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MOVEMENT DISORDERS (T. SIMUNI, SECTION EDITOR)

Structural Imaging in Parkinson's Disease: New Developments

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Abstract

Purpose of Review To review the advances in structural imaging for the diagnosis, prognosis, and treatment of Parkinson's disease (PD) during the last 5 years.

Recent Findings Structural imaging using high-field MRI (≥ 3 T) and new MR sequences sensitive to iron and nigral pigments have achieved to assess in vivo pathological surrogates useful for PD diagnosis (notably decreased nigral neuromelanin and loss of dorsal nigral hyperintensity, increased nigral iron content, diffusivity, and free-water), prodromal diagnosis (decreased neuromelanin signal in the locus coeruleus), and PD progression (with increasing nigral iron content (increasing R2* rate) and nigral damage (increasing free-water)). Additionally, evaluation of atrophy in small monoaminergic nuclei is useful for prognosis, including cholinergic basal forebrain nuclei atrophy for cognitive impairment.

Summary New advances in multimodal structural imaging improve diagnosis, prognosis, and prediction of invasive treatment outcome in PD, and may further benefit from machine learning and large scale longitudinal studies to better identify prognostic subtypes.

Keywords Parkinson's disease · MRI · Neuromelanin · Prodromal diagnosis · Machine learning

Introduction

Substantia nigra depigmentation and intracellular deposition of alpha-synuclein aggregates in Lewy bodies and Lewy neurites are the diagnostic hallmarks of Parkinson's disease (PD), albeit post mortem [1–3]. Notwithstanding this neuropathological gold standard, patients, their caregivers, physicians, and researchers alike need timely information for the diagnosis, prognosis, and treatment of PD. In vivo brain imaging, using non-invasive investigation methods including magnetic resonance imaging (MRI) and transcranial sonography, has the potential to solve this conundrum and help untangle the multiple neurodegenerative processes underpinning the variable expression of motor and nonmotor symptoms in symptomatic or prodromal PD.

Classically, standard anatomical imaging using T1-weighted MRI (1.5 T and 3 T) is considered as normal except for atrophy, even in advanced PD patients. However, new developments in structural imaging in the last 5 years have achieved to greatly improve both the spatial resolution and specificity, using high-field (3 T) and ultra-high-field (≥ 7 T) MRI with accelerated acquisition, combined with new MR sequences sensitive to neuromelanin or iron. This enables targeted investigation of small brainstem nuclei (~ 10^2–10^3 mm^3) and, in combination with functional imaging (using SPECT and PET), may inform on dysfunction of monoaminergic projections (dopaminergic, serotonergic, cholinergic, and noradrenergic), which are precociously altered in PD.

In this review, these new developments are presented according to four objectives relevant for patients, physicians, and researchers:

1- Improve the diagnosis and differential diagnosis of Parkinson's disease.

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2- Move toward the prodromal diagnosis of PD and identify the premanifest patients likely to benefit from disease-modifying intervention in the future.
3- Improve the prognostic markers of PD progression specifically for debilitating motor and nonmotor PD complications.
4- Identify the predictive markers of treatment response, in particular for invasive therapies.

Structural Imaging Advances for PD Diagnosis

Clinical diagnosis of PD remains challenging, even for experts [4]. Diagnosis is particularly error-prone in the early stage of PD and in patients with mild motor symptoms and dysautonomic, axial, or cognitive deficits, which overlap with other neurodegenerative parkinsonian disorders, including synucleinopathies (dementia with Lewy bodies (DLB), multiple system atrophy (MSA)) and tauopathies (progressive supranuclear palsy (PSP), corticobasal corticobasal degeneration (CBD)). Updated diagnostic criteria issued in 2015 by the Movement Disorder Society now incorporate nonmotor symptoms and may achieve greater accuracy [5, 6]. Importantly, these criteria newly set that normal functional neuroimaging of the presynaptic dopaminergic system is sufficient to exclude PD diagnosis (most commonly assessed using [^{123}I]-Ioflupane SPECT DaTscan^{TM})). However, neither functional nor structural imaging is recommended for PD diagnosis for now [7], although future developments of structural imaging may change this view notably for early diagnosis.

Advances in Structural Imaging of the Substantia Nigra

An intuitive place to look for abnormalities specifically related to PD is the substantia nigra (SN), where neurodegeneration is preferentially located in the pars compacta (and nigrosome-1) as demonstrated in pathological studies and results in the massive loss of dopaminergic striatal projections ($\geq 50\%$). However, in vivo imaging of the SN and its subdivisions is notably difficult due to its limited size and low contrast in standard T1-weighted MR imaging [8], rendering its structural segmentation and the evaluation of atrophy as a surrogate of dopaminergic cell loss challenging. Yet, the advent of high-field MRI and novel sequences sensitive to nigral pigments and iron deposition have now unleashed high-resolution nigral imaging and provided qualitative and quantitative measure of structural damage in the SN (Fig. 1 and Table 1).

-Neuromelanin-Sensitive Imaging

First, qualitative changes mirroring structural damage are visualized as a reduction in size and signal intensity in the SN using neuromelanin-sensitive imaging (based on its paramagnetic properties probed using high-field T1-weighted spin-echo MR sequences). This results from a decrease in neuromelanin-containing dopaminergic neurons and neuromelanin content in the SN, in contrast to the normal accumulation of neuromelanin as a by-product of dopamine and noradrenaline oxidative metabolism responsible for the pigmentation of the SN and the locus coeruleus (LC). Moreover, greater decrease in the normalized neuromelanin volume of the anterior, posterior, and whole SN correlates with global PD-related impairment [9], and with motor impairment and disease duration in the SN pars compacta [10]. In addition, greater volume reduction [11] and signal decrease [12] is observed in the SN contralateral to the more clinically affected side, mirroring motor asymmetry in PD and possibly the severity of dopaminergic cell loss, also present in patients with PSP [10]. However, it was recently demonstrated that neuromelanin also declines with age in healthy individuals after 50 years, both in the anterior and posterior SN [13] and the LC [14], which may limit its discriminative power for differential diagnosis.

-Iron-Sensitive Imaging

Second, structural damage to dopaminergic neurons in the SN pars compacta is visualized by the loss of an ovoid and dorsolateral hypersignal which likely corresponds to the nigrosome-1, a comma-shaped cluster of dopaminergic neurons undergoing early and massive (> 90%) neurodegeneration in PD [15]. This abnormality is preferentially evidenced using iron-sensitive MR sequences (T2*-weighted, Susceptibility-Weighted Imaging). These sequences contrast the nigrosome-1, a calbindin-negative, iron-poor, hyperintense area within the surrounding iron-rich and hypointense SN, labeled as the Dorsal Nigral Hyperintensity (DNH) or swallow tail in healthy individuals [16–18]. In PD, this hypersignal is reduced or lost, most often bilaterally, as recognized from 7 T MRI [17, 19] and confirmed in a recent meta-analysis [20] with an overall sensitivity and specificity of 97.7% and 94.6% (3 and 7 T) for PD versus controls, although sensitivity is lower at 3 T (94.6%). Moreover, DNH loss mirrors ipsilateral decrease in dopaminergic presynaptic striatal terminals [20] and is likely closely related to dopaminergic deficiency in neurodegenerative parkinsonian disorders, including DLB [21–23]. Most interestingly, loss of DNH is present in a subgroup of non-parkinsonian patients with RBD, who also had abnormal striatal dopaminergic binding [24]. Recent advances in high-resolution nigral imaging using ultra-high field (7 T) MRI may help resolve tinier structures

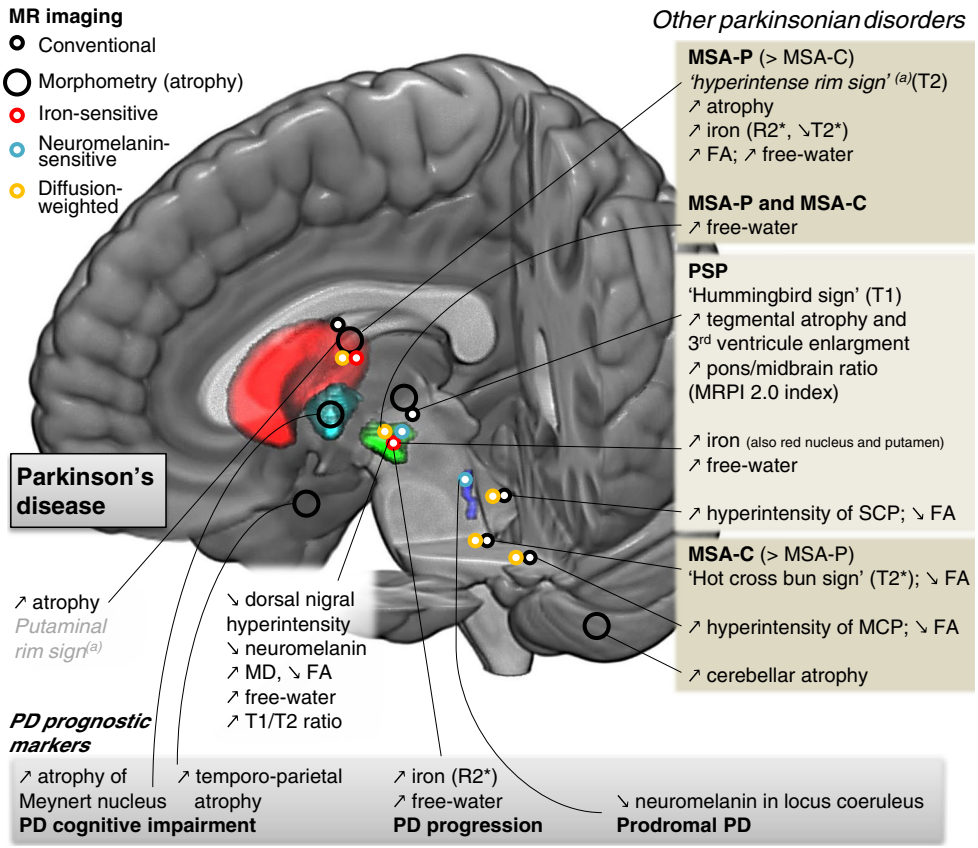

Fig. 1 Structural abnormalities in Parkinson's disease, multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). Structural abnormalities related to Parkinson's disease and other parkinsonian disorders are visualized using MR imaging in midbrain and basal ganglia (red: putamen (right); green: substantia nigra (right); blue: Meynert nucleus (right); violet: locus coeruleus (right)). [a]Hyperintense putaminal rim sign is also frequently found in PD. MSA, multiple system atrophy; MSA-C, MSA-cerebellar; MSA-P, MSA-parkinsonism; PSP, progressive supranuclear palsy; MRPI, magnetic resonance parkinsonism index

and identify the five nigrosomes in vivo [25], confirming post mortem findings using 9.4 T MRI [26]. However, rating the visibility of nigrosomes N2 to N5 is difficult and incompletely recapitulates the established histopathological progression pattern along the rostral, medial and dorsal axes [15]. Overall, semi-quantitative evaluation of the DNH has limitations, even at ultra-high-field (7 T), with up to 10% non-diagnostic scans (often due to motion-artifacts at 7 T) and experience-dependent rating [20]. Moreover, DNH is absent [18] or asymmetric [27] in a subset of healthy individuals (15 to 25%), notably males, lowering the specificity of the swallow tail sign. In particular, the proximity of micro-vessels and the superior cerebellar artery may cause susceptibility or pulsations artifacts in the midbrain, which may impede the visualization of DNH in healthy individuals [18, 28].

Third, quantitative measures hold the promise to achieve better sensitivity and follow the progression of nigral degenerative processes. Increased iron deposition in the SN is a good candidate [29] and can be measured from local field inhomogeneity causing faster signal decay in T2 and T2*-weighted MR and increased transverse relaxation rates R2 and R2*. Importantly, increased R2* in the SN in PD patients was shown to increase over a 3-year period and to correlate with the worsening of motor symptoms [30, 31]. Increased R2* was also associated with the presence of alpha-synuclein in the SN in one study across patients with PD, DLB, PSP, MSA, and CBS [32]. Although promising, these methods are increasingly supplanted by quantitative susceptibility mapping (QSM) with increased reliability [33], congruent with histologic validation of iron content [32, 34]. In particular, QSM enables to map the iron deposition within the SN in early PD patients confirming greater susceptibility values on the more affected side and in the posterior SN [35] and with PD-related impairment [36]. Recent comparison of R2* and QSM in PD patients shows the greater sensitivity of QSM to map the spatially heterogeneous iron deposition in the SN [37] and confirms that R2* longitudinally increases in the SN pars compacta and may mirror worsening of nonmotor symptoms, whereas QSM decrease in the SN pars reticulata correlates with motor change [38]. However, longitudinal progression over 18 months only occurred in more advanced patients, 5 years after diagnosis [38].

-Diffusion-Weighted Imaging

In addition, structural damage can be quantified using diffusion-weighted imaging, which maps the restriction to the free diffusion of water molecules resulting from the local architecture of brain tissue. As anticipated, nigral diffusivity is precociously altered in PD patients [39]. Recent meta-analyses confirm increased magnitude (increased mean diffusivity) and decreased directionality (decreased fractional

Table 1 Main MRI markers for the differential diagnosis of degenerative parkinsonian syndromes (Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, corticobasal syndrome)

	Conventional MRI	Neuromelanin-sensitive MR	Iron-sensitive MR	Iron-sensitive MR	Diffusion-weighted MR	Quantitative morphometry
	Qualitative markers (visual inspection)			Quantitative markers		
Typical sequences	T1, T2	T1-TSE	T2*, SWI	R2, R2*, QSM	DTI	T1
Parkinson's disease: substantia nigra		↘ Neuromelanin signal	↘ Dorsal nigral hyperintensity (nigrosome 1) (swallow tail sign)	↗ R2* ↗ QSM	↘FA, ↗MD ↗free-water	↗ T1/T2 ratio
Parkinson's disease: extra-nigral			Hyperintense rim sign	↗QSM in nucleus ruber, thalamus, and globus pallidus		Posterior putamen and caudate nucleus atrophy
Dementia with Lewy bodies			↘ Dorsal nigral hyperintensity (nigrosome 1) (swallow tail sign) (symmetrical)		↘ FA, ↗ MD in parieto-occipital white matter tracts ↘ FA in insular, posterior cingulate and visual association tracts (bilateral)	Posterior parietal, occipital and frontal lobe atrophy Preservation of medial temporal lobe (compared to patients with Alzheimer's disease)
Multiple system atrophy	Hotcross bun sign (MSA-C) ↘ Hyperintensity (T2) of MCP (MSA-C)		Hyperintense rim sign (MSA-P) Putamen hypointensity (T2*) (MSA-P)		↘ FA, ↗ MD in MCP (MSA-C) ↗ MD in putamen (MSA-P) ↗ Free-water in basal ganglia, thalamus, and cerebellum	MCP, pons and cerebellum atrophy (MSA-C) Putamen atrophy (MSA-P)
Progressive supranuclear palsy	Mesencephalon atrophy (hummingbird sign, morning glory flower sign)	↘ Area of neuromelanin--sensitive SN pars compacta	↗ Hypointensity (SWI) in the SN, red nucleus and putamen		↗ Free-water in basal ganglia, thalamus, and cerebellum	Midbrain atrophy ↗ Pons to midbrain ratio ↗ Magnetic Resonance Parkinsonism Index (MRPI 2.0)
Corticobasal syndrome						Frontal and parietal lobe atrophy (asymmetrical) Putamen atrophy

DTI, diffusion tensor imaging; *FA*, fractional anisotropy; *MD*, mean diffusivity; *MR*, magnetic resonance; *MCP*, middle cerebellar peduncle; *MSA-C*, MSA-cerebellar; *MSA-P*, MSA-parkinsonism; *SN*, substantia nigra; *SWI*, susceptibility weighted imaging

anisotropy) of diffusion processes corresponding to increased microstructural disarray in the SN [40, 41], although specific pathological processes cannot be directly inferred from diffusion-tensor models. Furthermore, new bi-tensor estimation methods consistently indicate increased free-water in the SN, which likely represent increased extra-cellular space resulting from nigral degeneration in early PD [42] and neurodegenerative parkinsonian disorders (MSA and PSP) [43]. Moreover, free-water increases in the posterior SN in PD patients over the first 4 years after diagnosis and correlates with putaminal dopaminergic deficiency [42, 44••, 45]. Interestingly, free-water also increases over 3 years in middle-stage patients, but only in the anterior SN, in line with the neuropathological progression pattern of nigral damage. Thus, free-water may represent a valuable progression biomarker in early PD, now validated in independent cohorts in multiple sites.

-Transcranial Sonography

Alternatively, SN hyperechogenicity corresponding to enlarged (> 0.20 cm^2) nigral echo using transcranial sonography may also mirror iron-related changes in PD. Transcranial sonography represent a cost-effective non-invasive method to aid PD diagnosis at bedside, with an overall sensitivity and specificity of 85% and 89% versus controls in a recent meta-analysis [46], but also in PSP and CBS. The increased SN echogenicity is correlated with striatal [^{123}I]-Ioflupane binding reduction [47] but not with disease severity [48], and may herald conversion to PD in healthy subjects [49]. Similarly to MRI, non-diagnostic scans amount to 10%, partly due to insufficient bone window in particular in older patients, and unexplained SN hyperechogenicity is present in 10 to 15% healthy controls.

In spite of these technical advances, the conundrum of a practicable, widely accessible and easily interpretable diagnostic biomarker is yet unmet, limiting routine use in standard clinical settings. Ease of implementation and interpretation is crucial to bridge this gap, as recently exemplified with a new, yet simple, method achieving fair diagnostic accuracy in early and middle-stage PD patients using the ratio of standard (3 T) T1 and T2-weighted images in the SN, representing a quantitative contrast sensitive to myelin content, although further validation is needed [50•].

Advances of Extra-Nigral Structural Imaging in PD

Pathological changes are not limited to the SN and extend to subcortical and cortical structures in neurodegenerative parkinsonian disorders, even in the early stage. In particular, dopaminergic projections to the basal ganglia are precociously altered in PD, both functionally and structurally, as recently highlighted from large-scale de novo cohorts such as the PPMI [51]. Dopaminergic denervation may underpin, at least partly, the preferential atrophy in the posterior caudate and putamen visualized using shape analysis in early PD [52–54] in addition to longitudinal diffusivity changes in the putamen [55], the brainstem and subcortical white matter [56]. Similarly, increased PD-related iron deposition in the globus pallidus using QSM correlates with increased levodopa use [36]. Remarkably, important changes in cortical glucose metabolism are visualized in PD using functional ^{18}FDG PET imaging, notably in the inferior parietal cortex, whereas cortical atrophy is heterogeneous and possibly delayed in PD [57]. Interestingly, frontal and posterior cortical gray matter thinning over time may be related to greater putaminal dopaminergic dysfunction in early non-demented PD patients [58], while cortical thinning in occipital cortex is related to longitudinal subcortical white matter diffusivity changes in PD patients but not in controls [59].

Overall, new methods in network analysis enable to track subtle changes distributed across the brain in PD by looking at co-varying atrophy in cortical and subcortical structures. This indicates that widespread changes are present even in de novo patients [60], spreading across an intrinsic network of functionally connected regions englobing the midbrain, basal forebrain, basal ganglia and medial temporal, insular, anterior cingulate, and frontal cortices. These changes also include reduced integrity in the anterior and posterior cingulate networks using gray matter density covariance patterns [61] and large-scale connectivity changes with increased clustering coefficient (Cp) and characteristic path length (Lp) using graph theory analysis [62], confirmed in resting state functional connectivity [63] despite alternate findings in early PD [64, 65]. Also, connectivity analysis support that cortical atrophy patterns recapitulating disease propagation may follow connectivity to early altered subcortical structures and herald cognitive impairment [66•]. Of note, technical challenges in tractography limit the ability to reliably isolate the nigrostriatal tract among corticospinal fibers and to compare anatomical connectivity strength [67].

Toward a Structural Biomarker for Prodromal Diagnosis of PD?

The recognition that disabling nonmotor symptoms (including mood disorders, REM Sleep Behavior Disorder (RBD), fatigue, constipation, hyposmia and urogenital disorders) and mild motor symptoms (tremor, balance) may precede PD diagnosis by a decade or more [68], and that dopaminergic deficiency is already massive (≥ 50%) at diagnosis [68], has led to the concept of prodromal PD, marked by progressive extranigral and nigral neurodegeneration. Advancing the diagnosis of neurodegeneration in PD holds the promise for timely therapeutic interventions to halt or even reverse the

neurodegenerative process when it begins, i.e., when brain damage is possibly the lowest. Of note, no such disease-modifying therapy is available for now, which in turn circumscribes the quest to acceptable, non-invasive, widely accessible, and cost-efficient prodromal markers. Although no prodromal symptoms are pathognomonic, recent advances demonstrate that high-risk population can be reliably identified using strong clinical predictors (polysomnography-confirmed RBD) or aggregate risk-score (including RBD, anosmia, dysautonomia) defining the prodromal diagnostic research criteria [69, 70], besides patients with inherited genetic mutations in identified families. Recent cohort studies demonstrate that most of the patients with RBD rapidly convert to overt degenerative synucleinopathies (≥ 30% after 4 years and ≥ 75% after 10 years), including PD and DLB with equal risk, whereas MSA is rare [70–72]. Importantly, it was recently demonstrated that patients with RBD have neuromelanin loss in the LC comparable to PD patients [73•], in addition to fully developed peripheral pathology (including cholinergic parasympathetic gut innervation and noradrenergic sympathetic cardiac denervation) but mostly preserved striatal dopaminergic functioning [74••], thereby recapitulating the early Braak stages (I and II) of pathological progression patterns in PD [75, 76].

Therefore, structural markers indicating extra-nigral neurodegeneration in the brainstem (in particular in the LC) are promising to early and reliably identify the patients who will convert to motor PD, before nigro-striatal dopaminergic denervation [77].

MRI Markers for Differential Diagnosis of PD

PSP Versus PD

First, standard structural imaging of the midbrain enables to gauge differences in the shape and volume of the mesencephalon to differentiate PSP from PD and MSA, recognized as the "hummingbird sign" and "morning glory flower sign" due to tegmental atrophy (Fig. 1 and Table 1). A recent and large study confirms that both signs are highly specific (≥ 97.7%) in patients with early clinical diagnosis of PSP versus PD or MSA, but insufficiently sensitive (35.3%) [78]. Quantitative measurements of midbrain atrophy hold the promise to overcome these issues, with increased pons to midbrain ratio in patients with PSP. Increased magnetic resonance parkinsonism index (MRPI), which represents the ratio of the pons to midbrain area multiplied by the ratio of the width of the middle to superior cerebellar peduncles (corresponding to midbrain atrophy), helps distinguish PSP from PD or MSA-P [79], predicts incident vertical supranuclear gaze palsy in PSP-P patients [80] and is greater in PSP patients with early vertical supranuclear palsy (PSP-Richardson syndrome) than in PSP-P [81]. This index was recently refined to take into account the enlargement of the third ventricle in PSP patients [82] and is greater and increases over time in patients initially diagnosed with PD but developing gaze abnormalities as in PSP-P [83]. Similarly, automated calculation of midbrain volumes using probabilistic (Bayesian) segmentation shows midbrain atrophy in PSP but not in PD and controls, independently of smaller SN pars compacta in PSP versus PD patients using neuromelanin imaging [10], and greater hypointensity in the SN, red nucleus, and putamen using SWI, likely corresponding to greater iron deposition [84].

MSA Versus PD

Differential diagnosis may be particularly difficult for patients with MSA and predominant parkinsonian (MSA-P) or cerebellar symptoms (MSA-C). Structural MRI markers consistently pinpoint the specific infra-tentorial damage in MSA-C (Fig. 1 and Table 1), including the "hot cross bun" sign visualized at the pons level resulting from selective loss of myelinated transverse pontocerebellar fibers and preservation of the corticospinal tract, although sensitivity is low [85, 86]. In addition, abnormalities of the middle cerebellar peduncles are observed in MSA-C, with decreased width, T2 hyperintensity, and microstructural diffusivity alterations [87, 88]. Variable findings indicate cerebellar gray matter atrophy both in PD and MSA, although cerebellar atrophy is likely more pronounced in MSA in association with decreased functional connectivity between the dentate nucleus and default-mode network [89]. Classically, putaminal abnormalities are observed in MSA-P, consisting in putaminal atrophy, T2* hypointensity (likely corresponding to greater iron deposition) and hyperintense putaminal rim (best seen using T2* sequences), with respective specificity/sensitivity of 87%/83%, 70/89%, and 90%/72% [88]. Notably, putamen and claustrum atrophy are often observed in patients with MSA-P within 5 years, but less so within the first 3 years [90]. Recent advances also demonstrate increased putaminal diffusivity in patients with MSA-P [91, 92]. Overall, more pronounced and widespread diffusivity changes are observed in PSP and MSA across infra- and supra-tentorial white matter tracts [87], with increased free-water in the SN, basal ganglia, thalamus, and cerebellum, but restricted to the SN in PD [43].

DLB Versus PD

Differential diagnosis of DLB versus other parkinsonian (PD dementia) or non-parkinsonian (Alzheimer's disease, frontotemporal dementia) degenerative syndromes compounded with cognitive impairment and hallucinations is notably difficult. Interestingly, the loss of dorsal nigral hyperintensity (swallow tail sign) is consistently observed both in DLB and PD [21–23], highlighting the selectivity of nigral damage in parkinsonian syndromes. Bilateral loss

increased specificity for DLB versus non-parkinsonian syndromes [23]. Additionally, increased nigral R2* may reflect deposition of alpha-synuclein across parkinsonian disorders including DLB [32]. Distinct gray matter atrophy patterns may also distinguish DLB from Alzheimer's disease (greater parietal, occipital and frontal atrophy and relative preservation of medial temporal lobe in DLB) [22, 93], in addition to microstructural alterations in parieto-occipital white matter tracts compared to healthy controls and in the pons and left thalamus compared to patients with Alzheimer's disease [94].

CBS Versus PD

Use of standard anatomical MRI typically evidences asymmetric cerebral atrophy in CBS, predominant in the frontal and parietal lobes and contralateral to the most clinically affected side, compounded with akineto-rigid parkinsonian syndrome and companion motor and nonmotor symptoms [95]. Importantly, a recent anatomical likelihood estimate meta-analysis highlights that atrophy in the premotor /supplementary motor area and posterior midcingulate/ frontomedian cortex seems to be specific for patients with pathologically confirmed cortico-basal degeneration [96], whereas widespread atrophy in the basal ganglia/thalamus, frontal, parietal, and temporal lobes is observed in CBS which may occur in patients with other neurodegenerative disorders [95].

Structural Imaging Advances for PD Prognosis

PD is characterized by important heterogeneity and variable progression to disabling motor and nonmotor complications, including motor fluctuations, dyskinesias, neuropsychiatric, and cognitive disorders. Stratification of risk is key to deliver individual prognostic information and design trials for disease-modifying drugs which could delay or prevent these debilitating complications. Importantly, variable expression of PD is likely underpinned by distinct pathological processes evolving over time [76, 97], and recent advances show that structural imaging may help anticipate this progression in vivo.

Structural Correlates of Global Impairment in Clinical Subtypes

Looking at clinically identified subtypes, it has long been postulated that patients with predominating axial impairment have worse prognosis, although prognostic value and pathological correlates are debated [98–100]. These patients have greater cortical [101] and subcortical [102] gray matter atrophy, albeit inconsistently [103]. New clinical clusters now include nonmotor symptoms which may mirror the heterogeneity resulting from non-dopaminergic degeneration [104]. In particular, PD patients with greater RBD, cognitive impairment, and dysautonomia at baseline have more rapid motor and nonmotor progression, named as "malignant-diffuse" subtype [100, 104]. Importantly worse prognosis relates to structural abnormalities with greater and widespread cortico-subcortical atrophy and greater dopaminergic progression in the caudate and putamen over 2.7 years in the diffuse-malignant subtype [100].

Structural Markers of Cognitive Impairment and Dementia

Besides the prediction of global impairment, prognosis of cognitive dysfunction is paramount in PD, as patients may be early impaired and later evolve to PD dementia, although this transition is not deterministic [105]. Dementia-risk is much higher in PD and almost 50% of the patients are demented by 10 years [105]. Progressive cortical thinning in the temporo-parietal cortex is believed to subserve the worsening of cognitive impairment in early PD [106]. Moreover, baseline temporal atrophy may predict conversion to mild cognitive impairment over 18 months [106], whereas left frontal, insular and bilateral caudate atrophy predict the conversion from mild cognitive impairment to PD dementia [107]. In addition, greater frontal cortical thinning over time is observed in newly-diagnosed patients with greater white matter hyperintensities load, which is believed to mirror subcortical vascular burden and amyloid angiopathy, and these patients also have greater cognitive decline [108]. Frontal mean diffusivity also increases over time in patients with mild cognitive impairment [109].

As recognized from Alzheimer's disease, cholinergic denervation plays a crucial role in the development of cognitive deficits and dementia. Although its evaluation is technically challenging challenging, atrophy of the small cholinergic nuclei in the basal forebrain comprising the nucleus basalis of Meynert is considered a surrogate for cholinergic depletion and has recently been demonstrated to predict global cognitive worsening over 2 to 5 years in two distinct studies [110•, 111•] and conversion to mild cognitive impairment within 5 years [110•]. Interestingly, increased mean diffusivity in the Meynert nucleus is a strong predictor of cognitive impairment which may herald atrophy [111•] and correlates negatively to the Stroop denomination score in association with reduced functional connectivity to the frontal cortex [112]. Furthermore, prediction of cognitive decline may be improved using multimodal information combining clinical risk factors, CSF amyloid pathology, functional (dopaminergic) and known genetic markers in early PD [113, 114], in addition to structural imaging indicating both diffuse cortical [115] and hippocampal atrophy [116].

Structural Imaging in Genetically Identified Subtypes of PD

Few studies have yet described the structural changes that occur in populations with identified genetic markers of prognostic value, as in patients with GBA mutations, who have greater cognitive decline and risk of dementia, in contrast to patients with LRRK2 mutations for example [105]. However, widespread atrophy in the frontal, anterior cingulate, and middle temporal cortex is found at baseline in de novo PD patients with the COMT Val/Val genotype [117], who have greater risk of cognitive decline [115] possibly due to greater COMT activity and reduced dopaminergic tonus. In addition, patients with LRRK2 and Parkin mutations have increased R2* signal compared to idiopathic PD patients, corresponding to increased iron deposition in the SN, and in asymptomatic carriers compared to healthy controls [118]. This contrasts with slower motor decline observed in LRRK2 carriers [119] although dopaminergic decline is similar compared to idiopathic PD patients [120].

Toward Structural Imaging-Derived Prognostic Subtypes?

In contrast to Alzheimer's disease [121], no study has yet investigated the progression in patients from imaging-defined subgroups. However, to our knowledge, only one team has used hierarchical clustering of structural images and identified cortical atrophy patterns related to cognitive performance, albeit different in non-demented [122] and de novo patients [123].

Structural Imaging Advances for Treatment in PD

Invasive therapeutic strategies using deep brain stimulation have dramatically changed the management of motor fluctuations, dyskinesias and tremor. Importantly, these methods have narrow therapeutic range and their efficacy is crucially determined by the good positioning of the electrodes in small target structures, notably the subthalamic nucleus (STN), internal globus pallidus (GPi), or ventral intermediate nucleus (VIM), whereas stimulation in surrounding white matter tracts may cause adverse effect. Although challenging, accurate registration of pre- and post-operative imaging is crucial to determine the precise contacts of electrodes and has benefited from improved high-resolution pre-operative MRI and post-operative CT scan, automated software solutions [124] and atlas correspondence [125, 126]. This allows to model the three-dimensional stimulation field and establish its structural connectivity pattern based on normative connectome data [127], demonstrating that DBS efficacy depend on long-distance modulation in remote area and that good motor outcome can be predicted from structural connectivity to the supplementary area, superior frontal gyrus, and cerebellum, in line with other studies [128]. Interestingly, a prospective (preoperative) tractography approach to select stimulation contacts has been shown to improve subgenual anterior cingulate cortex DBS results for resistant depression [129] and individualized deterministic tractography-guided targeting could as well be applied to DBS in PD.

These advances may also help to identify the stimulation sweet spot and refine the connectivity pattern for less commonly used or under investigation DBS sites, including the Meynert nucleus stimulation for cognitive impairment [130] or pedunculopontine nucleus for freezing of gait [131].

Conclusions and Perspectives

Overall, considerable advances have been achieved to improve PD diagnosis, predict disabling complications and improve invasive treatment outcome, using non-invasive in vivo structural imaging. In particular, high-resolution MRI and new sequences specific to biological substrates (iron, neuromelanin) disclose subtle and focused changes in the brainstem and basal forebrain nuclei, basal ganglia, and cerebral cortex, which herald clinical symptoms and inform dynamic pathological processes. Undoubtedly, multimodal MR imaging enables to rapidly and repeatedly assess brain structure, which opens promising perspectives for disease-modifying interventions that necessitate to reliably and precociously diagnose PD patients, likely combining multiple markers [132, 133], identify prognostic subgroups, and assess surrogates of their pathological progression. Recent advances in large-scale and multivariate analysis using machine learning will definitely help to manage this new data deluge and open new avenues in classification and multivariate pattern recognition useful for the diagnosis [134], prognosis and treatment of PD. This has been recently highlighted in [135] using multivariate classifiers for structural imaging and clinical characteristics to predict response to dopaminergic treatments, which would be instrumental to predict unfavorable prescription profiles, as for dopaminergic agonists and impulse control disorders. We hypothesize that careful implementation of machine learning relying on high-quality clinical and MRI data hold the greatest promise in domains where unexplained heterogeneity is high, in particular to identify new prognostic subtypes, and that dimensional reduction in clinical, genetic, and imaging data cannot be circumvented in the quest of meaningful, human-interpretable, time- and cost-efficient biomarkers.

Compliance with Ethical Standards

Conflict of Interest Stéphane Prange reports grants from Fondation pour la Recherche Médicale and from Association France Parkinson during the conduct of the study. Dr. Prange also reports non-financial support from Abbvie and TEVA, outside the submitted work. Stéphane Thobois reports grants from France Parkinson and Fondation pour la Recherche Médicale, personal fees from Aguettant, Boston, Medtronic, TEVA and Novartis, non-financial support from Abbvie, and Zambon, outside the submitted work. Elise Metereau declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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