Update on Molecular Imaging in Parkinson's Disease

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Abstract Advances in radionuclide tracers have allowed for more accurate imaging that reflects the actions of numerous neurotransmitters, energy metabolism utilization, inflammation, and pathological protein accumulation. All of these achievements in molecular brain imaging have broadened our understanding of brain function in Parkinson's disease (PD). The implementation of molecular imaging has supported more accurate PD diagnosis as well as assessment of therapeutic outcome and disease progression. Moreover, molecular imaging is well suited for the detection of preclinical or prodromal PD cases. Despite these advances, future frontiers of research in this area will focus on using multi-modalities combining positron emission tomography and magnetic resonance imaging along with causal modeling with complex algorithms.

Keywords Parkinson's disease · Positron emission tomography · SPECT

Introduction

Parkinson's disease (PD) is a prevalent neurodegenerative disorder with high clinical heterogeneity, although classically characterized by motor (bradykinesia, tremor, and

rigidity) and non-motor manifestations such as rapid eye movement sleep behavior disorder (RBD), constipation, and cognitive deficits. The diagnosis of PD remains a challenge for clinicians relying primarily on clinical profiles that are difficult to differentiate from other disorders with overlapping manifestations, especially at its early stage. Therefore, objective measurements such as positron emission tomography (PET) imaging may be helpful for increasing the accuracy of early diagnosis. Recently, dopamine (DA) transporter (DAT) imaging and a smell test were included in the criteria for PD diagnosis by the international Movement Disorder Society [1] as key components of exclusion or supportive items. Over the past 25 years, the molecular imaging of PD has advanced substantially, improving our capacity to better understand its pathogenesis, make a more accurate diagnosis at an earlier stage, make differential diagnoses, and monitor its progression. With continuing efforts and advances in the field, imaging strategies hold promise in identifying the treatment effects of potential disease-modifying agents or interventions for PD, indications greatly needed in the field. Here, we summarize the updates on molecular imaging in PD, mainly focusing on single photon emission computed tomography (SPECT)/PET imaging and briefly covering functional magnetic resonance imaging (fMRI) in this field as well.

Targets of Molecular Imaging in PD

Imaging the Dopaminergic System

The conventional methods for imaging the dopaminergic system include the estimation of: (1) L-aromatic amino-acid decarboxylase (AADC) activity with ¹⁸F-fluoro-L-

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dopa (FD), which also reflects the FD uptake and the capacity of ^{18}F -fluorodopamine (FDA) storage in presynaptic vesicles [2]; (2) reuptake of DA, which can be evaluated by DAT density using a variety of radiotracers; and (3) DA receptors—techniques used for the measurement of postsynaptic receptors can also provide information regarding the concentration of synaptic DA [3].

Imaging AADC Activity

FD imaging was the first approach introduced into the clinical setting to assess the presynaptic dopaminergic pathway. It is a good reflection of the *in vivo* consumption of FD and its conversion to FDA. A prolonged scanning protocol shows the FD egress rate, which reflects DA turnover [4]. Striatal levels of FD uptake correlate well with declining substantia nigra (SN) cell counts [5]. However, this imaging approach may underestimate the degree of DA depletion due to an upregulation of AADC activity, ostensibly due to compensatory responses, and found in early PD patients [6].

Imaging DAT Function

The DAT is expressed specifically on the presynaptic membrane of DA neurons and is responsible for the reuptake of DA from the synaptic cleft. DAT binding is the most widely used technique for imaging striatal DA function. However, the DAT is commonly downregulated in early disease stages resulting in an overestimation of degeneration [7], although with this understanding it can potentially aid the clinician in making an early diagnosis of PD. Another disadvantage of DAT imaging is that the DAT binding is easily affected by pharmaceutical treatments (e.g. amantadine and modafinil) [8, 9] and normal ageing [10]. A wide variety of ligands with PET or SPECT, including ^{11}C -CFT, ^{11}C -RTI-32, ^{123}I -FP-CIT, ^{123}I - β -CIT, ^{123}I -altpopane, and $^{99\text{m}}\text{Tc}$ -TRODAT-1, have been put to clinical use and proven useful in predicting the integrity of DA neurons. SPECT is more cost-effective with a lower resolution than PET scanning. Among these ligands, ^{123}I - β -CIT has the highest striatal-to-cerebellar uptake ratio but has slow distribution kinetics. To avoid longer scan times, the FP-CIT radioligand was developed to have more rapid binding kinetics [11].

Imaging Dopamine Receptors

Molecular imaging techniques are available for the measurement of postsynaptic dopaminergic function, and can provide rich information about DA transmission.

Postsynaptic DA receptors consist of two major families, the D1 family (D1 and D5) and the D2 family (D2,

D3, and D4). Investigations of the D1 receptor system using the radioligands ^{11}C -SCH23390 and ^{11}C -NNC112 indicated no differences in D1 receptor density between PD patients and healthy controls [12, 13], possibly due to low selectivity of these D1 receptor radioligands [14]. Assessment of D2-like DA receptors is the most widely studied: for example, ^{11}C -raclopride (RAC) competes with endogenous DA and is a good reflection of striatal synaptic DA concentration [3], while higher-affinity ligands including ^{11}C -FLB 457 and ^{18}F -fallypride can be used to estimate extra-striatal DA concentrations [15]. Imaging these receptors can be used to monitor the synaptic DA level following pharmacological or regulatory changes [16, 17]. For example, there is an upregulation of DA receptors in early untreated patients [18], possibly due to the reduced DA release and decreased receptor binding. However, disease progression and dopaminergic treatment result in downregulation of DA receptors as measured by ^{11}C -RAC [18, 19]. Furthermore, studies have demonstrated that D3 receptor overexpression, as measured by ^{11}C -PHNO, likely plays a role in levodopa-induced dyskinesias [20].

Imaging the Monoaminergic System: Vesicular Monoamine Transporter 2 (VMAT2)

VMAT2 is responsible for taking up DA into presynaptic vesicles and is a valid imaging target for determining PD severity [21]. VMAT2 is not restricted to packaging DA into the synaptic vesicles; it is expressed by various monoaminergic neurons and is involved in the vesicular trapping of a wide variety of neurotransmitters including DA, serotonin, norepinephrine, and epinephrine [22]. However, a large majority of VMAT2 binding is in dopaminergic terminals. Commonly used imaging ligands are ^{11}C -dihydrotetrabenazine (DTBZ) and its more recently commercially-used ^{18}F analog. Its superiority over DAT tracers is that it is less influenced by compensation or pharmacological regulation [23]. Nevertheless, this notion has been challenged by a recent finding indicating that vesicular DA concentration can affect VMAT2 binding [24]. A previous study has shown that the symptomatic threshold of PD is 38%–48% of the normal binding potential for ^{11}C -DTBZ, 47%–62% for ^{18}F -FD, and 29%–44% for ^{11}C -methylphenidate (^{11}C -MP) due to compensation [7].

Imaging Other Neurotransmitters Involved in PD

PD involves dysfunction in multiple neurotransmitter systems, in which the dopaminergic system is the most affected or at least the most investigated. Other systems implicated in PD include the serotonergic, cholinergic, noradrenergic, and opioid systems [25]. Among these,

imaging cholinergic activity can be performed by using cholinesterase substrates such as *N*- ^{11}C -methyl-piperidin-4-yl propionate (^{11}C -PMP). In PD patients with dementia (PDD) who reveal more severely affected cholinergic function than patients with Alzheimer's disease, the reduced uptake of PMP in cortical regions is more extensive in PDD patients [26]. Patients with non-demented PD and RBD exhibit significant decreases of acetylcholinesterase hydrolysis in neocortical and limbic cortical and thalamic areas compared to subjects without RBD symptoms [27]. PD patients with postural instability have been found to have reduced ^{11}C -PMP uptake in the thalamus and cerebral cortex [28], which is consistent with modulation of gait by the pedunculopontine nucleus, a principal cholinergic input to the thalamus. Moreover, imaging of cholinergic dysfunction with *N*- ^{11}C -methylpiperidin-4-yl acetate PET has shown that cholinergic deficits are distributed throughout the cortex and are consistent with the DA loss in PD [29].

The selective serotonin transporter PET ligand ^{11}C -3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile has been used to assess the role of serotonin in PD. Its binding has been shown to be decreased in subcortical and cortical areas in PD patients without depression [30, 31], but surprisingly is increased in the raphe nuclei and limbic areas in PD patients with depression [32]. In PD patients presenting with visual hallucinations, on the other hand, serotonergic activity has been shown to be increased in several cortical regions using the selective 5-hydroxytryptamine receptor 2A ligand, ^{18}F -setoperone PET [33].

Notably, ^{18}F -AV-1451, a recently developed PET radiotracer that putatively binds to neuromelanin, has shown decreased pigmented neurons in the SN of PD patients compared to age- and sex-matched controls, and that this correlates with a reduced signal for the striatal DAT (measured by ^{123}I -FP-CIT SPECT) [34].

Metabolic Network

Different from the imaging techniques directly reflecting dopaminergic or other neurochemical pathways, PET imaging of energy metabolism using ^{18}F -fluorodeoxyglucose (^{18}F -FDG) reflects neuronal and synaptic function more generally [35], making it possible to investigate highly interconnected regions and networks. In a form of principal components analysis, PD exhibits a characteristic network characterized by increased pallidothalamic, pontine, and cerebellar metabolism, that is associated with decreased metabolism in the premotor cortex and posterior parietal cortical regions [36, 37], termed the PD-related pattern (PDRP). Since its first identification, the PDRP has been validated across multiple independent cohorts [38–40] and has been identified in non-human primates

with experimental parkinsonism induced by MPTP exposure [41, 42]. The expression values of the PDRP correlate significantly with motor rating scores (akinesia-rigidity [43]), but not with tremor [36]. While the PDRP does not correlate with tremor, a PD tremor-related pattern has been identified with ordinal trends canonical variates analysis, and is characterized mainly by increases in the cerebellum and primary motor cortex [44]. Furthermore, network studies have revealed a PD cognition-related pattern (PDCP), which is characterized by decreased metabolism in the frontal and parietal association regions and increased metabolism in the cerebellar vermis and dentate nuclei [45]. The expression of the PDCP is correlated with executive and memory performance but not with motor score [43, 45]. All these studies provide support for metabolic imaging to be used to understand and study the regions and networks involved in motor, tremor, and cognitive functions in PD.

Microglial Activation

Neuroinflammation and microglial activation have been found to play an important role in the pathogenesis of PD [46, 47], in which translocator protein (TSPO) is a potential biomarker [48] that can be imaged and quantified by ^{11}C -PK11195 PET. A previous study revealed increased microglial activation localized to the brainstem in early-stage PD patients, and this correlated with motor dysfunction and the degree of DA denervation as measured by ^{11}C -CFT binding potential [49]. Binding of ^{11}C -PK11195 on PET was also found to be increased in other widespread regions in PD patients [50], although this finding is inconsistent [47]. It remains controversial whether ^{11}C -PK11195 uptake is correlated with disease severity [49, 50]. To overcome the current limitations of PK11195, which has low-affinity binding to TSPO and a poor signal-to-noise ratio, next-generation TSPO radiotracers have been produced, namely, ^{11}C -PBR28 and ^{18}F -FEPPA. These radiotracers have been used to reflect different TSPO binding affinities based on a genetic polymorphism [47, 51]. The inter-patient heterogeneity due to genetic polymorphism leads to confusion of quantitative comparison between subjects [52]. Taking this polymorphism into account could potentially guarantee a better interpretation of TSPO PET results. Nevertheless, it remains to be determined whether microglial activation is a cause or consequence of PD, although epidemiology indicates that there is a reduced risk of developing PD in those taking anti-inflammatory agents [53]. Nonetheless, a better understanding of inflammation and all possible factors contributing to PD and its progression may help in the development of disease-modifying therapies.

Proteinopathy

Analogous to imaging β -amyloid or tau in Alzheimer's disease, the ability to image α -synuclein is of great importance in gaining insight into the pathophysiology of PD and to track α -synuclein-based disease-modifying treatments. To date, tremendous efforts have been made in this regard [54], yet no viable radioligand has been validated and made available for detecting α -synuclein in the brain. The main obstacles appear to be due in part to the intracellular localization of α -synuclein deposition and the poor specificity of potential tracers [55]. Novel and more specific compounds or even radiolabeled antibodies are under development to overcome these shortcomings.

^{11}C -labelled Pittsburgh Compound B by PET has been extensively investigated in imaging fibrillary amyloid in Alzheimer's disease. Since there is also amyloid deposition in PD dementia, it has been shown to be variably related to the cognitive impairment in PD. In support of this, amyloid deposition is reported to be more marked in dementia with Lewy bodies than in PD dementia [56] and the cognitive dysfunction might be associated with increased cortical and striatal β -amyloid deposition [57, 58] and expression of the ApoE4 allele [59]. Together with neurotransmitter disruption, proteinopathy might be an independent contributor to cognitive impairment in PD [60]. With regard to tau imaging, several relatively selective radiotracers such as ^{18}F -THK523, ^{18}F -THK5117, ^{18}F -THK5105, ^{18}F -THK5351, ^{18}F -AV1451(T807), and ^{11}C -PBB3 have been developed and shown to be valuable in discriminating tauopathies including progressive supranuclear palsy (PSP) and cortico-basal degeneration (CBD) from idiopathic PD [61, 62].

Magnetic Resonance Imaging (MRI)

MRI has been widely applied in investigating PD because of its noninvasive profile, high spatiotemporal resolution, and widespread availability. Several functional MRI techniques are being extensively explored to investigate their value in understanding the pathogenesis and improving accurate diagnosis for PD [63, 64]. Nonetheless, they are not yet established enough for translation into clinical practice, largely due to the considerable variability in MRI acquisition parameters and inconsistent interpretation of data across studies.

Diffusion Tensor Imaging (DTI)

By measuring the random motion or diffusion of water molecules in brain tissue, especially neuronal fibers, DTI is an approach useful for analyzing white matter integrity and connectivity [65–67]. Two crucial parameters are measured

by DTI, mean diffusivity (MD) and fractional anisotropy (FA). FA is an important measure, representing an orientation distribution of the motion of water molecules, with a faster diffusion along the axons and fibers than that perpendicular to them. In PD patients, a decreased FA and increased MD have been correlated with the severity of dysfunctional microstructural tissue [68], and the connectivity of the SN to the basal ganglia and thalamus was shown to be reduced using the approach of tracking diffusion-based fibers [69, 70]. Moreover, DTI might be helpful in making a differential diagnosis between PD and atypical parkinsonism in the clinical setting [71]. Recently, DTI measures have provided more reliable and comprehensive analysis [72] based on global analysis like voxel-based analysis or tract-based spatial statistics, together with other advanced approaches such as neurite orientation dispersion and density imaging.

Blood Oxygen Level-dependent (BOLD)/Amplitude of Low Frequency Fluctuations (ALFF)

Functional connectivity in the brain using BOLD can be measured in resting-state fMRI (rs-fMRI) or task-state fMRI; however, rs-fMRI is currently preferred to reflect the intrinsic functional connectivity networks [73]. As a specific BOLD measure, ALFF is detected at ~ 0.01 Hz– 0.1 Hz in different regions of the brain in a synchronized manner, reflecting the functional connectivity networks among subregions [74, 75]. Patients with PD have a decreased ALFF in the striatum and increased ALFF in the midbrain, and the pattern in each low-frequency band between 0.027 Hz and 0.073 Hz is distinct and more robust in the basal ganglia and midbrain than other frequency bands [76].

Arterial Spin Labeling (ASL)

ASL-MRI assesses cerebral tissue perfusion based on imaging magnetically-labeled protons as an endogenous tracer of blood flow [77]. In PD patients, symmetrical hypoperfusion has been reported to be more affected in the posterior cortex than in the anterior cortex, dominantly in the parieto-occipital regions and dorsolateral prefrontal cortex [78–81]. Potentially, ASL-MRI might serve as an alternative to ^{18}F -FDG PET glucose metabolic patterns in PD [81, 82] due to their significant overlap.

Clinical Applications

Early Diagnosis

Patients with RBD are at a higher risk of developing disorders associated with α -synuclein accumulation

[83, 84]. VMAT2 imaging in these patients shows a decreased binding ratio but falls short of the threshold for the emergence of motor symptoms [85]. This indicates that RBD is an early marker of α -synucleinopathy in progress in PD and this hypothesis has been tested in follow-up studies where DAT imaging of non-motor RBD patients has detected a progressive denervation of the nigrostriatal pathway [86]. ^{18}F -FDG imaging shows a more global change involving the cortex in idiopathic RBD patients, corresponding to hypermetabolism in the hippocampus/parahippocampus, cingulate, supplementary motor area, and pons, but hypometabolism in the occipital cortex/lingual gyrus [87]. An RBD-related metabolic network resembling the PDRP has also been reported. However, differences between the RBD-related covariance pattern (RBDRP) and the PDRP exist, RBDRP activity decreases while PDRP activity increases with disease progression from prodromal RBD to advanced PD. This suggests that RBDRP is a very early-stage imaging biomarker for idiopathic RBD patients, while the PDRP is more suitable for patients with PD [88]. The PDRP in idiopathic RBD patients has been reported to be elevated in recent studies [88, 89]. In a long-term clinical follow-up study of 17 idiopathic RBD patients, Holtbernd *et al.* (2014) reported that individuals with higher PDRP expression at baseline are more likely to develop PD/dementia with Lewy bodies (DLB); in addition, 3 idiopathic RBD patients who had a subnormal network activity at baseline, developed multiple system atrophy (MSA) two to four years later. Furthermore, a logistic regression model based on PDRP expression and age at baseline accurately predicts phenoconversion to PD/DLB [89]. In summary, these findings suggest that the PDRP is a potential marker for predicting the phenoconversion of RBD to PD and thus could be used in the early diagnosis of PD.

For symptomatic PD patients with a genetic mutation, PET imaging with a focus on dopaminergic dysfunction shows a resemblance to idiopathic PD patients [90, 91]. Meanwhile, clinicians have drawn much attention to asymptomatic mutation carriers. DAT imaging presents evidence of dopaminergic pathway dysfunction in asymptomatic carriers of the *LRRK2* R1441G mutation [92]. In another cohort of carriers with an *LRRK2* G2019S mutation, abnormal DAT binding measured by ^{123}I -FP-CIT SPECT was detected and appears to be a better indicator of the future development of motor symptoms than the finding of SN hyperechogenicity [93]. In unaffected *LRRK2* mutation carriers, increased DA turnover (measured by FD), which is sensitive to compensatory changes, occurred early compared to typical dopaminergic imaging approaches (^{11}C -MP or ^{11}C -DTBZ) [94]. Similarly, ^{18}F -dopa imaging showed a reduced uptake in both Parkinson-associated and PINK1-linked mutation carriers [95, 96],

indicating a promising prospect of validating the diagnosis in these patients prior to the occurrence of motor symptoms.

Patients showing non-motor clinical features including olfactory dysfunction, mood disorders, constipation, and sleep disorders are at a higher risk of developing PD [97]. Molecular imaging is helpful in predicting the onset of PD in these high-risk populations. A combination of imaging techniques including low ^{123}I -metaiodobenzylguanidine (MIBG) uptake and screening of non-motor symptoms such as mild memory loss, autonomic failure, RBD, and psychiatric symptoms may aid in the early diagnosis of PD [98]. This was highlighted in a prodromal PD imaging study, in which an array of assessments including DAT deficits on SPECT, hyposmia, gender (male), and constipation were used to identify patients with a diagnosis of prodromal PD [99]. Retrospectively, it has been reported that expression of the PDRP increases approximately two years before the appearance of PD motor symptoms [100]; in patients with Hoehn and Yahr stage one, the expression of PDRP activity increases in the clinically unaffected hemisphere, supporting its potential usefulness in the prodromal diagnosis of PD [101].

Differential Diagnosis

Differential diagnosis of PD from other atypical parkinsonian syndromes can be difficult. These diagnostic difficulties have prompted the further development of novel imaging techniques.

Approximately 50%–60% cell loss in the SN and 70%–80% depletion of DA in the striatum have occurred by the time motor symptoms appear [102] and molecular imaging modalities serve as important techniques in revealing these abnormalities. Dopaminergic imaging is particularly useful in establishing the diagnosis of PD. Presynaptic imaging including VMAT2, DAT, and AADC correlates well with the loss of SN cells revealed by postmortem analysis [5, 103, 104] and is a reliable indication of impaired DA function. All of these DA imaging markers provide a similar pattern of uptake reduction in mild PD patients, with DA function showing an uneven pattern of depletion in the striatum and with the hemisphere contralateral to the more affected limb being more significantly affected in PD patients than in age-matched controls. The reduction of uptake is most prominent in the posterior putamen [105, 106]. Therefore, it is useful in aiding the differential diagnosis between essential tremor, drug-induced parkinsonism, vascular parkinsonism, dystonic tremor, and PD, since the non-PD patients do not show this PD pattern.

Nevertheless, differentiating PD from atypical parkinsonian syndromes remains challenging. To illustrate this point, MSA patients suffer a decline of D2 receptors while

PD patients show relatively normal postsynaptic function [107], but this technique is not diagnostically specific and the alteration of presynaptic and postsynaptic binding alone is not sufficient to discriminate PD from other atypical parkinsonian syndromes.

MIBG imaging may prove useful in this regard. Sympathetic nerve function is relatively preserved in MSA and PSP but is more damaged in PD patients [108]. In addition, one meta-analysis concluded that MIBG is potentially useful for differentiating PD from other forms of neurodegenerative parkinsonism [109].

^{18}F -FDG PET is another promising tool to discriminate PD from atypical parkinsonian syndromes. Studies with statistical parametric mapping analysis contrasting healthy controls, PSP, MSA, and CBD cases showed consistent patterns of regional metabolic changes quite different from the PD metabolic profile [110]. In routine clinical practice, the visual assessment of a ^{18}F -FDG PET scan may, at times, be helpful for differential diagnosis. Furthermore, visual assessment combined with individual voxel-based statistical maps (three-dimensional stereotactic surface projection technique) was helpful for differential diagnosis of neurodegenerative parkinsonism in a one-year follow-up study [111]. With the help of automated classification procedures and quantification of spatial covariance values, the disease-related pattern can be extremely efficient for the differential diagnosis from atypical parkinsonian syndromes, such as MSA, PSP, and CBD, each of which has a specific disease-related pattern [110, 112, 113]. The expression scores for each pattern can be calculated in individual cases, but their distinction is not perfect and some overlap exists between different disease groups [114]. Therefore, the combination of pattern scores in statistical models may have better differential effects. In a logistic two-step model, which differentiated PD from non-PD as the first step, followed by differentiation between MSA and PSP in the non-PD group, the diagnostic accuracy was relatively high even for patients with a short symptom duration [115]. Other methods, such as relevance vector machine analysis, have also been applied for single-case classification. In the study of Garraux *et al.* (2013), in which 120 patients with parkinsonism were recruited, the relevance vector machine showed high differentiation performance for PD *versus* non-PD (sensitivity, 93%; specificity, 83%), but limited classification of MSA, CBD, and PSP [116].

Disease Progress Monitoring

The Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr scale are clinical assessments to monitor disease progression in PD. However, rating scores vary among clinicians and are significantly affected by the treatment option. In dopaminergic imaging, uptake of

tracer follows a near exponential decline and the asymmetric decrease in tracer binding diminishes with disease progression [117, 118]. However, the rate of progression reported in presynaptic dopaminergic imaging has been inconsistent and discordant [119, 120]. Therefore, a more objective and precise means of assessment is urgently needed. The changes in ^{18}F -FDG PET can be used to monitor disease progression. In ^{18}F -FDG PET imaging, several regions of metabolic change are consistent with disease progression, including a metabolic increase in the subthalamic nucleus (STN), the internal globus pallidus (GPi), the dorsal pons, and the primary motor cortex. As disease progresses, decreased activity in the prefrontal and inferior parietal regions is detected [43]. In network analysis, expression of the PDRP, which is already elevated at baseline in contrast with healthy controls, increases progressively as the disease evolves, and the change in PDRP expression correlates with a concurrent decline in striatal DAT binding measured by ^{18}F -FP-CIT PET and increased motor ratings [43]. These points, in addition to the high level of reproducibility [37] and correlation with clinical improvement [121], make the PDRP a promising biomarker to track PD progression.

Monitoring Treatment Effects

PDRP expression may be useful for monitoring treatment responses. The PDRP is not responsive to placebo [122]. In contrast, consistent reduction in PDRP expression is revealed during L-dopa therapy and deep brain stimulation (DBS) of the STN [121], validating the use of this modality of molecular imaging in the evaluation of therapeutic efficacy.

Dopaminergic medication is effective in reversing the deficits in motor-related pathways, represented by a marked decrease in UPDRS motor scores [119] and a significant decline in PDRP expression [123]. Functional MRI also suggests that a partially-normalized functional connectivity is present after dopaminergic therapy [124]. In short, motor circuit abnormalities due to denervation of dopaminergic neurons in PD patients involve several functional brain regions, and this disruption can be improved in response to exogenous DA intake.

The pathological basis of PD is the neurodegeneration of nigrostriatal DA cells. Therefore, transplantation of DA neurons into the striatum seems rational and promising. PET imaging has proven useful for the assessment of the clinical outcome of grafted cell lines. Prior investigations using transplantation of fetal DA neurons have exhibited some promising prospects: the grafted tissue can alleviate the motor symptoms, improve the overall UPDRS motor score, reduce the use of dopaminergic medication, and increase striatal ^{18}F -dopa uptake [125–127]. ^{11}C -raclopride PET has also revealed that the grafted tissue can remain

functional for as long as 10 years and provide sufficient endogenous DA [128]. However, these promising results were inconsistent in another randomized controlled trial [129]. In addition, the occurrence of troublesome dyskinesia in transplanted PD patients also hinders the application of this technique [129]. The pathogenesis of this side-effect remains to be further explored. Excessive DA release into the synaptic cleft and inappropriate serotonin/DA levels may contribute to graft-related dyskinesias [130]. Other cell-based therapies include autologous induced pluripotent stem cell-derived (iPSC) neurons. Investigations using primates have revealed that the grafted tissue is able to provide functional improvement detected in ^{11}C -CFT PET [131]. Currently, the efficacy and safety of iPSC cells need to be further explored.

The surgical effects of DBS are well-established [132]. Patients with DBS show a reduced expression of the PDRP, corresponding to a suppression of abnormal network activity [121, 133]. A normalized ^{18}F -FDG uptake is evident in the GPi, representing a relatively controlled firing pattern from the STN [121, 134]. Nonetheless, despite its superiority in relieving motor symptoms and treating dyskinesia, PD patients implanted for DBS display a comparable decline of FD uptake as in other PD patients [135], indicating that STN DBS may be ineffective in slowing disease progression.

The therapeutic effects of possible disease-modification modalities can also be evaluated by molecular imaging. A preliminary study of the efficacy of GM1 ganglioside highlighted that a slowing of DAT signal loss measured by ^{11}C -MP is present and in some cases showed DAT signal improvement [136]. These results are encouraging but further study is required.

Reflecting Pathogenesis

If used properly, imaging techniques can also provide complementary assessment of disease pathogenesis. For example, imaging α -synuclein may be helpful for objectively assessing α -synuclein accumulation and evaluating immunotherapy for α -synuclein in future clinical trials. In a study combining biomarkers from cerebrospinal fluid and VMAT2 imaging, the authors concluded that there is a significant correlation between VMAT2 binding and pathogenic protein aggregation [137]. Therefore, molecular imaging might be helpful in reflecting pathogenesis if developed and used properly.

Future Perspectives

Approaches using molecular imaging represent the best opportunities and tools to gain insight into understanding pathogenesis and further provide objective biomarkers for

assessing parkinsonian disorders despite the shortcomings and caveats presented here. A promising strategy includes developing novel probes targeting the pathological deposition of α -synuclein, but challenges remain. Meanwhile, it is important to better understand the complex interplay between proteinopathy and network disruption. Moreover, further validation is needed in earlier and accurate diagnosis, objective monitoring of disease progression, and therapeutic efficacy in clinical and research settings.

Currently, cutting-edge technologies using hybrid PET/MRI are emerging to substantially improve the strengths of radionuclide imaging by incorporating the benefits that come with MRI, improving the spatial and temporal resolution which otherwise would be poor when using PET alone. Emerging artificial intelligence-based techniques are attempting to resolve the objective judging of ^{18}F -FDG pattern abnormalities in complex network imaging strategies and other molecular imaging modalities in PD. These have appeared on the horizon in dermatology [138], where trained convolutional neural networks with images and diagnosis as inputs can reliably identify the most common and deadliest skin cancers [138]. Potentially round-the-clock and portable-device-based artificial intelligence holds the promise of much more easily accessible diagnostic care.

Summary

In the clinical setting, precise diagnosis of patients with PD requires much effort, especially during the pre-motor stage. It is important to include several molecular imaging techniques to aid in the diagnostic decision-making process. Scanning of DA levels helps to distinguish PD patients from those with an intact nigrostriatal system. Through quantitative analysis of the metabolic pattern in ^{18}F -FDG PET, we are able to differentiate idiopathic PD from atypical parkinsonian syndromes. ^{18}F -FDG PET is also capable of *in vivo* measurement of the treatment response and disease progression. Finally, molecular imaging targeting α -synuclein has great promise and continued attention is warranted for the development of new PET tracers.

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