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Review

Imaging Biomarkers in Prodromal and Earliest Phases of Parkinson's Disease

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Abstract. Assessing imaging biomarker in the prodromal and early phases of Parkinson's disease (PD) is of great importance to ensure an early and safe diagnosis. In the last decades, imaging modalities advanced and are now able to assess many different aspects of neurodegeneration in PD. MRI sequences can measure iron content or neuromelanin. Apart from SPECT imaging with Ioflupane, more specific PET tracers to assess degeneration of the dopaminergic system are available. Furthermore, metabolic PET patterns can be used to anticipate a phenoconversion from prodromal PD to manifest PD. In this regard, it is worth mentioning that PET imaging of inflammation will gain significance. Molecular imaging of neurotransmitters like serotonin, noradrenaline and acetylcholine shed more light on non-motor symptoms. Outside of the brain, molecular imaging of the heart and gut is used to measure PD-related degeneration of the autonomous nervous system. Moreover, optical coherence tomography can noninvasively detect degeneration of retinal fibers as a potential biomarker in PD. In this review, we describe these state-of-the-art imaging modalities in early and prodromal PD and point out in how far these techniques can and will be used in the future to pave the way towards a biomarker-based staging of PD.

Keywords: MRI, PET, neuroimaging, Parkinson's disease, progression, diagnosis, prodromal, biomarker

INTRODUCTION

In Parkinson's disease (PD), a biomarker-based diagnosis like in Alzheimer's disease is currently not established. However, an early and specific diagnosis predicated on a biomarker-based staging in prodromal and early stages of the disease would be of great importance. This would offer the possibility to include patients early in clinical trials and objectively monitor disease progression [1]. Proposals for biomarker-based staging of PD have been previously introduced and follow a similar concept, but differ in terms of consideration of genetic PD and neurode-

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generation apart from the nigrostriatal dopaminergic system [2, 3]. In the following, we review the state of the art regarding imaging biomarkers in the prodromal and early stages of PD. Table 1 summarizes these imaging modalities with a special focus on their use in clinical practice. Furthermore, we discuss future perspectives of these biomarkers and the extent to which they can facilitate the way toward a biomarker-based diagnosis and disease staging.

STATE OF THE ART

Magnetic resonance imaging (MRI)

Gray matter (GM) atrophy is a cardinal sign of neurodegeneration which may be depicted by structural MRI using T1-weighted sequences. A typical GM atrophy diagnostic pattern has not yet been conclusively established in PD [4, 5]. More pronounced changes can be observed in PD with manifested cognitive decline [6], with the most consistent early PD-specific pattern of brain atrophy has been identified using deformation based morphometry and partial least squares [7]. The authors described a "PD-specific atrophy network" involving particularly subcortical, but also cortical regions. Individual variation in this atrophy pattern was not only correlated with PD symptoms, but also with CSF biomarkers and predicted scores in the motor and nonmotor domains. Moreover, this network predicted disease trajectories according to another longitudinal study [8]. Notably, using the same methods, a distinct atrophy pattern has been reported in isolated REM sleep behavioral disorder (iRBD) [9]. The same group also showed that cortical regions with greater structural and functional connectivity to the "PD-related atrophy network" demonstrated greater cortical atrophy over the 1-year period [10] hinting at protein spread along the brain's neuronal connectome.

Changes in white matter fiber integrity can be assessed using single-tensor diffusion imaging (DTI). The two most common DTI parameters used are mean diffusivity (MD) and fractional anisotropy (FA). While decreased FA and increased MD are usually found in PD and interpreted as decreased fiber integrity [11], other possible underlying mechanisms include e.g. axonal degeneration, demyelination, and larger axonal diameter. DTI changes in substantia nigra (SN) have been rather controversial [12]. The assumption of the Gaussian distribution of water diffusion is the greatest limitation of DTI. Diffusion kurtosis imaging (DKI) as an extension of DTI can overcomes this limitation. In a TNWT-61 genetic mouse model of PD, increased kurtosis in the thalamus was positively corelated with the total alpha-synuclein signal in the region [13]. Using this method in humans, the same group demonstrated increased diffusion kurtosis in the SN and the motor and premotor cortices in early PD [14]. Conversely, kurtosis decreases in cortical GM, decreased fiber integrity as assessed by FA and MD, and gross atrophy as assessed by DBM were dominant features of cognitively impaired PD patients as compared to early cognitively normal PD. Taken together, early increases of kurtosis in early PD likely reflect increased hindrance to water diffusion potentially caused by α-synuclein deposition. In more advanced PD with cognitive impairment the changes are in the opposite direction likely reflecting neurodegeneration.

A two-compartment diffusion model, free-water imaging, was implemented in iRBD [15] and in early PD [16], finding that the free water component may be increased in the posterior SN as compared to HC. This indicator of early neurodegeneration has been interpreted as likely reflecting neuro-inflammation-related oedema, blood–brain barrier disruption or atrophy (Fig. 1, FW).

Another MRI technique depicts iron in the brain and particularly in the substantia nigra pars compacta (SNc). It uses iron sensitive sequences such as T2* relaxometry or susceptibility weighted imaging (SWI) detecting an oval hyperintensity within the dorsolateral SN which constitutes the nigrosome-1. This dorsal nigral hyperintensity (DNH), also called the 'swallow tail sign', is detectable in individual healthy controls (HC), but is reduced or lost in PD due to increased iron deposition in this region [17] (see Fig. 1, DNH). Absence of DNH has been shown already in about two thirds of iRBD patients [18]. Unfortunately, the method currently only provides a qualitative ('yes' or 'no') answer and not a quantification of pathology, as with presynaptic dopaminergic imaging (see below).

Quantitative susceptibility mapping (QSM) enables quantification of iron in the brain, congruent with histologic validation of iron content [19]. It is a more sensitive measure than R2* relaxometry in terms of detecting nigral iron increase due to PD, as QSM accounts better for local tissue susceptibility than R2* [20]. Changes in SN have already been described in iRBD and may be present years before the onset of PD [21]. QSM may also be assessed in the parcellated striatum—one study reports that

Table 1
Imaging Biomarkers assessing neurodegeneration in early PD and their use in clinical routine

Modality	Assessment of PD-related neurodegeneration	Availability and clinical use
Structural MRI	• Excluding secondary parkinsonism.	• Broadly available and established in clinical routine. • Included in MDS PD criteria.
	• Detection of cerebral atrophy patterns.	• Broadly available and established in clinical routine.
Iron-sensitive MRI T2*, SWI, QSM	• Quantifiable iron depositions in PD.	• T2* and SWI are broadly available, QSM not.
	• Swallow Tail Sign (dichotomous).	• Not established in clinical routine.
Neuromelanin-sensitive MRI	• Quantifiable degeneration of substantia nigra and locus coeruleus.	• Not broadly available, not established in clinical routine.
Diffusion MRI	• Changes in WM integrity/ GM microstructure	• Not broadly available, not established in clinical routine for diagnostic purposes.
Functional MRI	• Task-based activations, functional connectivity	
DaT-SPECT	• Quantifiable degeneration of dopaminergic terminals.	• Established in clinical routine.
DOPA-PET PE2I-PET		• Included in MDS PD criteria. ◊ DaT SPECT: Broadly available. ◊ DOPA: Available. ◊ PE2I: Limited availability.
FDG-PET	• PD-related metabolic patterns.	• Broadly available, but not established in clinical routine.
TSPO-PET	• Imaging of microglia activation (inflammation).	• Not broadly available, not established in clinical routine.
Acetylcholine-, Serotonin-, Noradrenalin-PET	• Quantifiable degeneration of the cholinergic, serotonergic and noradrenergic system.	• Not broadly available, not established in clinical routine.
MIBG-Scintigraphy/-SPECT	• Quantifiable sympathetic denervation of the heart.	• Available and established in clinical routine. • Used mostly for differential diagnosis (PD vs. MSA). • Supportive criterium in MDS PD criteria.
OCT	• Quantifiable degeneration of retinal fibers.	• Available. Not established in clinical routine.

changes in the caudal motor striatum can be identified at the single-subject level with good accuracy [22] (see Fig. 1, QSM).

Another promising MRI method is neuromelanin sensitive (NMS) MRI. It is well known that dopaminergic neurons in SNc and noradrenergic neurons in locus coeruleus (LC) contain the pigment neuromelanin. The source of NM contrast is the NM binding to iron, which is paramagnetic. Therefore, reduced NMS signal can be observed in the posterolateral motor areas of SN in early PD and iRBD compared to HC with good classification accuracy [23], and even 5–6 years before the onset of symptoms of PD (see Fig. 1, NMS) [21]. LC-MRI signal loss could also be found at early PD and in iRBD [24].

We find it important to at least briefly mention functional MRI. A recent study [25] showed global (whole-brain) network changes in a large sample of early mild drug naïve PD patients as compared to HC. At the connectome level, the authors described impaired basal ganglia connections particularly to the sensorimotor, default mode, and visual networks in PD, which fits well with the connectome spreading model of brain pathology. Based on more recent literature, it seems that the default mode network 'enhancement or inhibition' in PD is driven by specific phenotypes such as hallucinations and cognitive impairment, respectively [26, 27].

Imaging of the presynaptic dopaminergic system

It is assumed that the motor symptoms of PD occur when about 50% of nigrostriatal dopaminergic neurons are degenerated. However, newer results indicate that the loss of dopaminergic terminals seems to be more around 30% after adjusting for age [28]. Imaging of the dopaminergic system therefore offers the possibility to assess neurodegeneration even in preclinical and prodromal phases of PD and represents a powerful biomarker in these earliest disease stages.

Several different tracers for positron emission tomography (PET) and single photon emission

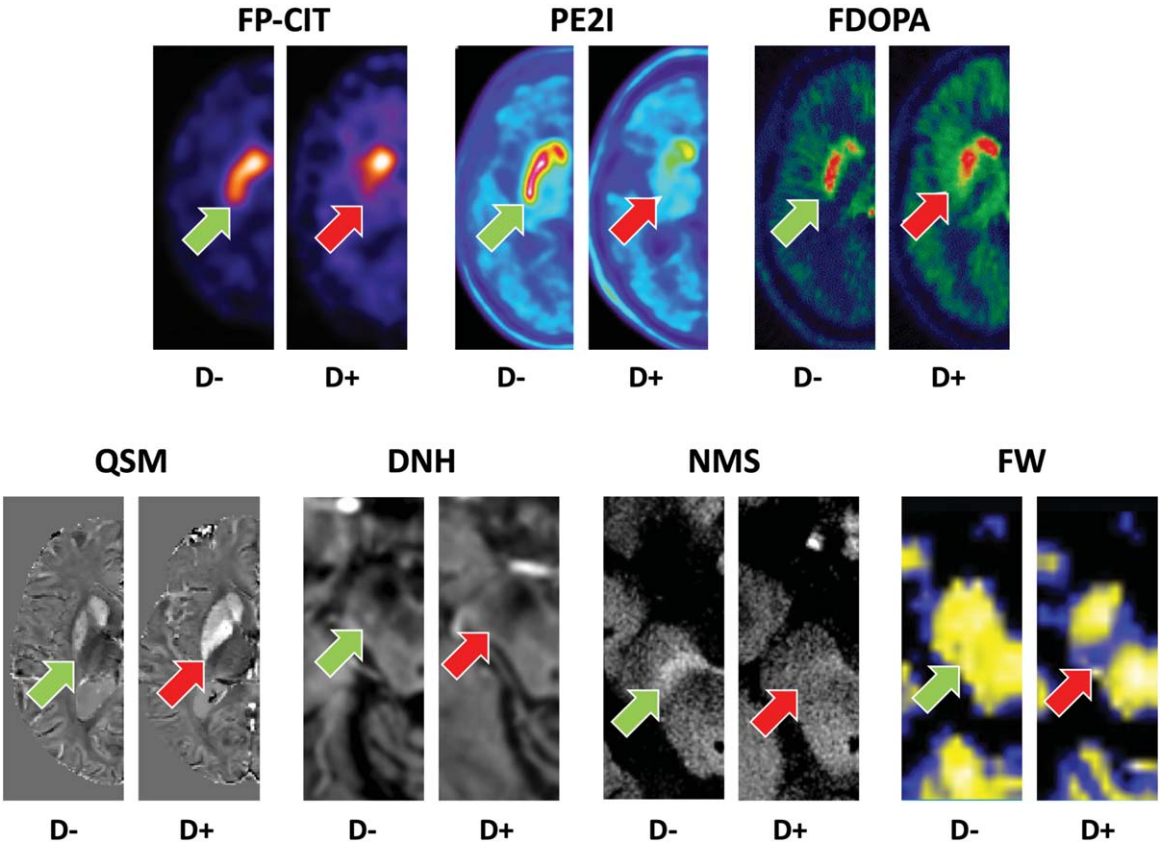

Fig. 1. Imaging Biomarkers of Dopaminergic Degeneration in PD. Various PET or MRI modalities can capture dopaminergic degeneration (see Table 1 for availability and use in clinical routine). Examples of normal (D–) and pathological (*D+*) findings. Red arrows indicate abnormality. Normal findings pointed out with green arrow. All images are in axial orientation. FP-CIT: dopamine transporter SPECT using [123I]FP-CIT; PE2I: dopamine transporter PET using [18F]FE-PE2I; FDOPA: presynaptic dopamine turnover PET using [18F]DOPA; QSM: Quantitative susceptibility mapping MRI of iron load the striatum. DNH: Dorsal nigral hyperintensity in SWI or T2* MRI, a.k.a. 'swallow tail sign'. NMS: Neuromelanin-sensitive MRI of the substantia nigra; Courtesy Stephane Lehericy, Rahul Gaurav (Paris Brain Institute, France). FW: Free water diffusion MRI of the posterior substantia nigra; Courtesy David Vaillancourt (University of Florida, USA).

computed tomography (SPECT) of the presynaptic dopaminergic system are available. The most commonly used in clinical routine is SPECT imaging of the dopamine transporter (DaT) with [123I]FP-CIT (see Fig. 1, FP-CIT). However, the novel highly selective DaT PET-tracer [18F]FE-PE2I represents a promising alternative (see Fig. 1, PE2I). Apart from DaT imaging, quantification of presynaptic dopamine turnover with [18F]DOPA offers another possibility to measure nigrostriatal dopaminergic degeneration [29] (see Fig. 1, FDOPA).

DaT imaging can be visually interpreted and additionally confirmed by a semiquantitative analysis. A z-score below –2 for striatal binding ratios has been defined as an abnormal threshold during semiquantitative analysis [30, 31]. However, especially in prodromal PD, less conservative thresholds might be necessary to detect the earliest phases of nigrostriatal degeneration. A recent study could show that for differentiating PD a z-score cut-off below –1.27 of the posterior putamen of the more affected hemisphere shows the highest accuracy [32]. However, the type of tracer and imaging modality also seem to play an important role in early and prodromal PD. With the higher resolution of PET and the higher selectivity of [18F]FE-PE2I for DaT a higher diagnostic accuracy can be achieved as compared to [123I]FP-CIT [33]. It could be shown with [18F]DOPA-PET and functional MRI that dopaminergic degeneration in early PD follows a somatotopic pattern, that is, an upper limb-related degeneration in the putamen and a progression over 2 years to the less affected hemisphere [34]. In this regard it is worth mentioning the interesting link between DaT and DOPA imaging. Asymptomatic patients with familial PD showed a downregulation of DaT while [18F]DOPA-

PET revealed an upregulated dopamine turnover [35, 36].

A very important topic is the association of DaT imaging in prodromal PD with phenoconversion to clinical PD. A longitudinal study showed that patients with iRBD with a DaT-specific putamen binding ratio below 48% had significantly higher short-term risk of developing PD [37]. Another study could demonstrate that a putaminal uptake decrease of at least 25% predicted Parkinsonism after 3 years [38]. Interestingly, it could be shown that those iRBD patients with DaT reduction did not differ in demographic or clinical features at baseline [39]. However, DaT SPECT signal was correlated with REM sleep without atonia measures [40]. To conclude, iRBD patients with reduced DaT binding have a high risk for (earlier) phenoconversion to clinical PD independent of other demographic or clinical features. It could be shown that PD patients with iRBD show, compared to PD without iRBD, a more symmetric reduction of dopaminergic terminals [41]. However, this finding was not supported in data of the PPMI cohort [5]. Interestingly, another study indicated that right-handed patients with iRBD have a left-hemispheric predominance of subclinical nigrostriatal dysfunction, which was also shown in clinically established PD [42]. Due to these inconsistent findings, the pattern of DaT reduction in iRBD, i.e., more symmetric or lateral reduction, warrants further investigations. In addition to iRBD, idiopathic hyposmia (iH) is also a prodromal marker of PD. Patients with iH who had abnormal DaT-SPECT at baseline and those who developed abnormal DaT-SPECT at follow-up had the highest rate of phenoconversion to PD [43, 44]. Olfactory disfunction itself showed a moderate correlation with dopamine turnover in the putamen [45].

It should be emphasized that the negative predictive value of DaT imaging is greater than the positive predictive value, which means that a normal DaT-SPECT practically excludes conversion to clinical PD in the near future [46, 47]. Hence, DaT-SPECT might gain great importance as a surrogate endpoint in clinical trials in prodromal PD [1]. In this regard, it is worth mentioning that imaging of vesicular monoamine transporter 2 with [18F]AV-133 might be an interesting biomarker to monitor the disease progression during therapeutic trials [48]. We want to point out that dopaminergic imaging can be influenced by some drugs, which includes the risk of false-positive results [49, 50]. Importantly, dopamine replacement therapy has no impact on DaT binding [50].

Imaging of inflammation–translocator protein

There is robust evidence that neuroinflammation plays a significant role in the development and progression of PD and other neurodegenerative disorders. The inflammatory response of the brain is crucially driven by activation of microglia [51]. Neuroinflammation can be demonstrated *in vivo* with PET ligands targeting the 18 kDa translocator protein (TSPO). TSPO is mainly expressed in the mitochondrial outer membrane of microglia and its expression is greatly increased when microglia are activated. Several teams have reported widespread increases in microglial activation in PD [52]. Even the earliest patients have shown widespread microglia activation targeting the brainstem, basal ganglia, and frontal cortex [53]. The presence of microglial activation in brain regions susceptible to Lewy body pathology has also been detected in patients with iRBD [54, 55], and in asymptomatic carriers of genetic mutations linked to PD (*GBA1* and *LRRK2* mutations) [56, 57]. In patients with iRBD, increased load of microglial activation in the substantia innominata, the major source of cholinergic input to the cortex, correlated with cortical cholinergic dysfunction measured with [11C]Donepezil [58]. In *GBA1* mutations carriers, interestingly, microglial activation in the SN correlated with hyposmia and seemed to precede the loss of striatal dopaminergic terminals measured with [18F]DOPA-PET.

Metabolic imaging

Metabolic imaging in preclinical and prodromal PD is commonly done with [18F]FDG-PET and can be used to evaluate disease related pathological patterns.

A recent study compared the iRBD-related pattern with the established PD-related pattern. The two patterns overlapped and the iRBD-related pattern was significantly expressed in PD patients compared to controls [59]. In a further step, the Scaled Subprofile Model and Principal Component Analysis (SSM-PCA) was used to predict phenoconversion of iRBD to PD by deriving a conversion pattern to PD. This pattern showed a sensitivity of 87% and a specificity of 72% discriminating converters from nonconverters and this conversion pattern was validated in an independent cohort [60, 61]. A multimodal study that combined PD-related pattern expression, DaT imaging, and olfactory tests could show that pattern expression was higher in iRBD with iH and in

patients with reduced DaT binding [62]. The expression of the suprathreshold PD-related FDG pattern and an increase in this pattern over time may indicate a greater short-term risk of phenoconversion to PD [63]. Interestingly, short-term conversion was explicitly driven by occipital hypometabolism at baseline in iRBD [64]. Additionally, hypometabolism in occipital and parietal areas was associated with mild cognitive impairment (MCI) in iRBD, which is also a predictor for phenoconversion to PD [65]. Additionally, the perfusion phase of other PET or SPECT tracers can be used to acquire equivalent information to FDG-PET [29, 66].

Imaging of acetylcholine

Posterior cortical cholinergic degeneration is prominent already in non-demented, de-novo Parkinson's disease [67, 68], with evidence of a posterior to anterior progression over time [69]. GBA-mutation carries with PD, who are at greater risk for early cognitive decline, express a more widespread reduction of cortical cholinergic denervation despite normal cognition [70]. Increasing cortical cholinergic dysfunction specifically characterised a group of iRBD patients with cognitive decline in another study with a small sample [71]. Grey matter density of the basal nucleus of Meynert, the main origin of cortical cholinergic innervation, was significantly reduced in 35 iRBD patients and reduction was associated with poorer performance in a working memory task [72].

Imaging of serotonin

The degeneration of serotonergic innervation in striatal and extrastriatal brain regions is considered an early feature of PD [73]. However, people living with PD but without depression, apathy, or anxiety may have a relatively preserved serotonergic system [74]. Loss of serotonergic innervation of the limbic cortico-striatal system in PD has been linked to the presence and severity of apathy and anxiety associated with lower [75]. Apathy in PD was associated with lower serotonin transporter binding in the basal ganglia [76]. Serotonin transporter signal integrity in the dorsal raphe nucleus was shown to correlate with apathy severity in prodromal PD [77]. Overall, it seems that serotonergic deficits, which can be monitored with brain imaging, may precede motor deficits and identify those patients with a risk of apathy, anxiety, and depression.

Imaging of noradrenaline NA

Currently, the integrity of the noradrenergic system is studied either analyzing neuromelanin-dependent MRI signal of the small locus coeruleus— the principal origin of noradrenergic neurons of the brain, or using PET radioligands targeting receptors or transporters of noradrenalin. Interestingly, studies have rather consistently shown a dissociation of locus coeruleus integrity as measured with MRI and integrity of noradrenergic cortical terminals using PET [78, 79]. A widespread cortical (motor cortex and insula) and subcortical (thalamus and putamen) reduction of NA receptors has very recently been described [79]. NA transporters do not appear to be dramatically reduced in prodromal PD, with some evidence for moderately reduced availability of NA transporters in the sensorimotor cortex and the thalamus [80]. In general, there is not much evidence for a distinctive role for NA imaging biomarkers in prodromal or early PD.

Imaging of heart and gut

It is now well accepted that there is severe neuronal pathology in PD also outside the brain, mostly affecting the autonomous nervous system of the heart (noradrenergic) and gut (cholinergic) [81]. It has been speculated that pathology may in fact enter the brain via the vagus and the olfactory nerve [82]. (Dys-)function of the enteric nervous system can be objectified by imaging either directly with transmitter imaging (e.g., using [11C]-donepezil) or indirectly and less specific using enteric passage times for radiologic markers. Colonic, but not gastric transfer times seem to be a sensitive marker of enteric autonomous dysfunction in the prodromal and early PD phase [83, 84].

To measure the sympathetic denervation of the heart, SPECT or scintigraphy with iodine radiolabelled MIBG are established methods. Despite relevant shortcomings of the method, it has been used to subcategorize PD into two to three subcategories [85, 86]. The dichotomy of a "brain-first" (no sign of sympathetic denervation at diagnosis) and "body-first" (sympathetic denervation at diagnosis) subtype has received a lot of attention, but is not uniformly supported [5, 87]. Although cardiac imaging is not the only factor that differs between these hypothetical subtypes, it is considered the most critical distinction around the time of PD diagnosis [85]. Interestingly, more severe sympathetic dener-

vation may also differentiate GBA-PD from sporadic PD [88]. Using a clustering approach including cardiac MIBG imaging, another group recently defined a cardio-cortical and a dopamine dominant type [85]. The finding that plasma α-synuclein levels correlated with cardiac sympathetic denervation, but not with nigrostriatal degeneration may also be seen as adding to the circumstantial evidence for a relative dissociation between "peripheral" and "central" PD [89]. Critically, when using this imaging method, it should be considered that drug interactions can significantly influence MIBG uptake, see also [90, 91].

Optical coherence tomography (OCT)

Ophthalmological complaints are common in PD and often precede the onset of motor symptoms. Retinal impairment has also been described in PD from the very early stages of the disease [92]. OCT provides accurate measurements of mean macular thickness (MMT) and thinning of the peripapillary retinal nerve fiber layer (RNFL). In general, these studies have shown that patients with PD have a significant reduction in RNFL and MMT compared to HC, although other studies have failed to find any difference [93, 94].

A recent study in iRBD patients has shown that RNFL and most macular retinal layers were significantly thinner compared to HC. Interestingly, the values observed in iRBD were between those observed in PD and HC [95]. Conversely, another study found no OCT abnormalities in PD patients with LRRK2 mutation and LRRK2 non-manifesting carriers, suggesting that LRRK2-PD could be distinguished from idiopathic PD by absent or less retinal nerve involvement even at the prodromal stage [96].

FUTURE PERSPECTIVES

For MRI biomarkers, as for all other modalities, it will be interesting to bring them into the perspective of the suggested biomarker-based definition of PD [2, 3]. While the traditional domain for MRI could be seen as the evaluation of neurodegeneration *per se*, specific evaluation of biomarkers signaling degeneration of the dopaminergic system is now more relevant than ever. Moreover, imaging will be needed to visualize early spatial brain alterations related to neurodegeneration and brain compensation. To achieve this, harmonization of data acquisition and analytical approaches is warranted for the use of QSM, NMS, fMRI, and various diffusion methods in clinical practice. Moreover, MRI has also potential to study pathophysiological mechanisms of toxic protein spreading [97]. MRI techniques not only have potential as preclinical PD biomarkers, but more work is needed to prove their utility in predicting early disease phenoconversion, monitoring specific PD symptoms with time, and predicting disease clinical subtypes and disease trajectories. Although some works suggest utility of the above-mentioned MRI methods in, e.g., early differential diagnosis of PD versus atypical parkinsonian syndromes [98], machine learning and AI approaches will have to be further corroborated.

Dopaminergic imaging can already be used as an endpoint reflecting neurodegeneration of the nigrostriatal dopaminergic system in the preclinical and prodromal phases of PD. A previous proposal elaborated the role of aggregated α-synuclein in CSF as well as imaging of dopaminergic degeneration as promising biomarkers for a staging system in PD [2]. Along these lines, dopaminergic imaging represents a valuable tool for biomarker-based staging, where patients with aggregated α-synuclein (S) in absence of substantial dopaminergic (D) system degeneration ($S+$ D–) can be identified. This group might represent a promising candidate for therapeutic trials against α-synuclein and subsequent neurodegeneration. In addition, in some patients with iRBD, dopamine transporter density stays normal for a longer time than in others. This indicates underlying factors that prevent or promote nigrostriatal degeneration, which would be imperative to investigate as therapeutic targets.

Future imaging studies investigating neuroinflammation should aim to clarify the actual nature of microglia activation in prodromal PD, as there is evidence that there might be two peaks of microglial activation: an early peak with a protective function and a later pro-inflammatory peak [99]. Therefore, it is crucial to understand when and which subtype of microglia is relevant in prodromal stages. Imaging neuroinflammation has provided a rationale for the trial of anti-inflammatory agents to prevent the progression of iRBD to parkinsonian syndromes. In this line, a Phase 2a study in participants with iRBD (ClinicalTrials.gov Identifier: NCT05904717) will start soon to evaluate whether 12-week treatment with PXS-4728, a very potent and highly selective inhibitor of the enzyme Semicarbazide-Sensitive Amine Oxidase (SSAO), can reduce levels of microglia activation, as measured by PET.

FDG-PET currently has already demonstrated in a research context that a concrete metabolic pattern may indicate iRBD patients at immediate risk for phenoconversion. Further investigation is needed for the relevance of occipital hypometabolism in iRBD patients. It is necessary to disentangle whether this is more relevant as a biomarker for phenoconversion to PD or for cognitive decline.

Cortical cholinergic denervation has been implicated with the development of dementia in PD. However, while there is some evidence for it being a necessary precursor to dementia in PD, the evidence is far from conclusive. It seems clear that early-stage PD already comes with significant loss if cholinergic input to the posterior cortex, but we need to have a better idea about when this process starts in the prodromal phase and how strongly cholinergic denervation in certain parts of the brain is associated with consecutive cognitive decline. If this can be firmly established, imaging biomarkers of cholinergic denervation may ultimately serve as a surrogate endpoint for the development of dementia in PD.

It seems clear that serotonergic denervation is involved in non-motor symptoms such as apathy and anxiety. As the disease develops, serotonergic innervation may also significantly contribute to motor phenomena, including dyskinesias. However, it is currently unclear, what role imaging biomarkers of the serotonin system may play in the prodromal or early PD phase.

Cortical and subcortical noradrenergic innervation plays a physiological role in many motor and non-motor functions that are affected in PD. However, it has yet to be established, how NA imaging biomarkers can be used to monitor PD in the prodromal or early stage.

There is evidence for great heterogeneity in when cardiac imaging is pathologic during the course of PD, which certainly questions the utility of this biomarker as a surrogate endpoint in clinical trials. However, when only considering prodromal PD as characterized by iRBD, there is some evidence that a pathological MIBG may almost always precede pathological DaT SPECT and may therefore be considered as a non-clinical milestone in the prodromal disease progression [100].

It is intriguing that OCT could potentially be used as a simple non-invasive biomarker of PD pathology. Future studies will also be needed to investigate the possible relationship between structural changes in the retina and disease severity or time to phenoconversion to motor PD in prodromal cases to understand whether OCT can also be used to monitor disease progression.

Currently, there is no validated PET tracer for α-synuclein in PD. For a detailed review on imaging of α-synuclein, see [29]. The tracer [18F]ACI-12589 represents a promising candidate for imaging of α-synuclein in MSA, but showed only very limited binding in PD [101]. In the light of current developments around α-synuclein seeding assays in CSF [102] and the potential use of α-synuclein PET tracers [101], a biomarker-based disease staging in terms of α-synuclein and (dopaminergic) neurodegeneration may be possible in the near future [2].

CONCLUSION

Plenty of imaging methods are available to assess and quantify different facets of neurodegeneration in PD. Currently, biomarkers that may serve as an endpoint in clinical trials surrogating for the therapeutic effect on the development of motor symptoms in the prodromal phase are at the center of interest. While there are many interesting candidates, DaT-SPECT currently is the most broadly available, most established in clinical routine and most validated biomarker for this use case. However, in light of a biomarker-based definition of "neural synucleinopathy" as an entity, biomarkers capturing the advent of other disease features (e.g., dementia) remain important to develop and validate.

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CONFLICT OF INTEREST

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