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Longitudinal Progression Markers of Parkinson's Disease: Current View on Structural Imaging

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Abstract

Purpose of Review Advances in neuroimaging techniques pave a rich avenue for in vivo progression biomarkers, which can objectively and noninvasively assess the long-term dynamic alterations in the brain of Parkinson's disease (PD) patients. This article reviews recent progress in structural magnetic resonance imaging (MRI) tools to track disease progression in PD, and discusses specific criteria a neuroimaging tool needs to meet to be a progression biomarker of PD and the potential applications of these techniques in PD based on current evidence.

Recent Findings Recent longitudinal studies showed that quantitative structural MRI markers derived from T1-weighted, diffusion-weighted, neuromelanin-sensitive, and iron-sensitive imaging have the potential to track disease progression in PD. However, validation of these progression biomarkers is only beginning, and more work is required for multisite validation, the sample size for use in a clinical trial, and drug-responsiveness of most of these biomarkers. At present, the most clinical trial-ready biomarker is free-water diffusion imaging of the substantia nigra and seems well established to be used in disease-modifying studies in PD.

Summary A variety of structural imaging biomarkers are promising candidates to be progression biomarkers in PD. Further studies are needed to elucidate the sensitivity, reliability, sample size, and effect of confounding factors of these progression biomarkers.

Keywords Parkinson's disease · Progression · Biomarkers · Structural MRI · Diffusion-weighted MRI · Free-water

Introduction

Parkinson's disease (PD) is the second most prevalent progressive neurodegenerative disorder, with an estimate of seven to ten million people affected worldwide [1]. Its rising prevalence with age and associated economic and social burden present a major challenge to healthcare networks worldwide [2].

The crucial pathological features of PD are progressive loss of dopaminergic neurons within the substantia nigra pars compacta (SNpc) and Lewy pathology [3]. By the time of motor symptom onset, more than 60% SN neurons may have been lost and nearly 80% of dopamine is reduced in the striatum [4–6]. Lewy pathology consists of abnormal aggregates of α-synuclein proteins, called Lewy bodies and Lewy neuritis, which are found throughout cortical and subcortical brain regions [7]. The typical motor symptoms mostly reflect dysfunction of the dopaminergic nigrostriatal pathway, whereas the various non-motor features are likely caused by diffuse

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pathology, which affects brain regions outside the basal ganglia and neurotransmitters other than dopamine.

Since the first description of PD in 1817, efforts have been directed toward the development of treatments to slow down the rate of neurodegeneration or even halt the disease progression of PD. However, all current interventions are symptomatic treatments and have limited therapeutic benefit for disease progression. Clinical trials have primarily focused on clinical scales to measure symptom changes, but teasing apart symptomatic effects from disease-modifying effects is virtually impossible. Meanwhile, most clinical scales are subjective, and it is unknown whether a linear relationship exists between clinical scales and the progression of PD-related pathology. To circumvent this problem, biomarkers that can objectively detect brain changes related to PD and monitor these changes as the disease progresses need to be studied, and this represents a critical need for future clinical trials of PD.

The current imaging techniques applied in PD can be mainly classified as structural and functional. A common structural imaging technique used in PD is magnetic resonance imaging (MRI), and the MRI-derived structural biomarkers include biomarkers of brain atrophy and neuromelanin-sensitive signal changes on T1-weighted imaging, biomarkers of tissue microstructure changes on diffusion-weighted imaging, and biomarkers reflecting iron deposition extracted using R2* measurement. Other techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional MRI (fMRI) are examples of functional neuroimaging techniques, and are not a focus of this review.

This article reviews the latest progress in structural neuroimaging tools to track and predict disease progression in PD. We will discuss what criteria a neuroimaging tool needs to meet to be a progression biomarker for PD, and discuss the validation of these progression neuroimaging tools in PD based on current evidence.

Progression Imaging Markers of PD-Related Alterations in Brain Structure

T1-Weighted MRI

The rapid advances in MRI technologies and methodological approaches make it possible to perform increasingly sophisticated investigations of brain morphometry. Depending on the question of interest, one or more of a variety of methodologies can be used to quantitatively measure different aspects of brain structure, including volumes of regions of interest (ROI), tissue density, surface area, or topology.

To date, several methodological approaches have been applied to T1-weighted images to assess longitudinal structural changes in global or regional brain structure between groups of different individuals or within individuals. One frequently used approach is voxel-based morphometry (VBM), which allows a voxel-wise estimation of brain changes in either gray or white matter, and assessment of group differences in the density or volume across the entire brain with a high regional specificity [8]. Studies using whole-brain VBM analyses have reported progressive regional atrophy in several brain regions including the hippocampus, occipital fusiform gyrus, and precuneus, when compared within PD patients at different time points [9–11]. However, it is difficult to establish whether longitudinal gray matter (GM) changes are specific to PD, because no healthy-matched controls were assessed in these studies.

Currently available studies with control subjects and PD with follow-up periods ranging from 1.5 to 3 years have consistently reported that PD patients have greater total GM volume reduction in the early to mild stages [12–14]. However, studies using whole-brain VBM analyses failed to find significant difference of rates in regional GM volume loss between early-stage PD patients and controls over a period of time up to 3 years [14–16]. Although Ibarretxe et al. found PD patients showed greater GM volume loss than controls in the left inferior lateral occipital cortex and left angular gyrus over 3 years, these results did not survive the correction for multiple comparisons [14]. This indicates the possibility that whole-brain VBM analysis may not be sensitive enough to detect different rates of regional brain alterations between PD patients and matched controls, or subtle short-term changes in brain structure. However, using a ROI-based method, studies have shown accelerated rates of regional brain atrophy in the amygdala over 35 months [14], and in the hippocampus over 2 years in PD patients compared to controls [13]. This indicates the possibility that whole-brain VBM analysis may not be sensitive enough to detect different rates of regional brain alterations between PD patients and matched controls, or subtle short-term changes in brain structure.

Tensor-based morphometry (TBM), another voxel-wise structural analysis technique, identifies structural differences from the gradients of deformation fields that warp images to a common anatomical template [17]. Tessa et al. applied TBM to assess progressive atrophic changes in 22 PD patients [18]. They found even cognitively intact PD patients showed significantly higher yearly atrophy rates in the prefrontal cortex, anterior cingulum, caudate, and thalamus than controls over 3 years in the early stages of disease [18]. These results indicated that cognitively preserved PD patients showed progressive cortical and subcortical atrophic changes in regions related to cognitive functions and that these changes are already detectable in the early stages of the disease.

Different from VBM analysis, which provides a mixed measure of cortical GM including cortical surface, cortical folding, and cortical thickness, cortical thickness analysis has the advantage of providing a quantitative value that represents a physical property of the cortical mantle and has been commonly used to

capture the PD-specific cortical progression pattern [14]. However, longitudinal studies using cortical thickness analysis reveal conflicting results. Yau et al. found PD patients in the early stage presented significantly greater cortical thinning than controls in parts of the left occipital and bilateral frontal lobes and right motor-sensory cortex over 1 year [19]. Mak et al. reported that de novo PD patients without cognitive impairment developed greater percentage of cortical thinning in the left caudal middle frontal cortex than controls over 18 months [20]. Other studies did not find significant cortical thinning differences between PD patients and controls over 45 months [21], 4 years [22], and 6.4 years [23]. The exact reason for these discrepancies is not known but different ways of quantifying longitudinal changes in cortical thickness applied may influence results [14]. Longitudinal changes have been assessed based on the average change (average thickness change from baseline to follow-up) [19], temporal average (the average thickness between baseline and follow-up) [14], percent change (the rate of thinning divided by the baseline thickness) [14, 20], symmetrized percent change (the rate of thinning divided by the average thickness) [14, 21, 22], and annual rate of cortical thickness change [23]. To facilitate comparisons across studies, it is necessary to use the same measure or to perform complementary analyses with other longitudinal measures in the future.

When using the same measure to capture the longitudinal changes of cortical thickness in PD, the results are still controversial. Ibarretxe-Bilbao et al. [14] used symmetrized percent change to quantify the cortical thickness alterations over time, and found PD patients without cognitive dysfunction presented a faster rate of cortical thinning with a bilateral frontotemporal pattern over 35 months. Another two studies using the same measure failed to find significant differences of progression rates between PD patients and controls over 45 months and 4 years respectively [21, 22]. One possible reason for this might be that patients in the latter two studies had more advanced ages (mean age of 59.5 years and 61.4 years, respectively) and longer disease durations (6.5 years and 4.9 years) at baseline [21, 22], than patients in the earlier study (the average age was 55.9 years and the average disease duration was 2.97 years) [14]. Age and disease duration are likely to be independent factors for disease progression [24]. In contrast to controls, the accelerated annual rate of cortical GM changes, measured by cortical GM volume and cortical gyrification, respectively, was found only in PD patients with medium disease duration (1–5 years), but not in PD with short (< 1 year) or long disease duration (> 5 years) [25•, 26]. These results may reconcile the controversial findings relating to cortical GM changes associated with PD, and guide the choice of more sensitive stage-dependent biomarkers. In interpreting these findings, one should bear in mind that PD is known for its clinical heterogeneity. In contrast to healthy controls and PD patients without cognitive impairment, PD patients with mild cognitive impairment (MCI) show more extensive atrophy and faster rates of cortical thinning in frontal and temporoparietal cortices, including hippocampus atrophy over 18 months [20]. These findings suggest that structural changes as detected by these methods are more common in subgroups of PD with additional cognitive symptoms.

Regardless of the various factors affecting comparison across studies, accelerated total GM loss and frontal cortical thinning seem to specifically associate with the PD degeneration process in the early and moderate stage [14, 19, 20, 23, 25•, 27], whereas extensive and faster cortical thinning in temporoparietal cortices in addition to frontal atrophy appears to be a consistent finding in PD patients with MCI [20, 28].

Depigmentation of the substantia nigra is a significant pathological feature of PD and is related to loss of neuromelanin, which has paramagnetic properties resulting in signal increase on a specific T1-weighted MRI sequence, which is also called neuromelanin-sensitive T1 MRI (NMI). So far, only one study evaluated longitudinal changes on NMI in PD patients [29]. Keita Matsuura et al. examined the longitudinal changes on NMI in 14 patients over 2.3 years [29]. They found that the total area and contrast ratio of SNpc on follow-up NMI were significantly smaller than those on initial NMI, and the total area and contrast ratio of the SNpc negatively correlated with disease duration. These results indicate that NMI may be a potential tool for detecting neuropathological changes over time in PD patients, but the small sample size and lack of controls limit the generalization of these results.

Diffusion-Weighted MRI

Diffusion-weighted MRI (dMRI) is sensitive to microstructural tissue changes that alter the regional diffusion of water molecules [30, 31]. Diffusion tensor imaging (DTI) estimates microstructural integrity by measuring diffusion tensor with four different metrics including mean diffusion (MD), fractional anisotropy (FA), radial diffusion (RD), and axial diffusion (AD). MD represents the general diffusion and FA its directionality. AD and RD describe diffusion along the main and transverse axes, respectively [30, 32].

Several longitudinal studies employed a standard DTI processing to assess voxel-wise differences of DTI metrics along principle white matter tracts using tract-based spatial statistics (TBSS) in PD patients [9, 27, 33]. Diez-Cirarda et al. found decreased WM FA mostly in the corpus callosum and corticospinal tract, and increased MD and RD in the posterior thalamic radiation and optic radiation in early PD patients over 18 months [9]. However, when compared with healthy controls, Melzer et al. and Rossi et al. used TBSS and failed to identify significant DTI changes in early to moderate PD patients over 1 year and 2 years, respectively [27, 33]. It should be noted that there were no controls in the first study, and the latter two studies used a relatively low number of diffusion-encoding directions (28 and 20, respectively).

Using a ROI approach that may be more sensitive at detecting regional alterations, longitudinal studies have reported microstructural changes in PD but with inconsistent results. Lenfeldt et al. [34] investigated DTI changes in three subareas of SN in 122 PD patients at three time points over 5 years, and found that nigral FA and AD were higher in PD patients than those in controls at baseline and follow-ups, but no evolution in nigral FA was observed over 5 years. In contrast to these results, Loane et al. [35] investigated the effect of disease progression on SN and striatal diffusion metrics in 18 early-stage PD over 19 months. They found that at baseline, PD patients and controls did not differ in terms of FA or MD in the striatum or SN, but by follow-up, decreased FA and increased MD in SN had significantly deviated from the controls [35]. Zhang et al. [36] explored the extended to explore the annualized rates of DTI changes in 118 WM and subcortical ROIs in 122 early-stage PD patients over 1 year. They found that PD have higher rates of FA reduction was associated with higher rates of FA reduction and RD and AD increases predominantly in the SN, midbrain, and thalamus compared to healthy controls [36]. These conflicting results lead to a debate regarding the potential for nigral FA as a progression biomarker in PD. This debate is reinforced in two recent systematic reviews stating a high degree of variability of nigral FA changes [37, 38]. Inconsistent methodologies of delineating the SN and heterogeneity of samples may partially explain the controversial results. The effect of extracellular water on classic diffusion measures may also be a reason.

Recently, a bi-tensor dMRI model was developed to separate the diffusion properties of extracellular water (i.e., free-water) from those of water in brain tissue (free-water-corrected DTI) [39, 40]. The presence of free-water can cause a higher degree of isotropy, possibly driving a decrease in FA and increase in MD values [41]. In single site and multisite cohort studies, free-water in the posterior SN (pSN) was consistently elevated in early-stage PD when compared with healthy controls [42••, 43•, 44•, 45]. Furthermore, longitudinal studies across multiple sites and scanners showed that free-water in pSN increased over a 1-year period of time in early-stage PD but not in controls [42••], replicating the initial observation by Ofori et al. [44•], and also found that free-water in pSN continued to increase over 2 and 4 years in PD [42••]. These results demonstrated that pSN free-water is a valid progression biomarker in early-stage PD.

Diffusion kurtosis imaging (DKI) was developed as an extension of DTI to quantify the non-Gaussian distribution of water diffusion. This technique represents a promising approach for accessing neurodegenerative diseases. So far, one study has assessed the effect of disease progression on DKI measures in PD patients over time [46]. The authors examined longitudinal DKI changes in the basal ganglia, thalamus, midbrain, pons, red nucleus, and WM and found that only a decrease in FA in the putamen of early-stage PD patients was significantly different from the changes observed in healthy controls over 2 years. No correlations were found between change in DKI parameters and change in UPDRS III, H&Y, and MMSE. However, based on previously published studies, DKI tends to show inconsistent results in brain regions involved in the basal ganglia circuit in PD [46], and thus the validity of DKI measures to be a biomarker in PD needs further study.

Iron-Sensitive Imaging

Evidence from post-mortem studies demonstrates selective increase of iron in the SN in PD [47, 48], suggesting that measurement of regional iron content in the SN may provide an indication of the pathological severity of the disease. There are two MRI methods used to visualize iron deposition in PD. Most studies are based on a T2* sequence and report the R2* value (1/T2*) as a measure of total non-heme iron content [49]. Several studies have assessed the disease progression effect on R2* changes over time but with controversial results. Some studies found increased nigral R2* over 2 years [50] and 3 years [51] in PD patients, while other studies reported no longitudinal changes in nigral R2* over 2 years [33] and 3 years [52]. The influence of clinical heterogeneity on R2* value [53] and the wide variance of R2* at each time point [52] likely partially explain the conflicting findings. A study by Du and colleagues suggests that by separating PD into early (< 1 year), middle (1 to 5 years), and late stage PD (> 5 years), only the late-stage PD group showed increased R2* in SNpc over 18 months compared with a control group [54]. Another MRI technique is susceptibility-weighted imaging (SWI), which generates contrast based on phase images and can reflect the iron content in the brain. Using this method, it was found that PD patients showed hypointensity and slightly increasing relaxation in the SNpc over 2 years [33]. The non-quantitative analysis used in this study may reduce the sensitivity to detect iron content changes. This limitation is being addressed with the recent development of quantitative susceptibility mapping (QSM), which computes the underlying susceptibility of each voxel as a scalar quantity. Some studies have suggested that QSM is more sensitive to estimate brain iron levels in PD patients than R2* [55, 56], but in the study by Du and colleagues [54], the QSM measures in SNpc did not change over 18 months in PD, whereas R2* measures did increase in late-stage PD. Further studies are needed to test whether it is a promising method to track disease evolution.

Which Structural Imaging Tool Has the Potential to Be a Progression Marker in PD?

Much has been discussed about which features a biomarker for PD progression should have [57–59]. There is a consensus as to the qualifications an ideal PD progression biomarker should meet: changes with PD neurodegeneration, sensitivity

to small changes in disease progression, satisfactory test-retest repeatability and across-multisite reproducibility, not influenced by symptomatic treatment, relating to or predicting a clinical outcome, having robust longitudinal data linking it to disease progression, easy accessibility, and inexpensive to measure. Here, we discuss which structural imaging techniques have demonstrated obvious potential in monitoring disease progression based on available evidence (Table 1).

Does the Biomarker Describe a Biological Process That Changes with PD Neurodegeneration?

Progression biomarkers are expected to detect neuropathological features and mechanisms underlying neurodegeneration in PD and to correlate with disease progression in order to allow the monitoring of disease status. PD is a complex neurodegenerative disorder in which many different pathophysiological processes have been found in the nigrostriatal pathway and other brain regions. Advanced MR contrast and imaging analysis techniques have improved visualization and objective quantitative assessment of different brain structures, and make it possible to detect in vivo brain longitudinal changes in PD.

Cortical degeneration in PD can be followed using voxel-based techniques and cortical thickness measurements that can detect alterations in the volume, density, and thickness of the gray matter in the cortex [14, 19, 60]. Results from imaging studies in PD animal models have supported the application of structural MRI to assess brain alterations in PD patients. Local tissue volume changes in the substantia nigra have been detected by whole-brain VBM using 7-T MRI in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys [61]. An in vivo MRI study in a rat proteasome inhibitor model of PD has detected thinning of the primary motor and somatosensory cortices [62].

Subcortical white matter deficits in PD can be captured using diffusion-weighted imaging, which can detect changes in water diffusion in biological tissues, and fiber tract-specific reconstruction. Techniques such as diffusion imaging, iron-sensitive imaging, and neuromelanin-sensitive imaging can investigate microstructural changes in deep brain nuclei. Microstructural changes in the substantia nigra have been identified by diffusion imaging in the two commonly used rodent models of PD, the 6-hydroxydopamine (6-OHDA)-treated rat [63] and the MPTP-treated mouse [64]. Diffusion imaging also revealed altered diffusion in nigrostriatal regions, and diffusion tractography detected fiber loss in the nigrostriatal pathway in MPTP-treated monkeys [65]. T2*-weighted imaging in 6-OHDA-treated rat model of PD revealed T2* hypointensities in the striatum, the area that histological analysis confirmed the existence of iron accumulation [66]. These studies indicate that all of these above structural imaging biomarkers have the potential to reflect an important biological process in PD.

Is the Biomarker Sensitive to Reflect Small Changes in Disease Progression?

An ideal progression biomarker should not only be able to identify the disease-specific changes more than that expected by healthy aging, but also be sensitive to reflect small changes in disease progression. There is currently no evidence to suggest what the minimum duration of a surrogate biomarker should be in order to detect small changes in disease progression. For maintaining low costs in clinical trials, the shorter the time period that a biomarker detects disease progression, the more useful the biomarker would be for disease-modifying trials.

The majority of current structural imaging studies that investigated longitudinal changes in PD were generally followed for 2 to 3 years, with the range of 1 year to 6.4 years.

Table 1 Performance of currently available structural MRI tools to track disease progression in the early stage of PD

Criteria	T1-weighted MRI			dMRI			Iron-sensitive imaging	
	VBM	Cortical thickness	NMI	One tensor	Bi-tensor	DKI	R2*	QSM
1. Describe PD neurodegeneration	✓	✓	✓	✓	✓	✓	✓	✓
2. Sensitive to reflect small changes in disease progression	✖	NA	NA	NA	✓	NA	✖	✖
3. Good test-retest reliability	✓	✓	✓	✓	✓	NA	✓	✓
4. Reproducible across multisites	NA	NA	NA	✓	✓	NA	NA	✓
5. Not influenced by symptomatic treatment	NA	NA	NA	NA	✓	NA	NA	NA
6. Relate to clinical outcome	✓	✓	NA	NA	✓	NA	NA	NA
7. Robust longitudinal data allowing sample size calculations	NA	NA	NA	NA	✓	NA	NA	NA
8. Be relatively inexpensive and easy to use	✓	✓	✓	✓	✓	✓	✓	✓

VBM, voxel-based morphometry; *dMRI*, diffusion-weighted MRI; *DKI*, diffusion kurtosis imaging; *NMI*, neuromelanin-sensitive imaging; *QSM*, quantitative susceptibility mapping; *NA*, has not been studied sufficiently to draw a conclusion; *check mark*, yes; *X mark*, no

Although whole-brain VBM analysis could reveal the global GM volume loss over 1.5 years [12], it is not sensitive enough to capture regional cortical and subcortical GM changes even over 3 years [9, 14, 15] in early and mild PD. The ROI approach seems to be able to detect striatal GM volume changes over time in PD, as faster volume loss in the putamen and caudate has been found in PD patients over 3 years [26], but these results are in contrast to several prior studies that reported no changes in basal ganglia volumes over 19 months [28] and 35 months [14]. These contradictory findings may raise the possibility that the ROI approach could detect longitudinal striatal volume changes but need a long enough follow-up duration. Regardless the conflicting results revealed by cortical thickness studies in PD, the different rates of cortical change in different disease durations might suggest that cortical thickness has the potential to measure the progressive cortical atrophy in the relatively early stage of PD [26]. As for SN, in contrast to the high degree of variability of single-tensor DTI metrics, bi-tensor free-water imaging consistently showed that the elevated free-water in the posterior SN increased over 1 year in early stages of PD but not in controls across multiple sites and cohorts, and demonstrated free-water imaging could sensitively track the SN degeneration changes in a 12-month period [42••, 43•]. Given the conflicting and limited evidence on NMI and iron-sensitive imaging to measure SN longitudinal changes, the sensitivity of these imaging tools needs further investigation.

Is the Biomarker Reliable and Reproducible Across Centers?

The reliability of an imaging biomarker must be established by demonstrating its repeatability and reproducibility. The repeatability refers to the reliability of the biomarker to repeatedly measure the same feature under identical or nearly identical conditions, and it is often investigated by the test-retest and scan-rescan studies. Reproducibility refers to the reliable consistency of a biomarker across sites that may be expected in clinical practice. The increased repeatability and reproducibility allow for smaller sample size in studies evaluating biomark of disease progression or treatment effects, which is particularly important when planning large multisite studies.

Prior studies have showed that the diffusion metrics derived from single-tensor dMRI have good repeatability and reproducibility in healthy controls, but the test-retest reproducibility worsens with smaller ROI volumes [67, 68, 69•]. Recently, Albi et al. evaluated and compared the test-retest reproducibility of dMRI measures in a longitudinal multisite healthy elderly participants scanned in two sessions at least 1 week apart, using the standard single-tensor DTI and bi-tensor free-water elimination [69•]. They found free-water elimination significantly improves test-retest reproducibility on all four DTI metrics (FA, MD, AD, RD) in most ROIs in the brain consistently across MRI sites, and most of the significant improvements in reproducibility following free-water elimination were on smaller ROIs [69•]. The improved reproducibility suggests that free-water-corrected DTI measures have higher sensitivity than conventional DTI measures to detect both within- and between-group effects related to microstructural changes [69•].

The test-retest variability of VBM results was evaluated with an ROI approach, and all ROIs from 3-T data exhibited good reliability [70]. However, Hidemasa et al. found that scanner drift and inter-scanner variability significantly affected longitudinal morphometric results from VBM and could cancel out actual longitudinal (2-year) brain volume changes [71]. The test-retest reproducibility of the substantia nigra with NMI has recently been investigated in 11 subjects who underwent two NMI scans. Volume and MT contrast of SNpc showed good reproducibility (ICC, 0.94 and 0.81, respectively) in interscan measurements [72]. For the iron-sensitive imaging, ROI-based QSM measurements and R2* also showed good reproducibility over the same scanner and over different scanners in the basal ganglia for healthy subjects [73, 74]. The cortical thickness measures could be highly reliable when MRI instrument and data processing factors are controlled [75]. The intraclass correlation coefficient (ICC) was used to assess scan-rescan reliability of the two commonly used pipelines in cortical thickness analysis. ANTs thickness pipeline and the FreeSurfer thickness pipeline produced an ICC value of 0.98 and 0.97, respectively, indicating good scan-rescan reliability for both pipelines [76]. Although most of these above imaging tools showed quite good reliability in healthy controls, the reliability of a biomarker in PD needs to be further investigated in PD patients.

The test-retest study on Parkinson's PPMI data reported that most large white matter fascicles in PD subjects, such as corpus callosum and corticospinal tract, could be evaluated with fairly good test-retest repeatability, whereas fascicles that connect small deep nuclei (caudate, putamen, thalamus) to larger functional cortical areas (associative, limbic, sensorimotor) [77] are much less reproducible. Using free-water dMRI, free-water in the posterior substantia nigra was found to be elevated in PD compared to that in controls across multisite cohorts [42, 43•, 44•], and increased over 1 year in PD but not in controls across multisites and scanners [42••, 44•]. Furthermore, free-water in the posterior SN was found to consistently increase across multiple sites in PD subjects at de novo baseline, 1 year, 2 years, and 4 years [42••]. These results demonstrated free-water in posterior SN has good reproducibility in PD patients.

Does the Biomarker Monitor Disease Progression Without Being Biased by Symptomatic Treatments?

An evaluation of possible confounding factors on the biomarker should be performed, as understanding the influence of these

factors on the biomarker would aid sample size calculation and allow a rigorous analysis of results by adjusting for these factors. Among these factors, it is essential to elucidate the effects of symptomatic therapy on imaging markers because most PD patients recruited in neuroprotective clinical trials will be on symptomatic treatment, and the symptomatic treatments can change throughout a trial. An ideal biomarker for disease-modifying clinical trials should not be influenced by symptomatic treatment, and this would simplify the trial design by recruiting patients both on and off medication. The effects of anti-parkinsonian medication on free-water dMRI measures have been recently tested. Chung et al. found that free-water and free-water-corrected FA in key nigrostriatal structures are not influenced by administration of acute anti-parkinsonian medication in PD [78]. These results provided evidence that neuroimaging measurements such as dMRI free-water and free-water-corrected FA are well-suited disease progression biomarkers to reflect the chronic state of basal ganglia in PD. The effects of symptomatic drugs on other structural imaging biomarkers need to be investigated in the future.

Does the Biomarker Relate to Clinical Outcome?

Although changes in the structural imaging markers may represent changes in the underlying disease process, the rates of change of a marker may or may not correlate with that of clinical metrics during the time period of interest. Whereas validation of biomarkers against clinical outcomes is ultimately essential, and if the baseline level or the change of the biomarker within a short-term correlated with a long-term clinical progression, the biomarker would be particularly useful in evaluating the efficacy of disease-modifying therapeutics. Ray et al. reported that PD patients with reduced volumes of nucleus basalis of Meynert at diagnosis suffered greater global cognitive decline over 2 years, and had increased risk of early development of progressive cognitive impairment leading to PD dementia up to 5 years later [79]. These results suggested the volumetry of the nucleus basalis of Meynert might be a biomarker to stratify the patients in clinical trials of cognitive treatments in the early stage of PD. Using free-water dMRI, the 1-year and 2-year increase in free-water in the pSN predicted subsequent 4-year progression on the Hoehn and Yahr staging system in PD [42••]. This finding suggests that if a medication were able to slow down the elevation of SN free-water, then the long-term motor progression may be slowed as well.

Are There Robust Longitudinal Data That Allow Sample Size Calculations for the Biomarker to Measure Disease Progression?

To pave the way for application of a progression biomarker in progression clinical trials, longitudinal data on a sufficient number of patients should be available to allow the estimation of sample size and power for a clinical trial. Sample size estimates derived from power calculations are primarily influenced by the proposed size of the effect of interest (e.g., group difference in rate of structural change) and the variance of the data derived from the particular measure used [80]. As the variance of the data is mainly contributed by sample biological variability and measurement variability, only the effect of confounding factors such as age, sex, or symptomatic treatment being addressed and the reliability of the measurement being established could enable the performance of power calculations for multicenter clinical trials. However, longitudinal structural imaging studies that to provide estimates of sample sizes for putative disease-modifying therapies for PD have only recently begun to appear in the literature. The utility of free-water measurement and DaTscan as biomarkers in clinical trials of a possible disease-modifying therapy has been recently compared. Power calculations suggested that free-water in the pSN showed comparable sensitivity as functional imaging markers such as putamen DAT binding measurement derived from DaTscan in a 2-year clinical drug trial with two arms (placebo and active drug), with estimates of 88–104 subjects per arm for free-water in pSN and 151–158 subjects per arm for DaTscan SBR in putamen (50% reduction from drug, statistical power = 90%) [42••]. Mak et al. reported whole-brain atrophy and ventricular enlargement required substantially smaller sample sizes compared to global cognitive decline (MMSE) for detecting significant differences over time in PD-MCI patients versus controls [12]. To detect a 20% reduction, 186 and 223 patients per arm are required for whole-brain atrophy and ventricular enlargement respectively [12]. In contrast, 2974 patients per arm are required to detect an equivalent degree of slowing of global cognitive decline. These estimates demonstrate that imaging-based measures need a smaller sample size and are thus more sensitive than clinical symptomatic measures in disease-modifying clinical trials.

Longitudinal studies with long-term follow-up are needed to observe the pattern of biomarker changes with disease progression, and this not only will help to address the biomarker variance but also guide the choice of imaging biomarkers in a clinical trial. The recent longitudinal study identified that loss of cortical gyrification was not obvious at baseline but accelerated over 3 years in PD with disease duration between 1 and 5 years, but not in patients with longer disease duration [25•]. These findings indicated that the measurements of cortical folding might be more sensitive to monitor disease progression in the early stage. When measuring the striatal atrophy in PD patients with different disease duration over 3 years, the annual volume changes in the putamen and caudate were accelerated in the first several years and appeared to reach plateau 5–10 years after diagnosis [26]. These findings suggested that striatal atrophy has the potential to gauge early but not

later on progressive changes. Free-water in pSN was observed to increase in drug-naïve PD patients and continued to increase over 4 years [42••], while the findings in patients with much longer disease duration (mean disease duration 7.1 years at study entry) showed longitudinal increases in anterior but not posterior SN free-water over 3 years [45]. These results demonstrated that free-water in SN could track the disease progression in different disease stages and indicated a shift of free-water changes from posterior to anterior SN with disease progression. Further serial imaging studies are needed to examine the changing pattern of other structural imaging biomarkers.

Conclusions

Substantial progress has been made in neuroimaging studies of PD and provided a variety of structural imaging biomarkers that possess the potential to monitor longitudinal disease progression in PD (Table 1). However, the possible validation of most progression biomarkers remains to be performed. Based on current available evidence, the most promising structural MRI biomarker is free-water in the SN, which meets most of the criteria required for a progression biomarker and seems well established with a reasonable sample size to be used in disease-modifying clinical trials in PD (Table 1). Other modalities are also promising progression biomarkers but require further validation. Further studies are needed to elucidate the sensitivity, reliability, and effect of confounding factors of these biomarkers. Alongside these issues, other factors should also be considered when validating these progression biomarkers. As PD is a clinical heterogeneous and pathological progressive disorder, each structural MRI modality may have its own advantage in tracking disease progression with pathoanatomic specificity and disease stage-dependent sensitivity. It is necessary to explore the pathoanatomic specificity and the natural history of each biomarker that changes with disease progression.

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Compliance with Ethical Standards

Conflict of Interest Dr. Jing Yang and Dr. Roxana G. Burciu declare that they have no conflicts of interest. Dr. David E. Vaillancourt reports grants from NIH, NSF, and Tyler's Hope Foundation during the conduct of the study, and personal honoraria from NIH, National Parkinson's Foundation, Sanofi, and Northwestern University unrelated to the submitted work. Dr. David E. Vaillancourt reports a patent 62/486,580 is pending.

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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- •• Of major importance

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