

## Neuroimaging advances in Parkinson's disease

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## **ABSTRACT**

**Purpose of review:** Neuroimaging in Parkinson's disease is an evolving field, providing *in-vivo* insights into the structural and biochemical changes of the condition, although its diagnosis remains clinical. Here, we aim to summarize the most relevant recent advances in neuroimaging in Parkinson's disease to assess the underlying disease process, identify a biomarker of disease progression, and guide or monitor therapeutic interventions.

**Recent findings:** The clinical applications of imaging technology increasingly allow to quantify pigments (iron, neuromelanin) on MR imaging, proteins (tau), cell markers (phosphodiesterase, microglia) and neurotransmitter receptors (dopamine, serotonin, noradrenalin, cholin) via PET protocols, activity maps by resting-state and task-dependent functional MRI, as well as microstructural changes (free water) through diffusion-based assessments. Their application provides increasing insight on the temporal and spatial dynamics of dopaminergic and other neurotransmitter systems as well as anatomical structures and circuits in PD. An expanding list of PET tracers increases the yield of functional studies.

**Summary:** This review summarizes the most recent, relevant advances in neuroimaging technology in PD. In particular the combination of different imaging techniques seems promising to maximise the scope of future work, which should, among others, aim at identifying the best imaging marker of disease progression.

key words: PET, SPECT, MRI, imaging, Parkinson's disease

## **INTRODUCTION**

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's dementia[1,2]. Initially perceived as a condition affecting the motor system by  $\alpha$ -synuclein-mediated loss of dopaminergic neurons in the substantia nigra (SN)[1], current knowledge about associated cognitive, neuropsychiatric and non-motor symptoms has led to increased interest in cholinergic, serotonergic, noradrenergic and other neurotransmitter systems[3,4]. For some time advanced neuroimaging has been an invaluable tool to investigate *in-vivo* changes in PD[5]. But while voxel-based morphometry MRI has previously detected volume changes in cortical and subcortical areas[6], state-of-the-art neuroimaging nowadays provides a window into the (micro-) structure and function of neuronal networks and surrounding glia [7, 8\*].

The aim of this review therefore is to summarize the most relevant recent developments in both structural and functional neuroimaging in PD pertaining to certain aspects: (1) the detection of underpinning neurobiological processes, (2) the use of different neuroimaging techniques as biomarkers of disease progression, and (3) the application of imaging to guide and monitor therapeutic interventions.

## **DETECTION OF UNDERLYING NEUROBIOLOGICAL PROCESSES**

Neuroimaging continues to be a powerful tool for the *in-vivo* study of disease related pathophysiology and recent developments in PD corroborate this.

### **Neurotransmitter systems**

It has been apparent for some time that the degeneration of neurons in PD is not limited to the Substantia nigra, but only recent developments of respective tracers allow the detailed *in-vivo* study of additional neurotransmitter systems (see Table 1).

#### **Dopaminergic system**

Although quantification of pre-synaptic dopaminergic function is part of daily clinical practice[9], the exact anatomical pattern and longitudinal dynamics of signal changes are increasingly described: a substantial meta-analysis of 142 studies using PET or SPECT to assess presynaptic dopaminergic function confirmed consistently larger decreases in binding in posterior > anterior putamen > caudate nucleus (CN) across ligands for aromatic L-amino-acid decarboxylase (AADC), dopamine transporter (DaT) and vesicular monoamine transporter 2 (VMAT2) – overall disease severity correlated closest with dopaminergic terminal loss in the CN[10\*\*,11]. Focusing on the physiological equivalent of SPECT signalling, a large study reported post-mortem numbers of nigral neurons in PD and atypical parkinsonian conditions *not* to correlate with [<sup>123</sup>I]FP-CIT or [<sup>123</sup>I]b-CIT tracer binding[12\*], which contrasts with previous observations[13]. This suggests that these tracers actually reflect striatal changes such as axonal dysfunction or reduced DaT expression, rather than the number of intact nigral neurons.

Similarly, the dynamics of changes among tracer targets are increasingly studied: a substantial meta-analysis reported a consistently smaller reduction in 6-[<sup>18</sup>F]fluoro-L-dopa measuring AADC in both CN and putamen compared to DaT and VMAT2 levels, suggesting either less severe loss or even compensatory up-regulation of AADC in PD[10\*\*]. An analysis of a large number (n=210) of healthy control DaTSCANs indicated a relatively higher DaT concentration in women, as female striatal volumes are slightly lower, but DaT quantification similar between sexes[14].

Nigro-striatal dopaminergic loss as quantified by DaT, has also been used to study pathophysiological changes only accessible to advanced imaging techniques by means of correlation analysis: one study on the basis of diffusion tensor imaging (DTI) reported a negative correlation between fractional anisotropy of the SN and putaminal dopamine transporter signal over time[15\*], while another cross-sectional study described that on neuromelanin-sensitive sequences, SN volume correlated best with nigro-striatal innervation loss[16]. Both studies detected micro-structural changes based on correlations with established DaT quantification. Similarly, the severity of dopaminergic degeneration correlated with changes in diffusion measurements in the striatum in a primate MPTP model[17].

Today, the *in-vivo* study of dopaminergic degeneration is able to detect the temporal and spatial dynamics of tracer changes and serves as a basis for the explorative study of novel imaging approaches.

### **Serotonergic system**

Although serotonergic dysfunction is known to occur in PD, *in-vivo* quantification has been achieved only recently. [<sup>123</sup>I]FP-CIT exhibits non-specific, extrastriatal binding for presynaptic serotonergic transporters[18,19\*] and hence has been used to assess its involvement in the pathogenesis of non-motor symptoms. One study found significant differences in hypothalamic binding between PD and atypical parkinsonism, suggesting a different pattern of serotonergic pre-synaptic receptor involvement between these conditions[20]. More specifically, the same team reported a negative association of levels of anxiety with low [<sup>123</sup>I]FP-CIT binding in the thalamus in a large sample of *de novo* PD patients[19\*]. A similar negative correlation between right CN [<sup>123</sup>I]FP-CIT SPECT tracer binding and anxiety has been reported in a large, controlled cohort of *de novo* PD patients[21], confirming an earlier observation[22].

Although the above mentioned results are in line with the hypothesis of anxiety mainly being linked to a serotonergic dysfunction in earlier and a dopaminergic dysfunction in later disease stages[20], this remains to be proven in larger, and ideally longitudinal samples.

### **Noradrenergic system**

Noradrenergic projections almost exclusively originate from the locus coeruleus (LC), playing a role in cognitive attention, sleep cycle regulation and autonomic function. The application of neuromelanin-sensitive MRI sequences to identify pigmented cells of the LC[23\*] and [<sup>11</sup>C]MeNER PET to characterize noradrenalin transporters[24] allowed a study comparing PD patients with and without rapid eye movement sleep behaviour disorder (RBD) and controls, revealing most pronounced reductions for both signals in the PD+RBD group[23\*], supporting an earlier neuromelanin-based study[25] (see Figure 1). In terms of dynamics, first evidence indicates that the reduction in neuromelanin-content might be greater in the LC than SN [16], possibly reflecting the progression of neuropathology according to the Braak hypothesis[27]. Although of minuscule anatomical size, the noradrenergic system and the implications of changes to it, is now accessible to state-of the art imaging.

### **Cholinergic system**

There has been a debate over the anatomical and functional aetiology of cognitive symptoms in PD, which present most frequently as executive, and in later stages more wide-spread dysfunction including memory impairment[28]. A noticeable PET-based contribution is the finding that it might be the interaction between CN dopaminergic and cortical cholinergic denervation to explain PD cognitive decline and dementia[29,30\*\*]. The data seems to suggest a possible compensatory over-activity of the cortical cholinergic system for CN dopaminergic degeneration in early disease stages, before cognitive symptoms become apparent with cholinergic decline. This challenges the previously proposed dual syndrome hypothesis, which distinguishes dopaminergically mediated fronto-striatal executive impairments and cholinergically mediated memory symptoms[28].

## **Protein aggregates**

PD neuropathology is dominated by the presence of  $\alpha$ -synuclein deposits, although  $\beta$ -amyloid and tau have been implicated in cognitive impairment in PD[31\*,32\*]. Recent publications seem to support a role for both tau and  $\beta$ -amyloid only in advanced stages of cognitive impairment[31\*, 32\*, 33], most noticeably in dementia with lewy bodies[31\*]. Anatomically, precuneus and inferior temporal gyrus tau tracer uptake has been reported to be associated with this [34], adding to our understanding of mixed pathology in PD.

## **White matter involvement**

Overt white matter (WM) lesions have been implicated with the development of both cognitive symptoms and gait disorder in PD. The reported observation of an association between WM lesions and neurogenic orthostatic hypotension[35] supports the notion that extreme blood pressure changes might contribute to the development of cognitive symptoms through WM lesions[36]. Small vessel involvement, defined as lacunes or WM hyperintensities, have equally been linked to cortical thinning and cognitive impairment[37]. **Greater WM lesion load is reported among patients presenting with postural instability and gait difficulty compared to a tremor-dominant phenotype[3, 18].**

**Furthermore, computational and theoretical advances allow for a more comprehensive assessment of microstructural changes and network disruptions: A meta-analysis of 39 DTI studies comparing data from 1087 PD patients and 768 healthy controls identified consistent changes within subcortical (SN) and cortical areas (cingulate and temporal cortices) as well as white matter fibre tracts (corpus callosum and cortico-spinal tract)[7]. Prospective high-resolution 3 Tesla DTI imaging and graph theory detected reduced connectivity in mesolimbic–striatal pathways, within the basal ganglia, the sensorimotor circuits and also the limbic system in a cohort of treatment naïve patients[11]. Another study suggested more prominent WM lesions along the cerebello-thalamo-cortical pathway in tremor-dominant PD patients[17]. A large study of advanced PD patients also identified DTI changes in diffuse basal ganglia and frontoparietal networks among PD patients with mild cognitive impairment[24]. Taken together, these findings point towards an early, progressive degeneration initially evident only at a microstructure level[25].**

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### **Neuroinflammation**

A number of findings suggest a role of the immune system in PD pathoetiology[1]. Activation of microglia may be evaluated through novel PET radioligands, such as [<sup>18</sup>F]FEPPA, although first, moderately sized studies in PD were not able to show signal differences in comparison to healthy controls [38,39]. [<sup>11</sup>C]PBR28 imaging, however, revealed a reduction in microglia activation after treatment with a selective myeloperoxidase inhibitor in PD although this report included no control subjects for comparison[40]. Indirect indications of inflammation have also been detected by signs of blood brain barrier breakdown, evident as microbleeds and gadolinium leakage[41].

### **Phosphodiesterases**

Phosphodiesterases are enzymes highly expressed on striatal medium spiny neurons, metabolizing cAMP and cGMP, the second messengers of dopamine receptors. First studies employing specific radioligands, such as [<sup>11</sup>C]IMA107 binding to phosphodiesterase 10A[42], showed lower binding activity in the basal ganglia of PD patients compared to controls, and a negative correlation with disease duration and severity[43]. The same group adopted [<sup>11</sup>C]rolipram, assessing phosphodiesterase 4 levels, and reported lower binding in

caudate, putamen, hypothalamus and cortex to correlate with spatial working memory deterioration[44\*\*]. Positing phosphodiesterase expression as a marker of striatal dopaminergic terminal loss, it would be interesting to study its decline longitudinally and compare its dynamics with DaT and other markers of dopaminergic degeneration in the future.

### **Functional MRI**

The application of functional MRI (fMRI) studies in PD is still an evolving field, with a considerable heterogeneity of paradigms and patient subgroups being studied. Nevertheless, a methodologically sound, recent meta-analysis of resting state fMRI studies indicated reproducible, increased functional connectivity in the left postcentral gyrus[45]. While this might highlight this area to be explored further,, the conclusive interpretation of results of task-dependent fMRI studies[46] remains challenging, still.

## **IMAGING MODALITIES AS BIOMARKER OF DISEASE PROGRESSION**

Monitoring disease progression is a prime aim in PD imaging research, but although there have been some developments, it remains to be seen which modality might emerge as the most exact measure.

### **Iron-content**

Brain tissues physiologically contains iron, >90% of which is stored in the form of ferritin, and the basal ganglia (Globus Pallidus (GP) > Putamen > Caudate) are particularly rich in iron. Imaging studies have shown that ferritin accumulates throughout the basal ganglia in a linear fashion as a function of age[47]. Iron-sensitive MRI sequences including SWI, 3D FLAIR, T2\*, R2 and R2\* relaxation, as well as quantitative susceptibility mapping (QSM) or adiabatic T1rho have been increasingly applied to study iron-content and -metabolism in PD[48]. Overall, QSM has been suggested to be more sensitive than R2\* to detect deep cerebral nuclei iron quantity[48,49], allowing the visualization of the dorsolateral nigral hyperintensity or nigrosome-1 within the SN. A meta-analysis of 16 studies suggested this assessment to be the most sensitive and specific imaging protocol to date to differentiate PD patients from controls and possible suitable to differentiate degenerative from non-degenerative parkinsonism[50\*]. Nigral hyperintensity has also been corre-

lated with disease progression and reported to predict DaTSCAN measures in PD[51,52], but also idiopathic RBD[53].

Disease severity, as measured by clinical characteristics ranging from UPDRS-III, H&Y stage, depression and anxiety to levodopa equivalent daily dose, has been reported to correlate with iron load in SN on SWI[54\*], R2\* sequences[55], and QSM[48,56]. Iron load, especially in the caudal region of the SN (R2\*) has been reported to be particularly higher in patients with freezing of gait in both cross-sectional[49] and longitudinal samples[55]. Taken together, as an epiphenomenon of the underpinning neuropathological process, iron accumulation seems to be a good candidate to follow disease progression in PD.

Regarding extranigral tissue in PD in comparison to controls, iron load was found increased in GP and putamen on SWI-weighted sequences[54\*], and red nucleus (RN)[48], GP[48] and thalamus[48] on QSM quantification[48]. A QSM-based study described iron signal changes only in SNc in early disease stages, whereas more prominent involvement of RN and GP were apparent in more advanced patients[57]. Only one study reported whole brain iron level assessments - using a cross-sectional protocol it reported higher QSM values in dorsal pons and a number of cortical areas, arguably following the topographical progression of  $\alpha$ -synuclein deposition[58].

Iron content therefore seems to emerge as a powerful imaging tool with high diagnostic accuracy (nigral hyperintensity), good correlation with clinical characteristics and good spatial as well as longitudinal temporal resolution.

### **Neuromelanin**

Neuromelanin is an insoluble pigment and by-product of catecholamine-synthesis. Its production is Fe<sup>3+</sup>-mediated and appears to be governed by cytosolic content of dopamine or other catecholamines and is therefore predominantly located in SN and locus coeruleus. Quantification of neuromelanin to follow disease pro-

gression has been investigated widely. The histologically known pattern of SN neuronal changes affecting postero-lateral aspects of SNc earlier/more than anterior-medial ones has been replicated with neuromelanin imaging[59–61]. Similarly, the progression of loss of SWI-hyperintensity from nigrosome-1 to nigrosome-4 seems to follow disease progression[62]. Neuromelanin loss has also been correlated with UPDRS[59,60] and MDS-UPDRS scores[61], H&Y stages[61] and disease duration[63].

Hence, neuromelanin appears to be a promising imaging biomarker for PD progression, if confirmed prospectively.

### **Substantia nigra Free Water**

Free water measurements are an advanced diffusion-based modelling approach, measuring the fractional volume of unconstrained diffusion. The recent development of a bitensor modelling technique allows to acquire the fractional signal of water from a single voxel. The detection of posterior SN free water was able to distinguish PD patients from controls[64,65\*\*] and in a multisite study showed to correlate with H&Y stages, MDS-UPDRS part III and cognitive performance [66]. This appeared to be independent of acute dopaminergic medication[67]. First longitudinal data indicated that posterior SN free water increases over time and can predict bradykinesia severity and MOCA scores[68], which was validated in a larger, international study [65\*\*](see Figure 2). By and large, all of the above suggests that SN free water might become a valuable tool to monitor PD progression.

### **DaTSCAN**

It is generally accepted that DaT measurements correlate with the degree of dopaminergic cell loss, however its exact dynamics across disease stages has not been clear. A recent study implied different velocities of midbrain neuromelanin-signal loss measured via [<sup>18</sup>F]AV-1451 PET [69\*], versus striatal dopaminergic loss ([<sup>123</sup>I]FP-CIT SPECT) in early PD[70]. Together with further evidence[71\*], this has been interpreted to indicate that in humans nigral cell loss and striatal tracer uptake *in-vivo* correlate closely only up to a nigral cell loss of 50%. Beyond this, the dynamics of neurodegeneration and tracer uptake seem to follow a more loose correlation, as also observed in MPTP-treated monkeys[72]. Accordingly, the majority of longitudinal

PET studies[10\*\*] point to a negative exponential dopaminergic loss in PD, consistent with the nonlinear pattern previously described for the progression of motor symptoms, with faster progression in the first symptomatic disease phase[10\*\*]. This is in keeping with the „dying back“ concept, describing axonal and terminal degeneration in the striatum before neuronal cell loss in SN[73]).

## **GUIDING AND MONITORING THERAPEUTIC INTERVENTIONS**

We have noted some developments in the application of imaging used for therapeutic interventions in PD.

### **Functional neurosurgery**

Both deep brain stimulating and advanced lesioning[74] rely on the correct pre-surgical identification of target structures. One report proposed STN visualization to benefit from using QSM over T2\*-weighted images[75] (see Figure 3). Similarly, advanced high angular resolution diffusion-based imaging has been proposed to improve VIM nucleus targeting in tremor patients[76\*]. Probably the most innovative addition to functional stereotactic neurosurgery has been the development of the publicly available “DBS Intrinsic Template Atlas”[77\*\*] – this combination of subcortical brain manual segmentation, automatic multimodal probabilistic maps, co-registration with histology as well as STN and GP internus functional sub-segmentation according to structural connectivity, offers potential advantages for future functional neurosurgical trials[77\*\*].

Another set of studies investigated the effect of both anatomical and functional connectivity after STN-DBS and validated the findings in a second, independent data set[78\*\*]: apart from replicating that STN-DBS has an effect on SMA and medial prefrontal cortex activity, authors reported that both types of connectivity explained 26.2% of clinical variance in intervention outcome. They concluded that their findings support the idea of focusing surgical treatment not only on specific brain regions, but also on network nodes[78\*\*].

Finally, of more practical relevance, the development of a new coil system able to reduce DBS lead absorption might alleviate safety concerns for post-DBS MRI monitoring[79].

### **Levodopa/carbidopa intestinal gel (LCIG)**

Continuous delivery of levodopa via LCIG provides more stable levodopa levels in blood with respective clinical advantages over pulsatile oral intake, which is advantageous in advanced PD cases. A small pilot study documented a sustained significant reduction in striatal [<sup>11</sup>C]raclopride binding, suggesting sustained higher dopamine levels during LCIG infusion[80].

### **Apomorphine**

One study examined the effect of apomorphine infusions as add-on therapy using resting state PET over a 6 month period: induced changes in this relatively small sample (n=12) were documented throughout motor, cognitive and limbic networks and appear compatible with the notion that metabolic changes in PD could be reversed by continuous dopaminergic treatment [81].

### **Rehabilitation**

A randomized trial of cognitive rehabilitative approaches documented improved executive function, visual memory and functional but no structural changes on functional MRI after three months of integrative cognitive rehabilitation[82\*], persisting at 18 months[83].

## **SUMMARY**

In this review we provide an update on current applications of state of the art neuroimaging in PD. The expansion of the current *in-vivo* imaging armamentarium increasingly allows the comparison and cross-validation of different imaging modalities. It seems that the increasing number of radionuclide-based proto-

cols assessing microglia activation, protein accumulation and receptor density as well as the combination of established and novel approaches drive developments in this field of movement disorder research. Providing distinct and complementary information, in particular the combination of these techniques will most likely advance our understanding of the pathophysiology of PD disease processes in the future. Among other, future work should focus on identifying the best marker to monitor disease progression.

**KEY POINTS:**

- The increasing number of available PET tracers marking neurotransmitters, proteins and cell populations dramatically increases the scope for future studies.
- Iron content, neuromelanin and substantia nigra free water content seem to emerge as potential markers of disease progression along conventional DaT scans.
- The combination of different imaging modalities is increasingly applied and allows deeper insights into the pathophysiology of the condition..

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**ABBREVIATIONS:**

AADC	aromatic L-amino-acid decarboxylase
CN	caudate nucleus
DaT	dopamine transporter
DBS	deep brain stimulation

DTI	diffusion tensor imaging
GM	grey matter
GP	globus pallidus
LC	locus coeruleus
LCIG	levodopa/carbidopa intestinal gel
MRI	magnetic resonance imaging
PET	positron emission tomography
QSM	quantitative susceptibility mapping
RBD	rapid eye movement sleep behaviour disorder
RN	red nucleus
SN	substantia nigra
SPECT	single-photon emission computed tomography
STN	subthalamic nucleus
SWI	susceptibility weighted imaging
VIM	ventral intermediate nucleus of thalamus
VMAT2	vesicular monoamine transporter 2
WM	white matter

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FIGURE CAPTIONS:

Figure 1 - Noradrenergic system evaluated by [<sup>11</sup>C]MeNER PET. Column “A” displays tracer uptake on a section including the raphe nucleus, while columns “B” and “C” display sections including red nucleus, hypothalamus and thalamus. [modified from Nahimi et al.[24]]

Figure 2 – Monitoring of PD progression: SN free water content. As one of the most promising markers to quantify disease progression, SN free water has been evaluated in a longitudinal study over 4 years [modified from Burciu et al.[65\*\*]].

Figure 3 – Comparison of STN visualization for DBS direct targeting. Examples of identifying the STN (marked by red and blue marks) by standard T2\* sequences (panel A) or newly proposed QSM sequences (panel B) [modified from Alkemade et al.[75]].

Table 1: Overview of PET tracers currently used in PD imaging research. (for exhaustive list, see supplementary material in Politis' review[5])