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MRI biomarkers of motor and non-motor symptoms in Parkinson's disease

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Abstract

Parkinson's disease is a heterogeneous disorder with both motor and non-motor symptoms that contribute to functional impairment. To develop effective, disease modifying treatments for these symptoms, biomarkers are necessary to detect neuropathological changes early in the disease course and monitor changes over time. Advances in MRI scan sequences and analytical techniques present numerous promising metrics to detect changes within the nigrostriatal system, implicated in the cardinal motor symptoms of the disease, and detect broader dysfunction involved in the non-motor symptoms, such as cognitive impairment. There is emerging evidence that iron sensitive, neuromelanin sensitive, diffusion sensitive, and resting state functional magnetic imaging measures can capture changes within the nigrostriatal system. Iron, neuromelanin, and diffusion sensitive measures demonstrate high specificity and sensitivity in distinguishing Parkinson's disease relative to controls, with inconsistent results differentiating Parkinson's disease relative to atypical parkinsonian disorders. They may also serve as useful monitoring biomarkers, with each possibly detecting different aspects of the disease course (early nigrosome changes *versus* broader substantia nigra changes). Investigations of non-motor symptoms, such as cognitive impairment, require careful consideration of the nature of cognitive deficits to characterize regional and network specific impairment. While the early, executive dysfunction observed is consistent with nigrostriatal degeneration, the memory and visuospatial impairments, the harbingers of a dementia process reflect dopaminergic independent dysfunction involving broader regions of the brain.

Keywords

Parkinson's disease; MRI; Imaging; Biomarker; Motor; Non-Motor

1. Introduction

Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder, with more than 6 million people currently diagnosed, a prevalence that has more than doubled between 1990 and 2015 [1,2]. Classically, PD is diagnosed by evaluating the presence of motor features, including bradykinesia (slow movement), rest tremor, muscle

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rigidity, and gait abnormalities. Non-motor features, such as cognitive impairment, sleep disorders, and constipation are found early in the disease course and can significantly contribute to patient disability and even increase mortality [3,4]. To develop effective, disease-modifying treatments for both the motor and non-motor symptoms of PD, early, accurate diagnosis and prognostic/monitoring indicators are necessary. This is challenging as the onset and progression of motor and non-motor symptoms is variable [5,6] with certain subtypes of individuals exhibiting a more pronounced decline [7]. Diagnostically, it is informative to differentiate PD participants from controls. However, it is more difficult to clinically distinguish PD from atypical parkinsonian disorders (APD), including multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD); thus a true diagnostic biomarker needs to also differentiate PD from these APDs.

There are diverse approaches to biomarker investigation which include physiological/clinical assessments, genomic/proteomic/metabolomic/RNA methodologies (often collectively referred to as CSF and blood biomarkers) and imaging approaches [8]. CSF and blood biomarkers [9,10] and PET/SPECT Imaging biomarkers [11–13] have been reviewed at length elsewhere. There has recently been substantial developments in new MRI methodology. The current review aims to present the most promising imaging biomarkers. This is not intended to be an exhaustive review, but rather a practical overview that provides information for identifying the appropriate imaging metric for the question being asked and the utility of potential biomarkers to characterize specific aspects of the motor and non-motor symptoms of PD.

2. Is the imaging metric appropriate for the question being asked?

Most imaging biomarkers have examined dysfunction of the nigrostriatal pathway as it is responsible for the cardinal symptoms of PD (bradykinesia, rigidity, tremor). The primary neuropathology includes the misfolding and aggregation of α-synuclein (α-Syn) in the substantia nigra (SN) and degeneration of nigrostriatal dopamine neurons. Motor symptoms emerge after 50-70% loss of the dopaminergic neurons in the SN [14,15] resulting in dopaminergic denervation of the striatum. It is thought that α-Syn aggregation typically begins in the caudal brainstem and progresses rostrally [16,17] (Fig. 1A), and the progression is found to correspond with increased non-motor symptoms, such as cognitive impairment [18]. Specifically, non-motor symptoms are not solely driven by the degeneration of the dopaminergic nigrostriatal system, but by multifocal involvement of broader network dysfunction depending on the symptomatic presentation [19]. Neuroimaging may be particularly useful to monitor regionally specific pathological progression and resultant dysfunction in both the motor and non-motor symptoms. To review the available MRI metrics and current research, the following sections focus on the specific imaging modalities that are sensitive to either structural or functional variations in the 1) SN (brainstem level neuropathology) and the basal ganglia and 2) limbic and neocortical regions. Within each of the following sections we introduce each imaging modality and the literature relevant to evaluate its utility as a diagnostic biomarker (e.g. can it differentiate PD from controls and APDs) and a monitoring biomarker (e.g. can it reliably measure disease progression). For biomarker definitions, please refer to Table 1.

3. SN and basal ganglia

Recently, several scan sequences and analytic techniques have emerged that can detect PD associated changes in the SN and basal ganglia such as increased iron load, abnormal shape, abnormal diffusion, anatomical connectivity, and functional connectivity (Table 2). Each of these techniques provides distinct, but often complementary information regarding the SN and basal ganglia. The utility of these measures may vary depending on the stage of disease and the possible extent of dysfunction. For instance, the earliest dopaminergic neuronal loss within the substantia nigra occurs in the nigrosomes (clusters of dopaminergic neurons; N1 – N5) [14,20]; within A9 in the caudal and ventrolateral tier of substantia nigra pars compacta (SNc) and progresses to neighboring regions (A8 and A10; Fig. 1B) [15,19]. It is important to consider biomarkers with this in mind. Presumably, there may be a substantial loss of N1 dopaminergic neurons early in the stage of the disease course, but this likely hits a “floor level” early on and therefore may not serve as a monitoring biomarker later in the disease course. Furthermore, patients with APDs typically have neuronal degeneration in the SN and other midbrain structures, but without the presence of Lewy bodies [21]. Diagnostically, it is critical to determine whether a biomarker can differentiate SN disruptions specific to PD rather than a general reduction seen across PD and ADPs.

3.1. Structural Morphometry

Conventional imaging can be used to quantify the volumes of subcortical structures (putamen, caudate, globus pallidus, thalamus; Fig. 2B) [22,23]. There are inconsistent findings regarding the ability of subcortical volumes to differentiate PD and controls [24,25]. However, the midbrain and putamen volume were found to differentiate PD from MSA or PSP was 97.4% [26]. Based on T1-weighted imaging, subcortical nuclei shape analysis of the putamen and caudate nucleus differentiate PD relative to controls and might relate to motor symptoms, suggesting shape may be more sensitive than volume to detect changes in PD [27]. Examination of the midbrain structures, such as the SN, is challenging due to the limitations of the contrasts of the conventional T1 and T2 images. Only recently, automated midbrain segmentation has been developed (midbrain, pons, medulla oblongata, superior cerebellar peduncle) [28]. Midbrain volumes characterized using this method were significantly lower in PSP patients relative to PD patients and controls, suggesting that it may be a useful measure for differentiating APD [29]. For a review of structural segmentation currently available see Ref. [30]. Together, these studies suggest that differences in structural morphometry are subtle in PD relative to controls, with more pronounced differences observed in MSA and PSP. There is some suggestion that shape analyses may be more sensitive to differentiate controls and PD and track disease progression. Overall, structural morphometry approaches have yielded inconsistent results and further research is necessary to understand the utility of these approaches.

3.2. Iron and neuromelanin sensitive MRI

T2* weighted Imaging—Histochemical studies have demonstrated elevated iron accumulation in the SN in PD patients [31]. MRI scan sequences can quantify iron due to its paramagnetic property which changes the relaxation behavior of tissue and introduces changes in susceptibility and microscopic field gradients [32,33]. Specifically, iron levels in

vivo cause signal changes in T2 and T2*, and can be quantified in a variety of ways [34,35], with initial focus on relaxation rates (R2* = 1/T2*; R2' = R2*-R2 [36–38]), collectively referred to as relaxometry [39]. Using these early measures, PD demonstrated elevated iron levels in the SN [36,38,40,41]. Increased iron levels observed postmortem were related to the R2* values [31]. A combination of R2* measures and diffusion metrics (described below) have been helpful in differentiating PD and APD [42,43]. There have been mixed reports of whether R2* can capture PD progression [44–46].

The R2*contrast captures variance of the magnetic field that is generated by local as well as surrounding tissue susceptibility (capturing local and surrounding signal). This has led to the development of a novel MRI modality, quantitative susceptibility mapping (QSM) which removes the effects of susceptibility of the surrounding tissue through deconvolution, providing a superior measure of local tissue magnetic properties [47–49]. Both R2* and QSM have been found to be reliable [50]. QSM generally demonstrates a greater sensitivity to differentiate PD from controls relative to R2* methods [51–54]. Recently, examination of R2* and QSM obtained in vivo with postmortem pathological findings in the SN found that both measurements correlated positively with iron, however R2* was additionally associated with a-Syn aggregation and neither measure related to the presence of tau in the SN [55]. This is the first MRI measure that has been linked to α-Syn pathology in the same specimen. Longitudinal analysis of these same measures suggests that while both R2* and QSM were elevated in PD relative to controls, only the R2* measure changed longitudinally, but only in the "late" group which consisted of PD participants that had been diagnosed for greater than 5 years [46].

Nigrosome Imaging—While the aforementioned studies typically examine the broader regions of the SN (e.g. the entire SN, or SNc), the increased spatial resolution obtained using higher magnetic field strength (7T; *ultra-high field*) allow for the examination of structures as small as the individual nigrosomes within the caudal and ventrolateral tier (A9) of the SNc (Fig. 1B), the regions affected earliest in PD [56]. Examination of the presence of N1 (referred to as the swallow-tail sign) using T2*-weighted imaging at 7T provides high sensitivity (100%), specificity (87-100%), positive predictive value (91-100%), and negative predictive value (100%) in differentiating PD from controls [56–58]. However, similar rates of diagnostic differentiation were recently obtained using 3T MRI, suggesting that it is not necessary to obtain images at the ultra-high field strength [59–63]. The loss of nigrosome signal is common in APDs [64,65], indicating that this technique may not differentiate PD and APDs [66,67].

Neuromelanin Imaging—Neuromelanin is produced as oxidative products downstream from L-DOPA [68]. It accumulates inside specific autophagic organelles, accumulating over the lifespan in the soma of dopaminergic neurons in the SN [68,69]. It is only cleared from tissues following cell death via microglia, evident in PD [70,71]. Neuromelanin sensitive MRI (NM-MRI) relies on quantitative magnetization transfer (MT) and T1 effects and is sensitive to NM-positive dopamine neurons (T1-weighted fast spin echo; T1w FSE; [72,73]). Neuromelanin may be more sensitive to capturing the SNc whereas T2* better captures the SNr [74] (Fig. 2). NM-MRI is consistently decreased in the SN in PD patients

relative to controls [72,75–79]. Additionally, there is a decrease in neuromelanin concentration in postmortem SN tissue of PD patients relative to controls [80]. However, currently, the NM-MRI measurements' specificity and sensitivity to differentiate between PD and APD [29,79,81,82] and essential tremor [83] warrants further investigation. Preliminary evidence suggests that longitudinal change in neuromelanin signal in PD could serve as a marker of disease progression [66,84].

In summary, all of these measures have high sensitivity and specificity in distinguishing PD relative to controls with inconsistent results differentiating PD from APD [66]. While nigrosome imaging is sensitive to changes early in the disease course [85], it may be limited changes after the initial decline early in the course of PD. In contrast, NM-MRI, T2* and QSM measures of the nearby regions may better characterize change over time [46] and serve as useful monitoring markers.

3.3. Diffusion MRI

Diffusion Tensor Imaging—Diffusion MRI is sensitive to the diffusion of hydrogen protons, modeled most commonly with the diffusion tensor model (DTI) [86,87]. Metrics derived include: mean diffusivity (MD) which reflects the diffusion in all directions within a voxel and fractional anisotropy (FA) which reflects the extent in which there is directional diffusion [88]. Hydrogen protons are widespread in the brain and therefore these metrics can examine not only iron-rich areas, but the entire brain. Interpretation therefore varies depending on which region of the brain. For instance, changes in DTI metrics in the SN (decreased FA and increased MD) indirectly measure neuronal degeneration as it likely results in a decrement of the microstructural integrity and diffusivity of water molecules [89]. Multiple meta-analyses indicate that PD patients exhibit significantly lower FA values and higher MD values in the SN [88,90,91]. These effects are observed in *de novo* patients, with reports of 100% sensitivity and specificity of differentiating PD from healthy controls [89].

Free Water Imaging—More recently, a novel bi-tensor diffusion analysis model (referred to as free water) can separate the diffusion properties of water in brain tissue from those of water in extracellular space [92]. All forms of parkinsonism exhibit elevated free water in the SN, however, MSA and PSP (and not PD) demonstrate a broad network of free water changes, suggesting this measure may be helpful in differentiating these disorders [93]. This approach typically uses microregions of interest within the SN, often 2 × 2 voxels in size that are hand-drawn. Nonetheless, free water values have been correlated with motor symptom severity [94,95], increase longitudinally within 1, 2, and 4 years of being diagnosed with PD [96–98], predict the rate of motor progression [96], and are not affected by antiparkinsonian medication [99] highlighting that they may be a useful monitoring biomarker.

Structural Connectivity—While FA, MD, and free water metrics characterize diffusion within individual voxels, diffusion imaging can also be used to quantify the integrity of the white matter fiber tracts in the brain [100]. This approach can be used to differentiate the parallel organization of functionally segregated basal ganglia and frontal cortex circuitry that

had been described anatomically [101] (Fig. 1C), with distinct parallel loops that included the posterior (sensorimotor), anterior (associative), and ventral (limbic) compartments [102]. Examination of structural connectivity in PD finds disruption in the motor loop, but it is unclear how well this information can differentiate PD from HC and APD, or how well it can track disease progression at this time [103]. Additional research is necessary to identify either network based metrics or individual connections that may serve as useful biomarkers of structural connectivity.

3.4. Resting state functional MRI (fMRI)

Resting state fMRI detects blood-oxygen-level-dependent (BOLD) low-frequency spontaneous fluctuations across the brain while an individual is at rest, and can be used to study functional connectivity within and across spatially distributed brain networks. The most validated analytical approach examines the resting state fMRI Parkinson's Disease Related Pattern (fPDRP), which was initially characterized using PET [104–107]. Similar to PET, there are significant increases in fPDRP expression in PD relative to control subjects [108], however, further research is necessary to evaluate its utility as a diagnostic and monitoring biomarker. At this time, there are numerous additional analytical approaches taken to examine rs-fMRI in PD, that suggest widespread dysfunction in PD, but also numerous inconsistencies based on recent reviews [104,109]. This is partially related to the impact of various preprocessing approaches and observations showing rs-fMRI varies as a function of medication status [110]. Further, networks appear to dynamically adapt to disease progression and functional brain circuitry dysfunction may differ dependent on the nature of the motor symptoms [111]. Indeed, investigation of more targeted analytic approaches will be necessary to identify potential diagnostic and monitoring biomarkers, which is discussed further in the next section.

4. Limbic and neocortical regions

The aforementioned studies examine dysfunction of the nigrostriatal pathway. However, non-motor symptoms are driven by multifocal involvement of limbic and cortical regions depending on the nature of the symptoms [19]. Imaging characterization of regional changes associated with non-motor symptoms may serve useful as monitoring indicators and will help to better understand the mechanisms underlying divergent clinical presentations. An exhaustive review of this literature is beyond the scope of this article. Here, we briefly focus on imaging approaches to examine the cognitive dysfunction in PD as a means to illustrate how various imaging sequences and analytical approaches can be applied.

Cognitive dysfunction is a common and debilitating feature of PD, with approximately 20% of PD patients meeting criteria for mild cognitive impairment (MCI) at diagnosis, over 40% of patients developing MCI within 6 years [112], and 80% of those who survive two decades progressing to PD dementia [113,114]. These cognitive deficits change over the course of disease, with a variable progression impacting different regions of the brain. Unlike the clear role of the SN in motor symptoms, a "cognitive deficit" cannot be treated as uniform dysfunction of any single brain region, but rather there are domain-specific deficits that correspond to regional and network dysfunction. Examination of regional brain structure and

function related to specific cognitive domains is necessary to accurately characterize neuropsychiatric symptoms in PD.

Early in the disease course PD patients may not experience fully developed cognitive deficits but rather exhibit subtle executive dysfunctions, initially requiring highly sensitive tests to detect [115]. The executive dysfunctions observed in PD are characterized by deficits in internal control of attention, working memory, set shifting, planning, inhibitory control, dual task performance, and a range of decision--making and social cognition functions [116]. The emergence of these executive dysfunctions are thought to reflect the involvement of associative fronto-basal ganglia loops [117,118]. Deficits associated with this system are considered to be potentially dopamine dependent [119] and in some patients even mild levels of impairment might result in disability [120]. Task fMRI, which measures changes in the BOLD signal when an individual is engaged in a task, has yielded mixed results regarding the divergent functional activation patterns during executive functioning tasks [121]. However, there is an indication that PD patients can exhibit compensatory activation [122,123] prior to the development of the cognitive dysfunction, suggesting a possible avenue for future research and intervention.

Dopamine independent cognitive dysfunction, such as memory and visuospatial changes, are better predictors for future development of PD dementia [119,124]. These impairments are thought to reflect the progression of α-Syn from the brainstem to cortical regions, but may also be related to emerging age-related pathology [125]. Resting state fMRI has identified a cognition related rs-fMRI PD-related pattern [108] and reduced connectivity in networks relevant to cognition, most consistently within the default mode network [126]. Hippocampal atrophy may serve as a biomarker of initial cognitive decline in PD, including impaired memory encoding and storage [127,128]. Most recently, 7T hippocampal subfield imaging indicated a significant relationship between memory performance and CA1, suggesting that it may characterize memory [129]. Much work is needed in this area to understand the mechanisms of dopamine independent cognitive dysfunction and their relationship to underlying neuropathology.

These studies are presented as a means to highlight the complexity in studying PD-related non-motor symptoms, and cognition in particular. While aspects of cognitive dysfunction are related to the neurodegeneration of the fronto-striatal circuitry, the development of memory and visuospatial deficits, the harbingers of dementia, require further investigation. Careful consideration of the age of the individual, stage of disease, associated genetic risks, and nature of the cognitive symptoms are necessary to develop and utilize biomarkers for the cognitive symptoms in PD.

5. Considerations

The use of MRI biomarkers exhibit several potential advantages, for clinical trials as well as clinical practice, as the MRI is a noninvasive imaging technique that does not require the injection of contrast agent or radiation exposure, and thus can be repeated many times during a longitudinal study. Furthermore, MRI scanners are already part of routine medical care and easily accessible. However, there are limitations of these methods that need to be

carefully considered when translating to use for clinical trials. Specifically, there are several issues related to scalability. Many of the iron/neuromelanin sensitive and diffusion measures discussed here currently require manual outlining of the SN (and corresponding sub-regions) and/or an expert read by a radiologist (in the case of nigrosome imaging), both of which are labor intensive processes. Further, manual segmentation creates enormous variability due to between-rater differences and drift effects overtime, a major limitation for clinical trials. Fortunately, automated segmentation and quantification approaches are being developed and future research should focus on validating these measures prior to clinical trial implementation [38,55,130,131].

fMRI has relatively high spatial and reasonable temporal resolution, and can be acquired in the same session as structural MRI. However, unlike structural MRI, fMRI is highly sensitive to dopaminergic medications and is best performed when patients are in a practically defined ‘off’ state [110]. Further, there is a large amount of post-processing necessary to interpret resting state fMRI and this technique is very sensitive to the effects of motion and preprocessing strategies. While single site studies show very few individuals exceeding head motion parameters, with no differences between PD and older neurologically normal adults [110], head motion control has been difficult to scale to multisite studies. Hopefully this can be overcome as emerging standardization will facilitate automated processing [132].

6. Summary and conclusions

MRI biomarkers exhibit an enormous potential to characterize disease processes in PD. Particularly promising measures that capture PD related changes in the SN include iron, neuromelanin, and diffusion sensitive measures. However, there remains a need to validate these markers against pathological data and determine their reliability, how sensitive they may be in detecting pre-clinical changes, their ability to differentiate PD and APDs, as well as capture longitudinal progression. Unlike the clear role of the SN in motor symptoms, a “cognitive deficit” cannot be treated as uniform dysfunction of any single brain region, but rather there are domain-specific deficits that correspond to regional and network dysfunction. Much work is necessary to identify biomarkers in this domain.

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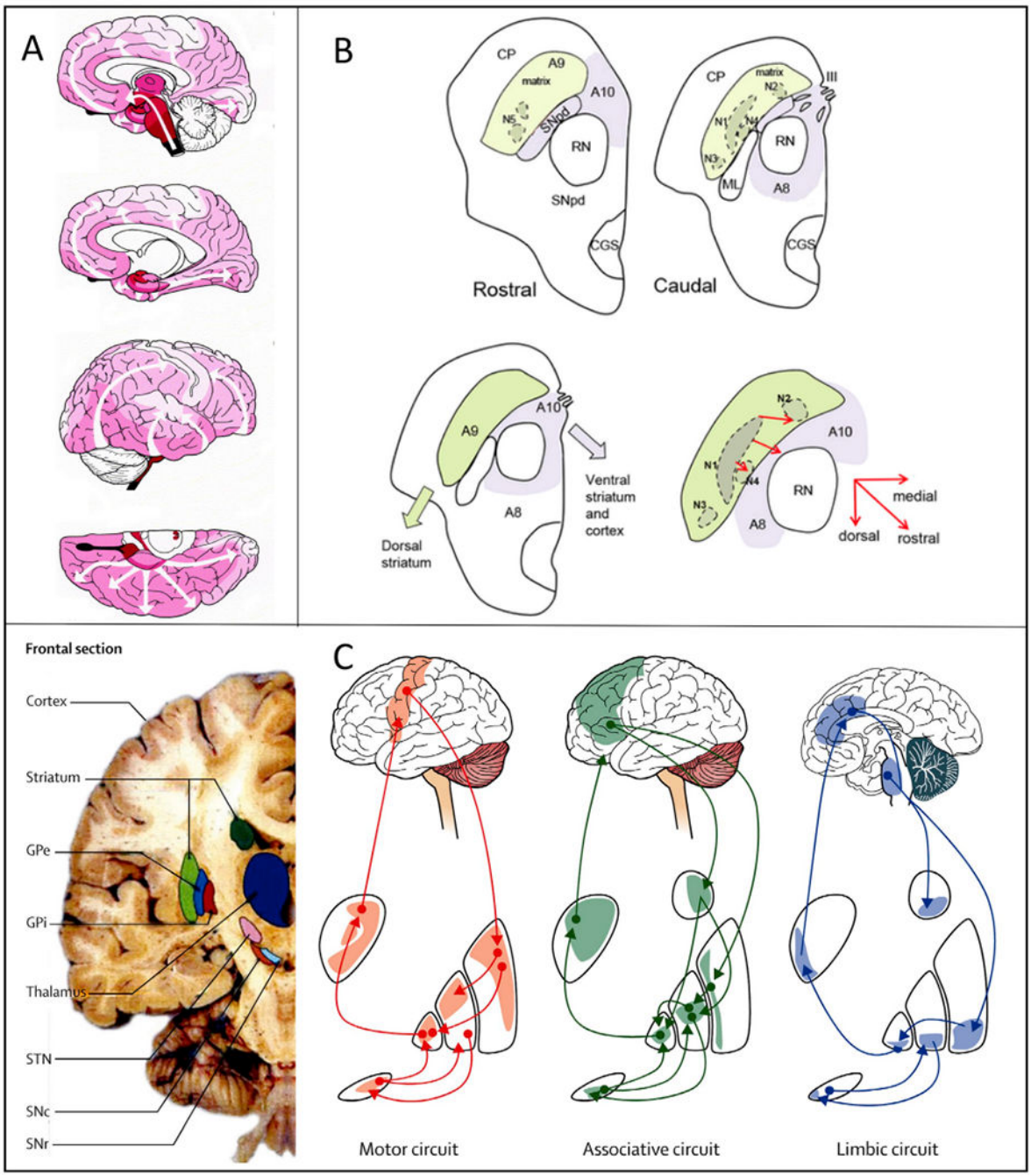

Fig. 1. Neuroanatomy Relevant to Parkinson's Disease

A. Braak staging of α-synuclein pathology. At death, PD patients exhibit the following stages of α-Syn pathology: stage I olfactory bulb only (8.6%), Stage IIa brainstem predominant (15.4%), stage IIb – limbic predominant (13.6%), stage III brainstem and limbic (31.8%) and stage IV neocortical (30.7%) [133]. While not all patients with pathology will exhibit clinical symptoms [16,134], the progression of neuropathology generally corresponds to the progression of both motor and non-motor symptoms [18]. B. The SN is subdivided into the ventral pars reticulata (SNr) and the dorsal pars compacta

(SNc), the latter is composed of dopaminergic neurons. The SNc is further divided into the dorsal and ventral tier, with the loss of dopaminergic neurons occurring first in the caudal and ventrolateral tier (A9; [15,19]). Within A9, there are five nigrosomes (clusters of dopaminergic neurons; N1 – N5), with N1 exhibiting the earliest loss of dopaminergic neurons [14]. Dopaminergic neuronal loss typically spreads to neighboring groups from the N1 in PD (A10; A8; [20]). C. Fronto-subcortical loops comprise the motor, associative, and limbic domains, which respectively transit through the posterior, anterior, and ventral striatum, thus segregated functionally and anatomically. GPe = globus pallidus externa. GPi = globus pallidus interna. STN = subthalamic nucleus. SNc = substantia nigra pars compacta. SNr = substantia nigra pars reticulata. *Adapted with permission from:* [16,74,117].

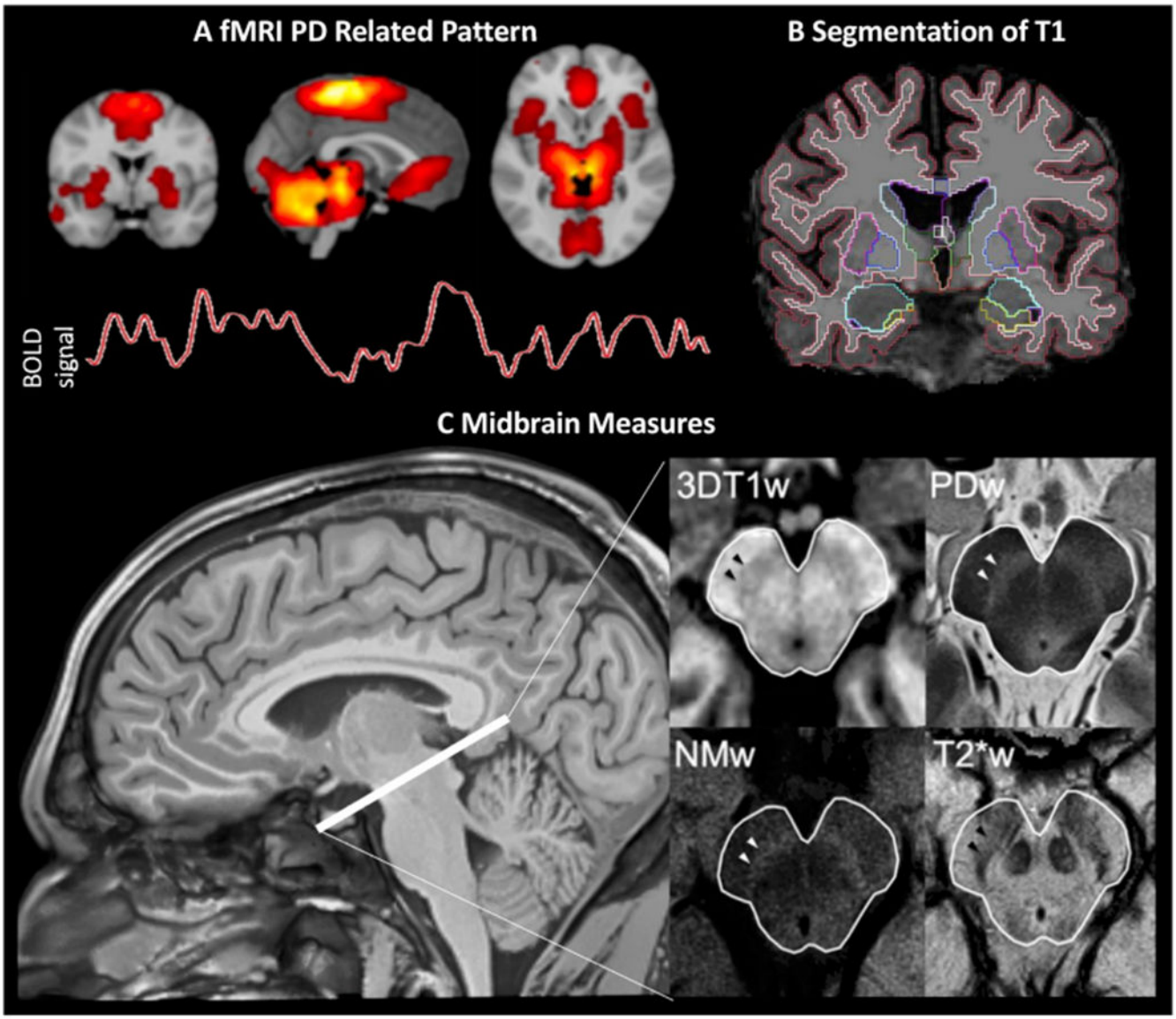

Fig. 2. Common MRI methods used to study Parkinson's disease.

A. Parkinson's Disease Related Pattern (PDRP) identified with rs-fMRI. PDRP identified in rs-fMRI (fPDRP, left) is shown on the MNI 152 template. fPDRP is characterized by increased activity in the basal ganglia, thalamus, cerebellum/pons, anterior cingulate cortex (ACC), and supplementary motor area (SMA). B. Example cortical and subcortical segmentation of a T1-weighted image. C. Normal MR anatomy of the SN at 3T. Left: Parasagittal T1w image showing the level of the axial slice. Right: Axial slice passing at the level of the midbrain and the SN (arrowheads). The SN appears hypointense in three-dimensional T1-weighted MP2RAGE (3DT1w) and in two-dimensional T2*weighted images (T2*w) and hyperintense in neuromelanin T1-weighted spin-echo images (NMw) and proton density-weighted (PDw) images. The contours of the midbrain are outlined in white. *Adapted with permission from:* [74].

Table 1

Biomarker Definitions

In the United States, FDA-NIH Joint Leadership Council published a resource which includes biomarker definitions to facilitate harmonization of terms used in translational science and medical product development [Biomarkers, Endpoints, and other Tools (BEST) Resource; [126]].

Biomarker: A defined eharaeteristie that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives. Categories of biomarkers include:

- *Susceptibility/Risk Biomarker:* A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.
- *Diagnostic Biomarker:* A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.
- *Monitoring Biomarker:* A biomarker measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.
- *Prognostic Biomarker:* A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.

Reasonably Likely Surrogate Endpoint: An endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials, but without sufficient clinical data to show that it is a validated surrogate endpoint.

Validated Surrogate Endpoint: An endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit.

Table 2

Description and summary of each imaging modalitys

Structural Morphometry	
Description	• Techniques used to quantify features of brain regions such as volume and shape. •Typically utilize T1 or T2 images optimized to differentiate structural boundaries.
PD versus HC	• PD patients demonstrate subtle changes in basal ganglia structures, with variable difference from HC. • Useful to investigate regional changes associated with non-motor symptoms.
PD versus APD	• Greater differences have been observed between PD and APDs, such as MSA and PSP.
Iron Sensitive Imaging	
Description	• Techniques sensitive to iron (e.g. T2*, SWI) in the SN and can detect changes at the level of the nigrosome. • Advanced techniques such as QSM will be helpful to quantify these changes.
PD versus HC	• Evidence to suggest moderate-to-high specificity and sensitivity to differentiate PD from HC. • Nigrosome imaging can detect early changes. • Quantification of iron changes in the broader SN may capture longitudinal change.
PD versus APD	• Changes in these measures are observed in APDs and PD, warrants further investigation.
Neuromelanin Sensitive Imaging	
Description	• Techniques sensitive to neuromelanin (e.g. T1 FSE; MT) detect changes in different aspects of the SN than iron sensitive imaging.
PD versus HC	• Similar to iron-sensitive measures, evidence to suggest moderate-to-high specificity and sensitivity to differentiate PD and HC. • Quantification may capture early and longitudinal change.
PD versus APD	• Changes in these measures also observed in APDs and PD, warrants further investigation.
Diffusion MRI	
Description	• Techniques sensitive to diffusion of hydrogen protons, useful as these measures are not restricted to areas rich in iron or neuromelanin. • Previous measures utilize DTI, quantifying FA and MD. • More recent measures examine Free Water metrics. • Connectivity between regions of the brain can be also be derived.
PD versus HC	• DTI and Free water exhibit moderate-to-high specificity and sensitivity to differentiate PD and HC. • Longitudinal data suggests utility as a monitoring biomarker to track longitudinal change.
PD versus APD	• Signal in SN may not differentiate PD from APDs, but broader changes beyond the SN in MSA and PSP observed. • Combined measurement may help differentiate PD and APD.
Resting State and Task MRI	
Description	• Detects low-frequency fluctuations of BOLD signal either at rest or when an individual is engaged in a task. • Numerous analytical approaches available, including comparison of activation patterns during tasks and functional connectivity within and across spatially distributed brain networks.
PD versus HC	• Inconsistent results, partially attributed to numerous analytical approaches. • The signal is sensitive to PD medications and networks dynamically adapt as disease progresses. • Useful to understand mechanisms of non-motor symptoms.

PD versus APD	• Requires systematic investigation.

Abbreviations: PD, Parkinson's disease; HC, Healthy Controls; APD, Atypical Parkinsonian Disorder; MSA, Multiple System Atrophy; PSP, Progressive Supranuclear Palsy; SWI, susceptibility weighted imaging; SN, substantia nigra; QSM, Quantitative Susceptibility Mapping (QSM); T1 FSE, T1-weighted fast spin echo; MT, magnetization transfer; SN, substantia nigra; DTI; diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; BOLD, blood-oxygen-level-dependent.