces challenges due to the requirement for specialized equipment and expertise. Recognizing the need for standardization, Morbelli et al. (2020) proposed consensus guidelines for [18F]FDOPA PET imaging in PD [90]. Their recommendations covered various aspects of the imaging procedure, including patient preparation, tracer administration, image acquisition protocols, and data analysis methods. These guidelines aim to improve the consistency and comparability of results across different centers, potentially facilitating larger multi-center studies and more widespread clinical application of [18F]FDOPA PET in PD management.

Other PET radiotracers: While [18F]FDG and [18F]FDOPA have been the mainstay PET radiotracers for PD, other radiotracers have been explored and ongoing research efforts are focused on developing novel radiotracers. For example, Pavese et al. (2006) further elucidated the relationship between dopaminergic function and clinical symptoms in PD using [11C]raclopride PET, which provides insights complementary to [18F]FDOPA PET [91]. In their study of 16 patients with advanced PD, the researchers investigated the correlation between levodopa-induced clinical improvement and in vivo synaptic dopamine release [91]. Patients underwent [11C]raclopride PET scans both off medication and after a single oral dose of levodopa (250 mg levodopa/25 mg carbidopa). The study found that levodopa administration led to significant reductions in [11C]raclopride binding potentials in both the caudate and putamen, indicating increased synaptic dopamine levels. Importantly, results indicated improvements in individual UPDRS motor scores correlated significantly with reductions in putaminal binding potential, suggesting a direct relationship between striatal dopamine release and motor symptom alleviation. Further analysis revealed rigidity and bradykinesia symptoms were alleviated and showed correlation with putaminal dopamine release. There was no improvement shown in tremor or axial symptoms. Additionally, patients who experienced larger changes in putaminal binding potential were more likely to develop dyskinesias.

One area of active application is the use of PET radiotracers targeting pathological protein aggregates, such as alpha-synuclein and tau, which are implicated in the formation of Lewy bodies and neurofibrillary tangles, respectively. These radiotracers enable the in vivo visualization and quantification of protein misfolding and aggregation, providing further understanding of the molecular mechanisms of neurodegeneration in PD. Several promising alpha-synuclein PET tracers have shown selective binding to alpha-synuclein aggregates in animal models and a small subset of patients [92, 93]. These tracers could potentially aid in the differential diagnosis of PD from other synucleinopathies, such as dementia with Lewy bodies and multiple system atrophy, and facilitate the evaluation of disease-modifying therapies targeting alpha-synuclein pathology. Similarly, research using tau PET tracers to identify and quantify tau pathology in PD and related tauopathies was explored [94-98]. While tau aggregates are not a primary hallmark of PD pathology, a subset of PD patients have been observed to have increased aggregates [99, 100].

PET radiotracers targeting specific neurotransmitter systems, such as serotonin, norepinephrine, and acetylcholine, are being actively investigated as potential biomarkers for non-motor symptoms in PD [101]. By visualizing the integrity and function of these neurotransmitter systems, researchers aim to elucidate the neural circuits and molecular pathways underlying cognitive, neuropsychiatric, and autonomic dysfunctions associated with the disease. For instance, serotonin transporter (SERT) PET tracers have been used to assess serotonergic dysfunction in PD, which has been shown to be associated with the
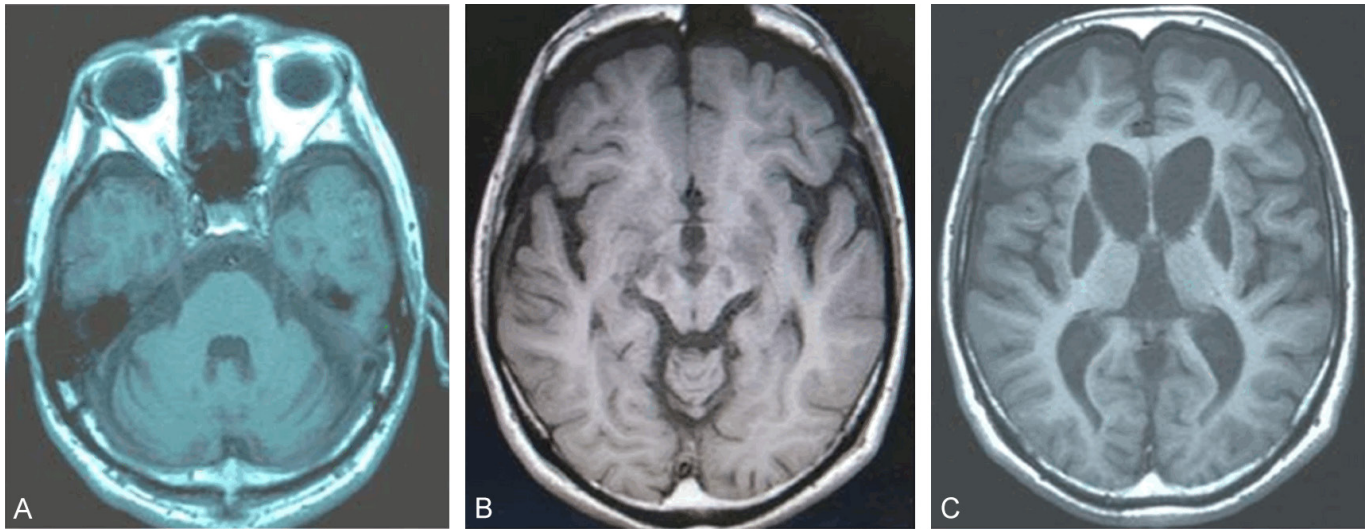
Figure 3. T1-weighted MRI scans of a 42-year-old Parkinson's disease (PD) patient reveal distinct neuroanatomical changes. A. A cross-sectional image at the level of the pons shows notable atrophy of the cerebellar cortex. B. A midbrain section highlights hypointense alterations within the substantia nigra. C. An image at the level of the basal ganglia demonstrates symmetrical hypointense signals within the head of the caudate nucleus and the globus pallidus. Reproduced from Ohta E, Takiyama Y. MRI findings in neuroferritinopathy. Neurology research international. 2012;2012(1):197438. © 2012, with permission under Creative Commons Attribution 4.0International Public License (https://creativecommons.org/licenses/by/4.0/legalcode) [6].

development of anxiety, cognitive impairment, and depression [102-105]. Similarly, norepinephrine transporter (NET) PET tracers have been explored for their potential to evaluate noradrenergic deficits in PD, which may contribute to autonomic and neuropsychiatric symptoms [106]. Additionally, PET radiotracers targeting the cholinergic system have been investigated as potential biomarkers for motor function loss and cognitive impairment in PD [107, 108].

Another promising area of research is the development of PET radiotracers targeting neuroinflammatory processes, such as microglial activation and astrogliosis [109, 110]. Neuroinflammation is increasingly recognized as a key contributor to neurodegenerative diseases, including PD. Radiotracers targeting the 18-kDa translocator protein (TSPO), which is upregulated in activated microglia, have been widely explored for imaging neuroinflammation in PD [109, 111]. These tracers have demonstrated increased binding in brain regions affected by PD pathology, suggesting their potential utility as biomarkers for neuroinflammatory processes. Additionally, PET tracers targeting other neuroinflammatory markers, such as cyclooxygenase (COX) and matrix metalloproteinases (MMPs), are under investigation for their potential to provide complementary insights into the neuroinflammatory cascade in PD [109].

Magnetic resonance imaging for evaluation of PD

Structural and functional MRI techniques also play distinct roles in PD. Structural MRI provides high-resolution images of brain anatomy, aiding in differential diagnosis by revealing macrostructural changes [112]. While not able to detect subtle molecular neurodegenerative-related changes in early PD, advanced structural techniques can identify alterations in key regions such as the substantia nigra and basal ganglia [113]. Conversely, functional MRI (fMRI) attempts to approximate neuronal activity by directly measuring blood-oxygen-level-dependent (BOLD) contrast, which reflects local hemodynamic changes coupled to neuronal activation. fMRI maps brain function by analyzing dynamic spatiotemporal neural activity patterns, revealing both region-specific activations and intrinsic functional networks. In the evaluation of PD, fMRI assesses functional alterations within the basal ganglia-thalamocortical circuits. Unlike structural MRI, functional MRI can reveal abnormal patterns of brain activation or connectivity even when structural imaging appears normal [114, 115].

While MRI is not a central diagnostic modality for PD, it is crucial in excluding other potential causes, such as structural lesions, tumors, or vascular pathologies that could mimic the clinical presentation of the disease [116-120]. Conventional structural MRI sequences can provide valuable insights into the structural integrity of the brain regions affected by PD, including the substantia nigra, basal ganglia, putamen, and globus pallidus [121]. This atrophy can be explained by the degeneration of dopaminergic neurons and the associated loss of neuronal volume. While atrophy can be a non-specific finding and may be present in other neurodegenerative disorders or even normal aging, its presence with relevant clinical symptoms can support the diagnosis of PD [122] (**Figure 3**).

Further image analysis of atrophy in PD patients using various quantitative techniques, including voxel-based
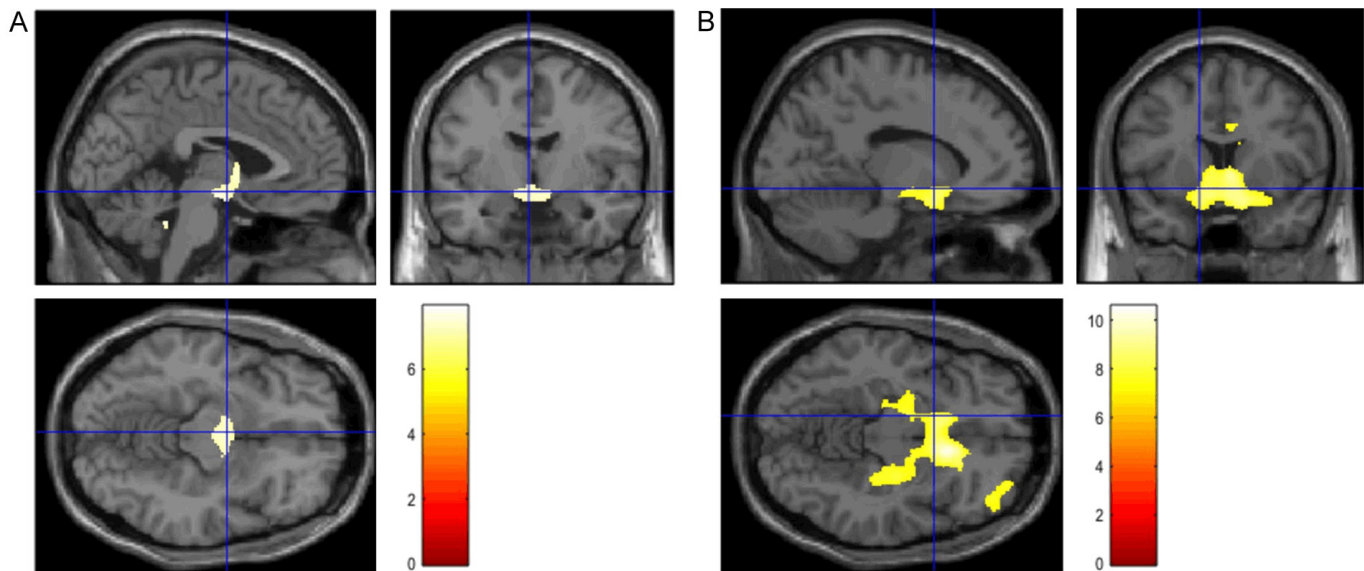
Figure 4. The results of voxel-based morphometry analysis reveal areas of significant structural differences between groups using the contrast of gray matter volume (group 1 > group 2). A. The analysis compares healthy control groups and individuals with early-stage PD. B. Similarly, a comparison between the healthy control group and participants with late-stage PD highlights brain regions where gray matter volume differs significantly between the groups, with the healthy control group serving as the reference for comparison against both early and late stages of PD. Images created by SPM12, Welcome Trust Centre for NeuroImaging, London, UK (http://fil.ion.ucl.ac.uk/spm/software/spm12/). Reproduced from [7].

morphometry (VBM) and tensor-based morphometry (TBM), have been applied [7, 113] (**Figure 4**). These techniques enable precise measurements and mapping of regional volume changes, providing valuable insights into the spatial distribution and temporal progression of atrophy [123]. Studies employing VBM and TBM have consistently reported significant volume reductions in the thalamus, substantia nigra, caudate nucleus, putamen, and cortical areas in PD patients compared to healthy controls [7, 124]. Moreover, the degree of atrophy in specific brain regions positively correlates with disease duration, motor symptom severity, and cognitive impairment, suggesting its potential as a biomarker for disease progression and subtyping [125, 126].

In addition to atrophy, increased or decreased signal intensity on various MRI sequences may be related to pathological processes such as abnormal iron deposition, neuronal loss, gliosis, or alterations in tissue microstructure [6, 127]. One of the most observed signal alterations in PD patients is the presence of hypointense regions within the substantia nigra on T2-weighted and T2*-weighted sequences [128] (**Figures 5** and **6**). This hypointensity is primarily attributed to the increased iron deposition due to disease progression, which is proposed to occur due to oxidative stress [127, 129]. The pattern and extent of iron deposition in PD patients have also revealed a characteristic "swallow-tail" or "wing-beating" hypointense region in the substantia nigra [130]. Additionally, increased iron deposition has been observed in other basal ganglia structures, such as the putamen and globus pallidus, as well as in cortical regions. While iron deposition is a common finding in PD, it may also occur in

normal aging and other neurodegenerative conditions, limiting its specificity for PD diagnosis [129, 131-133]. However, when combined with clinical symptoms and other imaging findings, the pattern and distribution of iron deposition can aid in differential diagnosis [134, 135].

Lastly, MRI has been useful to identify psychiatric comorbidities in PD patients. Reijnders et al. (2010) conducted a voxel-based morphometry study on 55 PD patients to explore apathy and its correlation to brain structure [136]. Results indicated higher apathy scores were correlated with lower gray matter density in multiple cortical regions, which include the insula, bilateral precentral gyrus, precuneus, inferior frontal gyrus, inferior parietal gyrus, and the right posterior cingulate gyrus [136].

Advanced MRI techniques

In recent years, researchers have advanced other MRI techniques, such as the MR Parkinsonism Index (MRPI), Diffusion Tensor Imaging (DTI), and Quantitative Susceptibility Mapping (QSM), that hold promise for enhancing the diagnosis and monitoring of Parkinson's Disease (PD) [11, 137, 138]. The MRPI is a quantitative MRI technique that utilizes T2-weighted imaging to assess basal ganglia abnormalities in PD patients [122]. By analyzing the signal intensity ratios between various basal ganglia structures, such as the globus pallidus, putamen, and substantia nigra, the MRPI generates a numerical score that reflects the degree of basal ganglia degeneration [139]. The MRPI is based on the premise that the degeneration of dopaminergic neurons and associated changes due to iron deposition and tissue microstructure lead to
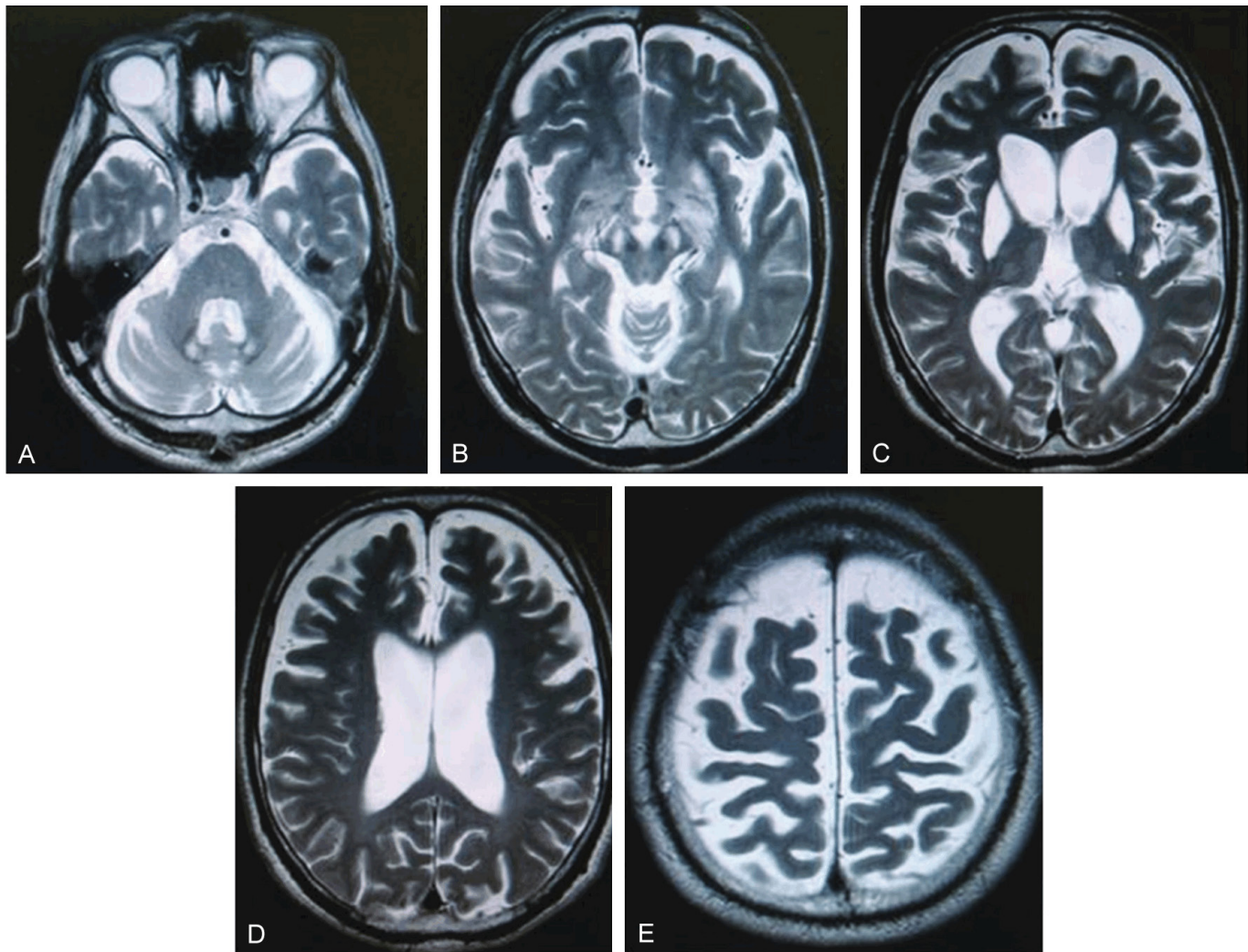
Figure 5. T2-weighted MRI scans (TR 3,440 ms/TE 89.4 ms) of a 42-year-old patient show specific neuroimaging findings. A. A cross-sectional view at the pontine level displays bilateral, symmetric signal loss with central hyperintense abnormalities in the dentate nucleus, along with cerebellar cortical atrophy. B. The midbrain section reveals symmetric high signal intensity in the substantia nigra and a reduced signal change in the red nucleus. C. At the level of the basal ganglia, there is a hyperintense signal surrounded by a hypointense band affecting the putamen and pallidum, along with hazy high signal changes in the bilateral inner thalamus. D. A section through the central lateral ventricles is shown. E. A cerebral cortex section indicates no evident signal changes. Reproduced from MRI findings in neuroferritinopathy. Neurology research international. 2012;2012(1):197438. ©2012, with permission under Creative Commons Attribution 4.0International Public License (https://creativecommons.org/licenses/by/4.0/legalcode) [6].

alterations in the T2 signal intensity within the basal ganglia [140]. By quantifying these signal intensity changes and their ratios between different structures, the MRPI aims to capture the specific pattern of substantia nigra degeneration in the midbrain relative to the pons. Several studies have evaluated the diagnostic accuracy and clinical utility of the MRPI in PD [139, 141-143]. One article indicated a pooled sensitivity of 96% and a specificity of 98% for the MRPI in differentiating PD patients from progressive supranuclear palsy (PSP) [144]. Additionally, the MRPI has been shown to correlate with various clinical measures of disease severity, such as the Unified Parkinson's Disease Rating Scale and Hoehn and Yahr stages [145]. Despite these promising findings, further research in larger subject pools and across different disease stages is necessary. One limitation of QSM would be

the influence of orientation dependence in the white matter due to susceptibility. Orienting for multiple images may lead to patient discomfort, limited clinical feasibility, and increased scanning time [146-148]. Another limitation would be the limited application of QSM to just midbrain landmarks and basal ganglia where changes in susceptibility are commonly observed.

DTI, an advanced MRI technique, measures the diffusion of water molecules within brain tissues. By analyzing the directionality and magnitude of water diffusion, DTI can provide valuable information about white matter tract structural integrity and brain region connectivity [11] (**Figure 7**). In the context of PD, DTI has been extensively utilized to detect microstructural changes and loss of dopaminergic neurons by analyzing alterations in water diffusion properties within white matter tracts connecting
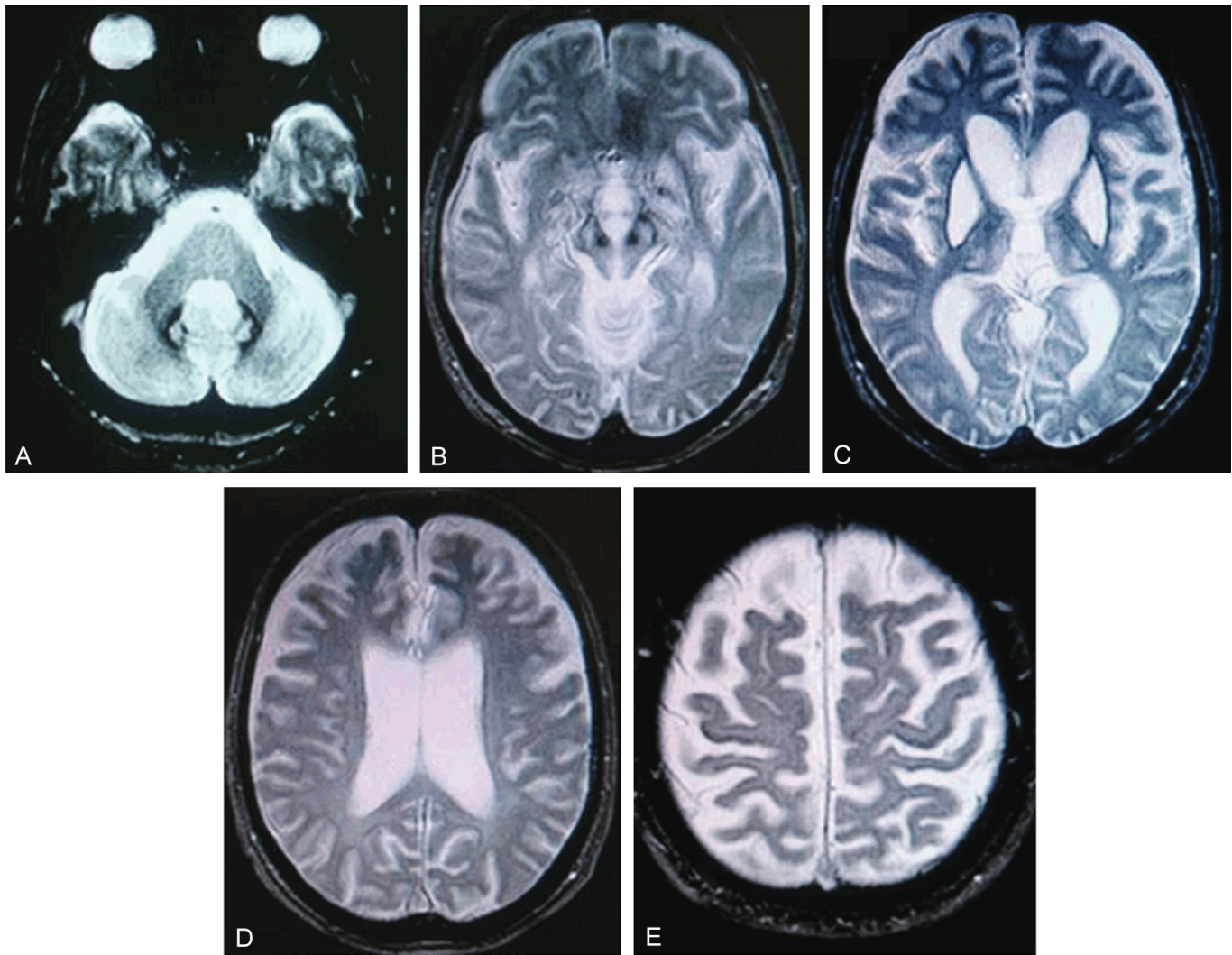
Figure 6. T2-weighted gradient echo sequence images (TR 400 ms/TE 25 ms) of a 42-year-old patient reveal specific abnormalities. A. The pontine level cross-section shows more pronounced signal loss with central hyperintense lesions in the dentate nucleus, more evident than in T2-weighted imaging (T2WI). B. The midbrain section highlights distinct hypointense changes in the red nucleus. C. The basal ganglia exhibit cystic degeneration characterized by a peripheral rim of signal loss, along with bilateral hyperintense abnormalities surrounded by mild hypointensity in the thalamus. D. A section through the central lateral ventricles is depicted. E. The cerebral cortex demonstrates evidence of iron deposition, which is observed as signal loss. Reproduced from MRI findings in neuroferritinopathy. Neurology research international. 2012;2012(1):197438. © 2012, with permission under Creative Commons Attribution 4.0International Public License (https://creativecommons.org/licenses/by/4.0/legalcode) [6].

the substantia nigra and other affected regions [149]. These changes in diffusion patterns reflect the degeneration of axonal projections and disruption of neural circuitry associated with PD pathology. DTI investigations in individuals with PD have consistently demonstrated reduced fractional anisotropy (FA) and elevated mean diffusivity (MD) across multiple white matter structures, including the substantia nigra, midbrain, and nerve fiber tracts connecting to the basal ganglia and cortical regions [11, 150, 151]. These diffusion abnormalities are believed to represent the disruption of white matter integrity and axonal degeneration associated with the disease process.

Furthermore, DTI measures have been correlated with damaged white matter tracts in patients who have cogni-

tive impairment, suggesting their potential as biomarkers for disease progression and treatment monitoring [152-154] (**Figure 8**).

Additionally, DTI has shown promise in detecting early microstructural changes that may precede macroscopic atrophy or other structural abnormalities, potentially enabling earlier diagnosis and intervention [12]. Conversely, DTI findings in PD are not always disease-specific, as similar patterns of white matter alterations have been observed in other neurodegenerative disorders, including Alzheimer's disease [155, 156]. Nonetheless, the integration of DTI with other neuroimaging modalities and clinical data may enhance its diagnostic utility and provide a more comprehensive understanding of the functional and structural alterations linked to PD [157].
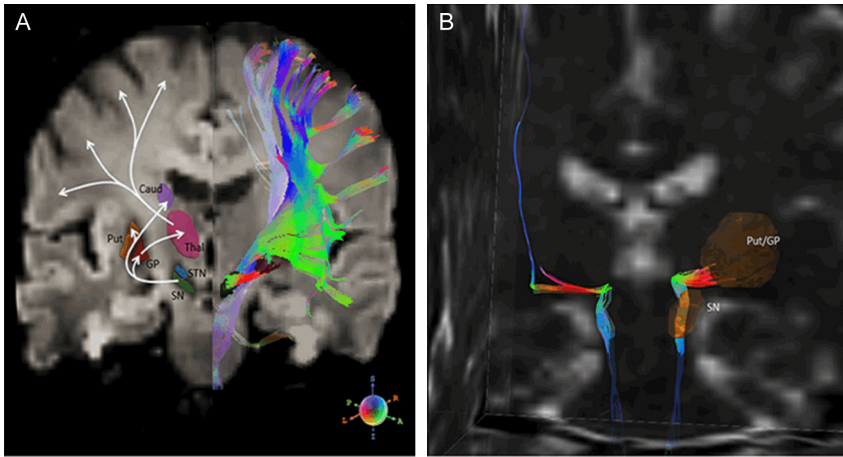
Figure 7. A. The left panel depicts the basal ganglia nuclei along with the direct and indirect pathways implicated in motor function. The right half-panel features diffusion tensor tractography (DTT) streamlines, highlighting the pathways traversing the substantia nigra. B. This section focuses on the isolation of the nigrostriatal tract, which connects the substantia nigra with the inferior putamen and globus pallidus in a healthy individual. The DTT streamlines within the right hemisphere illustrate the anatomical connections of the nigrostriatal tract, originating at the brainstem and substantia nigra, and passing through the putamen and globus pallidus. Some fibers further connect to the thalamus, ultimately projecting to the premotor cortex. The fiber orientation is visually represented using three primary colors: red, green, and blue. It is important to note that DTT does not provide information regarding the directionality of these fibers, whether afferent or efferent. Reproduced from Zhang Y, Burock MA. Diffusion tensor imaging in Parkinson's disease and parkinsonian syndrome: a systematic review. Frontiers in neurology. 2020 Sep 25;11:531993. © 2020, with permission under Creative Commons Attribution 4.0International Public License (https://creativecommons.org/licenses/by/4.0/legalcode) [11].
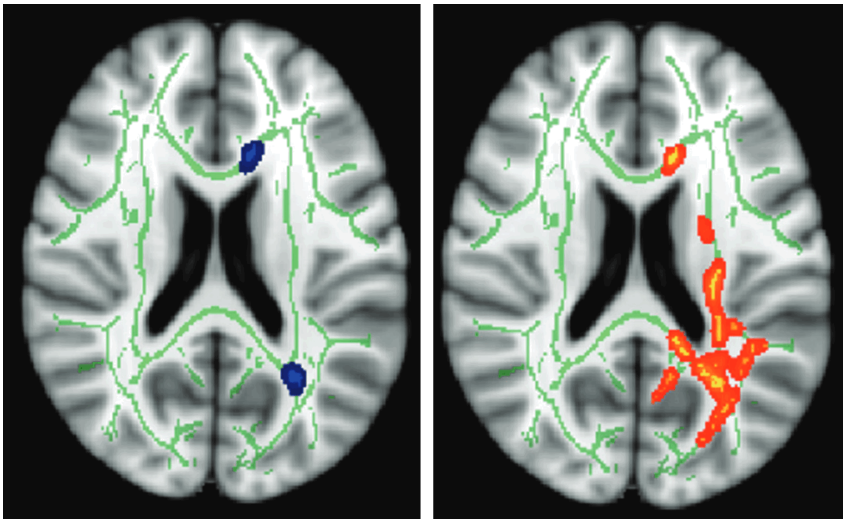

Figure 8. The region of interest (ROI) analysis involves measuring fractional anisotropy (FA) values from the anterior and posterior periventricular regions, which are highlighted in blue on the left side of the image, at baseline. On the right side, the figure illustrates tracts (highlighted in red-yellow) where significant differences in longitudinal FA changes are observed between the control and intervention groups. Reproduced from Stephen R, Solomon A, Ngandu T, Levälahti E, Rinne JO, Kemppainen N, Parkkola R, Antikainen R, Strandberg T, Kivipelto M, Soininen H. White matter changes on diffusion tensor imaging in the FINGER randomized controlled trial. Journal of Alzheimers Disease. 2020 Jan 1;78(1):75-86. © 2020, with permission under Creative Commons Attribution 4.0International Public License (https://creativecommons.org/licenses/by/4.0/legalcode) [12].

QSM is an advanced MRI technique that has gained significant attention in the field of PD neuroimaging [138, 158]. QSM utilizes the inherent magnetic properties of brain tissues to quantify the distribution of magnetic susceptibility sources, such as iron deposits, which are known to accumulate abnormally in PD pathology. QSM works by exploiting the differences in magnetic susceptibility between various tissue types, which are influenced by their chemical composition and microstructure [138, 158]. Iron, being a paramagnetic substance, induces local distortions in the magnetic field that can be measured and quantified using specialized QSM algorithms. In PD patients, QSM has consistently demonstrated increased magnetic susceptibility values in the substantia nigra, reflecting the elevated iron levels associated with the disease [159, 160]. Additionally, increased susceptibility has been observed in other basal ganglia structures, such as the putamen and globus pallidus, as well as in cortical and subcortical regions [161-163]. By quantifying the degree and distribution of iron accumulation, QSM can act as a biomarker for disease staging and monitoring therapeutic interventions aimed at modulating iron homeostasis. Furthermore, the combination of QSM with other advanced MRI techniques, such as DTI and functional MRI, may provide better insight into the structural and functional alterations associated with PD [164].

As imaging technologies continue to advance, higher field strengths are becoming widely accessible for clinical and research applications. Ultra-high field MRI, typically operating at field strengths of 7 Tesla (7T) or higher, offers significant improvements in spatial resolution and contrast compared to conventional clinical MRI systems (typically 1.5T or 3T) [165, 166]. The enhanced resolution and contrast of ultra-high field MRI can be particularly beneficial in the visualization of intricate structures like the substantia nigra, a critical region affected in PD pathology. Ultra-high field MRI has the potential to reveal subtle structural and functional changes that may be obscured or undetectable at lower field strengths, potentially enabling earlier and more accurate diagnosis of PD. One of the key

advantages of ultra-high field MRI in PD is the improved visualization and quantification of iron deposition in the substantia nigra and other affected areas of the brain. The increased sensitivity to magnetic field distortions at higher field strengths allows for better delineation and quantification of iron-related hypointensities, which could aid in differential diagnosis and disease monitoring. Furthermore, ultra-high field MRI provides enhanced spatial resolution for structural imaging, enabling more precise measurements of atrophy and volumetric alterations in the substantia nigra, basal ganglia, and other affected brain regions [167]. This increased level of detail could potentially uncover subtle anatomical abnormalities that may be missed at lower field strengths. Nonetheless, ultra-high field MRI is still a relatively new and evolving technology, with challenges related to increased magnetic field inhomogeneities, specific absorption rate limitations, and specialized hardware and software requirements [168].

Functional MRI (fMRI)

Functional MRI (fMRI) is a powerful neuroimaging technique that measures changes in blood flow and oxygenation levels, which serve as a proxy for neural activity [169]. One of the strengths of fMRI in PD is its ability to capture functional changes that may precede structural abnormalities, potentially enabling earlier diagnosis and intervention. In the context of PD, fMRI has been extensively utilized to elucidate alterations in neural functional connectivity and activity patterns associated with various brain networks, including the motor, cognitive, and limbic circuits and the motor and cognitive dysfunctions observed in the disease [169-171].

By mapping the functional networks involved in motor control, cognitive processing, and other brain functions affected by PD, fMRI can offer a better understanding of neural substrates that appear latent to PD clinical manifestations. Additionally, fMRI has the potential to identify functional biomarkers that could aid in the diagnosis and monitoring of PD, as well as the evaluation of therapeutic interventions targeting specific neural circuits [172]. For instance, decreased activation in the primary motor cortex, supplementary motor area, and basal ganglia has been observed during motor tasks, reflecting motor dysfunction in PD [169].

Furthermore, results of fMRI research indicate neural correlates of non-motor symptoms in PD, including cognitive impairment [173, 174]. Altered functional connectivity patterns have been observed in the default mode network, which is involved in introspective processes and self-referential thoughts, as well as in other cognitive and affective networks [175]. Additionally, fMRI has the capability to assess the efficacy of therapeutic interventions, which include deep brain stimulation or pharmacological treatments, on brain function and connectivity [171]. Conversely, fMRI findings in PD are heterogeneous, which

can lead to possible discrepancies due to various factors, such as disease stage, medication effects, and cognitive status [172, 173].

Magnetization transfer (MT) imaging

The technique for MT imaging relies on the principle of magnetization exchange between protons in free water and those bound to macromolecules [116]. By applying an off-resonance radiofrequency pulse, the magnetization of the bound protons is selectively saturated, leading to a decrease in the measured MRI signal due to the exchange of magnetization between the two pools. In PD patients, MT imaging has revealed decreased MT signal in certain brain regions, which can be attributed to lower macromolecule concentrations resulting from lower axonal densities and demyelinated lesions [116, 176, 177]. Additionally, several studies have reported decreased MT ratio (MTR) values in various brain regions of PD patients, including the neocortex, substantia nigra, basal ganglia, thalamus, and cortical areas [178, 179]. These decreases in MTR are thought to reflect a reduction in the macromolecular content of the affected tissues, potentially due to neuronal loss, axonal degeneration, and demyelination processes associated with the disease pathology [178].

The MT imaging technique has been utilized to further explore the correlation between changes in MTR and clinical measures of disease severity, cognitive impairment, and depression in PD patients [178, 180]. While MT imaging holds promise as a complementary tool for assessing microstructural alterations in PD, MTR changes are not entirely particular to the disease and can also be observed in other neurological disorders and normal aging [181].

Chemical Exchange Saturation Transfer (CEST)

Chemical Exchange Saturation Transfer (CEST) utilizes the selective saturation and indirect detection of specific metabolites and proteins [177]. The CEST technique relies on the exchange of magnetization between protons in mobile molecules (e.g., water) and protons in slowly tumbling molecules, such as proteins or metabolites [177]. By selectively saturating the resonance frequencies of these slowly tumbling molecules, the magnetization exchange process can be detected as a decrease in the MRI signal from the surrounding mobile protons.

In the context of PD, CEST has shown promise in visualizing dopaminergic neuron reduction in the substantia nigra, a characteristic of PD pathology [182]. CEST has been utilized to target and detect the exchange of magnetization between specific molecules associated with dopaminergic neuron degeneration and nearby water protons [182]. By selectively targeting these molecules, CEST has the capability to allow for further understanding of molecular-level information about the biochemical alterations associated with PD, potentially enabling earlier and more specific diagnosis. While CEST is a promising tech-

nique, its application in PD is in early development, so later research is necessary to validate its diagnostic utility and establish standardized protocols [183, 184].

Conclusion and future directions

The diagnosis of PD remains challenging due to its complex and heterogeneous nature. However, advanced neuroimaging techniques have significantly improved our understanding of the structural, functional, and molecular changes underlying the disease, providing crucial tools for early diagnosis, disease monitoring, and treatment evaluation. SPECT, PET, and MRI imaging play a major role in accurately distinguishing PD from other conditions and providing crucial information on the structural and functional changes occurring in PD. Integrating multimodal imaging approaches, combining SPECT, PET, MRI, and other methods, offers a comprehensive assessment of brain structure, function, and molecular changes in PD. Further effort must be made to leverage the mentioned imaging techniques by investigating longitudinal diagnosis and tracking disease progression. The rapid advancements in imaging technologies and the development of new radiotracers, coupled with multimodal approaches, will open new avenues for early detection, disease subtyping, and personalized treatment. As research continues to uncover PD's complex pathophysiology, neuroimaging will play a crucial role in translating these discoveries into improved patient care and outcomes for individuals affected by this debilitating disorder.

Disclosure of conflict of interest

None.

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