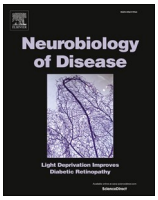
Neurobiology of Disease 164 (2022) 105626

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi



Clinical and imaging evidence of brain-first and body-first Parkinson's disease

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ARTICLE INFO

Keywords:
Parkinson's disease
Subtypes
Autonomic nervous system
Imaging
Biomarkers
Clinical markers
Genetics

ABSTRACT

Braak's hypothesis has been extremely influential over the last two decades. However, neuropathological and clinical evidence suggest that the model does not conform to all patients with Parkinson's disease (PD). To resolve this controversy, a new model was recently proposed; in *brain-first PD*, the initial α-synuclein pathology arise inside the central nervous system, likely rostral to the substantia nigra pars compacta, and spread via interconnected structures – eventually affecting the autonomic nervous system; in *body-first PD*, the initial pathological α-synuclein originates in the enteric nervous system with subsequent caudo-rostral propagation to the autonomic and central nervous system.

By using REM-sleep behavior disorder (RBD) as a clinical identifier to distinguish between body-first PD (RBD-positive at motor symptom onset) and brain-first PD (RBD-negative at motor symptom onset), we explored the literature to evaluate clinical and imaging differences between these proposed subtypes. Body-first PD patients display: 1) a larger burden of autonomic symptoms - in particular orthostatic hypotension and constipation, 2) more frequent pathological α-synuclein in peripheral tissues, 3) more brainstem and autonomic nervous system involvement in imaging studies, 4) more symmetric striatal dopaminergic loss and motor symptoms, and 5) slightly more olfactory dysfunction. In contrast, only minor cortical metabolic alterations emerge before motor symptoms in body-first. Brain-first PD is characterized by the opposite clinical and imaging patterns.

Patients with pathological LRRK2 genetic variants mostly resemble a brain-first PD profile whereas patients with GBA variants typically conform to a body-first profile. SNCA-variant carriers are equally distributed between both subtypes.

Overall, the literature indicates that body-first and brain-first PD might be two distinguishable entities on some clinical and imaging markers.

1. Introduction

Parkinson's disease (PD) is clinically defined by the presence of motor symptoms, i.e., bradykinesia plus tremor and/or rigidity (Postuma et al., 2015). These symptoms primarily arise as a consequence of dopaminergic deficiency in the nigrostriatal circuitry, and emerge when approximately 50% of striatal dopaminergic terminals are lost (Cheng et al., 2010).

Misfolded and aggregated α-synuclein (α-syn) is thought to play a major role in nigral dopaminergic neuronal loss. Such α-syn species can replicate in presence of native α-syn, travel ante- and retrograde in neurons, and exploit existing neuronal connections to propagate from cell to cell, suggesting that α-syn behaves similarly to prions (Brundin and Melki, 2017). Hence, due to the ability of misfolded α-syn to move and spread, affection of additional neurotransmitter systems is likely to occur before and after the clinically defined onset of PD.

The seminal Braak staging system (Braak et al., 2003) postulated that the initial α-syn brain pathology originates in the dorsal motor nucleus of the vagus and/or the olfactory bulb, possibly caused by an enteric and olfactory epithelial insult (Hawkes et al., 2007). The α-syn pathology subsequently propagates to the rostral brainstem and supratentorial systems. Although the pathophysiology of autonomic symptoms is far

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https://doi.org/10.1016/j.nbd.2022.105626
Received 31 August 2021; Received in revised form 4 January 2022; Accepted 7 January 2022
Available online 11 January 2022

from being established, damage to peripheral autonomic structures (Braak stage 1) is thought to lead to dysfunction (Chen et al., 2020b). In animal models, REM-atonia is mediated by the sublaterodorsal nucleus and precoeruleus region in the pons, and lesions in these areas lead to REM-sleep behavior disorder (RBD) (Braak stage 2) (Boeve et al., 2007). This framework may explain a premotor stage of PD originating in structures caudal to the substantia nigra and likely in the peripheral nervous system. RBD prior to or at onset of motor symptoms may serve as a central clinical indicator of this sequence.

However, robust evidence show that Braak staging is not valid for all Lewy pathology positive cases at post mortem, and that some cases do not display pathology in the DMV, despite having pathology in higher Braak stage structures including the locus coeruleus and substantia nigra (Jellinger, 2019; Kalaitzakis et al., 2008; Parkkinen et al., 2008). Additionally, less than half of PD patients have RBD at the time of PD diagnosis (Zhang et al., 2017), but the prevalence increases over time (Sixel-Doring et al., 2016). Second, RBD patients without parkinsonism exhibit severe autonomic degeneration, but almost half of early PD patients with unknown RBD status show normal cardiac sympathetic innervation (Kashihara et al., 2010; Knudsen et al., 2018; Miyamoto et al., 2006; Nagayama et al., 2005). This data points to the possibility that not all PD cases start with pathology in regions caudal to the substantia nigra as proposed by Braak, but pathology might start in other brain regions in a subset of patients.

As an attempt to resolve this controversy, it was recently hypothesized that PD comprises two subtypes: I) one subtype where α-syn pathology originates inside the brain and spreads via connected neuronal structures throughout the brain, and eventually involve the autonomic nervous system (*brain-first PD*), and II) another subtype where α-syn pathology originates in the enteric nervous system with subsequent propagation through the autonomic nervous system to the lower brainstem and from there to the rest of the brain (*body-first PD*) (Borghammer and Van Den Berge, 2019) (Fig. 1). Early in the disease course, the two subtypes are more likely to differ on several clinical and imaging markers, whereas in later disease stages the two phenotypes may converge due to increasing amounts and dissemination of α-syn pathology. Importantly, this framework assumes that misfolded α-syn originates at a single site in the nervous system and spreads from there

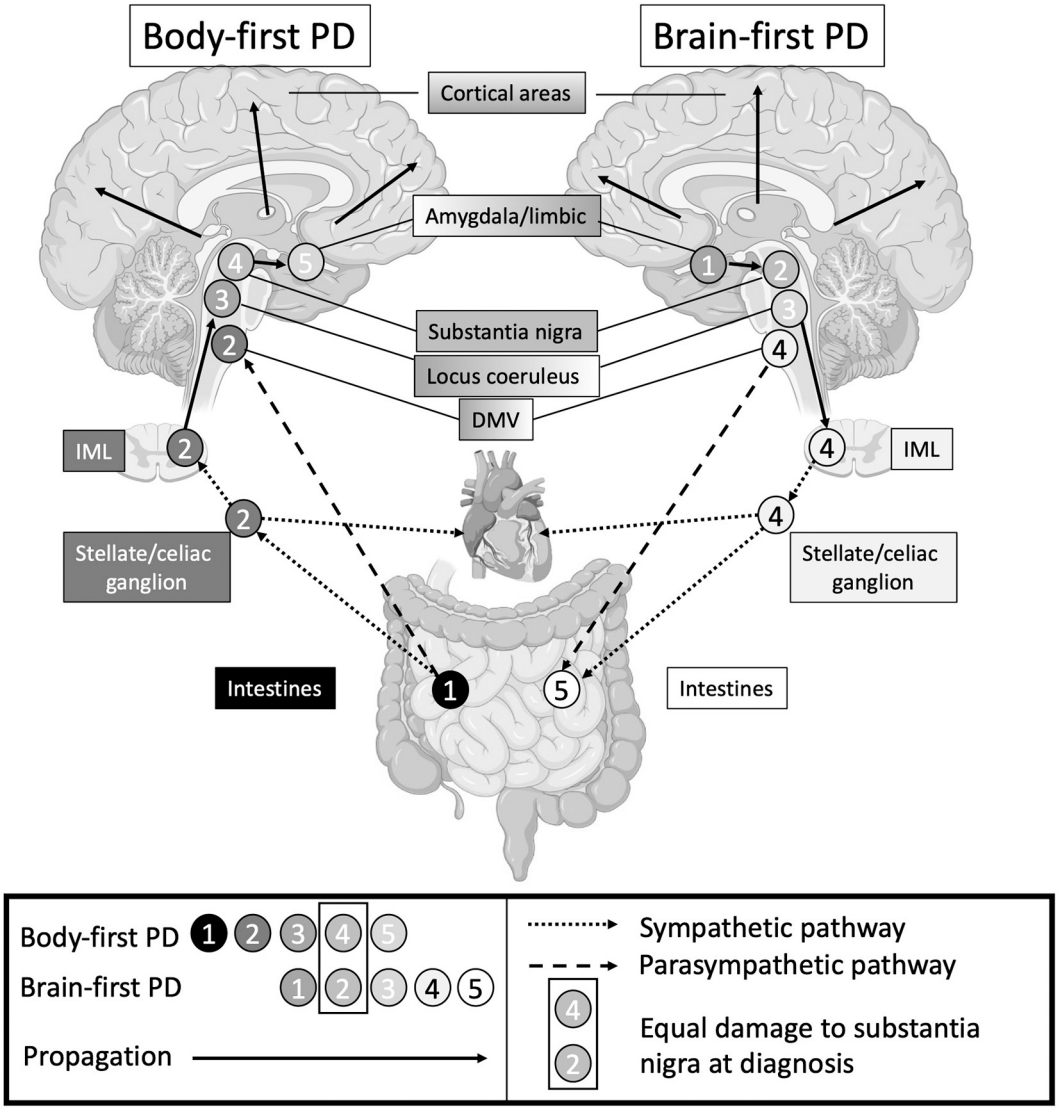

Fig. 1. Schematic depiction of hypothetical α-syn spreading patterns in the proposed brain-first and body-first PD model. The grey color scale is used to state the hypothetical degree of neuronal damage at diagnosis, i.e., black and dark grey resemble high degree of damage, and, conversely, white and light grey resemble low degree of damage. Note that the degree of damage in substantia nigra at diagnosis does not differ between the two proposed subtypes. Supratentorial spreading in body-first PD probably is rather symmetric, whereas in brain-first, the ipsilateral hemisphere to the initial pathology is affected before the contralateral hemisphere (not visualized in the figure). DMV = dorsal motor nucleus of the vagus. IML = intermediolateral cell column. Made with Biorender.com

via connected neurons in a rather stereotypical manner (Borghammer, 2021). The second assumption of the model is that α-syn pathology coincides with neuronal dysfunction and degeneration in PD, even though the exact interplay of α-syn pathology with other mechanisms (i.e., inflammatory processes) is yet to be elucidated.

In the following review, we will discuss available clinical and imaging evidence in the context of the brain-first and body-first hypothesis of PD. Neuropathological evidence for brain-first and body-first PD have been reviewed in another paper in this special issue (Borghammer et al., 2021).

2. RBD as a marker of body-first PD

In humans, RBD is believed to be caused by damage to pontine structures including the magnocellular reticular formation and locus subcoeruleus (Shen et al., 2020; Valencia Garcia et al., 2017). It is well established that isolated RBD (iRBD) is the strongest predictor for prodromal PD or DLB (Berg et al., 2015; Heinzel et al., 2019). Furthermore, nearly all iRBD patients exhibit marked cardiac sympathetic denervation predating damage to the nigrostriatal dopamine system (Kashihara et al., 2010; Knudsen et al., 2018; Miyamoto et al., 2006).

In the present review, we will therefore use pre-motor RBD (i.e., RBD that clearly antedates the emergence of parkinsonism) for body-first vs. brain-first dichotomization, since RBD has been the focus of many recent clinical and imaging studies. A body-first PD patient is thus defined as either an iRBD patient that later converts to PD (in the sense of a prodromal body-first PD patient) or a diagnosed PD patient with RBD (PD+RBD) including a reliable history of RBD symptoms clearly antedating the onset of motor symptoms. A brain-first patient is a diagnosed PD patient without RBD (PD-RBD) or a PD patient where RBD clearly emerged *after* onset of motor symptoms. Hence, timely and correct diagnosis of RBD by gold-standard video-polysomnography (PSG) is crucial in this framework. Of note, as stated above, more than half of PD patients do not have RBD at the time of PD diagnosis, which implies that the majority of PD patients are brain-first. Some studies compared iRBD to PD patients with unknown RBD status. The latter group is then assumed to be a mixed population of body- and brain-first patients.

However, it must be emphasized that premotor RBD should *not* be considered a perfect method to divide brain- and body-first PD. First, it is probable that not all body-first patients will develop overt clinical RBD. Some patients may only develop REM sleep without atonia but without the dream enactment behavior necessary for the RBD diagnosis (Sateia, 2014). Also, many published studies employed RBD questionnaires to diagnose RBD, which is inferior to gold standard PSG (Skorvanek et al., 2018). One study showed that sensitivity and specificity was highly depended on clinical sleep interview prior to RBD sleep questionnaire (RBDSQ) assessment; the group with pre-RBDSQ sleep history taking showed excellent sensitivity (0.90) and specificity (0.87) using a cut-off score of 5, whereas sensitivity (0.68) and specificity (0.63) was rather poor in the group without pre-RBDSQ sleep history taking (Stiasny-Kolster et al., 2015). Initial clinical sleep interview was not performed in any of the referenced RBDSQ-based studies in the present review. Another study found a very low sensitivity (0.44) and modest specificity (0.84) of RBDSQ in de novo PD using 6 as cut-off score (0.47/0.78 using 5 as cut-off) (Halsband et al., 2018). The authors concluded that RBDSQ could not reliably detect RBD in a de novo PD cohort. Therefore, questionnaire-based studies of RBD in PD should be interpreted with precautions, and are considered of lower scientific value than those with PSG-confirmed RBD diagnosis in the present review. However, these studies often employ large cohorts which to some degree compensate for the inaccuracy of the RBD diagnosis, i.e., an attenuated difference between PD+RBD and PD-RBD due to inaccurate RBD diagnosis may still be detectable in a larger study sample. Finally, the timing of RBD onset in relation to motor symptom onset is rarely mentioned, which would enable a better categorization of brain-first and body-first patients (if RBD emerges after onset of motor symptoms, the patient should be categorized as brain-first PD). Despite these circumstances, a PD+RBD group - based on questionnaire assessments - is assumed to be enriched with body-first PD patients, especially compared to a group of PD-RBD patients. We have listed information on RBD-assessment method, time since diagnosis in PD patients, and sample size in all reviewed studies where this information was available (Supplementary Tables 1A+B). In this review, questionnaire-based RBD is considered probable RBD (pRBD). To summarize, it is highly probable that some patients in the reviewed studies are miscategorized. This might lead to an attenuation of the true difference between brain-first and body-first PD on the clinical- and imaging markers.

Other methods of categorization could also have been employed, including biomarkers of neuropathology or neurodegeneration in the autonomic system preceding central nervous system (CNS) involvement. However, only a very small number of such studies are available. These will also be reviewed below.

3. Clinical evidence for brain-first and body-first PD

3.1. Motor symptoms

The PD diagnosis requires motor symptoms and typically translates to a clinical score of approximately 20 on the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III at the timepoint of diagnosis (Holden et al., 2018), whereas healthy aged persons exhibit a score of 5 on average (Keezer et al., 2016). As such, a threshold needs to be surpassed for a motor symptom-based diagnosis. It is therefore not surprising that brain-first and body-first PD do not differ in the overall MDS-UPDRS part III score at the time of diagnosis (Horsager et al., 2020). Averaged motor symptoms are therefore not a suitable clinical parameter to distinguish brain- and body-first patients, and cannot be used as evidence for or against the model. However, the brain-first and body-first model could be relevant to explain differences in the degree of motor asymmetry among patients: the body-first subtype is affected by ascending pathology, which may be more symmetrically distributed, since the vagal efferent projections show a high degree of left/right overlap throughout the gastrointestinal tract (Connors et al., 1983). Therefore, the subsequent brainstem and nigral pathology should also show more symmetric involvement, which would lead to more symmetric parkinsonism (Borghammer, 2021). In a study of 98 subjects, PD-RBD patients were significantly more likely to have asymmetrical onset of motor symptoms (95%) compared to PD+RBD patients where only 66% presented with asymmetrical motor symptoms (Romenets et al., 2012). Further, a study clustered PD patients into a malignant phenotype, where 60% had RBD and 21% had symmetrical motor symptom onset (Merola et al., 2020). In contrast, the benign phenotype only contained 46% RBD-positive patients and only 4% exhibited symmetrical onset of motor symptoms. Thus, RBD and symmetrical motor symptoms seem to correlate and indicate – by pathophysiological consideration of α-syn spreading – a body-first subtype.

Different motor subtypes have been proposed for PD, the most prominent being tremor-dominant and postural instability/gait difficulty phenotype. The brain-first and body-first model does not predict which motor subtypes emerge from each subtype. Nonetheless, some studies suggest that PD+pRBD are more likely to have a non-tremor dominant motor phenotype (Lee et al., 2010; Liu et al., 2019; Postuma et al., 2008; Romenets et al., 2012), but not all studies report such association (Pagano et al., 2018; Rolinski et al., 2014; Sommerauer et al., 2018; Vibha et al., 2011). Also, bradykinesia and rigidity generally present earlier than tremor in iRBD patients who phenoconvert to either PD or DLB (Fereshtehnejad et al., 2019). Therefore, the tremor-dominant motor subtype might be more pronounced in brain-first patients whereas the non-tremor dominant motor subtype might be more pronounced in body-first patients.

3.2. Autonomic dysfunction

Body-first PD patients should theoretically show damage to the autonomic nervous system and the lower brainstem structures earlier in the disease course compared to brain-first patients. This should be accompanied by a higher burden of autonomic symptoms, in particular gastrointestinal disturbances, urinary dysfunction, sexual dysfunction, and symptoms of orthostatic hypotension. However, it should be kept in mind that such symptoms in general are highly multifactorial, and may not necessarily be linked to neurodegeneration of a single system. Also, subjective symptoms are sometimes poorly correlated to its objective counterpart - the latter probably serving as the best measurement of an underlying neurodegeneration. For instance, objective measures of colonic transit time correlates poorly with subjective constipation (Knudsen et al., 2017b). Therefore, objective measures of autonomic manifestations, such as blood pressure for orthostatic hypotension diagnosis, may be of higher value in this context.

Fig. 2 depicts the relative distribution of various symptoms and clinical markers in brain- vs. body-first PD.

3.2.1. Gastrointestinal dysfunction

Gastrointestinal symptoms are very frequent in PD and include sialorrhea, dysphagia, bloating, early satiety, anorectal dysfunction, and, most commonly, constipation (Fasano et al., 2015). Since most studies only report constipation, and no other gastrointestinal symptoms, we only discuss constipation.

Constipation is reported by 28–80% of PD patients (Klingelhoefer and Reichmann, 2015; Knudsen et al., 2017b). However, more than 10 different definitions have been used in the PD literature, which may explain the highly variable prevalence estimates, impeding reliability of subjective constipation reporting (Knudsen et al., 2017b). Constipation in PD is thought to be, at least partially, caused by autonomic dysfunction (Reichmann et al., 2016). The brain-first and body-first PD model predicts that body-first patients suffer from more severe autonomic denervation - earlier in the disease course. Thus, constipation should be more prevalent and severe in body-first patients.

In two large studies comprising nearly 900 patients, the burden of self-reported constipation was significantly larger in PD+pRBD than PD-pRBD patients measured by MDS-UPDRS I. The first study showed higher frequency of constipation (58.8% vs. 40.7%) (Rolinski et al., 2014), while the other reported higher mean symptom score (0.58 vs. 0.32) (Pagano et al., 2018). Another large study of 141 PD patients reported constipation in 80% in the PD+pRBD group and 56% in the PD-pRBD group (Liu et al., 2017). A tendency towards a higher constipation frequency (70% vs 50%) and severity score (1.06 vs 0.81) was seen in PD+RBD with PSG-confirmation, but differences were not statistically significant (Romenets et al., 2012). In a similar study design, constipation frequency tended to be higher in PD+RBD (72%) than PD-RBD (50%) (Neikrug et al., 2014).

Of note, the most thorough review and meta-analysis on constipation found that 40–50% of PD patients are constipated and 11–14% of same-study controls (Knudsen et al., 2017b). Thus, studies which also included healthy controls generally finds that 30%-points more PD patients are constipated than the controls in the same study, e.g., 50% PD and 20% controls. Thus, the "background" constipation frequency should ideally be subtracted when PD+RBD and PD-RBD patients are compared. For instance, if a healthy control group in the study by Liu et al. had a constipation frequency of 20%, then 36% (56%–20%) of PD-RBD patients would have PD-related constipation. In the PD+RBD group, 60% (80%–20%), would have PD-related constipation. In this perspective, the higher constipation frequency in PD+RBD seems robust.

We found no significant difference in ROME III constipation scores between 13 de novo PD+RBD, 24 de novo PD-RBD, and 22 iRBD patients (Horsager et al., 2020). Similar results were reported previously (Leclair-Visonneau et al., 2017). However, a small but significant difference was found in the gastrointestinal section of the non-motor symptom scale (NMSS) between PD+pRBD and PD-pRBD patients, which was also reported in a study of 158 early, untreated patients (Liu et al., 2019). It should be noted that the NMSS gastrointestinal section includes assessment of sialorrhea, dysphagia, and constipation combined.

Finally, a large study reported constipation in 47% of 117 iRBD patients, and in 40% of 119 early untreated PD patients (with unknown RBD status) (Barber et al., 2017). This numerically lower frequency in PD patients compared to iRBD patients was not significant; however, separation of PD patients according to RBD-status might have revealed significant differences.

In summary, these studies indicate that constipation is more frequent and more severe in PD+pRBD patients compared to PD-pRBD patients although some findings in individual studies were not significant. Still, no studies have reported the opposite pattern. Also, iRBD patients seem to experience constipation at least to the same degree as "mixed" PD patients.

3.2.2. Urinary dysfunction

Optimal urinary function is provided by a complex neuronal interplay between the CNS (cerebral cortex, hypothalamus, pontine

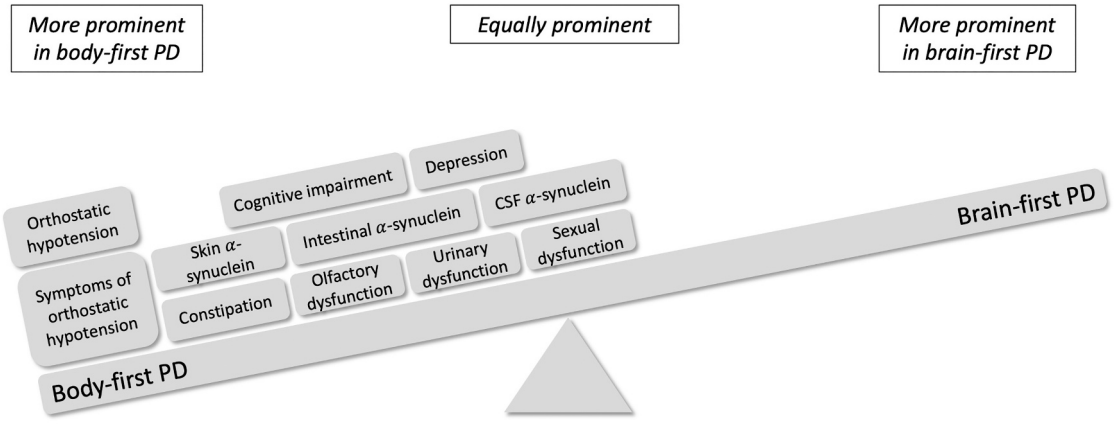

Fig. 2. A stylized rendition of the distribution of symptoms and biomarkers in the proposed body-first vs. brain-first PD subtypes. Boxes to the left reflect a disproportionate high burden in body-first PD. Boxes in the middle reflect an equal burden. It has to be noted that none of the depicted symptoms and markers are exclusive for one subtype. The relative positioning of the boxes is not to scale, but provides a qualitative impression of the results of the present review. Overall, patients with the proposed body-first PD subtype seem to carry a larger disease burden than brain-first PD patients.

micturition center, sacral spinal cord reflex center) and the peripheral nervous system that innervates the detrusor muscle and urethral sphincters (autonomic and somatic motor neurons) (de Groat, 2006). Damage to any of these structures could theoretically lead to urinary symptoms and may thus not necessarily be caused by peripheral autonomic denervation. Additionally, prostate gland changes are highly prevalent in the aged male, leading to a variety of urinary discomfort. Thus, brain-first and body-first PD patients may suffer equally from urinary symptoms.

As with gastrointestinal dysfunction, multiple different single symptoms are summarized under the umbrella term "urinary dysfunction" and multiple different subjective and objective tools are available. Not surprisingly, the prevalence of urinary symptoms in PD varies from 27%–85%, with nocturia, voiding frequency, and urgency being the most common features (McDonald et al., 2017). In the following, we will not distinguish between different symptoms, but rather investigate whether urinary symptoms in general are more prevalent and severe in body-first PD patients.

One study reported urinary incontinence by clinical interview in 4 of 17 PD+RBD patients compared to 0 of 11 PD-RBD patients (Donadio et al., 2018). Two large studies with nearly 900 patients also found higher burden of urinary symptoms on the MDS-UPDRS I in PD+pRBD patients. The first study reported higher frequency (70% vs. 59.6%) (Rolinski et al., 2014), while the other study reported higher mean symptom score (0.84 vs. 0.57) (Pagano et al., 2018). However, in 158 early untreated patients no difference in NMSS urinary section score was found between PD+pRBD and PD-pRBD (Liu et al., 2019). We also found no differences between 24 PD-RBD and 13 PD+RBD patients in the urinary section of both NMSS and SCOPA-AUT (Supplementary Table 2**).** Similarly, no difference in urinary symptom frequency or severity was reported in two studies with PSG-confirmed PD+RBD vs. PD-RBD patients (Neikrug et al., 2014; Romenets et al., 2012).

In summary, urinary symptoms may be slightly more prevalent in PD+pRBD, but the current evidence does not allow firm conclusions to be drawn. Studies with smaller patient samples with PSG-confirmed PD+RBD vs. PD-RBD showed no difference. Different urinary symptoms probably arise from different pathophysiological mechanism, and subjective reporting may not be optimal to depict urinary dysfunction caused by peripheral autonomic dysfunction compared to other causes.

3.2.3. Sexual dysfunction

Sexual function relies on intact autonomic innervation of the reproductive system; however, intact sexual function is also dependent on complicated (psycho-)physiological systems and mechanisms. In the updated MDS criteria for prodromal PD (Heinzel et al., 2019), erectile dysfunction (in men) yields the highest likelihood ratio (3.4) of all subjective prodromal markers, exceeding that of constipation, urinary dysfunction, and symptomatic orthostatic hypotension. Despite this, only few studies have reported on this symptom separately. One study found no difference in either erectile dysfunction frequency nor severity between PD+RBD and PD-RBD patients (Romenets et al., 2012). Similarly, another study using RBDSQ for RBD status reported no difference on the NMSS sexual dysfunction section (Liu et al., 2019). Further, we found no difference between 13 PD+RBD and 24 PD-RBD patients using the same questionnaire (Supplementary Table 2). One of two questions, however, enquires about the loss of interest in sex, which may not be a feature of autonomic dysfunction.

To summarize, the current limited data on sexual dysfunction do not differ between RBD-positive and -negative PD patients. Future studies are needed to study sexual dysfunction in more detail.

3.2.4. Orthostatic hypotension

In Parkinson's disease, orthostatic hypotension (OH) probably arises as a consequence of sympathetic degeneration, which is the efferent mediator of the baroreflex, responsible for stabilizing blood pressure when standing up (Freeman, 2008). Symptoms often include lightheadedness, dizziness, presyncope, and, in severe cases, syncope, but other patients may experience more vague symptoms including weakness or fatigue (Freeman, 2008). Nevertheless, patients with OH are often asymptomatic, and OH might be underestimated with questionnaires.

3.2.4.1. Symptoms of OH. Light-headedness upon standing has been reported to be significantly more prevalent in PD+pRBD than PD-pRBD patients (53% vs 36%) (Rolinski et al., 2014). Similarly, light-headedness score on MDS-UPDRS I, was significantly higher in the PD+pRBD group than in PD-pRBD (0.41 vs 0.24) (Pagano et al., 2018). In early untreated patients, a significantly higher score on NMSS cardiovascular section was found in PD+pRBD patients (1.03) compared to PD-pRBD patients (0.44) (Liu et al., 2019). Furthermore, a significantly higher frequency (61% vs. 39%) and severity (mean orthostatic symptom score: 0.89 vs. 0.44) of symptomatic orthostatic hypotension was found in 54 PD+RBD patients compared to 44 PD-RBD patients (Romenets et al., 2012). In addition, higher prevalence of dizziness was reported in PD+RBD (55.6) vs. PD-RBD (19.2) (Neikrug et al., 2014).

In contrast, we found no difference between PD+RBD and PD-RBD patients in the cardiovascular sections of NMSS nor SCOPA-AUT (Supplementary Table 2) (Horsager et al., 2020). One study evaluated the presence of orthostatic hypotension symptoms by reviewing medical records for pressor medication, and found a non-significant higher prevalence in PD+pRBD patients compared to PD-pRBD patients (6.2% vs. 1.4%) (Yoritaka et al., 2009). Finally, a large study observed postural light-headedness in 42% iRBD patients but only in 27% "mixed" PD patients, which was statistically significant (Barber et al., 2017).

In summary, the severity and prevalence of OH symptoms are generally higher in groups of PD patients presumably enriched with body-first cases, although score differences are generally of small magnitude.

3.2.4.2. Objective OH. The objective definition of OH is defined as at least 20 mmHg systolic or 10 mmHg diastolic blood pressure drop during the first 3 min of standing or on a head-up tilt-table test (Kaufmann, 1996). We found the prevalence of OH to be 31% in iRBD patients, 46% in PD+RBD patients, and 17% in PD-RBD patients; however, this trend was not statistically significant (Horsager et al., 2020). Three additional studies have reported significantly higher prevalence of OH in PD + RBD patients compared to PD-RBD patients (Donadio et al., 2018; Romenets et al., 2012; Sommerauer et al., 2018). In these studies, the prevalence ranged from 50 to 71% in the PD+RBD group, and from 7 to 29% in the PD-RBD group. Similarly, higher systolic blood pressure drop was reported in PD + RBD (12.2 mmHg) vs. PD-RBD (4.2 mmHg) (Sommerauer et al., 2018), and in PD+pRBD (9.3 mmHg) vs. PD-pRBD (4.7 mmHg) (Rolinski et al., 2014). In an iRBD cohort, a slightly higher systolic blood pressure drop was reported (5.3 mmHg) compared to a "mixed" PD group (3.8 mmHg), which was not statistically significant (Barber et al., 2017). Finally, only one study found no difference in orthostatic hypotension between PD+RBD and PD-RBD (Leclair-Visonneau et al., 2017).

In summary, these studies support that objectively defined OH is more prevalent and severe in body-first PD patients.

3.3. Olfaction

Hyposmia is among the most common non-motor symptoms in PD, and may antedate diagnosis by more than a decade (Fereshtehnejad et al., 2019). We found a higher frequency and severity of hyposmia in PD + RBD patients than in PD-RBD patients (mean sniffin' sticks score: 5.7 vs. 8.3) (Horsager et al., 2020). All 13 PD + RBD were hyposmic according to normative data, whereas 7 of 24 PD-RBD patients performed within normal range. This finding is supported by another study of 421 patients where a small but significant difference was found

between PD + pRBD and PD-pRBD patients on smell identification test (mean UPSIT score: 21.3 vs. 23.0) (Pagano et al., 2018). Similarly, a trend towards a lower smell identification score has been reported between PD + RBD and PD-RBD patients, but the difference was not statistically significant (mean sniffin' sticks score: 6.6 vs. 7.6) (Sommerauer et al., 2018). Finally, a study showed lower olfaction scores and lower frequency of hyposmia in de novo PD patients with cardiac sympathetic denervation measured by ^{123}I-MIBG scintigraphy (CC-SIT score: 6.0, frequency: 71%) than in patients with intact innervation (CC-SIT score: 7.1, frequency: 48%) (Kim et al., 2017). Importantly, questionnaire-based RBD was significantly overrepresented in the group with pathological scintigraphies. In contrast, two other studies encompassing 256 PD patients found no difference on smell identification tests between PD + RBD and PD-RBD (Romenets et al., 2012; Sixel-Doring et al., 2014). Similar results were found in PD + pRBD vs PD-pRBD patients (Rolinski et al., 2014). Further, no significant difference in hyposmia, assessed by interview, was reported between these groups (Liu et al., 2017).

Thus, body-first PD patients exhibit olfactory dysfunction at least to the same degree as brain-first patients. Also, body-first PD patients experience olfaction loss many years prior to onset of motor symptoms because the majority of iRBD patients have abnormal olfaction (Fantini et al., 2006; Miyamoto et al., 2010; Miyamoto et al., 2009; Postuma et al., 2019; Postuma and Montplaisir, 2006). How does this observation fit into the brain-first and body-first framework?

The dual-hit hypothesis proposed by Braak and colleagues suggests that an unknown pathogen enters the olfactory and intestinal epithelium and initiates a cascade of pathology traveling retrograde into the brain from both the olfactory bulb and the vagal parasympathetic projections to the gut (Hawkes et al., 2007). However, pathology of olfactory origin did not seem to spread into non-olfactory areas, and the staging scheme was thus based on the caudo-rostral propagation (Braak et al., 2003). In this framework, hyposmia and autonomic dysfunction should appear more or less simultaneously, which fits well with the clinical presentation of body-first patients.

Other lines of evidence suggest that olfactory dysfunction can also arise from *ante*rograde propagation of α-syn from brainstem to olfactory structures. First, the brainstem-to-nose route is supported by animal evidence, where α-syn seeds injected into the duodenum of wild-type rats lead to ascending α-syn pathology into the brainstem, and eventually reaching the olfactory bulb (Van Den Berge et al., 2021). Second, olfactory dysfunction is a significant predictor of incipient phenoconversion in iRBD patients (Iranzo et al., 2021; Postuma et al., 2019). This would be expected if the olfactory loss is caused by ascending pathology, for example through direct connections from locus coeruleus and substantia nigra neurons to the olfactory bulb (Hoglinger et al., 2015; Kebschull et al., 2016; Shipley et al., 1985). Third, in a cohort of patients with pure autonomic failure (PAF), a large fraction converted to either PD ($n = 6$), DLB ($n = 13$) or MSA (n = 6) during a 4-year follow-up period (Kaufmann et al., 2017). All converters, except one PD patient, had RBD. All PD and DLB converters exhibited olfactory dysfunction. However, 12 PAF patients did not convert within the follow-up period. None of these had RBD and all had normal olfaction. Intriguingly, their subjective reporting of autonomic failure duration was only 6 years, whereas those who converted to PD and DLB had autonomic symptoms for 14 and 10 years on average. It is thus conceivable that the remaining 12 non-converted PAF patients are at an earlier stage of α-syn disease and will eventually express RBD and hyposmia in the future course. If so, this evidence from PAF patients suggests that ascending pathology is, at least in part, the culprit behind olfactory dysfunction in body-first patients.

It has been hypothesized that the initial α-syn pathology of brain-first patients arise in the amygdala, which is highly connected to the olfactory bulb (Borghammer, 2021). However, due to the highly lateralized connections, propagating pathology would initially be restricted mainly to the same side. This would then lead to asymmetric olfactory bulb pathology early in the disease course. In support, early PD patients with right-sided motor symptoms perform worse on smell identification on the left side (Zucco et al., 2015). However, olfactory dysfunction might not be clinically apparent as the unaffected side could theoretically fully compensate for this deficit and olfactory testing are typically done on both nostrils at the same time. This would explain why brain-first patients can have normal sense of smell.

In summary, body-first patients may exhibit slightly more olfactory dysfunction compared to brain-first patients. This clinical discrepancy could theoretically be explained by initial unilateral olfactory dysfunction in brain-first patients, and either simultaneously α-syn affection of the nose and intestine ("dual-hit"), or more symmetric ascending brainstem-to-nose pathology in body-first patients. However, the current data on this topic is not sufficient to draw firm conclusions and future studies are needed to test these hypotheses. Importantly, such studies should carry out longitudinal assessment on prodromal patients and perform unilateral olfaction testing to uncover clinically silent unilateral olfactory loss.

3.4. Neuropsychiatric symptoms

Neuropsychiatric symptoms are various and highly common in Parkinson's disease. They include cognitive impairment, depression, anxiety, apathy, fatigue, hallucinations, and psychosis (Aarsland et al., 2009). Neuropsychiatric symptoms are believed to be multifactorial, caused by an interplay of neurotransmitter dysfunction, personality, and psychosocial prerequisites. Therefore, these symptoms may not necessarily provide evidence for the existence of the proposed brain-first and body-first model. However, in the following, we will briefly review two major symptoms, cognitive impairment and depression, in a brain-fist and body-first PD context.

3.4.1. Cognitive impairment

Neurotransmitter dysfunction may be the main driver for cognitive alterations in PD (Aarsland et al., 2021). Indeed, deficits of three neurotransmitter systems located in brain areas of early Braak stages, dopamine (Sawamoto et al., 2008) (Braak stage 3), noradrenaline (Sommerauer et al., 2018) (Braak stage 2), and acetylcholine (Pasquini et al., 2021) (Braak stage 3), are known to be related to cognitive decline in PD. However, co-occurrence of Alzheimer's disease pathology is a common feature in PD dementia and might accelerate α-syn pathology in limbic and neocortical regions (Johar et al., 2017; Smith et al., 2019). Additionally, brain atrophy of the neocortex is associated with cognitive decline in PD (Aarsland et al., 2021). Furthermore, non-modifiable risk factors like the APOE (encoding apolipoprotein E) ε4 allele, age, and male sex are described (Marinus et al., 2018; Tan et al., 2021). In contrast, high education mitigates cognitive decline (Chen et al., 2020a). Such factors, unrelated to the α-synucleinopathy, may either confound or attenuate a difference in cognitive decline between brain-first and body-first subtypes. Also, distinct clinical patterns of cognitive alterations are described, potentially reflecting varying etiologies and mechanisms (Dujardin et al., 2013; Pourzinal et al., 2020). Nevertheless, it is well recognized that cognitive impairment can occur in the prodromal stage of PD prior to motor symptoms, and it is part of the MDS research criteria for prodromal PD (Darweesh et al., 2017; Fengler et al., 2017; Heinzel et al., 2019).

iRBD patients show - on average - impaired visuospatial abilities and executive function (Ferini-Strambi et al., 2019). This observation is accompanied by neuroimaging data of reduced neuromelanin contrast of the noradrenergic LC of iRBD patients (Ehrminger et al., 2016), cholinergic denervation (Gersel Stokholm et al., 2020), and reduced dopamine transporter binding in iRBD patients with MCI (Arnaldi et al., 2021). MCI is also the strongest predictor for phenoconversion to dementia in these patients (Postuma et al., 2019). However, iRBD patients converting to dementia also showed stronger neocortical structural brain changes compared to patients converting to parkinsonism (Rahayel et al., 2021), which could fit to an underlying co-pathology in

addition to α-syn spread in this subgroup of iRBD patients.

PD + RBD patients show more impaired cognition and faster progression to dementia than PD-RBD patients (Jozwiak et al., 2017; Marion et al., 2008). PD + RBD patients showed reduced LC neuromelanin contrast compared to HC and PD-RBD (Garcia-Lorenzo et al., 2013; Sommerauer et al., 2018) and had reduced noradrenergic transporter density, which correlated with poorer cognitive performance (Sommerauer et al., 2018). This data is corroborated by studies relating LC integrity with cognitive performance in mixed PD samples (Li et al., 2019; Prasuhn et al., 2021). PD + pRBD patients exhibited reduced cortical acetylcholinesterase activity along with worse cognitive performance compared to PD-pRBD patients (Kotagal et al., 2012). Cognitive deterioration in PD is also associated with peripheral sympathetic cardiac denervation on ^{123}I-MIBG scintigraphy and orthostatic hypotension, both markers of a body-first subtype (McDonald et al., 2016).

In summary, body-first PD display higher degree of cognitive impairment than brain-first PD. In support, iRBD patients also exhibit cognitive decline. However, it has to be noted that iRBD patients convert, with approximately similar fractions, to PD and to a predominant dementia phenotype (i.e., PD-dementia and DLB) (Iranzo et al., 2014; Postuma et al., 2019). Additionally, intact cognition relies on a multitude of systems and non α-*syn*-related factors including APOE status and Alzheimer's disease co-pathology.

3.4.2. Depression

Depression is a frequent symptom in PD with an estimated prevalence of 35% (Aarsland et al., 2011). Depression is also acknowledged as a prodromal marker of PD in the current MDS research criteria (Heinzel et al., 2019). However, the pathophysiology is complex and not well established. Neuronal damage to the noradrenergic coeruleus-subcoeruleus complex and the serotonergic caudal raphe nucleus is thought to be involved (Aarsland et al., 2011). On the other hand, the limbic system and specifically the amygdala are key structures of emotional processing and such structures might be first involved in a brain-first PD subtype. In addition, psychosocial circumstances also contribute to depression. Hence, in a brain-first and body-first context, depression may not be easily sorted to one subtype and could arise in both in the prodromal stage.

An epidemiological study of 371 PD patients showed that males were more likely than the background population to receive a depression diagnosis in the 5 years prior to getting a PD diagnosis (Jacob et al., 2010). Interestingly, this effect was not present earlier than 5 years prior to diagnosis. This indicates that depression is a marker for prodromal PD. In support, one study showed higher prevalence of antidepressant use and higher score on Beck's Depression Inventory (BDI) in iRBD patients (32% and 10.3) than in a mixed PD group (12% and 7.6) (Barber et al., 2017). One study reported higher depression score on UPDRS I in PD + RBD (0.65) than PD-RBD (0.35) (Romenets et al., 2012). Similarly, two studies found a higher frequency of depression in PD + pRBD (27%–63%) compared to PD-pRBD (16%–24%), despite substantial interstudy variation (Liu et al., 2017; Rolinski et al., 2014). Further, one study found significantly higher scores on Hamilton Depression Rating Scale (HAMD) in PD + pRBD (10.8) compared to PD-pRBD (7.1) patients (Liu et al., 2019). However, not all studies report this association. We found no difference in BDI score between PD + RBD and PD-RBD patients (Horsager et al., 2020). Similar results have been reported previously (De Cock et al., 2007). Also, a large study found no difference in the use of antidepressant between 210 PD + RBD (20%) and 246 PD-RBD (16%) patients (Sixel-Doring et al., 2011).

It should be noted that RBD-like symptoms may be triggered by antidepressant use, but such cases probably reflect an underlying α-syn disease (Postuma et al., 2013). Thus, antidepressant use in prodromal PD patients may demask RBD earlier. One study showed that UPDRS I score in phenoconverted iRBD was not significantly elevated in the prodromal period compared to control values, and no difference was found in depression frequency between converters and non-converters (Fereshtehnejad et al., 2019). Furthermore, depression was not a predictor for phenoconversion in iRBD patients (Postuma et al., 2019). Thus, depression seems to be de-coupled from many other prodromal symptoms like hyposmia, cognitive decline, and autonomic dysfunction (Fereshtehnejad et al., 2019).

In summary, depression may be slightly overrepresented in body-first PD, but the current literature does not support depression as a strong marker for this subtype.

3.5. In vivo α-synuclein detection

In recent years, intense research has addressed the need for biomarkers, which enable exact and early diagnosis of synucleinopathies. Immunohistochemistry studies have, with varying success, microscopically visualized pathological α-syn aggregates in different tissue samples. However, novel methods for pathological α-syn detection in human tissues, including real-time quaking-induced conversion (RT-QuIC) and protein misfolding cyclic amplification (PMCA), seems to have higher diagnostic sensitivity.

3.5.1. Immunohistochemistry

Immunohistochemistry studies eligible for brain-first vs. body-first interpretation have been published on skin, intestinal, and salivary gland tissue, i.e., sites with dense autonomic innervation. Hence, body-first patients should theoretically display α-syn aggregates more often than brain-first patients. Two studies using gastrointestinal biopsies support this idea; one study found α-syn aggregates in colonic biopsies in 24% of iRBD patients but only 5% of PD patients with, presumably, mixed RBD-status (Sprenger et al., 2015). Another showed that 64% PD + RBD were α-syn positive compared to only 13% PD-RBD (Leclair-Visonneau et al., 2017). However, two studies found no difference in autonomic symptoms nor RBD-status in PD patients categorized based on presence/absence of α-syn pathology in intestinal biopsies (Leclair-Visonneau et al., 2019; Ruffmann et al., 2018).

Skin biopsies are easier acquired than intestinal biopsies and with less discomfort. In a recent study, 82% of iRBD patients were positive for α-syn aggregates in skin biopsies whereas 70% of "mixed" PD patients (disease duration >8 years) were positive (Al-Qassabi et al., 2021). Further, in two different studies using neck, thigh, and leg skin samples, all PD patients with orthostatic hypotension and all PAF patients were positive at all three sites (Donadio et al., 2018; Donadio et al., 2016). In contrast, PD patients without orthostatic hypotension displayed a different pattern of pathology with decremental frequency of positive samples from neck to thigh to leg. The authors described this pattern as centrifugal spread of α-syn pathology which resembles the idea of rostrocaudal spread of pathology in brain-first patients. In contrast, since PAF patients probably represent a prodromal phenotype of body-first PD, similar to iRBD (Borghammer and Van Den Berge, 2019), and 86% of the PD patients with orthostatic hypotension had RBD, it seems reasonable to infer that the pathology is widespread in the peripheral autonomic nervous system early in the disease course in the latter groups, which is in accordance with the body-first and brain-first hypothesis. However, two other studies found a higher frequency of α-*syn*-positive skin samples in a PD group with unknown RBD status compared to iRBD patients (Doppler et al., 2017; Miglis et al., 2021).

Salivary glands are fairly accessible to diagnostic biopsies. In two different studies on submandibular and labial salivary gland samples, α-syn pathology was detected in approximately half of iRBD, PD and dementia with Lewy body (DLB) patients (Iranzo et al., 2018; Vilas et al., 2016). Thus, α-syn is detectable in the premotor phase of body-first PD patients, and with similar detection rate as that seen in phenoconverted patients.

In summary, PD patients with RBD or orthostatic hypotension seem to show more frequent α-syn aggregates in peripheral tissue biopsies. In some studies, iRBD patients exhibit equal or higher frequency of α-syn pathology in tissue samples compared to "mixed" PD groups. Thus,

brain-first and body-first PD patients may be identified from immunohistochemistry studies, although some studies do not support this theory.

3.5.2. RT-QuIC and PMCA

Seeding aggregation assays including RT-QuIC and PMCA have proven very useful in the detection of pathological α-syn in tissues and biofluids. Applying cerebrospinal fluid (CSF) to these assays effectively separates synucleinopathies, including PD, from controls with a sensitivity of 75–100% and a specificity of 80%–100% (Donadio et al., 2021; Fairfoul et al., 2016; Garrido et al., 2019; Mammana et al., 2021; Manne et al., 2019; Rossi et al., 2020; Shahnawaz et al., 2020; van Rumund et al., 2019). In three different studies, 69 of 73 (95%) iRBD patients and 26 of 28 (93%) of PAF patients were positive on CSF RT-QuIC (Fairfoul et al., 2016; Iranzo et al., 2021; Rossi et al., 2020), which is approximately equal to the average of PD patients and imply that α-syn pathology has already entered the CNS in these prodromal cohorts. Since pathological a-syn theoretically can enter the CSF at many different CNS sites, these results are not easily interpreted in a brain-first vs. body-first context.

Samples from the olfactory mucosa using a nasal brush also showed misfolded α-syn in approximately 50% of PD and iRBD cases and only 12% of controls (De Luca et al., 2019; Stefani et al., 2021). Interestingly, in iRBD patients, a positive sample was associated with more severe hyposmia which was not the case in the PD group (Stefani et al., 2021). It is interesting to speculate on this discrepant association of α-syn aggregates in nasal brushes and olfactory function: the authors performed nasal brushes mostly in one nostril only, and as discussed earlier in the olfaction section, body-first PD patients may be prone to more symmetric pathology. If correct, detection of α-syn aggregates in one nostril of iRBD and PD + RBD subjects would therefore imply the presence of α-syn in the other nostril also - and hence, clinical hyposmia, which would not necessarily be the case in asymmetric brain-first PD.

PMCA and RT-QuIC have also detected misfolded α-syn in skin and gastrointestinal samples from PD patients (Donadio et al., 2021; Fenyi et al., 2019; Mammana et al., 2021; Wang et al., 2020). Such studies could be highly pertinent to elucidate whether brain-first and body-first PD subtypes exist, i.e., brain-first patients should theoretically be positive later in the disease course than body-first patients. However, none of the published studies have stratified patients based on RBD or autonomic dysfunction.

In summary, RT-QuIC and PMCA studies holds promise for future studies to illuminate propagation patterns of different PD subtypes; however, study designs and hitherto missing PD group subtyping hinders interpretation in the context of brain- and body-first PD.

3.6. Intestinal microbiome

While intestinal α-syn pathology was suggested to be caused by an unknown pathogen (Hawkes et al., 2007), such direct evidence of disease initiation remains to be identified, and might weaken the body-first part of the hypothesis. However, some evidence suggests that such a pathway is realistic. One study found intestinal α-syn accumulation during norovirus infection in children (Stolzenberg et al., 2017), and animal studies have shown that curli-producing *E. coli* bacteria can induce intestinal α-syn aggregation (Chen et al., 2016; Sampson et al., 2020). Recently, several studies on gut microbiome alterations in PD have been published. While such alterations theoretically could differ between brain-first and body-first PD patients, only one study compared PD + RBD to PD-RBD (Heintz-Buschart et al., 2018). Here, *Akkamansia* and *Prevotella* were more abundant in PD + RBD compared to PD-RBD although no difference in these taxa existed between iRBD patients and the collated PD group. Of note, iRBD patients generally exhibited significantly altered microbiome compared to healthy controls. This could indicate that *Akkamansia* and *Prevotella* could be more abundant in body-first subtype. *Akkamansia* bacteria may disrupt the mucosal barrier in the intestine (Derrien et al., 2004), creating a potential causal link between increased intestinal vulnerability and body-first PD. However, in the PD group *Prevotella* was more abundant than in healthy controls, and the opposite pattern is shown in most other studies (Haikal et al., 2019; Scheperjans et al., 2015). Future microbiome studies should stratify PD cohorts in brain-first and body-first subtypes, to reveal any significant differences, and discuss their findings in a mechanistic perspective. Of note, it should be kept in mind that intestinal disruption may not only be relevant in body-first PD, as translocation of gut-microbiome-derived lipopolysaccharides increase neuroinflammation which may be a relevant disease driver in brain-first PD as well (Fitzgerald et al., 2019).

3.7. Optical coherence tomography

Optical coherence tomography (OCT) enables detailed evaluation of retinal layer thickness. A meta-analysis of OCT studies in PD found significant thinning for the retinal nerve fiber layer, and the combined ganglion cell layer and inner plexiform layers (Chrysou et al., 2019). This corresponds to the layers where phosphorylated α-syn pathology have been identified postmortem in PD patients (Veys et al., 2019). Nevertheless, it is unknown how the pathology reaches the retina. If the α-syn pathology does not originate in the retina, anterograde spread through sympathetic neurons innervating retinal arteries from the superior cervical ganglion, could theoretically happen. However, intraocular arteries are devoid of sympathetic innervation (Laties, 1967), and inner retinal layers are primarily involved in PD. Alternatively α-syn could spread via photosensitive retinal ganglion cells from the suprachiasmatic nucleus where α-syn pathology have been observed in 69% of PD patients and in no controls (De Pablo-Fernandez et al., 2018). In a brain-first vs. body-first context, spread though the sympathetic nervous system would probably generate more severe retinal involvement in body-first PD patients. Conversely, spreading via ganglion cells would likely make brain-first PD patients more prone to (asymmetric) retinal layer thinning.

The first OCT study of patients with iRBD also included PD patients categorized into PD + RBD and PD-RBD. The authors reported significant retinal nerve fiber layer thinning in iRBD and PD + RBD patients compared to both PD-RBD and healthy controls. Furthermore, no difference was seen between PD-RBD and controls (Yang et al., 2016). This strongly suggest, that retinal involvement occurs early in body-first patients but probably *after* PD diagnosis in brain-first patients. Two other studies also found significantly decreased retinal layer thickness in iRBD patients compared to healthy controls (Lee et al., 2020; Rascuna et al., 2021). However, in one of these studies the retinal nerve fiber layer and ganglion cell layer was significantly thinner in PD patients with unknown RBD status compared to iRBD patients (Rascuna et al., 2021), which does not support that retinal layer thinning is more severe in body-first patients.

In summary, three studies consistently found retinal thinning in iRBD patients, which suggests that the retina is involved early in body-first PD patients. This also seems to parallel the findings of impaired color discrimination in iRBD patients (Fereshtehnejad et al., 2019; Postuma and Montplaisir, 2006), although the pathophysiology here might involve additional parts of the visual system. However, more studies are needed to decide whether OCT is a relevant biomarker to distinguish brain-first and body-first patients.

4. Imaging evidence for brain-first and body-first PD

Detailed assessment of changes in neurotransmitter systems in PD can be provided by different imaging modalities including radionuclide imaging and specific magnetic resonance imaging (MRI) sequences. In addition, computed tomography (CT) offers information on functional disturbances in the gastrointestinal tract, which are thought to be caused, at least in part, by underlying autonomic neurodegeneration.

Combined, these imaging measurements evaluate damage to structures at different levels of the autonomic nervous system and the CNS, thus enabling testing of the hypothesized brain-first vs. body-first PD model.

4.1. Parasympathetic nervous system

Parasympathetic neurons to the gastrointestinal canal originate primarily from the DMV, and a smaller part from the spinal sacral intermediolateral cell column. These cells use acetylcholine as the primary neurotransmitter.

Acetylcholinesterase density in peripheral organs can be visualized using 5-[^{11}C]-methoxy-donepezil (^{11}C-donepezil) positron emission tomography (PET) (Gjerloff et al., 2014), and intestinal ^{11}C-donepezil signal is thought to be an indirect measure of parasympathetic innervation. In iRBD patients, the colonic and small intestinal ^{11}C-donepezil signal was significantly lower than in healthy controls, and perhaps slightly lower (not statistically significant) than in PD patients with unknown RBD-status (Knudsen et al., 2018). Further, in de novo PD patients, colonic ^{11}C-donepezil SUV was significantly lower in PD + RBD than PD-RBD patients (Figure 3) (Horsager et al., 2020).

These data show that body-first patients display early parasympathetic degeneration, whereas de novo brain-first patients have relatively preserved parasympathetic innervation.

4.2. Sympathetic nervous system

Cardiac ^{123}I-MIBG scintigraphy is the most frequently used method to assess sympathetic denervation, and qualifies as a supportive diagnostic criterion for PD (Postuma et al., 2018). In early disease stages, a substantial fraction (~30–50%) of PD patients have normal cardiac ^{123}I-MIBG signal, but in later disease stages almost all patients develop cardiac sympathetic denervation (Chung and Kim, 2015; Kashihara et al., 2010; Kim et al., 2017; Nagayama et al., 2005; Satoh et al., 1999). Interestingly, eight studies have demonstrated that 87 of 95 (92%) iRBD patients exhibit pathological ^{123}I-MIBG scintigraphies (Barateau et al., 2018; Fujishiro et al., 2010; Gabilondo et al., 2019; Kashihara et al., 2010; Knudsen et al., 2018; Miyamoto et al., 2006; Paglionico et al., 2009; Sakakibara et al., 2019). Further, we found that de novo PD + RBD display a significantly lower cardiac ^{123}I-MIBG signal compared to de novo PD-RBD patients (Fig. 3) (Horsager et al., 2020). Two other studies support this finding as early-stage PD patients with decreased cardiac ^{123}I-MIBG signal had significantly higher RBD prevalence or RBDSQ scores than early-stage PD patients with intact cardiac sympathetic innervation (Kim et al., 2017; Yoo et al., 2021).

Together, these studies strongly support that cardiac sympathetic denervation is an early manifestation in body-first PD. In contrast, PD-RBD patients have more preserved cardiac sympathetic innervation early in the disease course. In line with spreading α-syn pathology over the disease course, prevalence of pathological ^{123}I-MIBG scintigraphies increases in brain-first PD, but this progressive sympathetic loss often occurs after motor onset.

4.3. Colonic dysfunction

An abdominal CT image can reveal increased colonic volume and transit time in patients with PD (Knudsen et al., 2017a). In short, colonic volume is defined by outlining the entire colon on the CT image, and colonic transit time is estimated by counting retained radiopaque markers ingested daily prior to the scan. The underlying mechanisms of colonic dysfunction are not entirely resolved, but probably involves autonomic dysfunction, medication and possibly decreased intestinal dopamine production (Fasano et al., 2015). Also, PD patients may be categorized into slow-transit constipation, anorectal dysfunction or a combination hereof, indicating a large heterogeneity in underlying pathophysiological mechanisms (De Pablo-Fernandez et al., 2019). However, in a brain-first and body-first context it seems reasonable to

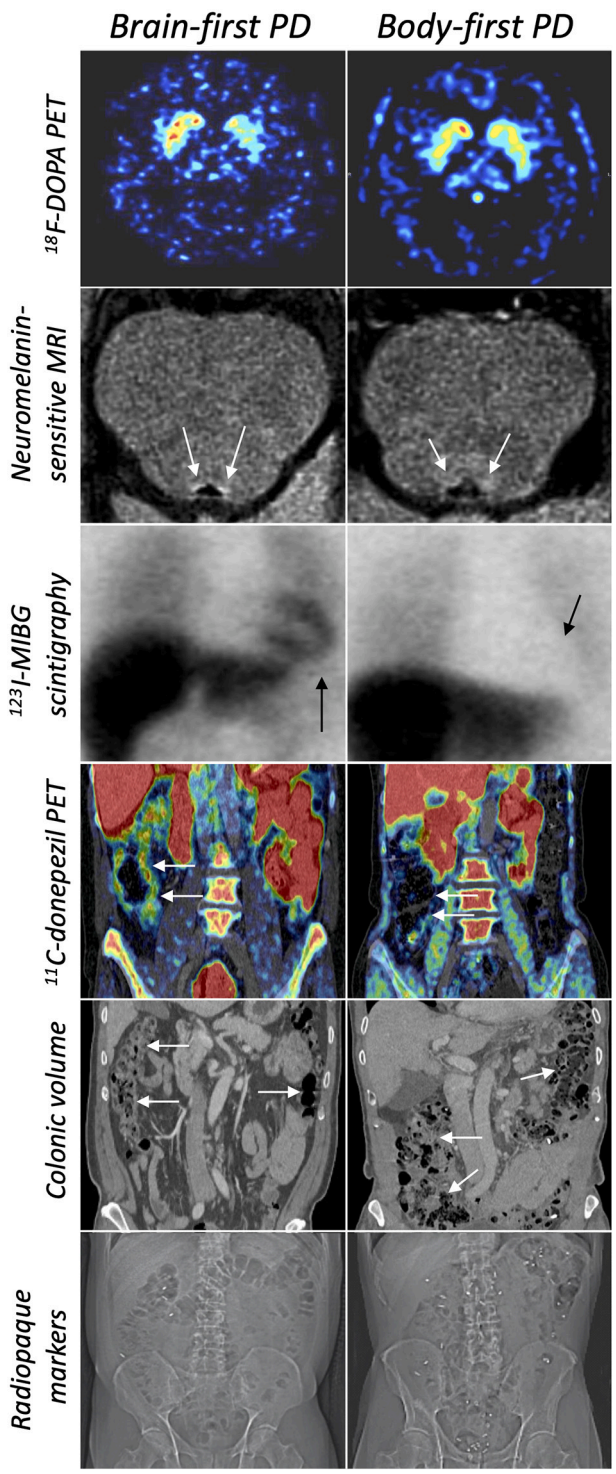

Fig. 3. Representative images of brain-first (left column) and body-first PD patients (right column). Brain-first PD patients display asymmetric striatal ^{18}F-FDOPA loss – body-first PD patients a more symmetric loss. Body-first PD patients display lower locus coeruleus signal on neuromelanin-sensitive MRI, lower cardiac ^{123}I-MIBG signal, and lower colonic ^{11}C-donepezil PET signal than brain-first PD patients (arrows). Larger colon volume and more retained radiopaque markers are seen in body-first PD patients compared to brain-first PD patients – both measures of colonic dysfunction.

hypothesize that objective colonic dysfunction is more pronounced in the body-first patients given the early involvement of the autonomic nervous system.

In iRBD patients, both colonic volume and transit time was significantly increased compared to healthy controls (Knudsen et al., 2019). This indicates that colonic dysfunction is an early manifestation in some body-first patients. Moreover, PD + RBD patients displayed significantly increased colonic volume and transit time compared to PD-RBD patients (Fig. 3) (Horsager et al., 2020). Interestingly, iRBD patients were on average comparable with PD-RBD patients. This could mean that autonomic denervation is not the sole factor responsible for colonic dysfunction in PD, since some brain-first patients with relatively preserved autonomic nervous system, also show slightly higher colonic volume and transit time compared to healthy controls.

4.4. Neuromelanin-sensitive MRI of the locus coeruleus

The locus coeruleus (LC) is situated in the upper dorsal part of pons and displays marked α-syn accumulation and cell loss in deceased PD patients (Giguere et al., 2018). Using neuromelanin-sensitive MRI, several studies have estimated the density of remaining neuromelanin (believed to be a marker of noradrenergic cell body density) by dividing the LC MRI signal intensity to a background reference - usually a region in the mid pons. Two studies demonstrated that iRBD patients display lower signal than healthy controls (Ehrminger et al., 2016; Knudsen et al., 2018). We found a lower signal in PD + RBD patients than PD-RBD, but the difference fell short of statistical significance ($p = 0.07$) (Horsager et al., 2020). However, two other studies reported significantly lower signal in PD + RBD compared to PD-RBD (Garcia-Lorenzo et al., 2013; Sommerauer et al., 2018).

These studies suggest that degeneration of LC cell bodies is tightly associated with a body-first PD subtype, which is in line with its location caudal to the substantia nigra.

4.5. Striatal dopaminergic imaging

iRBD patients show dopaminergic deficiency, but not to the same extent as PD patients (Baucknehet et al., 2018; Knudsen et al., 2018). In iRBD, a pathological dopamine transporter scan is associated with increased short-term risk of conversion to PD or DLB (Iranzo et al., 2017).

It was recently shown that iRBD patients and PD + RBD patients on average had significantly more symmetric ^{18}F-dihydroxyphenylalanine (^{18}F-DOPA) specific binding ratio compared to PD-RBD patients (Fig. 3) (Knudsen et al., 2021). Similarly, two other studies found more symmetric dopamine transporter scans in PD + pRBD patients than PD-pRBD patients (Cao et al., 2020; Chung et al., 2017). Further, three studies have shown a higher degree of symmetry in iRBD patients than in PD patients with unknown RBD status (Eisensehr et al., 2000; Eisensehr et al., 2003; Knudsen et al., 2021).

Thus, nigrostriatal dopaminergic degeneration seems to be significantly more symmetric in body-first PD than in brain-first PD. This observation supports the hypothesis that initial enteric pathology in body-first PD can spread symmetrically to the brainstem and therefore lead to more symmetric Lewy pathology and neurodegeneration.

4.6. Cortical ^{18}F-FDG PET

Cortical metabolic abnormalities can be visualized with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET. PD patents display an altered topographical metabolic profile (PD-related pattern) which correlates with disease severity (Eidelberg et al., 1994; Huang et al., 2007). Simplified, PD-related pattern consists of relative cortical hypometabolism and relative subcortical hypermetabolism. Although the physiological interpretation of this pattern is controversial (Borghammer et al., 2009), two studies have shown that the PD-related pattern is not expressed to the same degree in iRBD patients compared to PD patients - even when comparing with early PD stages (Huang et al., 2020; Meles et al., 2017). Interestingly, abnormal olfaction or dopamine transporter imaging (indicators of short term phenoconversion (Postuma et al., 2019)) was associated with higher degree of PD-related pattern in iRBD patients. Compared to normal controls, however, slightly increased PD-related pattern has been observed (Holtbernd et al., 2014).

The underlying pathomechanisms driving the expression of the PD-related metabolic pattern are not understood. However, the studies support that marked cortical metabolic alterations do not emerge before motor symptoms in body-first PD.

4.7. Diffusion-tensor MRI

Diffusion-tensor imaging studies can visualize microstructural brain tissue abnormalities. In three different studies, structural brainstem changes mostly restricted to the brainstem were detected in iRBD patients (Holtbernd et al., 2021; Scherfler et al., 2011; Unger et al., 2010). Moreover, Holtbernd and colleagues reported that structural brainstem changes in iRBD patients exceeded those of diagnosed PD patient with unknown RBD status. In line with these observations, structural changes were reported in PD + RBD patients compared with healthy controls (Garcia-Lorenzo et al., 2013). Interestingly, no changes were found between PD-RBD and healthy controls in that study. A recent study using advanced statistics and diffusion imaging to determine the sequence of microstructural changes found different trajectories according to RBD status in PD patients, resembling the brain- and body-first routes (Pyatigorskaya et al., 2021). However, two other studies found no structural brainstem differences between PD + pRBD vs. PD-pRBD (Ford et al., 2013) and PD + RBD vs. PD-RBD (Lim et al., 2016), but instead changes in a few supratentorial grey matter regions. Thus, the majority of studies using diffusion-based MRI metrics support that body-first PD display a higher degree of microstructural brainstem damage compared to brain-first PD. However, the literature is diverse, and these metrics might change during the process of neurodegeneration. More studies are needed in order to draw firm conclusions.

5. Genetics in a brain-first and body-first context

Genome-wide association studies have identified nearly 100 gene variants that account for 16–36% of PD risk hereditability (Nalls et al., 2019). Also, more than 20 monogenic causes of PD have been discovered with significant differences in clinical and neuropathological presentation (Deng et al., 2018; Schneider and Alcalay, 2017). Monogenetic PD only accounts for a minority of cases (Bloem et al., 2021). However, important information of the underlying pathophysiology is gained from studying these cases. Here, we will review some of the more common genetic variants in PD in a brain-first and body-first context.

5.1. LRRK2 (PARK8) variants

Over 80 variants have been reported in the leucine rich repeat kinase 2 (LRRK2) gene, and seven are known to be pathogenic, making these the most common genetic causes of PD (Deng et al., 2018). One study found a PSG-confirmed RBD frequency of 17% in LRRK2-PD patients, which was significantly lower than in non-carrier PD (53%) (Pont-Sunyer et al., 2015). Similar results were found in a cohort using clinical interview for RBD assessment: 11% of LRRK2 PD patients had pRBD, whereas 43% of non-carrier PD has RBD (Ruiz-Martinez et al., 2011). Also, no asymptomatic LRRK2 carriers had RBD. A low pRBD-frequency in LRRK2-PD was replicated in another study reporting a prevalence of 16%, whereas patients with pathogenic glucocerebrosidase (GBA) variants had higher prevalence of pRBD (50%) (Yahalom et al., 2019). Interestingly, pRBD was not observed in LRRK2 + GBA-PD, i.e., in patients with both pathogenic variants. This indicates a protective role of LRRK2 on pRBD risk. The opposite pattern was observed in a Chinese

study where 45% of LRRK2-PD patients and 28% of idiopathic PD had pRBD (Sun et al., 2016). However, in a cohort of 350 PSG-confirmed iRBD patients, no LRRK2 variants known to cause PD were observed (Ouled Amar Bencheikh et al., 2018).

In two studies of cardiac sympathetic innervation, 14 of 28 European LRRK2-PD patients had normal ^{123}I-MIBG scintigraphies (Gabilondo et al., 2019; Quattrone et al., 2008). Similar results were seen in Japanese patients, where 4 of 7 had normal scintigraphies (Hasegawa et al., 2009; Tomiyama et al., 2006). Of note, the three pathological cases in those studies were only slightly below the normal range. Finally, three studies totaling 53 LRRK2-PD patients showed that the cardiac ^{123}I-MIBG signal was significantly higher than in idiopathic PD cases (Ruiz-Martinez et al., 2011; Tijero et al., 2013; Valldeoriola et al., 2011). In the abovementioned studies, the motor symptom duration ranged from 2 to 26 years, but most studies reported an average just below 10 years. This is important in the brain-first vs. body-first context, since RBD or cardiac sympathetic denervation may have occurred after onset of parkinsonism in some of these LRRK2 cases, as the temporal evolution of symptoms was not reported in the studies.

In summary, LRKK2-PD patients display lower prevalence of RBD and frequently show normal or near-normal cardiac ^{23}I-MIBG signal, which is reminiscent of brain-first PD.

5.2. GBA variants

Pathogenic variants in the GBA gene leads to Gaucher's disease, the most common autosomal recessive lysosomal storage disease, but homo- and heterozygous variants also dramatically increases PD risk (Deng et al., 2018). Two studies have shown that pRBD prevalence is higher in GBA-PD than in idiopathic PD (Thaler et al., 2018; Yahalom et al., 2019). Compelling evidence also suggest that a substantial fraction of PSG-confirmed iRBD patients have pathogenic GBA variants: First, a large study reported a higher GBA-variant frequency in >1000 iRBD patients (9.5%) than in >3000 healthy controls (4.5%) (Krohn et al., 2020b). Second, in another cohort of 102 iRBD patients, the prevalence of pathogenic GBA variants was 13% (Honeycutt et al., 2019). Third, a study found a higher frequency of GBA variants in iRBD patients (2.6%) than in PD patients with unknown RBD status (0.9%) (Barber et al., 2017). Fourth, in a genome-wide association study, variations in locus TMEM175 were shown to induce decreased glucocerebrosidase activity, and was simultaneously significantly associated with both iRBD and PD (Krohn et al., 2020a). Finally, a longitudinal study of asymptomatic GBA variant carriers reported significantly increased RBD symptoms after a 2-year follow-up period (Beavan et al., 2015). In aggregate, these studies strongly link GBA variants to RBD – even in the premotor phase. In addition, cardiac ^{123}I-MIBG scintigraphy was abnormal in 10 of 11 GBA-PD patients (Itokawa et al., 2006; Lebouvier et al., 2014; Li et al., 2014).

Thus, it seems likely that patients with pathogenic GBA variants often display a phenotype resembling body-first PD.

5.3. SNCA (PARK1 and PARK4) variants

Several pathogenic variants have been discovered in the α-syn (SNCA) gene (Deng et al., 2018). Point variants and triplications show almost complete penetrance, whereas only 30–50% of duplication carriers develop PD (Schneider and Alcalay, 2017). One study reported RBD in 3 of 3 PD patients with SNCA duplications, but the disease duration ranged from 11 to 20 years, and the onset of RBD relative to motor symptoms was not reported (Konno et al., 2016). Another study found RBD in 7 of 10 patients with the pathogenic A53T variant, and with an average motor symptom duration of 4 years (Simitsi et al., 2021). In this study, no asymptomatic A53T variant carrier had RBD but one exhibited REM-sleep without atonia. Two large genome-wide association studies found SNCA variations significantly associated with iRBD (Bjornara et al., 2018; Krohn et al., 2020c). In support, a transgenic prodromal PD mouse model with the SNCA A53T variant displayed RBD-like behavior already at 5 months, but no motor symptoms at 18 months (Taguchi et al., 2020). In carriers of the E46K variant, 4 of 4 patients with PD and 1 of 2 asymptomatic carriers had pathological cardiac ^{123}I-MIBG scintigraphies (Tijero et al., 2013). The latter case indicates premotor involvement of the autonomic nervous system (Tijero et al., 2010). In a study of PD patients with SNCA duplications, 2 of 2 had abnormal ^{123}I-MIBG scintigraphies (Nishioka et al., 2006). Similarly, 2 of 2 symptomatic triplication carriers had abnormal cardiac innervation but 2 asymptomatic carriers had normal scintigraphies (Singleton et al., 2004).

In summary, pathogenic SNCA variations are to some degree associated with RBD and decreased cardiac sympathetic innervation; however, asymptomatic variant carriers rarely have RBD or abnormal ^{123}I-MIBG scintigraphies. Thus, the fraction of SNCA-PD patients conforming to a body-first phenotype may be similar or only slightly larger than in idiopathic PD.

5.4. PRKN (PARK2) variants

Homozygous and compound heterozygous variation in the parkin E3 ubiquitin protein ligase gene (PRKN) leads to inhibited protein degradation, and is a known cause of autosomal recessive early-onset PD (Deng et al., 2018). However, Lewy pathology is only present in ~30% of affected patients (Schneider and Alcalay, 2017). In a study of 14 PRKN-PD patients, none reported violent behavior during sleep (Yoritaka et al., 2011). Another study performed PSG on 10 PRKN-PD patients and found RBD in 6, but in all cases, RBD emerged many years after motor symptom onset (Kumru et al., 2004). With only few exceptions, PRKN-PD patients have relatively preserved cardiac sympathetic innervation even with average symptom duration ranging from 12 to 43 years (De Rosa et al., 2017; Gabilondo et al., 2019; Orimo et al., 2005; Quattrone et al., 2008; Suzuki et al., 2005; Tijero et al., 2015; Yoritaka et al., 2011). Of note, one study found abnormal ^{123}I-MIBG in 4 of 6 patients with heterozygous PRKN variants, but it is unclear whether these variations are actually pathogenic (De Rosa et al., 2017; Schneider and Alcalay, 2017). Furthermore, two studies reported a low burden of autonomic symptoms in PRKN-PD compared to PD patients in general (Tijero et al., 2015; Yoritaka et al., 2011).

Thus, PRKN-PD patients present a phenotype most similar to brain-first PD, but the early onset of motor symptoms and especially the common lack of Lewy pathology upon autopsy complicates the interpretation of PRKN-PD data.

6. Limitations

The presence of pre-motor RBD seems to be a strong tool to clinically dichotomize between brain-first and body-first PD, and to integrate clinical and imaging marker accordingly, when applied thoroughly. This entails that the RBD symptoms clearly appeared prior to motor symptoms, and that the RBD diagnosis is confirmed by PSG (Horsager et al., 2020). Currently, the large majority of studies do not fulfill both criteria and hence, separation of PD subgroups is somewhat blurred. Still, considerable differences in clinical and imaging markers of central and peripheral involvement are observed between iRBD and PD + RBD on the one hand, and PD-RBD patients on the other.

It has to be noted that some clinical symptoms, and to a lesser extent some imaging markers, cannot be sorted unambiguously to a brain- or body-first pathology. Some symptoms and imaging findings could arise as a consequence of both central and peripheral dysfunction, i.e., urinary and sexual dysfunction, or as a consequence of α-syn spreading from variable origins, i.e., olfactory dysfunction. On the other hand, some markers are clearly indicative of a peripheral pathology, i.e., direct detection of α-syn aggregates in peripheral tissues or cardiac denervation seen on ^{123}I-MIBG scintigraphies. However, in this review, we aimed to mainly include commonly collected markers in iRBD and PD+/-RBD patients and to discuss their occurrence in the context of the

brain-first and body-first hypothesis. Future studies using such clearly indicative markers to uncover central versus peripheral phenotypes of other clinical markers, such as urinary dysfunction, will facilitate a cleaner separation of PD subtypes.

As indicated in the main text, most studies dealing with non-motor symptoms in PD make use of questionnaire-based assessments - same holds true for RBD-assessment. However, consistency of subjective and objective measures is only moderate leading to bias in the separation of RBD versus no RBD. More importantly, some symptoms might not be reported by patients even in the presence of neuronal dysfunction (i.e., disturbed gut motility and cholinergic denervation in the absence of constipation as complaint).

Importantly, the brain-first and body-first hypothesis assumes that neuronal pathology and consequent dysfunction proceeds in a directed manner along neural connections, which are measurable by clinical and objective markers. However, this central assumption has yet to be proven in longitudinal studies. Future studies encompassing a thorough subtyping combined with longitudinal follow-up using objective readouts will add highly valuable data to the brain-first and body-first model. Such longitudinal studies are still warranted and will eventually prove or reject our hypothesis. Potentially, other assumptions could explain PD phenotypes with varying burden of non-dopaminergic neuronal dysfunction: In that sense, Bohnen and Postuma proposed 'pure motor' and 'diffuse' clinical subtypes based on cellular vulnerability as alternative explanation (Bohnen and Postuma, 2020). Specific nigral cellular vulnerability could elicit early and 'pure' motor symptoms in one patient while more resilient nigral neurons would allow RBD and other non-motor symptoms to emerge prior to parkinsonism in another patient. Indeed, the heterogeneity in the brain-first and body-first subgroups as illustrated in the present review, may be caused by different levels of individual cellular vulnerability in the cholinergic-, dopaminergic-, and noradrenergic system. However, the 'pure motor' and 'diffuse' subtypes does not explain motor- and dopamine transporter imaging asymmetry in patients without RBD. Actually, if nigral neurons were specifically vulnerable, it would be expected that both sides were affected rather simultaneously.

Most of the data presented in this review did not include direct detection of α-syn aggregates, but rather clinical symptoms or changes on imaging parameters. The relationship between the burden or distribution of α-syn pathology and appearance of clinical symptoms is not well understood. Furthermore, self-reported non-motor symptoms are prone to fluctuations and medication status, which are typically not controlled for in studies (Witjas et al., 2002). Also, some changes in imaging data, especially when measuring receptor density or enzyme activity, can be related to physiological or homeostatic adjustments and might not always reflect neurodegeneration (Lee et al., 2000).

The brain-first and body-first model relies on the assumption that initial α-syn pathology originate in a single location in either the brain or the gut (probably), and spreads from there along neuronal-networks. Lack of "gut-only" α-syn pathology has been proposed as evidence against the body-first hypothesis (Adler and Beach, 2016; Beach et al., 2021), but several factors may explain the absence of "gut-only" cases as described in detail previously (Borghammer, 2021). It was estimated that the probability of identifying a gut-only case (if such a case exists), would be less than 1% with current immunohistochemistry methods. Contrary, a few studies have shown pathology restricted to sympathetic ganglia, which could resemble a very early body-first subtype (Miki et al., 2009; Sumikura et al., 2015; Tanei et al., 2021). Nevertheless, a multi-side hit as initial inception might be possible or pathways apart of neuronal connections might contribute to spread of α-syn pathology. Such mechanisms might relate to variation of pathology and symptom burden in the overall concept of brain-first and body-first PD subtypes.

Additionally, the purported differences between brain-first and body-first PD subtypes should be most clear at early timepoints of α-syn pathology. Using iRBD is a powerful tool to study prodromal PD, but these patients resemble an early body-first subtype, and equivalent populations to study early changes of the brain-first subtype are lacking. It is likely that the prodromal phase in brain-first is very short and perhaps almost clinically silent before parkinsonism emerges. We therefore included a section on genetic PD, since some of these at-risk patient populations might be enriched with brain-first cases. However, genetic PD could also represent heterogeneous PD subtypes, which do not necessarily follow the brain-first and body-first model that is proposed for *idiopathic* PD. Future studies should attempt to recruit RBD-negative prodromal idiopathic PD patients and follow them longitudinally to phenoconversion to elucidate whether they always conform to a brain-first subtype of PD.

7. Conclusion

This review indicates that brain-first and body-first PD might be two distinguishable entities on some clinical- and imaging markers. Body-first patients display a higher burden of autonomic symptoms - in particular constipation and orthostatic hypotension – and have reduced cardiac sympathetic and colonic parasympathetic innervation. MRI studies have detected structural brainstem alterations including pronounced LC damage in body-first patients. The detection rate of skin and intestinal α-synuclein is also higher in body-first PD compared to brain-first PD. Dopaminergic imaging reveal more asymmetric nigrostriatal degeneration in brain-first PD – in line with the more asymmetric motor symptoms in this group. Finally, some monogenetic causes of PD often resemble a brain-first profile (LRRK2 and PRKN), whereas other monogenetic causes (GBA and SNCA) often create a clinical profile more in line with body-first PD.

Future studies are needed to investigate whether brain- and body-first profiles are caused by differing pathogenic mechanisms and etiologies (as suggested by the genetic data). Such knowledge will be crucial to realize the goal of personalized treatment and prevention strategies in the future.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2022.105626.

Funding

The study was supported by the Else Kröner-Fresenius-Stiftung (Michael Sommerauer) [grant number: 2019_EKES.02], and Lundbeck Foundation [grant number: R190-2014-4183].

Declaration of Competing Interest

None.

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