Single Photon Emission Computed Tomography/Positron Emission Tomography Molecular Imaging for Parkinsonism: A Fast-Developing Field

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The early differential diagnosis of Parkinson disease and atypical parkinsonism is a major challenge. The use of single photon emission computed tomography (SPECT)/positron emission tomography (PET) molecular imaging to investigate parkinsonism is a fast-developing field. Imaging biomarker research may potentially lead to more accurate disease detection, enabling earlier diagnosis and treatment. This review summarizes recent SPECT/PET advances in radiopharmaceuticals and imaging technologies/analyses that improve the diagnosis of neurodegenerative parkinsonism. We are currently witnessing a turning point in the field. Integrating molecular imaging as a diagnostic technique represents an opportunity to reassess the strategies for diagnosing neurodegenerative parkinsonism.

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The number of patients with neurodegenerative parkinsonism more than doubled between 1990 and 2015. It is projected to increase again by as much as 56% by 2030. It affects 1 in 120 people older than 45 years.[1] Neurodegenerative parkinsonism exhibits extensive clinical heterogeneity and comprises many different neurodegenerative diseases (Parkinson disease [PD], dementia with Lewy bodies [DLB], multiple system atrophy [MSA], corticobasal degeneration [CBD], progressive supranuclear palsy [PSP]). The differential diagnosis of parkinsonism during early disease still presents major challenges to clinicians.

The differential diagnosis can be narrowed down based on a combination of clinical and paraclinical features. Atypical parkinsonism is characterized by early onset (within the first 5 years) of symptoms that are unusual for PD.[2] In addition, response to dopaminergic treatment is reduced.[3] But it is only definitively diagnosed after postmortem pathological examination of the brain (gold standard for protein anomalies). The international diagnostic criteria for atypical parkinsonism are based on disease cohorts with postmortem brain data. The physician's diagnosis therefore relies on identifying patient features that correspond to the classification criteria. Compared to pathological examinations, this approach has a higher probability of diagnosing PD (>95% correlation) than atypical parkinsonism (approximately 70%).[4] There

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may also be some degree of variability between the progression of individual forms of atypical parkinsonism. However, these are relatively small compared to the differences in complications (falls, swallowing disorders, severity of dysautonomia) and survival periods between PD and atypical parkinsonism. Atypical parkinsonism requires more regular and multidisciplinary evaluations to prevent, detect, and treat complications compared to PD. The organization of health care therefore needs to be managed differently for these two conditions. Atypical parkinsonism patients have shorter median survival times (ranging from 6 to 7.4 years for PSP compared to 10.7 to >20 years for PD).[5,6] Although the multitude of neurodegenerative diseases that constitute parkinsonism are clinically similar, their underlying pathophysiological mechanisms are poorly understood. Molecular imaging that is routinely performed to assess neurodegenerative parkinsonism may provide additional diagnostic information and help clarify specific disease mechanisms (Fig 1).

Current Single Photon Emission Computed Tomography and Positron Emission Tomography Imaging in Routine Evaluation of Parkinsonism

Presynaptic Dopaminergic Imaging

The European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging recently published guidelines for dopaminergic imaging of parkinsonism.[7] These guidelines predominantly focus on two commonly used nuclear medicine examinations of presynaptic dopaminergic function, namely, single photon emission computed tomography (SPECT) using ^{123}I-labeled dopamine transporter ligands and positron emission tomography (PET) using ^{18}F-fluorodopa (Fig 2A). These differentiate neurodegenerative parkinsonism from other dementias (particularly DLB from Alzheimer disease [AD]), from other forms of parkinsonism (drug-induced, psychogenic, and vascular parkinsonism, whose diagnosis requires images to be fused with magnetic resonance imaging [MRI]) and from essential tremor. These scans can also detect early degenerative parkinsonism.[7] SPECT, with specific ^{123}I-labeled dopamine transporter ligands and ^{18}F-fluorodopa PET, detects different molecular dopaminergic targets. ^{123}I-labeled dopamine transporter ligands identify presynaptic dopamine active transporters (DATs). ^{18}F-fluorodopa PET visualizes L-dopa, which is subsequently decarboxylated to dopamine by the aromatic L-amino-acid decarboxylase. Both types of dopaminergic imaging need to take into account radiotracer–drug interactions prior to performing acquisitions. Current guidelines recommend discontinuing antiparkinsonian drugs before ^{18}F-fluorodopa PET imaging.[7] DAT and L-dopa targets decrease in parallel but not necessarily synchronously with progression of neurodegenerative parkinsonism.[8] This may be due to the presence of compensatory mechanisms in the presymptomatic and early symptomatic phases: a reduction in the number of presynaptic DATs, which increases the intrasynaptic availability of

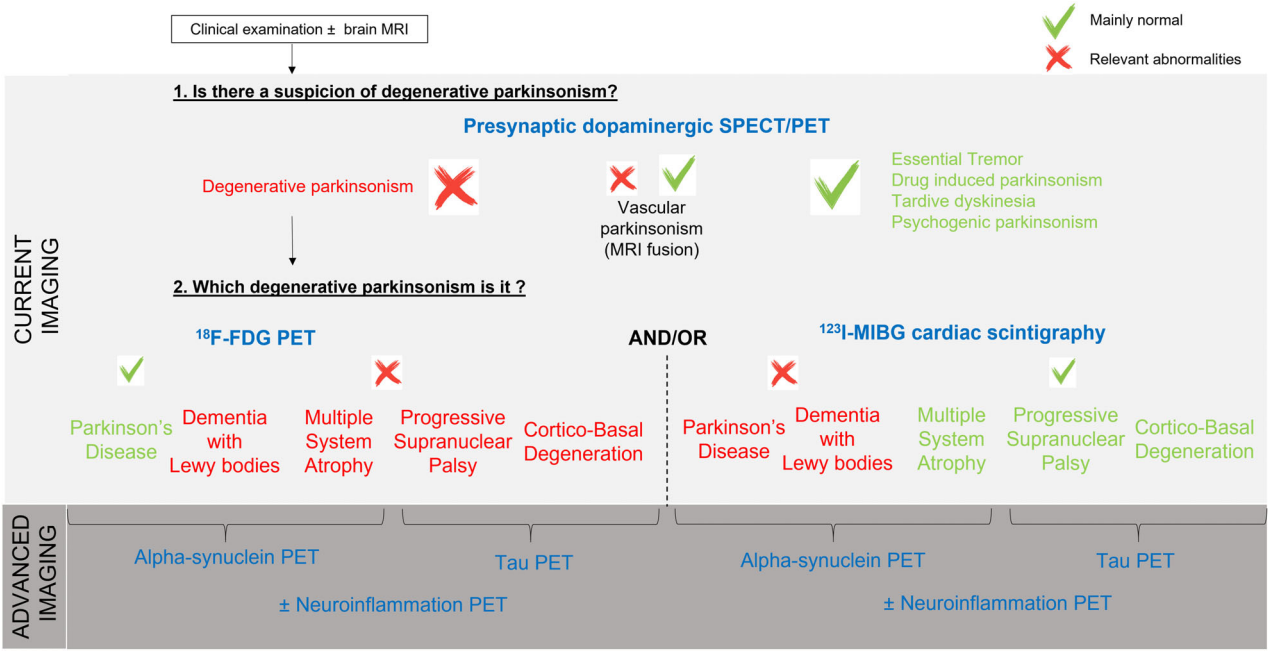

FIGURE 1: Flow diagram showing the rationale for performing single photon emission computed tomography (SPECT)/positron emission tomography (PET) molecular imaging in a patient with parkinsonism. FDG = fluorodeoxyglucose; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging.

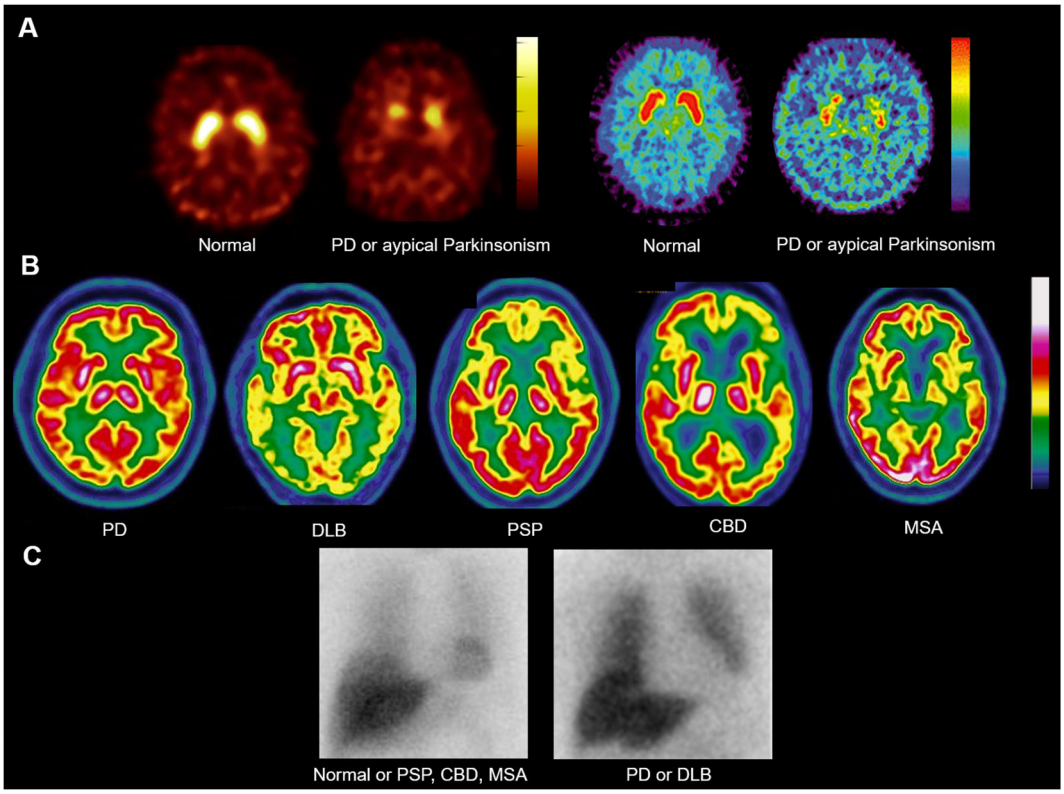

FIGURE 2: Representative single photon emission computed tomography (SPECT)/positron emission tomography (PET) images investigating parkinsonism from clinical routine practice radiotracers in normal subjects and patients with parkinsonism. (A) SPECT with ^{123}I-labeled dopamine transporter ligands (left panel) and ^{18}F-fluorodopa PET (right panel). (B) ^{18}F-FDG PET. (C) ^{123}I-metaiodobenzylguanidine scintigraphy. CBD = corticobasal degeneration; DLB = dementia with Lewy bodies; MSA = multiple system atrophy; PD = Parkinson disease; PSP = progressive supranuclear palsy.

dopamine, and an upregulation of the fluorodopa to dopamine conversion by aromatic L-amino acid decarboxylase in nerve terminals.[8,9] Clinical ^{18}F-fluorodopa PET studies focusing on the presymptomatic stage have confirmed the high sensitivity of the method.[10] Albeit performed on a relatively small number of patients, comparative study confirmed that SPECT and PET diagnose presynaptic dopaminergic deficiencies in early stage PD.[11] Fluorodeoxyglucose (^{18}F-FDG) PET and ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy are also routinely used to evaluate parkinsonism (see Fig 1).[12]

^{18}F-FDG PET

Brain ^{18}F-FDG PET images glycolytic metabolism in the brain. It may identify significant levels of brain dysfunction more consistently than any potential brain atrophies detected by MRI.[13] ^{18}F-FDG PET differentially diagnoses PD and parkinsonian "plus" syndromes at sensitivities and specificities greater than 75 and 90%.[14] This is particularly significant, because differential diagnoses based on dopaminergic imaging are somewhat limited for these entities.[15] ^{18}F-FDG PET provides a number of disease-specific metabolic patterns. DLB is characterized by the preservation of posterior cingulate metabolism (as opposed to posterior associative cortical hypometabolism in the occipital cortex). PSP is distinguished by prefrontal mesial, putamen, and pons hypometabolism. CBD displays asymmetrical frontoparietal hypometabolism. MSA exhibits a somewhat lesser extent of basal ganglia or cerebellum hypometabolism (see Fig 2B).[16]

^{123}I-MIBG Scintigraphy

^{123}I-MIBG scintigraphy/SPECT imaging targets the peripheral sympathetic noradrenergic stores. It can help differentiate PD/DLB (decreased cardiac binding) from MSA and PSP (normal binding) based on their sympathetic myocardial innervations (see Fig 2C). ^{123}I-MIBG scintigraphy differentiates PD/DLB from cognitive decline and/or parkinsonism (AD, MSA, PSP, frontotemporal lobe and vascular dementia) with a specificity of 91% and sensitivity of 94%.[17] Advances in ^{18}F-fluorodopa PET heart scans[18] and PET MIBG radiotracer analogues[19] may further enhance these performances. Current parkinsonism SPECT/PET diagnoses rely on a combination of dopaminergic imaging, ^{18}F-FDG PET, and ^{123}I-MIBG scintigraphy. Imaging biomarker research has the potential

to improve disease recognition and allow earlier diagnosis and treatment.[20] The development of in vivo biomarkers may be envisaged to follow the progress of personalized drug treatments. In vivo biomarkers may also become integrated in the earliest stages of parkinsonism rehabilitation. This review summarizes recent advances in radiopharmaceuticals and imaging technologies/analyses that improve the diagnosis of parkinsonism.

Advances in Radiopharmaceuticals

The new radiotracers developed for imaging of parkinsonism target either dopaminergic function or a pathological process.

New PET Radiotracers for Dopaminergic Imaging

New dopaminergic PET tracers target presynaptic DATs.[9,21,22] In addition to overcoming the technical performance limitations of SPECT, PET imaging of DATs with ^{18}F-FE-PE2I (N-[3-iodoprop-2E-enyl]-2β-carbo-^{18}F-fluoroethoxy-3β-[4-methylphenyl]-nortropane) allows routine performance of 10-minute static acquisitions only 30 minutes after administration of radiotracer. This represents a definite advantage over DAT SPECT imaging.[23] Another dopaminergic PET radiotracer that targets DATs, the [18F] (2S,3S)-methyl-8-([E]-4-fluorobut-2-en-1-yl)-3-(p-tolyl)-8-azabicyclo(3.2.1)octane-2-carboxylate, namely, ^{18}F-LBT-999, is being developed (Fig 3A).[24]

Additional molecular dopaminergic pathway targets are also being developed. ^{18}F-FP-DTBZ ([+]-α-9-O-[3-^{18}F-fluoropropyl]-dihydrotetrabenazine) is a PET radiotracer that specifically binds to VMAT2 (vesicular monoamine transporter type 2), an integral membrane protein that transports dopamine from the cytoplasm into synaptic vesicles.[25] This PET radiotracer is expected to suffer from the same limitations as ^{18}F-fluorodopa PET due to potential compensation phenomena at the early stages of PD. The iodobenzamide, ^{123}I-IBZM, is used for postsynaptic dopaminergic SPECT imaging and ^{11}C-raclopride, ^{18}F-fallypride, and ^{18}F-desmethoxyfallypride for PET imaging.[26] Postsynaptic dopaminergic imaging predominantly aims to differentiate PD from atypical parkinsonism.[26] Although radiotracers for this application are still in the research phase, one report already suggests that ^{18}F-FDG PET outperforms these postsynaptic dopaminergic radiotracers in terms of the differential diagnosis of PD/DLB and atypical parkinsonism.[15]

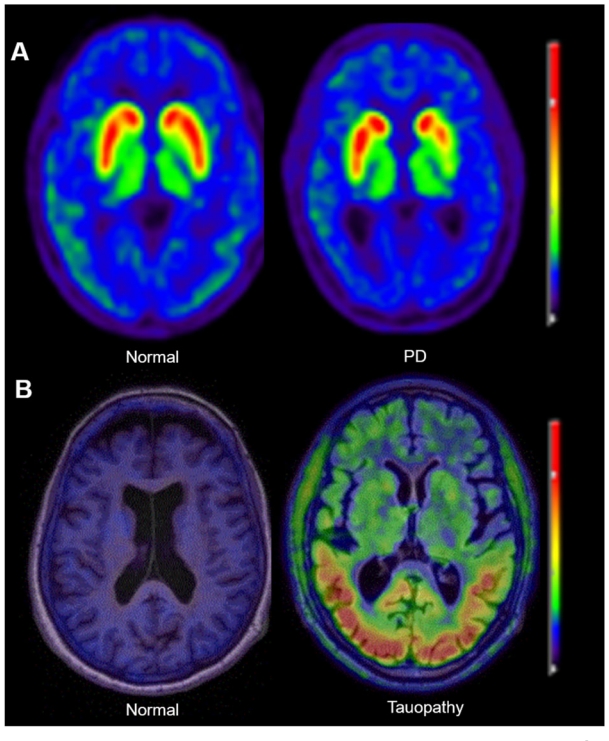

FIGURE 3: Representative positron emission tomography images investigating parkinsonism with new radiotracers. (A) ^{18}F-LBT-999 targeting the dopamine transporters in a normal subject (left panel) and a Parkinson disease (PD) patient (right panel). (B) ^{18}F-Flortaucipir targeting the tau protein in a normal subject (left panel) and a tauopathy patient (Alzheimer disease, right panel). LBT = Laboratoire Biophysique de Tours.

Tau PET Imaging

The cognitive proteinopathy field[27] has predominantly focused on imaging targets involved in the neurodegenerative process. Tau PET imaging is undoubtedly the best choice for the differential diagnosis of PD/DLB and other forms of atypical parkinsonism (see Fig 3B). The atypical parkinsonism PSP and CBD are tauopathies. PSP patients exhibit increased ^{18}F-AV-1451 signals in the pallidum, midbrain, dentate nucleus of the cerebellum, thalamus, caudate nucleus, and frontal regions compared to controls.[28] CBD patients have increased ^{18}F-THK5351 retention contralateral to the side with the greater cortical dysfunction.[29] These non-AD tauopathy deposits consist mainly of 4R tau, located in subcortical nuclei. Because AD is associated with 3R and 4R deposits, there is substantial clinical and neuropathological overlap between these tauopathies. Given that many regions of interest in corticobasal syndrome (CBS) and PSP largely coincide with off-target binding (eg, with monoamine oxidase B in the basal ganglia), there is substantial overlap of tracer binding load across the different diagnostic groups. This is particularly true for ^{18}F-AV-1451, which has been tested in the largest number of patients.[30] In CBS and PSP, tau burden determined by neuropathological assessment and in vivo ^{18}F-AV-1451 imaging yield inconsistent results. ^{18}F-AV-1451 PET, for instance, identifies in vivo areas with high postmortem tau in some brain areas but not

others. This presumably reflects a reduced sensitivity of the tracer to non-AD tau.[31,32] In vitro staining and/or autoradiography studies have, however, highlighted that tracers of the THK family do bind to CBS and PSP tau deposits to some extent, which is consistent with in vivo findings.[33] A new generation of more specific 4R tau tracers with less off-target binding is needed to improve the in vivo diagnosis of non-AD tauopathies.

α-Synuclein PET Imaging

Specific PET tracers targeting α-synuclein aggregates have great potential for diagnosing movement disorders but are currently exclusively in the research phase.[34] The identification of any additional transporter targets that facilitate movement across the blood–brain barrier is also required. The recently identified small, high α-synuclein affinity molecules are nevertheless not ideal lead compounds for PET radiotracer development. Although other different chemical entities that bind to α-synuclein, such as anle138b (^{11}C-MODAG-001), have been described, their selectivity for β-amyloid and tau fibrils still needs to be resolved.[35]

Neuroinflammation PET Imaging

There are a number of PET radiotracers that target neuroinflammation in parkinsonian disorders.[36,37] ^{18}F-DPA-714 and ^{18}F-GE-180 are translocator protein (TSPO) ligands. TSPO is an outer mitochondrial membrane protein expressed in activated microglial cells and macrophages in the brain. It is a marker of nervous system inflammation. Increased ^{18}F-DPA-714 and ^{18}F-GE-180 radiotracer uptake has been reported in the pons, basal ganglia, frontal and temporal cortex, and midbrain of PD patients compared to normal controls.[36] Although PET neuroinflammation imaging assesses one aspect of neurodegenerative parkinsonian disorder neuropathology (ie, TSPO expression), it is unable to diagnose specific parkinsonian disorders. There is no consensus about the optimal method for analyzing PET data or for selecting an anatomically defined reference region. This is because TSPO is expressed constitutively in the brain and because neurodegenerative pathologies are perhaps more widespread than previously assumed. The recent identification of populations of high- and low-affinity TSPO ligand binders has further complicated the issue.[37] The significance and potential clinical relevance of PET radiotracers targeting neuroinflammation requires further research.

Other innovative treatments that were initially identified in preclinical studies are currently being evaluated in a number of clinical trials. These include antibody-based treatments (anti–α-synuclein, antitau), iron chelators, and α-synuclein and tau aggregation inhibitors.[38] These

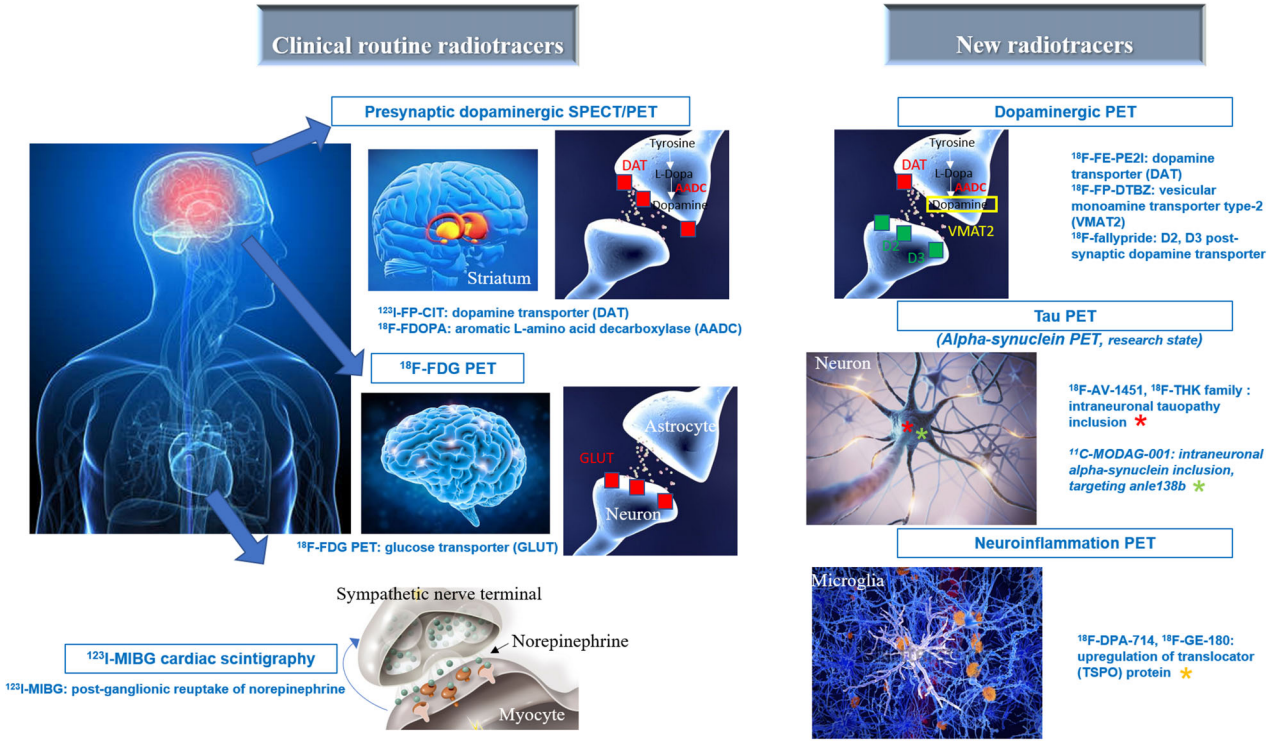

FIGURE 4: Pathophysiological mechanisms of single photon emission computed tomography (SPECT)/positron emission tomography (PET) radiotracers in neurodegenerative parkinsonism. FDG = fluorodeoxyglucose; MIBG = metaiodobenzylguanidine.

treatments could potentially influence the course of disease and improve patients' and caregivers' quality of life. It also highlights the importance of developing early PET brain neurodegeneration biomarkers that closely reflect the pathophysiology of these diseases, to rapidly identify patient profiles that would benefit from being included in these therapeutic trials. This would maximize the chances of offering patients a treatment that may potentially improve disease outcome. Figure 4 summarizes the pathophysiological mechanisms of SPECT/PET radiotracers used to assess neurodegenerative parkinsonism.

Advances in Imaging Technology

There have been major technological advances in both SPECT and PET imaging that have facilitated the use of neurotransmission imaging in the practice. First and foremost is the widespread deployment of hybrid systems for morphofunctional imaging.

The strongest neuroimaging associations are achieved with MRI. This approach integrates two devices into one system, enabling sequential and simultaneous bimodal acquisitions to be performed. These hybrid PET/MRI systems are, however, costly and currently not widely available. Alternatively, and perhaps more relevant in terms of current clinical practice, the data can also be fused after registering acquisitions performed on separate devices. This combination of information allows identification of striatal lesions that may impact the uptake of the radiotracer and development of bimodal correlations based on morphofunctional information.[39]

Large-field cadmium–zinc–telluride (CZT) SPECT cameras, which provide high performances in terms of count sensitivity, and spatial and energy resolution, are now also used for brain imaging.[40,41] Up to 2-fold shorter acquisition times, due to the lower number of counts required for ^{123}I-labeled dopamine transporter ligands SPECT imaging with large-field CZT cameras, have been reported.[40] The 360° detector ring configuration of CZT cameras may further enhance count sensitivity and image quality by providing focus acquisitions. Brain perfusion SPECT with 360° CZT cameras has recently been shown to provide high image quality in high-speed recording conditions.[41] These improvements allow short acquisitions of as little as 15 minutes, yield high image quality, and may challenge the cost-effectiveness of dopaminergic PET imaging systems. Additional specific CZT technology advances, such as absolute quantifications and dual isotope acquisitions, may further improve SPECT imaging.

The concomitant evolution of PET systems and digital PET technologies now offers marked improvements in image signal/noise ratios and contrast, and has significant potential for further enhancing spatial resolution.[42] Digital PET systems using silicon photomultipliers improve time-of-flight resolution, which facilitates routine dynamic PET recording.[43] This is particularly helpful to compute ^{18}F-fluorodopa influx constants (Ki) from brain time–activity curves of dynamic PET acquisitions. One advantage of Ki over the conventional ratio approach is that it provides a more direct measure of the ^{18}F-fluorodopa decarboxylation rate constant.[44] These dynamic acquisitions are also expected to come online for the newer dopaminergic PET radiotracers such as ^{18}F-FE-PE2I.[45] Further studies will be required to directly evaluate the additional value of such dynamic acquisitions over conventional static ratios for dopaminergic imaging of parkinsonism.

Advances in Image Analyses

Novel image analysis approaches may further enhance neurotransmission imaging of parkinsonism. Analyzing the metabolic connectivity of ^{18}F-FDG PET imaging in brain pathologies represents a significant shift from evaluating an underlying pathology of local neuronal function to improving the understanding of long-distance effects on interconnected neural systems.[46] The ^{18}F-FDG metabolic connectivity is based on voxelwise or region of interest methods with or without any a priori assumptions about the specific neurodegenerative disease, including PD.[46,47] When applied to resting-state ^{18}F-FDG PET scans of PD patients, this method identifies abnormal disease-related spatial covariance patterns (PD-related metabolic patterns [PDRPs]). PDRPs include numerous corticostriatopallidothalamocortical pathway components and are characterized by increased pallidal, thalamic, and pontine metabolic activity, coupled with relative reductions in the premotor cortex, supplemental motor area, and parietal association areas.[48] ^{18}F-FDG PET and multivariate classifications using PDRP features are objective, sensitive biomarkers of disease stage that may potentially detect treatment effects during PD progression.[49] These disease-related spatial covariance patterns are starting to be applied to atypical parkinsonism.[48] Prospective application of these models allowed determination of the probability of predicting PD, MSA, and PSP based on metabolic covariance patterns. The models were able to predict MSA with 90% specificity and an 85% positive predictive value.[50] PSP was predicted with 94% specificity and a 94% positive predictive value.[50] When a movement disorder specialist is not readily available, the application of such metabolic patterns improves the diagnostic accuracy by 10 to 15% for PD and 20% for atypical parkinsonism.[51] Compared to functional MRI (fMRI), metabolic ^{18}F-FDG PET patterns performed at the group level may

provide specific advantages. The cerebral metabolic rate of glucose measured by ^{18}F-FDG PET is known to precede the relative transient decrease in blood oxygen level–dependent signals without any magnetic limitations.[52] Group-level PET imaging is also expected to yield better signal-to-noise ratios, variance concentrations, and out-of-sample replications compared to single-subject–level fMRI. This is due to the unrivaled sensitivity of PET imaging to measure concentrations in the subpicomolar range. The ^{18}F-FDG radiotracer is also more commonly used and static imaging acquisitions are more easily applicable than dynamic ones.[53] These analytical approaches have now also been applied to dopaminergic imaging[54] and have been further validated in patients with movement disorders.[55,56] Molecular connectivity modeling approaches may improve our understanding of neurodegenerative movement disorder pathogeneses and provide a comprehensive strategy to identify the pathological networks involved. A combination of early perfusion scans to characterize spatial covariance patterns in PD and late striatal neuroreceptor binding scans were recently performed using ^{18}F-FP-CIT PET imaging. This original approach provides an alternative to ^{18}F-FDG PET for PD network quantification. This technique evaluates PDRP expression and DAT binding using a single tracer in one scanning session.[57]

Any discussion of recent advances in image analyses would be incomplete without the due consideration of artificial intelligence (AI). Radiotracers for SPECT/PET molecular imaging need to provide highly reliable binding specificities to achieve good signal-to-noise ratios. All molecular images are a compromise between the number of counts detected for generating a signal and the noise of nonspecific binding counts. This is particularly true for the new radiotracers that provide limited binding specificity (tau PET imaging, α-synuclein imaging, neuroinflammation imaging), at least until more selective radiochemicals are developed. AI-based methods may improve diagnostic assessments in the meantime. Several dopaminergic imaging studies using AI have reported accuracy of up to 90% for diagnosing PD. These automated learning approaches involve machine learning methods, based on textural analyses, for (1) differentiating PD and healthy subjects, (2) differentiating PD and vascular parkinsonism, and (3) discriminating between the different forms of atypical parkinsonism. A 2-center study using a linear support vector machine (SVM) model discriminated PD from healthy subjects with an accuracy of 82.5%.[58] This performance is similar to visual assessment by nuclear physicians.[58] A linear SVM model based on voxel values of statistical parametric images differentiated PD from vascular parkinsonism with 90.4% accuracy.[59] Both Nicastro et al and Iwabuchi et al were able to differentiate between the different forms of atypical parkinsonism by respectively using an SVM model or a classification and regression tree analysis.[60,61] Both approaches were based on FP-CIT uptake in caudate and putamen volumes of interest. CBD was correctly diagnosed with accuracies of up to 83.7% and PSP with accuracies of up to 94.4%. PSP was found to be associated with MIBG scintigraphy uptake. A higher degree of striatal impairment was observed in MSA parkinsonian-type patients and PSP. CBD patients showed a moderate reduction in uptake and a higher asymmetrical index.[60] DLB was associated with a lower level of impaired putamen to caudate ratio compared to the other forms of parkinsonism.[61] A fully automated artificial neural network based on deep-learning analyses of dopaminergic imaging has also been shown to diagnose PD with accuracies of >90%. This is similar to accuracies obtained by experienced physicians.[62] Although these deep-leaning approaches are better than those based on SVM algorithms in terms of diagnostic performance, they do not allow easy extraction of features used to classify patients with parkinsonism. Automated learning approaches also need further validation in clinical practice. This requires multicentric studies on well-characterized clinical cohorts. Extensive multicentric databases, which include healthy subjects as well as patients, will be needed to collect enough data to accurately perform these types of analyses.

To conclude, SPECT and PET molecular imaging is currently at a turning point and is consolidating its position in the diagnostic strategy of parkinsonism. The development of novel targeted radiopharmaceuticals, the improvement in performance of technical imaging systems, and the rapid evolution of new image analysis approaches improve the diagnosis of neurodegenerative parkinsonism. These innovations may potentially lead to more accurate disease detection, enabling earlier diagnosis and treatment.

Author Contributions

A.V. and E.G. contributed to the conception and design of the review; S.G. and S.F. contributed to the interpretation of studies included in the review; A.V., M.-J.R., and S.G. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

E.G. consults for amyloid PET imaging in AD (General Electric Healthcare).

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