Neuroimaging in Parkinson disease: from research setting to clinical practice

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Abstract | Over the past three decades, neuroimaging studies—including structural, functional and molecular modalities—have provided invaluable insights into the mechanisms underlying Parkinson disease (PD). Observations from multimodal neuroimaging techniques have indicated changes in brain structure and metabolic activity, and an array of neurochemical changes that affect receptor sites and neurotransmitter systems. Characterization of the neurobiological alterations that lead to phenotypic heterogeneity in patients with PD has considerably aided the *in vivo* investigation of aetiology and pathophysiology, and the identification of novel targets for pharmacological or surgical treatments, including cell therapy. Although PD is now considered to be very complex, no neuroimaging modalities are specifically recommended for routine use in clinical practice. However, conventional MRI and dopamine transporter imaging are commonly used as adjuvant tools in the differential diagnosis between PD and nondegenerative causes of parkinsonism. First-line neuroimaging tools that could have an impact on patient prognosis and treatment strategies remain elusive. This Review discusses the lessons learnt from decades of neuroimaging research in PD, and the promising new approaches with potential applicability to clinical practice.

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Introduction

Parkinson disease (PD) is the second most prevalent neurodegenerative disorder after Alzheimer disease (AD), and has high annual economic costs, estimated at around €14 billion in Europe.[1] In our increasingly ageing society, the prevalence of PD and the related pressure put on health-care systems are projected to grow substantially in the coming years.[2]

The main neuropathological characteristic of PD is the progressive loss of dopamine neurons in the substantia nigra pars compacta and the subsequent dopaminergic denervation in forebrain areas.[3] By the time a patient is diagnosed with PD, 30–50% of nigrostriatal neurons might have already been lost, representing striatal dopamine loss of nearly 80%.[4] However, the pathogenetic processes of PD are not limited to the dopaminergic system: diffuse pathology affects other, nondopaminergic, systems, such as the serotonergic,[5,6] glutamatergic,[7] opioid,[8] cannabinoid[9] and cholinergic[10] systems.

These processes account for a range of motor (bradykinesia, rigidity, tremor) and nonmotor (for example, fatigue and depression) symptoms in PD, each of which will affect a particular patient to varying degrees.[11] A plethora of studies from 30 years of neuroimaging research has attempted to link neuropathology with motor and nonmotor symptomatology *in vivo*, to aid differential diagnosis, to monitor disease progression, to investigate aetiology and pathophysiology, and to measure the effects and complications of various therapies.

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Neuroimaging—including MRI, PET and single-photon emission CT (SPECT)—rely on different principles that could be useful depending on the question asked and the research or clinical setting available. For many years, the main focus of neuroimaging studies in PD was the dopaminergic system, but recently there has been an explosion in the development of neuroimaging modalities, with more than a dozen MRI-based techniques (Table 1) and over 100 PET and SPECT radioligands available with potential applications to PD (see Supplementary Table 1 online). However, very few of these research achievements have been translated into clinical practice.

This Review highlights the most important findings from decades of research with neuroimaging techniques including MRI, PET and SPECT, and discusses their potential future roles in clinical practice.

Differential diagnosis

Although PD is the most frequent cause of parkinsonism, there are a number of other entities that mimic the clinical presentation of PD, each of which should be considered during differential diagnosis (Box 1).[12] Diagnosis is mainly based on observable symptoms, without an established role for neuroimaging. Despite the requirement for high precision in modern clinical practice, current approaches to the diagnosis of PD include the administration of medications, such as levodopa, and use of treatment response to confirm or refute the diagnosis. Such an approach could occasionally be inaccurate, raising additional burdens for patients,

Key points

- Neuroimaging has been used in Parkinson disease (PD) research for 30 years, but no guidelines have yet endorsed its routine use in clinical settings
- Single-photon emission CT and PET are equally effective at differentiating between degenerative and nondegenerative causes of parkinsonism; MRI and PET can differentiate between PD and atypical parkinsonism, but need sophisticated enhancement methods
- Dopaminergic and serotonergic PET can be used to monitor PD progression, motor and nonmotor symptoms, and complications, whereas cholinergic PET is currently the most sensitive approach for assessing PD dementia
- PET and other neuroimaging techniques should have a primary role in the development of protocols for new clinical trials, particularly those investigating cell therapy
- Hybrid PET–MRI technology could offer a revolution in PD imaging, but issues with image reconstruction need to be addressed before use in research and clinical settings can be considered
- High costs hinder the transfer of robust research techniques into clinical practice; however, these costs have not been directly compared with the costs deriving from misdiagnosis and flawed treatments plans

Table 1 | Potential neuroimaging techniques for clinical evaluation of PD

Imaging technique	Differential diagnosis	Other applications
Dopaminergic PET/SPECT	Degenerative and nondegenerative parkinsonisms Parkinsonian dementia (PDD or DLB) and dementia due to AD	Monitoring disease progression, including bradykinesia, rigidity, motor fluctuations and LIDs Estimation of preclinical PD years Patient selection for clinical trials* Monitoring graft survival after transplantation
Metabolic PET	PD and atypical parkinsonism (for example, MSA, PSP or CBD) Parkinsonian dementia (PDD or DLB) and dementia due to AD	Monitoring disease progression, including cognitive dysfunction and decline‡
Serotonergic PET	NA	Monitoring disease progression, including tremor, motor fluctuations and LIDs, and nonmotor symptoms (e.g. depression, weight dysregulation, fatigue and visual hallucinations) Graft preparation§ Monitoring graft-induced dyskinesias
Diffusion-weighted MRI	PSP and MSA-P from PD‖	NA
Structural MRI	PD, MSA and PSP (atrophy pattern recognition)	NA
Cholinergic PET	NA	Monitoring cognitive dysfunction Detecting subclinical dementia
Amyloid-β PET	NA	Monitoring cognitive dysfunction¶
Hybrid PET–MRI	NA	Simultaneous acquisition of complementary PET and MRI data

*For example, patients with ventral striatal dopaminergic deficits have worse outcomes than other patients with PD. ‡Patients with PD demonstrate distinct pathognomonic glucose metabolism distribution patterns related to disease progression and/or cognitive dysfunction. §Patient evaluation for cell composition of grafted tissue helps avoid excessive serotonergic grafting. ‖Differentiation on the basis of regional apparent diffusion coefficient values. ¶Dysfunction severity tends to be highest in patients with AD, followed by DLB and PDD. Abbreviations: AD, Alzheimer disease; CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; LIDs, levodopa-induced dyskinesias; MSA, multiple system atrophy; MSA-P, parkinsonian subtype of MSA; NA, not applicable; PD, Parkinson disease; PDD, PD dementia; PSP, progressive supranuclear palsy; SPECT, single-photon emission CT.

their carers and health-care systems. Greater precision might be gained from the use of neuroimaging; however, existing guidelines allow its use only as a supplementary tool, and mainly for the differentiation between PD and nondegenerative forms of parkinsonism (Box 2).

PET, SPECT and MRI have been repeatedly employed in research settings to increase the efficiency of differential diagnosis in patients with parkinsonism. PET and SPECT use a variety of radiotracers to quantitatively measure metabolic and neurochemical—for example, dopaminergic—changes in the brains of patients with PD (Figure 1), whereas MRI uses different sequences and contrasts to study brain structure and function (Figures 2 and 3).

Dopaminergic imaging

Differential diagnosis of conditions associated with disturbed dopaminergic functioning can be challenging, especially in the early stages. Many dopaminergic-specific radioligands have been developed to assist with differential diagnosis (Figure 4).[13] Dopamine transporter (DAT) imaging has largely been employed with SPECT, for example using the ^{123}I-FP-CIT ligand (also known as ^{123}I-ioflupane or DaTSCAN). DAT-SPECT typically reveals normal DAT levels in the caudate and putamen of healthy control participants and patients with essential tremor or with drug-induced or psychogenic parkinsonism, but reduced DAT levels are seen in patients with PD, PD dementia (PDD), multiple system atrophy (MSA) or progressive supranuclear palsy (PSP).

DAT-SPECT has high sensitivity (87–98%) and specificity (80–100%) for differentiating patients with parkinsonian syndromes (PD, MSA, PSP) from those with essential tremor and healthy controls (Figure 5).[14–18] However, DAT-SPECT is not efficient for the differentiation of PD from other degenerative parkinsonian syndromes such as MSA and PSP.[19–21] With regard to vascular parkinsonism, although some DAT-SPECT studies have suggested that the majority of patients with this disease have normal scans,[22,23] others have indicated that detectable vascular lesions in the basal ganglia or extrastriatal regions can be associated with reduced DAT binding in the striatum.[24,25]

Dopamine D2/D3 receptor SPECT, for example with ^{123}I-iodobenzamide (^{123}I-IBZM), has been employed to differentiate PD from other neurodegenerative parkinsonian syndromes. Early studies suggested a diagnostic accuracy of up to 90% for this approach,[26,27] but more-recent studies indicated a lower figure (75–82%),[28–31] suggesting that normal dopamine D2/D3 receptor availability does not exclude MSA or PSP from diagnosis.[32]

Currently, no financial reports are available that explore the cost-effectiveness of the clinical use of DAT-SPECT. A 2003 health economics report suggested that DAT-SPECT has greater sensitivity than clinical examination, but incurs higher costs up front.[33] However, these costs could be minimized in the long run by avoiding unnecessary treatment of people who do not have PD. A more recent report (from 2008) assessed the cost-effectiveness of DAT-SPECT for the differentiation of PD from essential tremor,[34] and found that use in patients with clinically uncertain parkinsonism generates savings to the health-care system, increases patients' time on potentially beneficial therapy, and limits unnecessary testing and flawed therapeutic schemes.

Box 1 | Differential diagnosis of idiopathic PD

Degenerative disorders
- Multiple system atrophy
- Progressive supranuclear palsy
- Corticobasal degeneration
- Dementia with Lewy bodies
- Genetic forms of PD
- Alzheimer disease

Nondegenerative disorders
- Essential tremor
- Dystonic tremor
- Exaggerated physiological tremor
- Tremor related to hyperthyroidism
- Vascular parkinsonism
- Drug-induced parkinsonism

Abbreviation: PD, Parkinson disease.

Some have suggested that loss of DATs might be more severe than loss of dopaminergic neurons in PD and, therefore, SPECT imaging might yield increased sensitivity.[35,36] However, the broader literature indicates that there is no real difference in diagnostic accuracy between DAT-SPECT and PET imaging of DATs via ^{18}F-CFT, and PET imaging of dopa decarboxylase (DDC; also known as aromatic-L-amino-acid decarboxylase) via ^{18}F-dopa.[37,38] Similarly, no difference in accuracy has been seen between SPECT and PET for measuring post-synaptic dopaminergic markers with ^{11}C-raclopride or ^{18}F-fallypride.[39,40] Also, findings from DAT-SPECT and DDC PET imaging are robustly correlated,[41,42] and these techniques did not differ significantly in their capacity to differentiate between newly diagnosed and advanced PD in the same group of patients.[42] As with SPECT, DDC PET can correctly distinguish PD-affected from healthy brains,[38] but cannot reliably differentiate PD from MSA or PSP (64–86% accuracy).[37,39,40] PET provides higher spatial and temporal resolution than SPECT, but at a higher cost.

Box 2 | Current guidelines for the use of neuroimaging in PD clinical practice

Routine use of molecular (SPECT and PET), structural (for example, CT and MRI) or functional (for example, fMRI, MRS) imaging, or transcranial ultrasound, has not yet been recommended for the differential diagnosis of PD and atypical parkinsonian disorders such as progressive supranuclear palsy and multiple system atrophy.

SPECT

^{123}I-FP-CIT SPECT scanning should be considered as an aid to clinical diagnosis when there is uncertainty between PD and nondegenerative parkinsonism and tremor disorders. ^{123}I-FP-CIT SPECT scanning should be available to specialists who have expertise in its use and interpretation.

MRI

MRI scanning is recommended for patients in whom it would be clinically helpful to identify the degree and extent of cerebrovascular disease—in particular, in subcortical brain areas including the basal ganglia—to differentiate idiopathic PD from vascular parkinsonism. MRI can also be useful for measuring the degree and distribution of brain atrophy in patients with features suggestive of an atypical parkinsonian disorder, and for detecting the presence of a structural lesion or lesions that may cause or contribute to parkinsonism, gait disorder and tremor.

CT

CT brain scanning is recommended in patients in whom it would be clinically helpful to identify the presence of one or more structural lesions that might cause or contribute to parkinsonism, gait disorder and tremor.

Abbreviations: fMRI, functional MRI; MRS, magnetic resonance spectroscopy; PD, Parkinson disease; SPECT, single-photon emission CT.

Metabolic imaging

Metabolic imaging can be applied to measure estimates of glucose use in the brain. Studies indicate that PET imaging of glucose metabolism using ^{18}F-FDG can, to varying extents, classify PD (75% sensitivity, 100% specificity), MSA (100% sensitivity, 87% specificity) and PSP (86% sensitivity, 94% specificity),[43] and has a reasonable ability to correctly categorize PD out of a pool of scans including patients with MSA, PSP and corticobasal degeneration (86% sensitivity, 91% specificity).[31]

Other metabolic PET studies showed 74% accuracy for distinguishing patients with PD from those with atypical PD or healthy controls. Accuracy could be increased to 95% by using topographical profile rating, a method for calculating abnormal regional metabolic covariance patterns in individuals with PD.[44] Network analysis of glucose metabolic PET is an innovative approach for the study of movement disorders, and can robustly differentiate between PD (84–95% sensitivity, 94–97% specificity), MSA (85–96% sensitivity, 96–99% specificity), PSP (88–91% sensitivity, 94–99% specificity) and corticobasal degeneration (96% sensitivity, 96% specificity).[45–47] Voxel-based glucose metabolic PET with automated image-based classification could also aid treatment planning for patients with early disease, and help identify patients for clinical trials.[47]

Although no financial data are available regarding the use of metabolic PET imaging in PD, it is of interest that incorporation of this technique into the clinical work-up of patients with cognitive decline yielded substantial cost savings in a European setting.[48] Similar reports are greatly needed for patients with PD and other parkinsonisms, given the potential benefits of this approach.

MRI-based techniques

In the context of PD, the most important role of conventional MRI is the identification of secondary parkinsonism resulting from structural lesions, including vascular parkinsonism, neoplasms and multiple sclerosis. MRI also has a routine and mandatory use in the planning of surgical interventions for PD, such as deep brain neurostimulator implantation.

MRI-based techniques, such as structural and morphometric MRI, diffusion-weighted imaging and magnetic resonance spectroscopy, have been evaluated for their abilities to aid differential diagnosis of PD. For example, structural MRI has shown that abnormal T2 hypointensity in patients with parkinsonian-dominant MSA (MSA-P) can differentiate these individuals from patients with PD with 88% sensitivity and 89% specificity.[49] Atrophy in the substantia nigra may also be evident on MRI, but not to a level of specificity that allows differentiation of early-stage PD from the healthy brain or other forms of neurodegeneration.[50]

Voxel-based morphometry has been shown to differentiate PSP from PD, MSA and healthy controls with

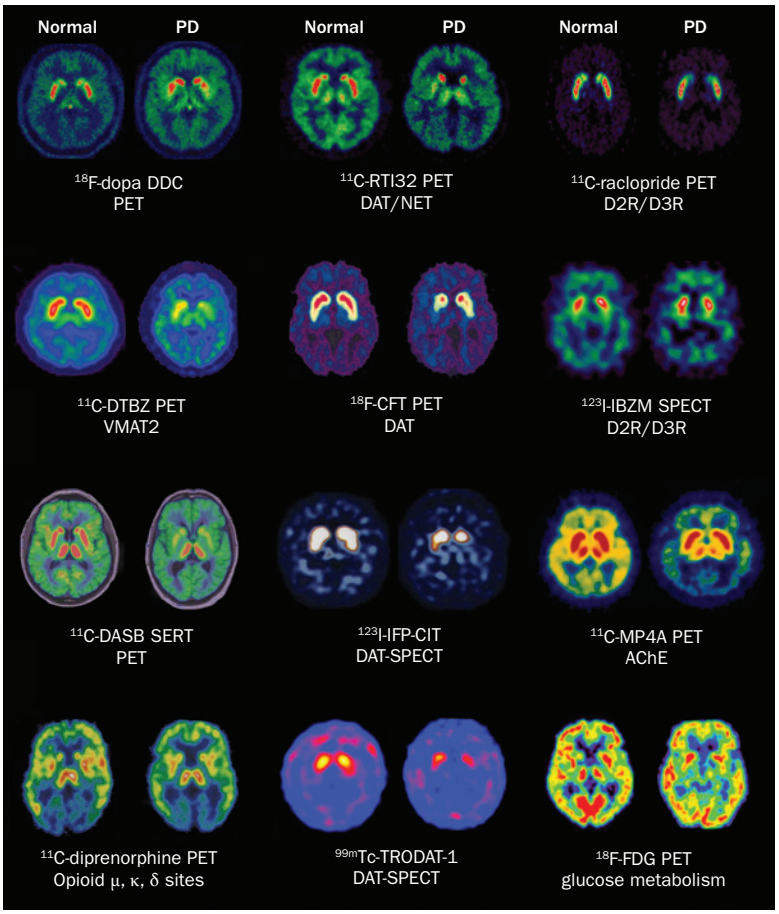


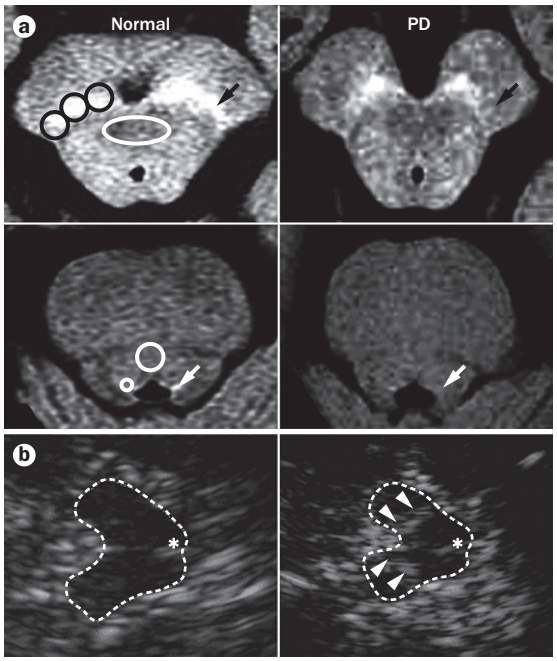
Figure 1 | Molecular imaging in patients with PD. PET and SPECT imaging techniques have revealed PD-associated alterations in DDC activity, DAT availability, NET availability, D2R/D3R binding capacity, VMAT-2 activity, SERT activity, AChE activity, opioid μ, κ, and δ binding site availability, and glucose metabolism. Abbreviations: AChE, acetylcholinesterase; D2R/D3R, dopamine D2 and D3 receptors; DAT, dopamine transporter; DDC, dopa decarboxylase; NET, noradrenaline transporter; PD, Parkinson disease; SERT, serotonin transporters; SPECT, single-photon emission CT; VMAT-2, vesicular monoamine transporter.

74–83% sensitivity and 79-94% specificity, mainly on the basis of atrophy in the cerebral peduncles of patients with PSP.[51,52] Voxel-based morphometry and diffusion tensor imaging were also able to discriminate between cerebellar-dominant MSA (MSA-C), MSA-P, PD, and healthy controls with 89% accuracy.[53] Fully automated pattern recognition analysis based on structural MRI has been used to predict disease state at the level of individual patients.[54] Distributed patterns of atrophy across a subcortical motor network yielded robust diagnostic classification of PD, MSA and PSP with 92% accuracy. Although this technique needs to be tested in larger studies, it shows promise, especially given the low costs of application.

Diffusion-weighted imaging using apparent diffusion coefficients has been found to robustly differentiate patients with PSP and MSA-P from those with PD with up to 90–100% sensitivity and specificity (Figure 6).[55,56] One study has also differentiated patients with MSA-P from patients with PD using magnetic resonance spectroscopy, which revealed proton density hyperintensity uniquely in patients with MSA-P (83% sensitivity, 100% specificity).[49] However, another study using this technique found no metabolic abnormalities in patients with early-stage PD.[57] Notable variability between studies of metabolite concentrations prevent conclusions about the use of magnetic resonance spectroscopy from being safely drawn.

Echogenic imaging

Transcranial sonography is a noninvasive imaging technique that does not require radiotracers and, potentially, has wide availability (Figure 2b). Common findings include a hyperechogenic substantia nigra in patients with PD,[58] and a hyperechogenic lentiform nucleus in patients with PSP, MSA or corticobasal degeneration.[59,60] Two studies have reported reasonable accuracy for transcranial sonography in the clinical diagnosis of PD (82–91% sensitivity, 82–85% specificity),[61,62] comparable to glucose metabolic PET in the same patients.[62]



◀ **Figure 2** | Subcortical imaging in PD. **a** | Neuromelanin-sensitive MRI of the substantia nigra pars compacta (upper panels), and the locus coeruleus and adjacent pontine tegmentum (lower panels). Compared with a healthy control (left panels), a patient with early PD (right panels) shows reduced signal intensity in the lateral part of the substantia nigra pars compacta (black circles and arrows) and locus coeruleus (small white circle and arrows). Large white oval and circle show no changes in the periaqueductal grey matter. **b** | Transcranial ultrasonography image of the mesenchephalic brainstem in a healthy control (left panel) and in a patient with PD (right panel), who shows hyperechogenic signals in the substantia nigra (arrows). Asterisk highlights the cerebral aqueduct. Abbreviation: PD, Parkinson disease. Part a reprinted from Ohtsuka, C. *et al.* Changes in substantia nigra and locus coeruleus in patients with early-stage Parkinson's disease using neuromelanin-sensitive MR imaging. *Neuroscience Letters* **541**, 93–98 (2013), with permission from Elsevier. Permission obtained for part b from Springer © Berg, D. J. *Neurology* **248**, 684–689 (2001).

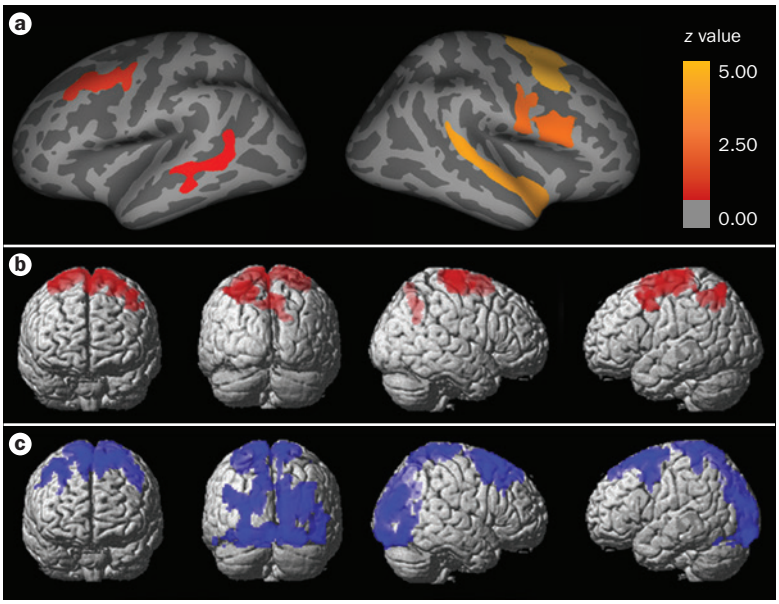


Figure 3 | Cortical imaging in PD. **a** | Cortical areas showing significantly greater thinning in patients with PD than in normal controls. **b** | Surface projection of clusters showing significantly decreased grey matter volume and **c** | significantly decreased cerebral blood flow in patients with PD compared with healthy controls. Abbreviation: PD, Parkinson disease. Permission obtained for part a from the Movement Disorder Society © Ibarretxe-Bilbao, N. *Mov. Disord.* **27**, 1746–1753 (2012). Parts b and c reprinted from Fernández-Seara, M. A. *et al*. Cortical hypoperfusion in Parkinson's disease assessed using arterial spin labeled perfusion MRI. *NeuroImage* **59**, 2743–2750 (2012), with permission from Elsevier.

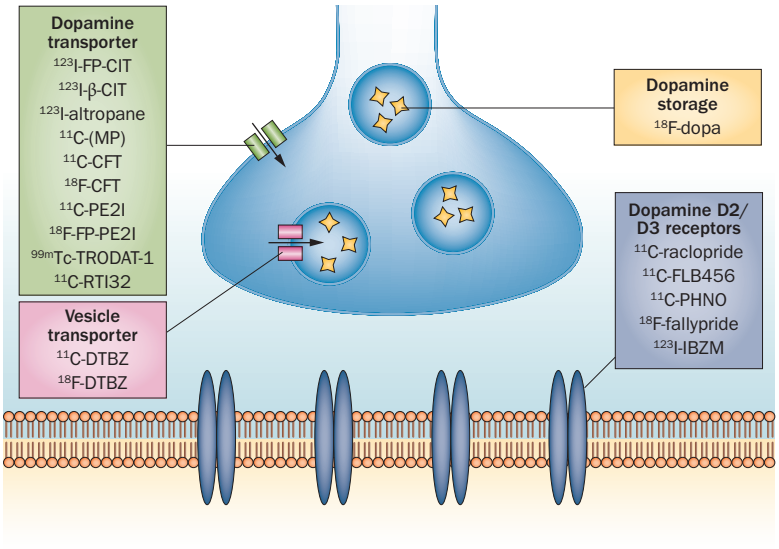


Figure 4 | Radiotracers for dopaminergic imaging. PET and single-photon emission CT can be used as molecular imaging techniques for presynaptic dopamine activity (including dopamine transporter, vesicle transporter and dopamine storage) and the postsynaptic dopaminergic system (D2/D3 receptors).

However, a large-scale study that assessed the ability of transcranial sonography to discriminate patients with degenerative and nondegenerative forms of parkinsonism or without parkinsonism showed only 40% sensitivity and 61% specificity for the diagnosis of PD, which was worse than DAT-SPECT (88% sensitivity, 68% specificity) in the same participants.[63] From these studies, it is not clear whether the diagnostic accuracy of transcranial sonography in early-stage PD is sufficient for routine clinical use and, therefore, more studies are needed.

General points

With respect to differential diagnosis, an important distinction among the various imaging techniques is whether they can achieve only between-group separation, as opposed to true diagnosis at the individual level. Individual diagnosis could be delivered by techniques that use a disease-specific pattern (as in glucose metabolic PET or structural MRI), or from which large data sets have been acquired from healthy and patient populations to define normal and disease-specific ranges for imaging biomarkers. Once a disease-specific pattern or range has been identified and validated, individuals can be categorized into groups, and the corresponding values can also be used for correlations with other disease-related measures.

Tracking disease progression

Several imaging techniques have shown promising sensitivity to disease progression in patients with PD (Figure 7). However, no single imaging modality can account collectively for the pathological processes underlying the development of motor and nonmotor symptoms in patients with PD—a situation that might change when α-synuclein PET becomes available.

Dopaminergic system

DDC PET using, for example, ^{18}F-dopa has shown that patients with PD have a mean annual decline in dopamine capacity that ranges from 8–12% in the putamen and from 4–6% in the caudate, which is considerably more than the decline typical of ageing (0.5% in the putamen and 0.7% in the caudate).[64,65] This decline in dopamine capacity is seen throughout the striatum, but has been demonstrated to start in the dorsal part of the caudal putamen contralateral to the clinically affected side.[4]

PET has also shown that early-stage PD is characterized by rapid progression of dopaminergic decline in the putamen, which has a posterior-to-anterior gradient and a side-to-side asymmetry between the less-affected and more-affected striatal structures. As the disease advances, progression of dopaminergic hypofunction becomes slower, and although the gradient is maintained, the degree of asymmetry diminishes.[66,67]

Presynaptic dopaminergic markers have been used in PET studies to indirectly estimate the preclinical duration of PD. At the time of symptom onset, evidence indicates that a period of approximately 6 years of dopaminergic decline has elapsed, totalling 30–55% losses of normal uptake in the putamen.[68,69] In individuals diagnosed with PD at a younger age, the preclinical period has been suggested to be longer. For example, PET imaging with ^{11}C-DTBZ, which targets vesicular monoamine transporter type 2 (VMAT-2), estimated a preclinical state lasting up to 17 years, and DAT PET (with ^{11}C-MP) has revealed a period of up to 13 years in patients with PD who were diagnosed at just over 50 years of age.[70]

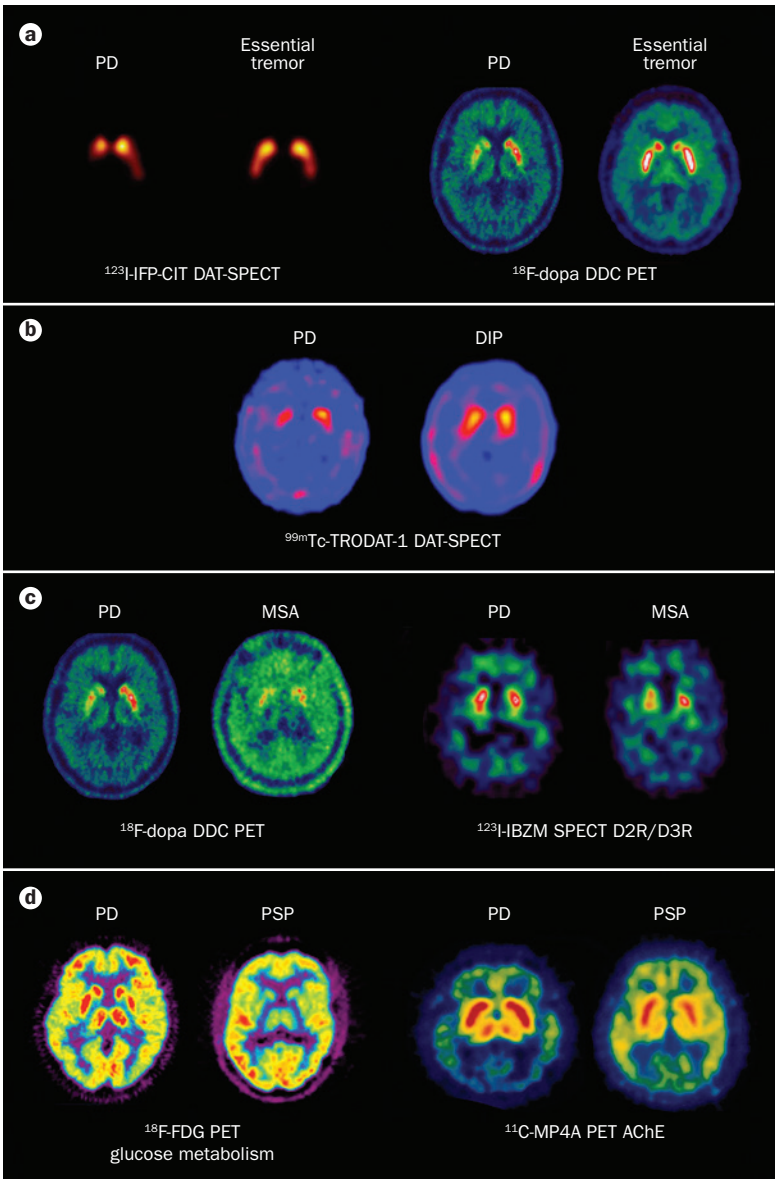


Figure 5 | Imaging for differential diagnosis. **a** | PD and essential tremor can be differentiated by measurement of DAT activity in the striatum via SPECT, or DDC activity via PET. **b** | DAT-SPECT scans of the striatum can also be used to differentiate PD from DIP. **c** | PET scans targeting DDC activity and D2R/D3R availability can help differentiate between PD and MSA. **d** | Glucose metabolism in the striatum and thalamus, and thalamic AChE activity, can reveal differences between PD and PSP. Abbreviations: AchE, acetylcholinesterase; D2R/D3R, dopamine D2 and D3 receptors; DIP, drug-induced parkinsonism; MSA, multiple system atrophy; PD, Parkinson disease; PSP, progressive supranuclear palsy.

Serotonergic system

The PET ligand ^{11}C-DASB selectively binds to the serotonin transporter (SERT), providing a measure of serotonergic activity. Patients with PD exhibit progressive, nonlinear loss of serotonergic function, which starts in the caudate, thalamus, hypothalamus and anterior cingulate cortex and expands into other areas in the basal ganglia, limbic system and cortex as the disease advances. The pattern of serotonergic denervation differs from the dopaminergic effects, as serotonin function is lost preferentially in the caudate throughout the course of the disease, and the putamen seems to be affected during the later stages.[5] The levels of decline between the serotonergic and dopaminergic systems are similar for the caudate (30–40% reductions), but there is attenuated serotonergic loss (20–30%) compared with profound dopaminergic dysfunction (70–80% reductions) in the putamen.[5,71]

Metabolic changes

PET imaging of glucose metabolism can also be used to track PD progression.[72] A clear PD-specific pattern has been identified, with changes in metabolic network activity occurring early in the disease course and progressing linearly. These changes involve increased metabolism in the subthalamic nucleus, globus pallidus, pons and motor cortex, and decreased metabolism in prefrontal and parietal areas. However, metabolic PET has an attenuated ability to track preclinical PD compared with dopaminergic PET, identifying periods of about 5 years.[73]

MRI measures

Several MRI techniques are being actively researched for their capacity to track PD progression *in vivo*; these include measures of cortical thickness,[74] regional cerebral blood flow,[75] functional connectivity,[76] diffusivity and fractional anisotropy,[77] and deposits of iron[78] or neuromelanin.[79] However, these techniques are currently far from ready for transfer into clinical practice.

Collectively, PET, SPECT and MRI provide a means to monitor molecular, structural and functional changes that reflect the progression of pathology in PD. It should be noted that these changes are not always independent; for example, changes in glucose metabolism revealed by PET and the blood oxygen level-dependent (BOLD) signal revealed by functional MRI (fMRI) could both reflect dysfunction in neurotransmitter systems. It is also important to account for the disease stage when using these imaging modalities to track PD progression. Convincing lines of evidence indicate that dopaminergic imaging is superior to other methods for assessing the progression rate in the preclinical period of PD. At the time of clinical diagnosis, however, dopamine in the putamen can be as low as 50–60% of the normal level, and may gradually exhibit a floor effect, with a slower rate of dopamine loss as the disease continues to progress. Therefore, PET and SPECT dopaminergic imaging may become gradually less sensitive to disease progression. By contrast, other PET and MRI techniques might be used to detect and measure metabolic, nondopaminergic, structural and functional changes that manifest gradually during the symptomatic stages of PD.

Motor correlates

Neuroimaging has revealed the pathological substrates of many of the motor and nonmotor symptoms of PD. These results have also highlighted potential mechanisms that could be targeted with novel treatments.

Bradykinesia and rigidity

PET and SPECT studies suggest that the development of bradykinesia and rigidity is primarily related to striatal

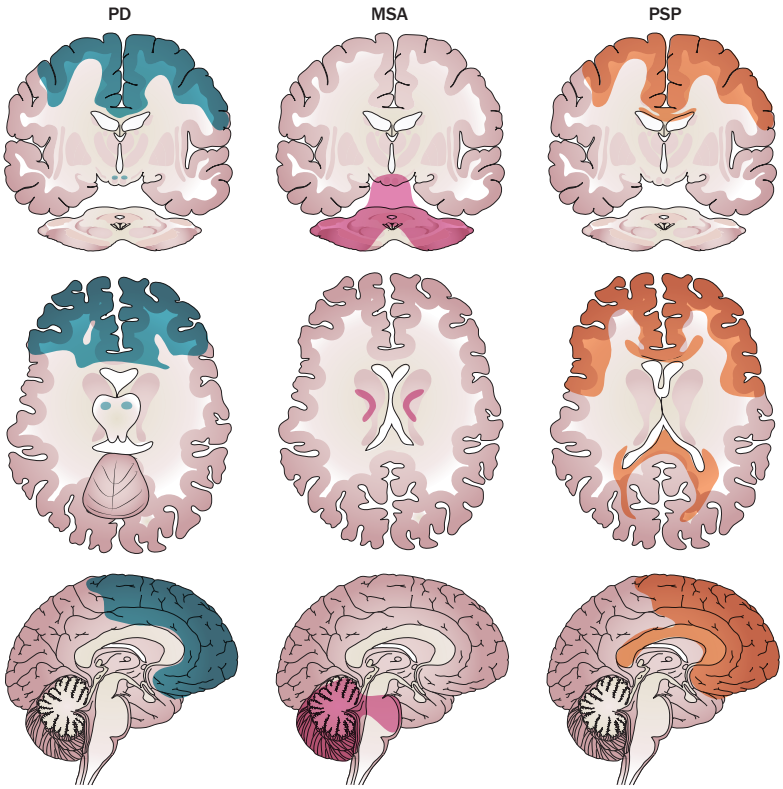


Figure 6 | Diffusion tensor imaging for differential diagnosis. This illustration, derived from diffusion tensor imaging studies,[77] shows the areas of the brain that tend to show significant alterations in fractional anisotropy associated with PD, MSA and PSP when compared with healthy controls. Abbreviations: MSA, multiple system atrophy; PD, Parkinson disease; PSP, progressive supranuclear palsy.

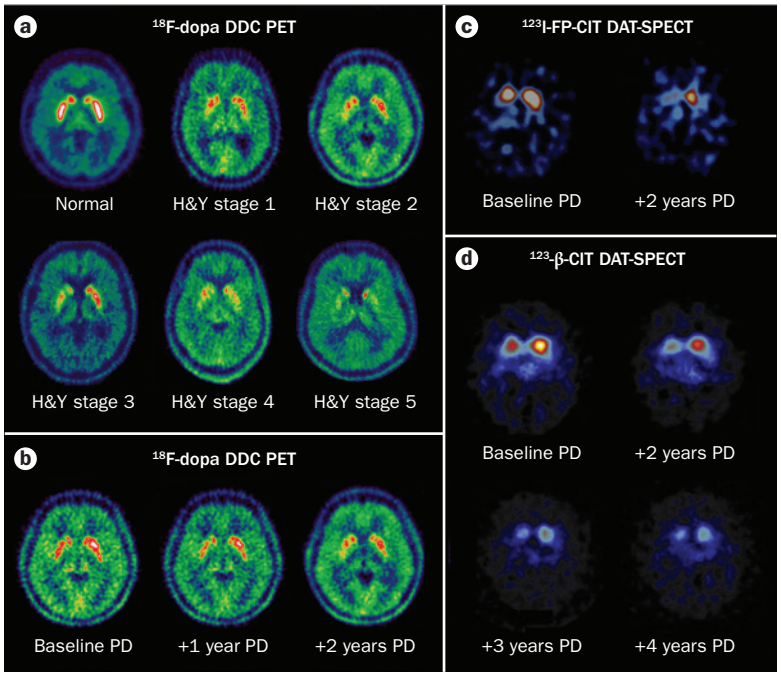


Figure 7 | Imaging disease progression. **a** | Striatal DDC activity reveals progressive decline in patients with PD as symptom severity—that is, H&Y score—increases. **b** | Serial imaging in the same patients with DDC PET or **c**,**d** | DAT-SPECT can show progressive loss of striatal dopaminergic activity. Abbreviations: DAT, dopamine transporter; DDC, dopa decarboxylase; H&Y, Hoehn and Yahr scale; PD, Parkinson disease; SPECT, single-photon emission CT.

dopaminergic deficits—an observation that is supported by the excellent response of these symptoms to dopamine drugs in the clinical setting. DAT-SPECT has shown correlations between dopaminergic decline and increased bradykinesia severity,[80,81] and DDC and VMAT-2 PET have revealed correlations between dopaminergic decline, bradykinesia and severity of rigidity.[68,82–85] Moreover, serial ^{11}C-raclopride PET scans have revealed that levodopa-induced striatal increases in dopamine release correlate with bradykinesia and rigidity.[86,87]

PET imaging of glucose metabolism has shown that PD-specific metabolic network activity correlates with ratings of motor impairment,[73] and fMRI studies have demonstrated reduced brain activity in the prefrontal cortex and pallidum of patients with the akinetic–rigid subtype of PD.[88] Serotonin-specific PET with either SERT or serotonin 1A (5-HT$_{1A}$) receptor tracers (such as ^{11}C-WAY100635) has indicated no correlation between loss of serotonergic function and bradykinesia or rigidity.[5,89]

Tremor

Tremor is one of the most challenging symptoms to manage in the clinic, as it has a poor and unpredictable response to dopaminergic treatment relative to bradykinesia and rigidity. Evidence is mounting that tremor may not be related to dopaminergic dysfunction. DAT-SPECT,[15] DDC PET,[82,90,91] VMAT-2 PET,[85] and serial dopamine D2/D3 receptor PET after levodopa challenge[86] have collectively shown that DAT availability, dopamine capacity and striatal dopamine levels do not correlate with tremor scores.

PET using SERT and 5-HT$_{1A}$ receptor binding has revealed that a decline in serotonergic function in raphe nuclei and striatum correlates with increased tremor scores.[89,92] SERT PET has also shown that patients with tremor-dominant PD have more-globally impaired serotonergic function than do those with akinetic–rigid PD, the opposite of what was observed with dopaminergic dysfunction.[92]

Imbalance, falls and freezing of gait

Imbalance, falls and freezing of gait become gradually more frequent as PD advances. Once established, these symptoms are usually refractory to treatment with dopaminergic medication. In line with this clinical observation, VMAT-2 and acetylcholinesterase PET (with ^{11}C-PMP) has shown that falls in PD are associated not with the degree of nigrostriatal dopaminergic denervation, but with significantly decreased cholinergic innervation in the thalamus.[93] Thalamic acetylcholinesterase activity derives mainly from neuronal terminals in the brainstem pedunculopontine nucleus, which play a central part in the control of movement.[94]

Balance problems can sometimes be aggravated by the adverse effects of dopaminergic medication, such as dyskinesias (see below); however, the pathophysiology of balance in patients with PD has not been imaged in great detail. Morphometric MRI has shown that freezing of gait is associated with cortical grey matter loss,[95,96] and with decreased fMRI BOLD signal in striatal and

extrastriatal regions during a virtual reality gait task.[97] Glucose metabolic PET imaging has revealed hypometabolism in the striatum and parietal cortex associated with freezing of gait in patients with PD.[98] Studies so far also suggest that freezing of gait is related to disruptions in the 'executive' attention network caused by atrophy and reduced functional connectivity, leading to impaired processing. In line with this notion, patients with freezing of gait exhibited significantly reduced scores on a variety of tests related to executive functions.[95–97]

Dyskinesias and motor fluctuations

After years of levodopa therapy, some patients with PD develop daily fluctuations in mobility, and disabling involuntary movements known as levodopa-induced dyskinesias. Several PET studies have attempted to understand the mechanisms underlying the development of levodopa-induced dyskinesias.[99]

DDC and DAT PET studies have shown that motor fluctuations and levodopa-induced dyskinesias in patients with PD are associated with reduced striatal dopamine function.[91,100] Presynaptic dopaminergic function regulates synaptic dopamine levels, and the gradual decline of this compensatory mechanism as PD progresses could alter the response to substantial rises in dopamine levels following a levodopa dose. In line with this notion, dopaminergic PET has shown that synaptic dopamine levels rise and fall sharply following a levodopa dose in patients with motor fluctuations and levodopa-induced dyskinesias,[101,102] and that rises in synaptic dopamine levels correlate with the severity of levodopa-induced dyskinesias.[86,87]

In light of the striatal dopaminergic denervation associated with advanced PD, maladaptive serotonergic mechanisms have been suggested to be responsible for dysregulated striatal dopamine levels and the development of levodopa-induced dyskinesias. This hypothesis was based on the ability of serotonergic terminals to store, convert and release dopamine, but in a dysregulated manner as they lack autoregulatory feedback for synaptic dopamine levels. PET studies assessing serotonergic function and dopamine release demonstrated a causal relationship between serotonergic function and excessive levodopa-induced synaptic dopamine levels in the striatum in patients with PD who regularly experienced levodopa-induced dyskinesias.[87]

PET has also revealed potential roles for other nondopaminergic systems in levodopa-induced dyskinesias, with observations including reduced striatal and extrastriatal μ, κ and δ opioid receptor sites,[8] reduced thalamic substance P,[103] increased striatal adenosine A_{2A} receptor availability,[104,105] and increased activation of striatal *N*-methyl-D-asparate receptors.[106] However, none of these studies reported correlations between these neurochemical effects and severity of levodopa-induced dyskinesias.

Nonmotor correlates

Nonmotor symptoms, such as depression, sleep problems and fatigue, are common in patients with PD, and represent a substantial burden for patients and health-care systems.[11,107] Although some initial indications from PET imaging suggested that nonmotor symptoms could relate to dopaminergic dysfunction in extrastriatal areas,[108] the current working theory indicates prominent involvement of nondopaminergic mechanisms. A 2012 PET study demonstrated that patients with PD who received fetal cell transplants showed restored dopaminergic function and major motor symptom recovery, but also experienced nonmotor symptoms including depression, fatigue, visual hallucinations and sleep problems. In these patients, serotonergic function was severely affected in raphe nuclei and several other brain regions involved in the regulation of sleep, arousal, satiety and emotion,[109] which suggests an important role for the serotonergic system in the development of nonmotor symptoms.

Depression is a major determinant of quality of life in patients with PD, and has a reported prevalence of up to 45%.[110] PET imaging of DAT and noradrenaline transporter activity (using ^{11}C-RTI32) has demonstrated reduced limbic noradrenergic and dopaminergic function in patients with PD experiencing depression compared with those without depression.[111] These reductions correlated with the severity of anxiety and apathy. PET studies using serotonergic markers have indicated significant reductions in 5-HT_{1A} binding capacity and increased SERT in limbic regions that correlated with depression scores in patients with PD.[112–115]

Sleep problems, broadly divided into disturbances of sleep or of wakefulness, are particularly common in patients with PD, with prevalence estimated up to 75%.[116] Reduced mesopontine monoaminergic capacity, revealed by DDC PET, correlates with inability to maintain rapid eye movement (REM) sleep, as measured by polysomnography, in patients with PD.[117] PET imaging has also shown an association between cholinergic denervation and REM sleep behaviour disorder in patients with PD, but failed to associate serotonergic or nigrostriatal dopaminergic denervation with this condition.[118] SERT PET has also failed to demonstrate a link between serotonergic dysfunction and sleep-disordered breathing.[119]

Chronic disabling fatigue is estimated to affect approximately one-third of patients with PD.[120] DDC and SERT PET have revealed reduced striatal and thalamic serotonergic function and reduced dopamine capacity in the caudate of patients with PD who experience fatigue compared with those who do not.[121]

Weight and appetite dysregulation are also common in patients with PD, affecting at least half of these individuals.[122] Abnormal weight changes are associated with increased SERT function in raphe and limbic structures.[123]

Visual hallucinations are the most common form of psychosis in PD, and tend to occur in late disease stages. The 5-HT_{2A} receptor PET ligand ^{18}F-setoperone has indicated increased 5-HT_{2A} availability in the ventral visual pathway and other cortical regions in patients who experience PD-related hallucinations.[124] Metabolic PET has also shown glucose hypermetabolism in the frontal cortex in these patients compared with those without psychosis.[125,126]

Although dopaminergic drugs are highly effective up to a certain stage of the disease, considerable evidence

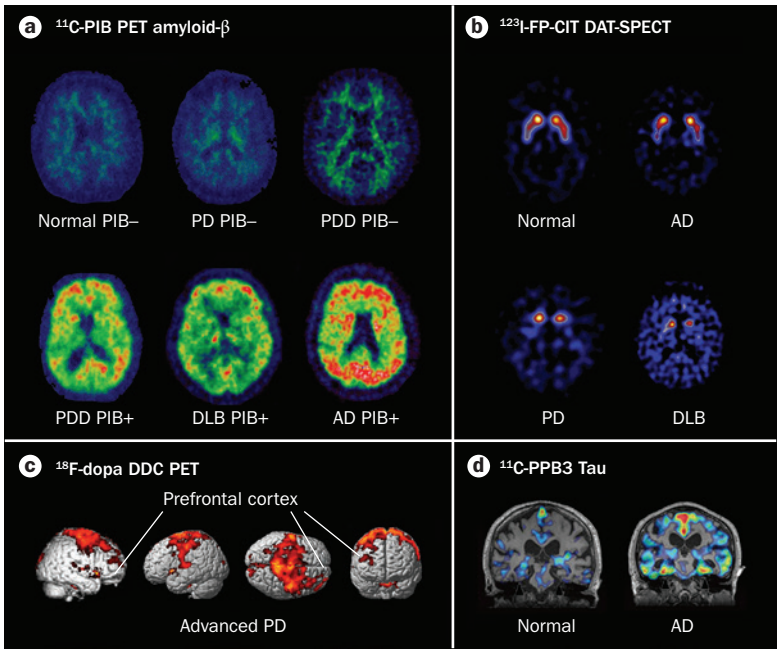


Figure 8 | Parkinsonism and dementia. **a** | PET imaging for amyloid-β reveals dissociable forms of PDD characterized by amyloid build-up. Deposits of amyloid appear in different regions in patients with PD, DLB or AD. **b** | DAT-SPECT scans reveal reduced DAT availability in patients with PDD or DLB compared with normal controls or patients with AD. **c** | Statistical parametric maps showing areas of cortex with significant decreases in DDC activity in patients with PDD relative to those with PD. **d** | ^{11}C-PPB3 binds selectively to tau inclusions in the hippocampal formation of patients with AD. Abbreviations: AD, Alzheimer disease; DAT, dopamine transporter; DDC, dopa decarboxylase; DLB, dementia with Lewy bodies; PD, Parkinson disease; PDD, PD dementia. Part d reprinted from Maruyama, M. *et al*. Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls. *Neuron* **79**, 1094–1108 (2013), with permission from Elsevier.

exists of addictive and compulsive behaviour—often with devastating consequences—after chronic exogenous dopamine exposure.[127,128] PET and fMRI studies have shown increased dopamine release and activation in the ventral striatum after levodopa challenge in a subset of patients with PD who experience so-called dopamine dysregulation syndrome, characterized by compulsive use of levodopa.[129] Similarly, increased dopamine release in the ventral striatum can be seen in patients with PD who exhibit mixed impulse control disorders[130] or pathological gambling.[131] Reduced cerebral blood flow (assessed by PET with $H_2{}^{15}O$) is also seen in limbic structures of patients with PD who gamble pathologically.[132] In PD patients with hypersexuality, fMRI has shown BOLD signal increases in brain networks that control reward, and decreases in areas associated with behavioural inhibition.[133]

Parkinson disease dementia

The prevalence of dementia in patients with PD is significantly higher than in the normal population, averaging around 30%,[134] and over 80% of patients develop dementia after 20 years of disease.[135] Dementia in PD might be a diverse entity, sharing a number of characteristics with dementia with Lewy bodies (DLB).[136] The latest guidelines consider patients presenting with parkinsonism more than 1 year before the onset of dementia as probably having PDD, and those developing parkinsonism and dementia concurrently as having DLB.[137]

PDD could be associated with several processes, including degeneration of subcortical cholinergic and dopaminergic projections, neocortical pathology associated with Lewy body and amyloid-β (Aβ) plaque deposition, and vascular pathology.[138] Also, functional polymorphisms in the catechol-*O*-methyltransferase gene, which influence dopamine storage, may contribute to cognitive deficits in PD.[139] PET and SPECT imaging have been employed on several occasions to explore PDD pathology *in vivo* (Figure 8).

Dopaminergic PET imaging

Patients with PDD exhibit decreased mesolimbic and mesocortical monoaminergic capacity, as revealed by DDC PET,[140,141] but do not show differences in striatal dopamine capacity[142,143] compared with cognitively normal patients with PD.

PD, PDD and DLB all feature nigrostriatal degeneration, and visual inspection of DAT-SPECT scans cannot aid discrimination between these disorders. Dopaminergic PET has revealed only subtle differences. DDC[143] and VMAT-2[144] PET show no differences between PDD and DLB. However, anatomical full-quantification analyses of DAT PET scans have demonstrated marked asymmetry of DAT-binding decline in the posterior putamen in patients with PD. This pattern is in contrast to DLB, which is associated with consistently bilateral reductions in caudate DAT sites.[145]

Glucose metabolic changes

Glucose metabolic PET can be used to distinguish between AD and PDD or DLB but, like dopaminergic PET, offers very little for the differentiation between PDD and DLB. For example, reduced metabolic activity in the medial occipital cortex has been consistently observed in patients with PDD or DLB, but this region seems relatively unaffected in patients with AD.[146,147] Metabolic PET imaging can distinguish DLB from AD with 90% sensitivity and 80% specificity, which is greater than for clinical diagnostic criteria applied retrospectively to the data from a medical chart review.[147,148]

More-sophisticated PET analysis has allowed the identification of a PD-related metabolic brain network that underlies the cognitive dysfunction in PD, extending beyond the occipital cortex to frontal and parietal areas.[72] However, even with more-advanced methods, discrimination between PDD and DLB has been difficult as they share similar metabolic patterns, except that decreased metabolic activity in the anterior cingulate is possibly greater in DLB than in PDD.[149]

Cholinergic PET imaging

Dopaminergic denervation alone seems insufficient to explain the development of PDD. PET imaging of acetylcholinesterase activity (for example, via ^{11}C-MP4A or ^{11}C-PMP uptake) has indicated that cholinergic

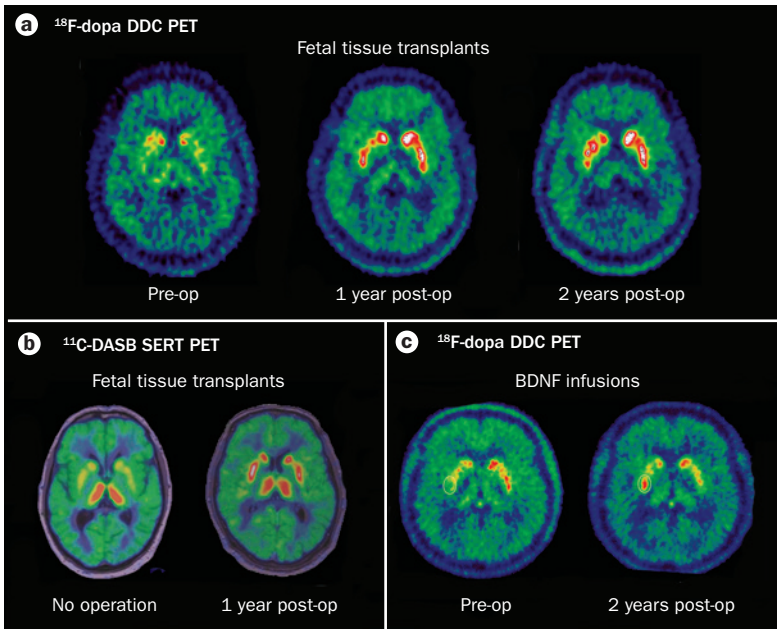


Figure 9 | Clinical trials in PD. **a** | Serial PET scans in one patient with PD show significant increases in striatal DDC activity 1 and 2 years after intrastriatal graft transplantation with dopamine-rich ventral mesencephalic tissue. **b** | PET reveals excessive graft-derived SERT binding in the striatum of a patient with advanced PD compared with a patient with PD who did not undergo surgery. **c** | Intraputaminal infusions of BDNF produce significant increases in putaminal DDC activity after 2 years in a patient with PD. Abbreviations: BDNF, brain-derived neurotrophic factor; DDC, dopa decarboxylase; op, operative; PD, Parkinson disease; SERT, serotonin transporter. Permission obtained for part c from Nature Publishing Group © Gill, S. S. *Nat. Med.* **9**, 589–595 (2012).

denervation is an early phenomenon in the course of PD, and is consistently more marked in PDD than in non-demented patients with PD.[10,142,150,151] Cholinergic PET may also be sensitive to subclinical dementia. In patients with PD who have not reached the threshold for PDD diagnosis, lower cortical acetylcholinesterase activity was associated with reduced cognitive performance scores for attention, memory and executive functions.[150] These cholinergic imaging studies are in agreement with post-mortem evidence suggesting that loss of forebrain cholinergic function is associated with PDD.[10,142,150,151] Overall, these findings indicate that appreciable cholinergic pathology underlies progressive cognitive decline in PD.

Amyloid-β PET

Postmortem analyses have shown that pathology typified by intraneuronal Lewy body inclusions can be complicated by the additional presence of Aβ deposition in some patients with PD.[152] PET imaging with the Aβ-sensitive ^{11}C-PIB (Pittsburgh compound B) has been very useful for tracking Aβ plaque load *in vivo*, and has demonstrated that the majority of patients with AD and many patients with DLB show increased cortical retention of Aβ.[153–156] However, Aβ pathology is infrequent in PDD (prevalence 15–20%) and largely absent in patients with early-stage PD. Aβ-positive PDD is associated with retention of Aβ mainly in cortical and striatal regions.[154,156,157] One PET study has shown that Aβ retention places patients with PD and mild cognitive impairment at increased risk of further cognitive decline in the future.[158] These findings indicate that despite relatively low Aβ levels compared with AD, Aβ deposition can contribute to cognitive impairment in PD.

Clinical trials

Several clinical trials investigating treatments for PD have used molecular imaging as a primary or secondary end point. Examples include the use of DAT-SPECT in comparing pramipexole with levodopa treatment (CALM-PD study)[159] and in comparing the effects of early versus late use of levodopa on clinical progression (ELLDOPA trial).[160] DDC PET has been used to compare ropinerole with levodopa in patients with newly diagnosed PD (REAL-PET study),[161] to study the efficacy of intraputaminal infusions of glial cell line-derived neurotrophic factor,[162] and to assess the efficacy of intrastriatal transplantation of dopamine-rich fetal ventral mesencephalic tissue in open-label[163,164] and double-blind[165,166] trials (Figure 9).

These studies revealed some discrepancies between the clinical effects of treatments and the imaging results. In the CALM-PD and REAL-PET studies, neuroimaging suggested a slower rate of disease progression with pramipexole and ropinerole than with levodopa, but clinical improvements were higher in the levodopa treatment groups.[159,161] In the ELLDOPA study, PD patients treated with levodopa showed more dopaminergic decline than did the placebo-treated group.[160] These findings suggest that dopamine agonists could be neuroprotective while levodopa could be neurotoxic, despite its higher symptomatic efficacy. However, it is also possible that the dopaminergic medication affected the imaging markers more than did the actual disease process, as levodopa depresses radioligand binding to DAT and DDC more than do dopamine agonists that act mainly postsynaptically.

Fetal tissue transplantation trials have aimed to resolve the dopaminergic denervation and neurotransmission deficits in patients with advanced PD.[167] Although DDC PET revealed significant increases in graft-derived striatal dopamine capacity in all trials, convincing improvements in clinical function were not consistently seen.[163–166] Moreover, results from these trials have generated controversy, as several of the patients with PD who received transplants subsequently developed postoperative graft-induced dyskinesias, which were present when patients were off medication. This phenomenon represented a major adverse effect, and may hinder the further development of cell therapy in PD.[165–173]

PET and SPECT imaging with markers of serotonin and dopamine suggest that patients with PD experiencing graft-induced dyskinesias exhibit excessive graft-derived serotonergic innervation, resulting in an unfavourably high ratio of serotonergic to dopaminergic terminals. A causative role for graft-derived serotonergic innervation in the development of graft-induced dyskinesias was shown in a subsequent experiment, wherein dampening of neurotransmitter release from serotonergic neurons with repeated doses of a 5-HT_{1A} receptor agonist was able to attenuate graft-induced dyskinesias.[170–172]

Cell replacement with fetal or stem cells remains a promising approach to provide long-lasting relief from the symptoms of PD.[174] In the past, DDC PET imaging was used solely to provide information regarding graft survival and growth, but a need now exists for optimized imaging protocols for future trials, including multimodal imaging that employs both dopaminergic and nondopaminergic PET and MRI-based methods to prevent and monitor adverse effects and to assess integration of the graft with the host brain.[175]

Hybrid PET–MRI

Hybrid PET–CT is an established imaging tool, and represents the state of the art for multimodal PET imaging in clinical settings. However, PET–CT technology has limitations, such as poor soft-tissue contrast and asynchronous data acquisition. Hybrid PET–MRI systems, in which a PET module is inserted inside an MRI scanner, have become commercially available in the past few years. This technique will allow simultaneous acquisition of MRI and PET data, thereby yielding temporal stability, spatial homogeneity, improved soft-tissue contrast, and greater spatial resolution.[176]

Proof-of-principle analysis of integrated and simultaneous collection of PET and MRI data has been very promising.[177] PET–MRI could have great potential for clinical imaging in multiple neurological disorders, including PD, and PET and MRI protocols might be developed to maximize the advantages of combining both modalities. Benefits for patient care might include more time-effective scanning, and limiting patient assessment to one session. Radiation exposure can be significantly reduced by using hybrid PET–MRI rather than PET–CT, as only the PET component requires potentially harmful radiation.

For clinical use, hybrid PET–MRI will allow synchronous recordings of morphological (such as T1 or T2* MRI) data or connectivity (such as diffusion-weighted or diffusion tensor imaging) data, together with metabolic data (obtained with ^{18}F-FDG PET, for example). These combinations could reveal correlations between structural and functional parameters that change over time. In research, hybrid PET–MRI can be used to simultaneously measure perfusion and BOLD signal (MRI) together with receptor-binding kinetics (PET) to collect complementary data regarding responses to treatments such as levodopa.

PET–MRI technology will not be ready for research and clinical settings until issues related to image reconstruction are resolved. In combined PET–MRI systems, PET attenuation correction and the creation of reliable attenuation maps are reliant on MRI, as a PET transmission source or a CT device cannot also be integrated. However, unlike CT measurements in PET–CT scanners, the MRI signal does not directly correlate with tissue density and, thus, cannot be converted by a simple transformation of intensity values. This limitation yields a spatially varying bias of the PET activity in PET–MRI images of the brain when bone tissue is not accounted for during attenuation correction.[144] Different methodologies have been suggested for the generation of attenuation maps based on MRI information;[179–181] however, the issue needs further refinement before widespread clinical or research use will be possible.

Conclusions

Decades of neuroimaging research have aimed to increase our understanding of the pathophysiology of PD, and to deliver tools that could inform patient management plans. An array of neuroimaging techniques with robust capabilities to measure biomarkers are available for use in a clinical setting (Table 1). For example, metabolic PET and structural or diffusion-weighted MRI can accurately discriminate PD from atypical parkinsonism—a common diagnostic problem in the clinic. Dopaminergic and serotonergic PET and SPECT techniques can follow the development of motor and nonmotor symptoms and complications as the disease progresses. Metabolic, cholinergic and Aβ PET methods are valuable tools for investigations into dementia, which frequently complicates the course of PD. Neuroimaging has also an important role in clinical trials, particularly those assessing the efficacy of cell therapies. It remains to be seen whether hybrid PET–MRI will add value to clinical brain imaging, but the potential advantage of simultaneous data acquisition is clear.

Despite these advances, current guidelines do not endorse the routine clinical use of neuroimaging in patients with PD. Several factors are hindering the transfer of neuroimaging techniques from the research setting to the clinic. For example, most research achievements have derived from studies using PET imaging, which—though a powerful molecular imaging technique—is expensive and not widely available, and in several cases requires an on-site cyclotron. Additionally, several PET and MRI techniques rely on sophisticated quantification, which requires specialized software and skilled technicians. However, clinical applicability of PET, in particular, is increasing because of the development of radioligands labelled with longer-half-life isotopes (for example, ^{18}F instead of ^{11}C) that have longer shelf lives, which are routinely used in clinical oncology imaging, and the recent introduction and approval of ^{18}F Aβ ligands for clinical practice.

No financial reports are available that directly compare expenses associated with widespread clinical use of neuroimaging with the expenses deriving from conventional examinations, potential misdiagnosis and flawed treatment plans. It will be important to assess whether wider availability of PET scanning, as well as automation and commercialization of PET compound synthesis and related analysis software, could influence future government policies with respect to health-care provision.

With regards to future research, PD remains complex, and will be impossible to fully treat while the underlying pathological mechanisms remain poorly understood. Several novel neuroimaging techniques will require further research before they can be recommended for routine clinical practice. The PET research community greatly anticipates the application of new tau ligands[182]

and the development of α-synuclein compounds, which could each accelerate the development of novel drug targets and preventative measures for PD and dementia.

One of the biggest challenges for the future is to bring together data from different investigational modalities and to identify mechanisms that are meaningful drug targets. Most research to date has focused on individual mechanisms, and far less effort has been devoted to bringing them together. Assessing an individual compartment of a complex biological process can only generate so much information. The future of neuroimaging research should focus on combining research modalities, such as through the use of advanced imaging technology with complex mathematics. Neuroimaging studies should be extended to combine wider clinical populations, genetics and deep phenotyping, pharmacology, and novel target identification and clinical trials. We should be able to analyse all these biological data through causal modelling rather than relying on correlations, because the causes of PD are fundamentally biological. Such an approach will facilitate identification of the pathogenetic signatures of the disease, and might finally reveal the key to curing and preventing PD.

Review criteria

Literature searches were performed on PubMed using the search terms "Parkinson", "positron emission tomography", "magnetic resonance imaging", "magnetic resonance spectroscopy", "diffusion tensor imaging", "diffusion-weighted imaging", "perfusion imaging", "functional magnetic resonance imaging", "resting-state functional magnetic resonance imaging", "voxel-based morphometry", "cortical thickness", "MRI", "PET", "CT" and "SPECT". Additional literature was retrieved from the reference lists of identified articles. Only papers in the English language published up to mid-2014 were selected for review.

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