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Neuroimaging of rapid eye movement sleep behaviour disorder and its relation to Parkinson's Disease

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Neuroimaging iRBD and PD patients with RBD

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Abstract (250 words maximum, unstructured)

Rapid eye movement sleep behaviour disorder (RBD) is a parasomnia characterized by the lack of normal skeletal muscle atonia during REM sleep. This disorder is considered a prodromal syndrome of alpha-synucleinopathies like Parkinson's disease (PD), where it affects more than 50% of PD patients. The underlying pathology of RBD has been generally understood to involve the pontine nuclei within the brainstem. However, the complete pathophysiology beyond the brainstem remains unclear as does its relationship with PD pathology. Therefore, this review aims to survey the neuroimaging literature involving PET, SPECT, and MR imaging techniques to provide an updated understanding of the neuro-chemical, structural, and functional changes in both RBD and PD patients comorbid with RBD. This review found neuroimaging evidence that indicate alterations to the dopaminergic and cholinergic system, blood perfusion and glucose metabolism in both RBD patients and PD patients with RBD. Beyond the brainstem, structural and functional changes were found to involve the nigrostriatal system, limbic system, and the cortex—suggesting that RBD is a multi-systemic neurodegenerative process. Future investigations are encouraged to follow RBD patients longitudinally using multimodal imaging techniques to enhance our understanding of this parasomnia disorder. Uncovering which

individuals are most likely to develop an alpha-synuclein disorder in the prodromal phase will improve patient outcomes and potentially aid in the development of novel treatments for patients affected by RBD.

Significance Statement (100 words maximum)

A significant majority of patients with REM sleep behaviour disorder (RBD) will eventually develop an alpha-synuclein disorder like Parkinson's disease (PD). Given the importance of RBD, this review paper aimed to synthesize the neuroimaging literature on the underlying neural mechanisms driving RBD, its conversion to synucleinopathies, and its manifestation within PD. This review found alterations to the dopaminergic and cholinergic system, blood perfusion and glucose metabolism in RBD patients and PD patients with RBD. Beyond the brainstem, structural and functional changes were found to involve the cortex, the nigrostriatal and limbic system—signifying that RBD is a multi-systemic neurodegenerative process.

Introduction

Rapid eye movement (REM) sleep behaviour disorder (RBD) is a parasomnia marked by the lack of normal skeletal muscle atonia during the REM stage of sleep, resulting in dream enacting behaviours. In many cases, these behaviours are associated with violent or aggressive dreams (Schenck, Bundlie, Ettinger, & Mahowald, 1986). The estimated prevalence of RBD in the

general population is between 0.5 to 1.25% (Haba-Rubio et al., 2018; Kang et al., 2013; Sasai-Sakuma, Takeuchi, Asai, Inoue, & Inoue, 2020; Sateia, 2014). This translates to 40 to 100 million expected patients worldwide, however, many cases go unrecognized (Sateia, 2014). The importance of idiopathic RBD is heightened because it is considered a prodromal syndrome of alpha-synuclein driven neurodegeneration (Iranzo et al., 2013). Given the understanding that this parasomnia may be an early manifestation of alpha-synuclein disease, we refer to idiopathic RBD as 'isolated' RBD (or simply known as 'iRBD') in this review (Högl, Stefani, & Videnovic, 2018).

The diagnostic gold-standard for iRBD is the polysomnography sleep test (Sateia, 2014). Through this assessment, the dream-enacting behaviours during REM sleep are associated with excessive electromyographic (EMG) activity. Specifically, either excessive tonic or phasic chin EMG activity or excessive limb EMG twitching are required for diagnosis (Sateia, 2014). However, overnight polysomnography is time consuming, costly, and in some cases, patient compliance may be difficult to achieve. Especially in research settings, a diagnosis of probable RBD can be attained with reasonable sensitivity and specificity through self-administered questionnaires such as the Mayo Sleep Questionnaire (Arnaldi et al., 2016; Boeve et al., 2011).

A significant majority of iRBD patients will eventually develop an alpha-synuclein disorder like Parkinson's disease (PD) or other disorders including dementia with Lewy bodies (DLB) or multiple system atrophy (MSA) after 15 years of follow up (Iranzo et al., 2013). Within the PD population, it has been estimated up to half suffer from not only the classical motor complications, but also symptoms of RBD (Yousaf, Pagano, Wilson, & Politis, 2018). Consequently, there is a need to detect *in vivo* biomarkers of neurodegeneration in iRBD and in PD patients comorbid with RBD to both better understand the pathogenesis and for clinicians to better be able to detect the development of the disease and provide timely treatment.

Given the importance of iRBD, there are significant interests in studying the underlying neural mechanisms driving this disorder, its conversion to synucleinopathies, and its

manifestation within PD (Campabadal, Segura, Junque, & Iranzo, 2021; Heller et al., 2017; Högl et al., 2018; Matzaras et al., 2021). The suspected pathophysiology of iRBD stems from the dysfunction of the subcoeruleus complex in the pons and is seen as one of the possible driving factors in initiating the clinical development (Boeve, 2010). However, the complete pathophysiology beyond the brainstem in iRBD and in PD with RBD remains elusive. Therefore, this review aims to synthesize the neuroimaging literature to provide an updated understanding on the neuro-chemical, functional, and structural brain changes in iRBD and in PD patients comorbid with RBD. It will focus on studies performed through positron emission tomography (PET), single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) modalities to explore this emerging topic of research.

To evaluate the literature gathered for the inclusion in this review, a main research question was formulated: "What are the underlying pathophysiological mechanisms associated with idiopathic RBD and in PD patients comorbid with RBD on the molecular, structural and functional level?" An English language electronic search using PubMed was completed, with papers drawn from its initiation to December 31st, 2021. Several search strategies were used where all had the subject headings (MeSH) and text words, which included: "REM sleep behaviour disorder," "idiopathic RBD," "Parkinson's disease," "neuroimaging," "PET," "SPECT," and "MRI." Additional articles were derived from the cited references of selected articles.

Molecular Imaging

Abnormalities of the dopaminergic system

Measuring dopamine transporter (DAT) activity is commonly achieved through SPECT imaging using either [^{123}I]FP-CIT or [^{123}I]IPT radioligands to assess striatal dopaminergic innervation in especially iRBD patients, along with PD patients with RBD. DAT is responsible for the reuptake of dopamine from the synaptic cleft back into the cytosol. DAT imaging has consistently found that patients with iRBD have reduced striatal DAT activity compared to healthy controls but

higher than PD patients without RBD (Arnaldi, De Carli, et al., 2015; Eisensehr et al., 2003; Zoetmulder et al., 2016). Relative to PD patients without RBD, PD patients with RBD had lower DAT binding in the caudate (Arnaldi, De Carli, et al., 2015).

Studies have correlated DAT levels with clinical measures. For instance, a study observed a positive correlation between olfactory function and DAT activity levels within the putamen in iRBD patients (Dušek et al., 2019). Stiasny-Kolster and colleagues (2005) found that two of the 11 iRBD patients in their study had both severe olfactory dysfunction and striatal DAT deficit. A more recent investigation found that the percentage of dermal structures with phosphorylated alpha-synuclein deposits negatively correlated with DAT binding and olfactory function but positively correlated with total likelihood ratio for iRBD patients to present prodromal PD (Doppler et al., 2017).

DAT activity level was also found to be negatively correlated with tonic and phasic muscle activity during REM sleep (Dušek et al., 2019). Zoetmulder and colleagues (2016) found an inverse relationship between DAT levels in the left putamen and the percentage of electromyographic activity in the mentalis muscle in iRBD patients, but this relationship was not observed for PD patients with and without RBD (Zoetmulder et al., 2016). Another study with iRBD patients found that muscle activity during REM sleep that lasted 0.5 seconds or longer in duration was associated with striatal DAT reductions (Eisensehr et al., 2003).

Like measuring DAT activity, measuring the availability of vesicular monoamine transporter 2 (VMAT2) within the basal ganglia provides another indication of pre-synaptic nigrostriatal denervation. VMAT2 is commonly indexed with [^{18}F]AV133 and [^{11}C]DTBZ PET radioligands. Studies have found that VMAT2 levels are lower in iRBD patients relative to healthy controls within the caudate and putamen (Albin et al., 2000; Beauchamp et al., 2020; Kotagal et al., 2012). However, interestingly, the VMAT2 levels are similar between PD patients with and without RBD as observed in two separate neuroimaging studies (Kotagal et al., 2012; Valli, Cho, Uribe, et al., 2021). Moreover, Valli et al. (2021) found a negative relationship

between motor severity in PD patients without RBD and VMAT2 availability in the left caudate, while this relationship was not present in PD patients with RBD.

There are few studies that examined the density and distribution of the amino-acid decarboxylase (AADC) enzyme in the pre-synaptic dopaminergic terminals. This enzyme is responsible for the synthesis of dopamine through the decarboxylation of L-DOPA and studies visualized this enzyme with the [^{18}F]DOPA PET radiotracer (**Figure 1**). Studies have found evidence that there is a reduction in AADC levels in iRBD patients relative to healthy controls within the putamen (Farmen et al., 2021; Knudsen et al., 2018; Stokholm et al., 2017) and the thalamus (Stokholm et al., 2018). PD patients without RBD are shown to have lower AADC levels within the striatum relative to iRBD patients (Stokholm et al., 2018). In addition to this reduction of AADC, multimodal studies also observed elevated microglial activation detected through [^{11}C]PK11195 PET radioligand within the occipital lobes and left substantia nigra in iRBD patients compared to healthy controls (Farmen et al., 2021; Stokholm et al., 2018, 2017; **Figure 2**). A recent study found that AADC levels within the putamen of iRBD patients negatively correlated with Toll-like receptor 4 levels on blood monocytes which are involved in innate immunity, but positively correlated with CD163^{+} myeloid cells (Farmen et al., 2021). In addition to immune system biomarkers, the acetylcholinesterase availability within the neocortex, indexed with the [^{11}C]donepezil PET tracer, was positively correlated with striatal AADC levels in iRBD patients relative to healthy controls (Stokholm et al., 2020). Another multimodal study observed positive correlation between AADC levels within the putamen and the [^{11}C]MeNER PET tracer binding within the thalamus, which reflects norepinephrine transporter availability (Andersen et al., 2020). This study additionally found reduction of the norepinephrine transporter in the primary sensorimotor cortex in iRBD and PD patients comorbid with RBD relative to controls (Andersen et al., 2020). Knudsen and colleagues used the same [^{11}C]MeNER PET radioligand and specifically observed reduced norepinephrine transporter availability within the left thalamus in iRBD patients relative to healthy controls, but not with PD patients unaffected by RBD (Knudsen et al., 2018; **Figure 1**).

Post-synaptically, the D2 receptors have also been explored with neuroimaging, but not to the same extent as DAT or VMAT2. A recent study looked at the extra-striatal D2 receptors with the [^{11}C]FLB-457 PET radioligand and found that PD patients with RBD had a significant negative relationship between D2 levels within the uncus parahippocampus and PD severity using the Hoehn and Yahr scale, but this relationship was not observed in PD patients unaffected by RBD (Valli, Cho, Masellis, et al., 2021). An older study was unable to detect any differences in striatal post-synaptic D2 receptor density between subclinical RBD, clinically manifest RBD and PD patients without RBD using the [^{123}I]IBZM SPECT tracer (Eisensehr et al., 2003).

Numerous longitudinal studies have found that a significant percentage of iRBD patients eventually convert to a synucleinopathy diagnosis of either PD, DLB or MSA. A study that examined AADC with the [^{18}F]FMT PET radioligand found that iRBD patients who converted to PD or DLB showed reduced bilateral putamen AADC levels during follow-up and their rate of decline between baseline and follow-up was steeper compared to iRBD patients that did not have a comorbid synucleinopathy (M. Miyamoto, Miyamoto, Saitou, & Sato, 2020). Numerous studies have found baseline DAT level deficits within the caudate and putamen in iRBD patients who converted to a comorbid diagnosis after 3 to 6 years of follow-up compared to healthy controls and iRBD patients that remained disease-free (Iranzo et al., 2017, 2020, 2011; Y. Li et al., 2017; T. Miyamoto et al., 2020). Recently, T. Miyamoto and colleagues (2020) found that 34% of iRBD patients developed PD and DLB at a 2.5 year follow-up. Furthermore, these patients had baseline striatal DAT deficit with a Z-score ≤ 2.5 compared to those who remained disease free (T. Miyamoto et al., 2020). Another study looked at the Parkinson's Progression Markers Initiative (PPMI) dataset that had iRBD data available and found that the risk of developing an alpha-synuclein disorder was significantly elevated in iRBD with DAT binding ≤ 48% of what is expected for age and sex, compared to iRBD patients above this cut off (Chahine et al., 2021). In PD, comorbid RBD only predicted motor symptom progression in PD patients which also had lower striatal levels of DAT and lower levels of alpha-synuclein within the cerebrospinal fluid (Pagano et al., 2018). The PPMI PD cohort with probable RBD had lower

DAT levels than PD patients without RBD over the 4 year follow-up period and also had faster decline of the dopaminergic terminal density (Y. E. Kim, Kim, Hwang, & Ma, 2020).

The presence of clinical features such as hyposmia, motor deficits and cognitive impairment work in tandem with iRBD symptomology to worsen disease outcome prospectively. A recent longitudinal study in iRBD patients observed that hyposmia at baseline was a symptom that correlated with faster decline of DAT levels within the putamen and caudate compared to iRBD patients with normosmia. Furthermore, this study also found that a combination of both hyposmia and a baseline PD-like pattern of DAT depletion predicted with 67% likelihood the conversion of these individuals to a future neurodegenerative disease within 4 years, wherein the majority were diagnosed with PD (Shin et al., 2020). Motor event frequency during sleep polysomnography was also found to be negatively associated with DAT levels in the caudate nucleus and putamen in iRBD patients (Nepozitek et al., 2021). Higher Mini-Mental State Examination score and lower striatal DAT binding in iRBD patients was also found to be associated with a higher chance of developing future motor-related parkinsonism while iRBD patients with the opposite pattern (i.e., lower Mini Mental State Examinations scores and higher striatal DAT binding) were more likely to develop dementia (Arnaldi et al., 2021).

Multimodal studies that used both SPECT and transcranial sonography (TCS) have found similar results to the PET studies. AADC activity measured with [^{18}F]FMT PET tracer was found to be lower in iRBD patients with pathological substantia nigra echogenicity compared to iRBD patients without substantia nigra echogenicity (M. Miyamoto et al., 2012). In a sample of 28 iRBD patients, 63% with mild motor abnormalities were strongly associated with substantia nigra hyperechogenicity and reduced striatal DAT levels (Rupprecht et al., 2013). Similarly, another study observed that a subset of their iRBD patients with reduced DAT levels in the striatum and those with substantia nigra hyperechogenicity were at short-term risk of developing a synucleinopathy including PD (Iranzo et al., 2010). Longitudinally, substantia nigra echogenicity size was larger both in the left hemisphere in right-handed iRBD patients with hyperechogenicity and among iRBD patients who developed a neurodegenerative disorder at a 5

year follow-up (Iranzo et al., 2020). However, another study examining PD patients with and without RBD was not able to detect any differences between these two groups in substantia nigra echogenicity nor any correlation between substantia nigra echogenicity and DAT binding levels creating some inconsistency in the literature (Mašková et al., 2020).

Abnormalities of the cholinergic system

A few studies have suggested that the cholinergic system may have a contributory role in the development of iRBD and PD with RBD, but the results are very heterogenous at the moment. Stokholm and colleagues (2020) found that iRBD patients had reduced acetylcholinesterase availability, indexed with [^{11}C]donepezil PET tracer, relative to controls within the superior temporal, occipital, cingulate and dorsolateral prefrontal cortices (Stokholm et al., 2020). The reduction of cortical acetylcholinesterase levels were also found to correlate with higher microglial activation, detected with [^{11}C]PK11195 tracer, in the substantia inominata in iRBD patients relative to controls (Stær et al., 2020). PD patients with probable RBD were shown to have cholinergic reductions within neocortical, limbic and thalamic regions compared to PD patients without probable RBD using the [^{11}C]PMP PET tracer (Kotagal et al., 2012). On the contrary, a study that measured the vesicular acetylcholine transporter (VAChT) with the [^{18}F]FEOBV PET radioligand found instead increased levels of VAChT within areas of the brainstem, midbrain, thalamus, deep cerebellar nuclei, paracentral lobule, anterior cingulate and orbitofrontal cortices in iRBD patients relative to controls (Bedard et al., 2019). Outside of the brain, a multimodal study explored the cholinergic gut innervation with the [^{11}C]donepezil PET tracer and cardiac sympathetic innervation with the [^{123}I]MIBG SPECT radioligand to assess the heart to mediastinum ratio in iRBD and PD patients while comparing to controls (Knudsen et al., 2018). The group of iRBD patients had significantly lower acetylcholinesterase availability in the small intestine and colon compared to controls; and relatively lower than PD patients, but the level of significance was not reached. In relation to the heart to mediastinum ratio, iRBD patients was significantly lower compared to controls, but no differences with PD patients were observed (Knudsen et al., 2018; **Figure 1**).

Changes in regional cerebral blood flow

Neuroimaging studies examining regional cerebral blood flow commonly used either [^{99m}Tc]ECD or [^{123}I]IMP SPECT tracers. These SPECT studies showed decreased perfusion in the frontal and tempo-parietal cortices, parieto-occipital lobe (precuneus), limbic lobe, and cerebellar hemispheres in iRBD patients relative to controls (Hanyu et al., 2011; Mazza et al., 2006). Evidence also points to elevated perfusion in iRBD patients in the pons and putamen bilaterally and in the right hippocampus (Mazza et al., 2006). In a 2 year longitudinal study of iRBD patients, they showed a decrease in regional cerebral blood flow in the medial areas of the parieto-occipital lobe and a significant decrease within the right posterior cingulate compared to healthy controls (Sakurai et al., 2014). Another larger longitudinal study of iRBD patients found baseline regional cerebral blood flow was higher in the hippocampus in patients that converted to PD or DLB within 3 years relative to those that did not. Furthermore, increased hippocampal perfusion correlated with worse motor and color vision scores in this same group of participants (Dang-Vu et al., 2012).

Amyloid deposition

There is a sparsity of studies that examined the role of beta amyloid deposition in iRBD pathology. H. Lee and colleagues (2020) measured the cortical amyloid beta levels using the [^{18}F]Flutemetamol PET tracer in a group of 23 iRBD patients and found that 4 patients were positive for amyloid and also showed elevated percentage of wake after sleep onset (WASO) compared to 19 amyloid negative patients. Global radioligand uptake also correlated with total sleep time, sleep efficiency, WASO, and N1 sleep. These sleep quality measurements are typically associated with brain regions involved in the default mode network, including the orbitofrontal, dorsolateral prefrontal and left temporal cortices (H. Lee et al., 2020).

Changes in glucose metabolism

Neuroimaging iRBD and PD patients with RBD

There have been a number of studies on iRBD patients that examined glucose metabolism in the brain using [^{18}F]Fluorodeoxyglucose (FDG). Multiple studies have found that iRBD have reduced glucose metabolism in the posterior part of the brain—particularly the occipital lobe compared to healthy controls (Carli et al., 2020; Fujishiro et al., 2010; Ge et al., 2015; Han et al., 2020; Meles et al., 2018; Wu et al., 2014). In addition, other investigations found hypometabolism within the middle cingulate cortex, parietal cortex (Meles et al., 2018), temporal cortex (Fujishiro et al., 2010; Meles et al., 2018; Wu et al., 2014), left anterior cingulate gyrus and right frontal lobe (Fujishiro et al., 2010). On the other hand, hypermetabolism was observed more anteriorly in iRBD patients relative to healthy controls involving the frontal cortex (Ge et al., 2015; Han et al., 2020; R. Kim et al., 2021; Liguori et al., 2019; Shin et al., 2020; Wu et al., 2014), temporal cortex (Ge et al., 2015; Liguori et al., 2019; Meles et al., 2018; Wu et al., 2014), thalamus (Meles et al., 2018), striatum (Han et al., 2020; R. Kim et al., 2021), lentiform nucleus and claustrum (Liguori et al., 2019). Other studies found more subcortical regions to have hypermetabolism including the midbrain, brainstem and cerebellum (Ge et al., 2015; Liguori et al., 2019; Meles et al., 2018; Wu et al., 2014). The Parkinson's disease related co-variance pattern, an abnormal metabolic brain network, was elevated in iRBD patients compared to controls (Holtbernd et al., 2014).

There is conflicting evidence regarding which brain areas have either hypo- or hypermetabolism in PD patients unaffected by RBD in relation to iRBD: one study found PD patients have lower occipital glucose metabolism (Han et al., 2020) while another instead found the reverse where PD patients to have higher occipital metabolism compared to iRBD patients (Carli et al., 2020). The iRBD metabolic related pattern was significantly expressed in PD patients compared to controls, but this pattern did not yield significant differences between PD patients with and without probable RBD (Meles et al., 2018). Relative to PD with RBD, iRBD patients showed elevated metabolic patterns in the premotor area (Shin et al., 2021; Yoon et al., 2019) and hippocampus (Yoon et al., 2019). Shin and colleagues (2021) observed that the glucose metabolism in PD patients with RBD was negatively correlated with olfactory function,

and this association was not found in PD patients without RBD. A recent longitudinal study found that the expression of a PD-related pattern of cerebral metabolism in iRBD patients increased over time: at the 4-year follow up, 4 out of 20 (20%) of iRBD patients in their sample with baseline PD-related pattern expression phenoconverted to PD (Kogan et al., 2020).

Some studies have also measured cerebral glucose metabolism with relationship to DAT binding. Studies of iRBD patients with abnormally low DAT binding correlated with higher PD-related glucose pattern expression. (Huang et al., 2019; Meles et al., 2017). A recent study of iRBD patients with mild cognitive impairment (MCI) had distinctive hypometabolism within the cuneus and precuneus, correlating with DAT binding, executive functioning and verbal memory compared to iRBD patients with normal cognition (Mattioli et al., 2021). PD patients with RBD, on the other hand, had lower DAT levels within the caudate and was associated with hypometabolism in posterior cortical regions along with relative hypermetabolism in anterior regions of the more affected hemisphere compared to PD patients unaffected by RBD (Arnaldi et al., 2016).

Abnormalities of the serotoninergic system

There were few studies that explored the serotonergic system in relation to iRBD, but limited evidence suggests it does play a significant contributory role in RBD. In comparison to controls, iRBD patients showed no differences in serotonin transporter levels within the brainstem and thalamus using the [^{123}I]FP-CIT SPECT tracer (Arnaldi, Famà, et al., 2015). Likewise in PD patients with probable RBD, there was no observable differences in serotonin transporter availability compared to PD patients without RBD measured with [^{11}C]DASB PET radioligand (Kotagal et al., 2012).

Summary of molecular abnormalities:

In contrast to the wealth of literature concerning iRBD patients, the molecular imaging of RBD in PD patients has been largely understudied. Despite this limitation, the present literature suggests a wide range of possible molecular changes in the dopaminergic and cholinergic system, blood perfusion, and glucose metabolism in both iRBD and PD patients with RBD. The striatal DAT levels in iRBD patients was in the middling: lower compared to healthy controls but higher than PD patients with RBD. A deficit of dopaminergic markers at baseline in iRBD patients was associated with a greater likelihood of developing an alpha-synucleinopathy over 3 to 5 years of follow up. The cortical acetylcholinesterase levels were at a greater loss in iRBD patients compared to controls and similarly, PD patients with RBD was at a greater loss relative to PD patients unaffected by RBD.

Literature relating to the regional cerebral blood flow was conflicting but suggested abnormal perfusion across the entire brain in iRBD patients relative to healthy controls. The glucose metabolism in iRBD patients was also dysregulated relative to healthy controls, with hypometabolism in the posterior parts of the brain and hypermetabolism in the anterior regions. Future studies are encouraged to explore this pattern with a larger sample size to elucidate cerebral blood perfusion alterations in iRBD patients and find if these anterior/posterior patterns of glucose metabolism also manifest in PD patients with RBD. The exploration of other molecular targets such as neuroinflammation is encouraged to provide a wider understanding of the underlying pathophysiology of RBD and its role in PD.

Structural Imaging Abnormalities

Literature investigating gray matter loss in iRBD patients has produced inconclusive and inconsistent findings that may question the utility of structural MRI techniques in untangling the iRBD signatures from normal aging processes (Heller et al., 2017). Within the striatum, one study showed larger putamen volume in iRBD patients relative to healthy controls (Chen et al., 2020) while another showed smaller volume (Ellmore et al., 2010). For the caudate, studies showed a volume decrease in iRBD relative to controls (Chen et al., 2020; Holtbernd et al.,

2021), but this finding was not replicated in another study (Ellmore et al., 2010). Outside of the striatum, posterior hippocampal atrophy was observed (Campabadal et al., 2019), however another study investigating the unsegmented hippocampi found iRBD patients had a larger volume compared to healthy controls. Increased volume was also observed in the thalamus (Chen et al., 2020) and amygdala (G. Li et al., 2021) in iRBD patients relative to controls. Certain subregions within the cerebellum showed to be larger in iRBD patients compared to healthy controls (Chen et al., 2020; Holtbernd et al., 2021) and PD patients (Holtbernd et al., 2021) while other studies instead found a decrease in cerebellar volume relative to healthy controls (Chen et al., 2020; Hanyu et al., 2012). Sample size of iRBD patients were usually small in these studies and differences in the analysis methodology could explain some of these inconsistent findings (Campabadal et al., 2021).

Gray matter volume differences in the brainstem offer more consistent results. Gray matter volume differences have been reported in a number of brainstem nuclei (G. Li et al., 2021) such as gray matter loss in the pontine tegmentum (Hanyu et al., 2012). A recent study noted increased locus coeruleus volumes in iRBD patients (Holtbernd et al., 2021). The locus coeruleus is perhaps the most consistent region to have gray matter loss in iRBD, with two studies finding neuromelanin signal intensity loss in this brain region in iRBD patients relative to healthy controls (Ehrminger et al., 2016; Knudsen et al., 2018). This suggests that neuromelanin-sensitive imaging may serve as a non-dopaminergic biomarker for synucleinopathies (Ehrminger et al., 2016).

Iron metabolism plays an important role in both synucleinopathy and normal aging as abnormal iron deposits damage neuronal functioning (Ward, Zucca, Duyn, Crichton, & Zecca, 2014). Iron can accumulate in neuromelanin molecules resulting in long-term sequestering of iron in these neurons, especially within the substantia nigra and locus coeruleus (Ward et al., 2014; **Figure 1**). A number of MRI sequences can detect iron depositions in the brain such as R2* or quantitative susceptibility mapping sequences, which have been employed to investigate PD and iRBD patients (Lehericy et al., 2017; **Figure 3**). A susceptibility weighted imaging (SWI)

study observed a significant portion of their iRBD sample had nigrosome-1 loss, reflecting abnormally elevated iron deposition within the substantia nigra compared to healthy controls (Zhang et al., 2021). In healthy controls, the substantia nigra has a hyperintense ovoid border in the dorsolateral part of the substantia nigra paired with a hypointense substantia nigra pars compacta which collectively is referred to as dorsolateral nigral hyperintensity (DNH) (Mahlknecht, Krismer, Poewe, & Seppi, 2017). In another SWI study, DNH in iRBD was found to be lower than healthy controls but higher than PD patients (Barber et al., 2020). In a similar fashion, Biondetti et al., (2020) used neuromelanin-sensitive MRI and found a gradient reduction of neuromelanin signal from healthy controls to iRBD to PD patients. This study further found that nigral neuromelanin intensity was correlated with motor, cognitive and behavioural measures reflecting a functional organization of the substantia nigra (Biondetti et al., 2020).

A recent longitudinal study uncovered chronological ordering in iRBD patients where striatal synaptic dopaminergic dysfunction was observed first, followed by abnormal iron metabolism in the substantia nigra pars compacta coupled with neuromelanin changes. This finding suggests an interrelationship between striatal dopaminergic dysfunction, nigral cell loss and increased iron content (Biondetti et al., 2021). Over a 1.5 year follow-up, another study found that iRBD patients with loss of nigral hyperintensities manifested symptoms of parkinsonism or cognitive disturbances and visual hallucinations consistent with dementia Lewy bodies with a hazard ratio of 7.13 (Bae et al., 2017). However, iRBD patients with DNH had reduced striatal DAT binding compared to controls (Bae et al., 2017; Frosini et al., 2017) but higher than PD patients (Barber et al., 2020). A multimodal imaging study found volumetric reduction of the substantia nigra coupled with neuromelanin-sensitive signal intensity and fractional anisotropy reductions as a measure of diffusion weighted imaging in iRBD patients compared to healthy controls (Pyatigorskaya et al., 2017). These three measures together proved to have a good diagnostic accuracy of 0.92 on the receiver operating characteristic curve in differentiating iRBD patients from healthy controls (Pyatigorskaya et al., 2017). Indeed, multimodal assessment of the substantia nigra using SWI with a 7 tesla MRI scanner has been

proposed as a reliable approach for monitoring neurodegeneration in iRBD (Frosini et al., 2017). Susceptibility-weighted imaging of subcortical iron deposits in the substantia nigra of iRBD patients may be a potential diagnostic biomarker with moderately high accuracy. Caution however should be advised for now as J. H. Lee and colleagues (J. H. Lee et al., 2014) found no iron deposition abnormalities by means of R2* values. This discrepancy could be due to the different techniques employed to quantify iron in the brain or the fact that most studies focused on a specific priori region of interest such as the substantia nigra while J. H. Lee and colleagues (J. H. Lee et al., 2014) assessed multiple subcortical structures limiting the ability to reach statistical significance.

Water molecules that do not encounter restrictions by the cellular environment or a directionality are known as free water, which is increased by neuroinflammation and brain atrophy linked to normal aging (Gullett et al., 2020) and neurodegeneration (Dumont et al., 2019). When assessing the free water within the substantia nigra (i.e., water molecules that do not display a directional dependence), a gradual pattern was observed where healthy controls had the least volume of free water, followed by iRBD and PD patients with the most (Zhou et al., 2021). Free water values in the posterior substantia nigra correlated negatively with DAT activity (Zhou et al., 2021). Longitudinally, free water values in iRBD increased over a 1.5 year period, thus suggesting a progression to PD values that was not observed in the healthy control group (Zhou et al., 2021).

Consistent with the iRBD literature reviewed earlier (Campabadal et al., 2021; Rahayel et al., 2018), PD patients with RBD had reduced thalamic volumes relative to PD patients without RBD and healthy controls using whole-brain voxel-based (Salsone et al., 2014) and deformation-based (Boucetta et al., 2016) morphometry approaches. However, a study using the PPMI dataset only reported lower right putamen volume in PD patients with RBD compared to PD without RBD and healthy controls (Kamps et al., 2019). This study was not able to detect differences in cortical regions between groups through the whole-brain voxel-based morphometry approach (Kamps et al., 2019). PD patients with RBD also demonstrate rightward cortical atrophy

particularly in the caudal sensorimotor area, supramarginal gyrus, superior temporal gyrus, temporal pole, and inferior temporal thinning extending to the fusiform cortex in comparison to PD patients without RBD (Rahayel et al., 2019). In relation to healthy controls, PD patients with RBD showed widespread cortical thinning characterized by a posterior predominant pattern which was also found with voxel-based morphometry together with basal ganglia, thalamus, hippocampus and cerebellum volume decrements (Rahayel et al., 2019). However, another study using the PD *de novo* PPMI cohort only reported bilateral inferior temporal thinning between PD patients with and without RBD and reported no subcortical differences (Yoon & Monchi, 2021). This discrepancy may be due to the fact that Rahayel and colleagues' (2019) study sampled mild PD patients already on medication while the PPMI cohort sampled unmedicated PD patients.

In a study also using the PPMI cohort, PD *de novo* patients with RBD displayed reduced volumes in the brainstem and deep gray matter structures, and both cortical volume decrements and increments in small clusters of voxels compared to PD patients unaffected by RBD (Boucetta et al., 2016). The authors relate such gray matter loss to cholinergic, GABAergic, and glutamatergic neuron depletion in the promotion of REM sleep and muscle atonia. A recent study on PD patients undergoing polysomnography confirmed RBD had higher cerebellar volume compared to PD patients unaffected by RBD in the vermis IV/V, and this was found to be associated with abnormal motor behaviour during REM sleep. In addition, reduced gray matter volume in the right superior occipital gyrus of PD patients with RBD was negatively associated with motor severity and positively associated with memory function (Jiang et al., 2021).

The Braak staging model for PD suggests that the brain degeneration progresses outwards from the brainstem to the cortex (Braak & Del Tredici, 2008; Braak et al., 2003; Jellinger, 2014). However, PD cortical atrophy has been extensively reported in the early stages of the disease (motor diagnosis usually takes place at Braak Stage III) even in the absence of overt cognitive impairment (Pereira et al., 2014; Uribe et al., 2018). A multimodal MRI study, using structural and neuromelanin sensitive sequences, aimed to assess these two hypotheses of PD subtypes:

from brainstem to cortex and second where cortical involvement is primed. Authors found that the group of PD patients with RBD had a neurodegeneration pattern consistent with the Braak brainstem-to-cortex model while PD patients without RBD fitted best with the cortex-to-brainstem model (Pyatigorskaya et al., 2021). Garcia-Lorenzo and colleagues (García-Lorenzo et al., 2013) found that PD patients with RBD had reduced neuromelanin signal intensity in the locus coeruleus which is consistent with the pathology found in iRBD patients (Ehrminger et al., 2016).

In a longitudinal PPMI study with an unbalanced sample size in each patient group, PD patients with RBD displayed reduced precentral and superior parietal thickness with a predominant left hemisphere atrophy (Yoon & Monchi, 2021). On the other hand, PD patients without RBD showed a more widespread atrophy decline in superior frontal, right inferior temporal, precentral, supramarginal, left superior, cuneus and lateral occipital areas. When comparing both subgroups, the left insula of PD patients with RBD suffered significantly more decline than the PD group across time. In addition, this study uncovered that the symmetrized percent of change (quantified change over 2 years) in the left caudate, pallidum and amygdala was greater in PD patients with RBD, suggesting a more pronounced gray matter loss. Unfortunately, in this study there was no control group to contrast the *per se* aging decline (Yoon & Monchi, 2021).

Male sex is risk factor for both iRBD and PD incidence, with around 80% of iRBD patients being male (Fernández-Arcos, Iranzo, Serradell, Gaig, & Santamaria, 2016) and the incidence of parkinsonism in males:female is 2:1 (Baldereschi et al., 2000). Oltra and colleagues (2021) explored the sex differences in disease incidence by stratifying the PPMI cohort. The authors found that male PD patients with RBD had greater global cortical atrophy and deep gray matter loss in the caudate, pallidum and brainstem regions compared to female PD patients with RBD. These males also had worse cognitive performance especially on speed processing measures compared to females (Oltra, Segura, et al., 2021). There are few studies which

examined the sex differences in iRBD and PD with RBD patients, and it merits for future studies to factor in sex difference into their analyses.

Summary of the structural alterations

Surveying the structural MR imaging literature revealed that abnormal iron deposits can be found in subcortical nuclei of the brainstem, a pathophysiological hallmark of iRBD, namely the substantia nigra and locus coeruleus. More importantly, a temporal ordering of iRBD pathology is proposed with striatal dopaminergic dysfunction precedes neuromelanin changes and abnormal iron metabolism in pars compacta (Biondetti et al., 2021). Multimodal imaging assessment of the substantia nigra (i.e., neuromelanin sensitive signal intensity, free water quantification, fractional anisotropy, DAT imaging, and gray matter loss) may be excellent diagnostic markers. In PD with RBD, the literature shows atrophy within limbic and basal ganglia regions compared to PD patients without RBD and healthy controls that is consistent with iRBD pathology. Future studies with larger sample size are encouraged to find effective biomarkers allowing for the better prediction of which iRBD subgroups will later convert to a synucleinopathy.

Resting State Functional Connectivity Abnormalities

In a multimodal study using resting-state MR and SPECT imaging, iRBD patients displayed a positive correlation between the mean regional homogeneity value and DAT tracer uptake ratio within the left putamen (G. Li et al., 2020). Another multimodal study uncovered that the functional connectivity predictive power in the basal ganglia was able to differentiate iRBD and PD patients from HC with a high sensitivity of 96% and moderate specificity of 74-78% in the absence of gray matter loss differences between groups. However, functional connectivity in the basal ganglia did not differentiate iRBD patients from PD suggesting a shared pathophysiology between the two conditions (Rolinski et al., 2016).

Another investigation showed that iRBD patients with motor impairment had decreased cortico-striatal functional connectivity and increased cortico-cerebellar functional connectivity

compared to both iRBD patients with normal motor function and healthy controls (Yamada et al., 2019). From the prodromal PD PPMI cohort that enrolled both iRBD and hyposmia patients, reduced intra- and inter hemispheric functional connectivity was reported in the striato-thalamo-pallidal network compared to healthy controls. This finding differentiated prodromal PD patients from controls with a sensitivity of 93% and specificity of 82%. However, these findings should be replicated in larger samples and with homogeneous participants with either iRBD or hyposmia instead of collapsing them into one group. This study also did a seed-to-whole-brain analysis where they showed iRBD patients had a reduced functional connectivity from the putamen as the seed with the pallidum and caudate nuclei compared to controls (Dayan & Browner, 2017). In a study with a smaller sample, Ellmore and colleagues (2013) found iRBD patients had significant differences in nigrostriatal (i.e., between the left substantia nigra and left putamen) and nigrocortical posterior-based (i.e., substantia nigra with right cuneus, precuneus and superior occipital gyrus) connectivity, discriminating iRBD from PD patients and healthy controls. However, these results did not survive correction for multiple comparison. A recent study found reduced connectivity between the brainstem seed and the bilateral posterior cerebellum, left temporal lobe and anterior cingulate region in iRBD patients relative to healthy controls (G. Li et al., 2021). Connectivity with the cerebellum and anterior cingulate regions negatively correlated with the autonomic function in iRBD patients (G. Li et al., 2021).

However, these previous studies did not cover the investigation of the whole-brain network. When using a whole-brain threshold-free node-based approach and graph theoretical measures, Campabadal and colleagues (2020) reported reduced cortico-cortical functional connectivity in posterior regions in iRBD patients compared to controls. This study additionally found that iRBD patients had reduced local measures of betweenness centrality in the left superior parietal region compared to controls, but global topological metrics did not differ between groups (Campabadal et al., 2020). In a larger study, iRBD patients relative to controls displayed reduced fronto-striatal connectivity within the executive control network, weaker midbrain-pallidum connectivity within the basal ganglia network, and reduced connectivity

within the sensorimotor network (Wakasugi et al., 2021). There were a few studies that found a relationship between functional connectivity and clinical measures in iRBD patients. One such study noted a correlation between the connectivity of the inferior temporal and the superior parietal regions with the speed processing cognitive measure (Campabadal et al., 2020). Another study uncovered that iRBD patients' global cognition score was associated with the functional connectivity in bilateral precuneus determined through multivariate pattern analysis (Byun et al., 2021). Interestingly, these different methodological approaches all highlight the posterior-based functional connectivity signatures (Byun et al., 2021; Campabadal et al., 2020) coupled with the classic fronto-striatal deficits (Wakasugi et al., 2021) in iRBD patients that is consistently observed in PD patients (Tang & Strafella, 2012; Valli, Mihaescu, & Strafella, 2017).

When using a seed-based approach of a priori regions of interest based on grey matter loss in PD patients with RBD, functional connectivity was lower between the right superior occipital gyrus and posterior regions including the left fusiform gyrus, left calcarine sulcus, and left superior parietal gyrus compared to PD patients without RBD. The reduced connectivity between the superior occipital gyrus and the superior parietal gyrus positively correlated with cognition (Jiang et al., 2021).

In a study that explored the whole-brain functional connectivity differences between PD patients with and without probable RBD using a threshold-free network-based approach, authors found that medicated PD patients with probable RBD had reduced functional connectivity between the right ventral posterior cingulate and left medial precuneus compared to PD patients without RBD. In addition, PD patients with probable RBD had reduced connectivity between the cingulate cortex and temporal, frontal, insular, and thalamic regions compared to healthy controls (Oltra, Campabadal, et al., 2021). These functional connectivity abnormalities were associated with the visuo-perceptual function in PD patients with probable RBD. The study also used graph theory analysis to find increased normalized characteristic path length, as a global graph measure, in PD patients with probable RBD compared with PD patients. This finding was also present when comparing PD patients with and without probable RBD stratified by the

presence of mild cognitive impairment (i.e., increased normalized characteristic path length in PD patients with probable RBD with MCI in comparison to PD patients with MCI and without RBD) (Oltra, Campabadal, et al., 2021). Having a longer path length means this network is less efficient overall in integrating information at the whole-brain level.

In another study investigating *de novo* patients from the PPMI dataset, PD patients with probable RBD, PD patients and healthy controls all displayed small world topology with intact global graph measures (J. Li et al., 2020), consistent with the previously described study involving iRBD patients (Campabadal et al., 2020). However, local measurements differentiated PD patients with probable RBD from PD patients, with the former having increased nodal efficiency in the thalamus and betweenness centrality in the left insula, but reduced betweenness centrality in the right dorsolateral superior frontal gyrus. Having a more efficient network in these brain regions may be compensating for the reduced thalamic volume they also observed while maintaining normal cognitive function despite disease pathology pressures. Furthermore, this study uncovered that nodal efficiency in the bilateral thalamus was positively correlated with RBD sleep questionnaire scores (J. Li et al., 2020). These network measure abnormalities unique to the PD with RBD group may be a potential pathological biomarker that merits further exploration.

In a study using independent components as inputs to compute windowed brain connectivity states, PD patients with probable RBD engaged in a brain pattern characterized by weaker positive couplings between the visual and default mode network, basal ganglia and default mode network, and within the default mode network itself compared to PD patients. Furthermore, PD patients with probable RBD dwelled significantly more time in the sparse state while the healthy controls dwelled more time in the connected state (Gan et al., 2021).

Summary of the functional alterations

These functional studies found evidence of disruptions in cortico-cortical, nigrostriatal, and striato-cortical functional connectivity in iRBD patients which was linked to the presence of cognitive

decline, autonomic dysregulation and motor impairment (Campabadal et al., 2020; Dayan & Browner, 2017; G. Li et al., 2021; Yamada et al., 2019). In line with structural MRI abnormalities, a cortical posterior-based functional connectivity signature (Byun et al., 2021; Campabadal et al., 2020) coupled with the classic fronto-striatal deficits (Wakasugi et al., 2021) and insular connectivity dysfunction linked to non-motor symptoms in PD (Christopher, Koshimori, Lang, Criaud, & Strafella, 2014; Christopher et al., 2013) was also observed in iRBD patients. These findings were consistently similar in PD patients with RBD, with whole-brain cortico-cortical and striato-cortical functional disruptions. Interestingly, along the PD course, global whole-brain architecture disruptions emerge within the subtype of PD patients with RBD (J. Li et al., 2020; Oltra, Campabadal, et al., 2021). Future studies using advanced analytical approaches such as machine learning and graph theory analysis are needed to better understand the underlying neural substrates driving iRBD and the role RBD takes in PD pathology.

Conclusion

This review revealed a wealth of multimodal neuroimaging evidence that indicate iRBD patients and PD patients suffering from RBD face alterations to the dopaminergic system, cholinergic system, blood perfusion and glucose metabolism. Outside the brainstem, structural and functional changes were found to involve the nigrostriatal system, limbic system, and the cortex—suggesting that RBD is a multi-systemic neurodegenerative process. Future studies are encouraged to follow iRBD patients longitudinally—even when they develop an alpha-synuclein disorder such as PD—using multimodal imaging techniques with multivariate analytical techniques. Taking novel steps may facilitate effective prediction of individuals who will develop an alpha-synuclein disorder and potentially aid in the development of new treatments for patients affected by RBD.

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Conflict of Interest

MV, CU, and AM declare that they have no conflict of interest. APS was a consultant for Hoffman La Roche; received honoraria from GE Health Care Canada LTD, Hoffman La Roche.

Authors' Contributions (CRediT)

Conceptualization: MV and APS; **Data Curation**: MV and CU; **Investigation**: MV and CU; **Writing – Original Draft**: MV and CU (equal); **Writing – Review & Editing**: MV, CU, AM, and APS; **Supervision**: APS; **Funding Acquisition**: APS.

Data Accessibility

Data sharing not applicable—no new data generated.

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Figure Legends

Figure 1: Representative images from healthy controls, iRBD and PD patients with the five imaging modalities are displayed here (Knudsen et al., 2018). (A) The [^{11}C]donepezil uptake within the gut, reflecting the cholinergic innervation, is reduced in iRBD and PD patients relative to controls. The arrows point to the transverse colon. (B) There is no uptake of [^{123}I]MIBG SPECT of the heart (indicated by an arrow) in iRBD and PD patients in comparison to controls. (C) Neuromelanin imaging of the locus coeruleus (LC; indicated with the arrows). The signal intensity and size are the highest in controls, but lower in both patients with iRBD and PD. (D) Thalamic norepinephrine transporter availability, indexed by the [^{11}C]MeNER radioligand, is lower in the patient groups relative to the controls. (E) Putamen [^{18}F]DOPA uptake (shown with arrows), which reflects AADC levels, is lower in some iRBD patients, but significantly reduced in PD patients compared to controls (Knudsen et al., 2018).

Reprinted from The Lancet, 17, Knudsen K, Fedorova TD, Hansen AK, Sommerauer M, Otto M, Svendsen KB, Nahimi A, Stokholm MG, Pavese N, Beier CP, Brooks DJ, and Borghammer P, In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study, 618-628, Copyright (2018), with permission from Elsevier.

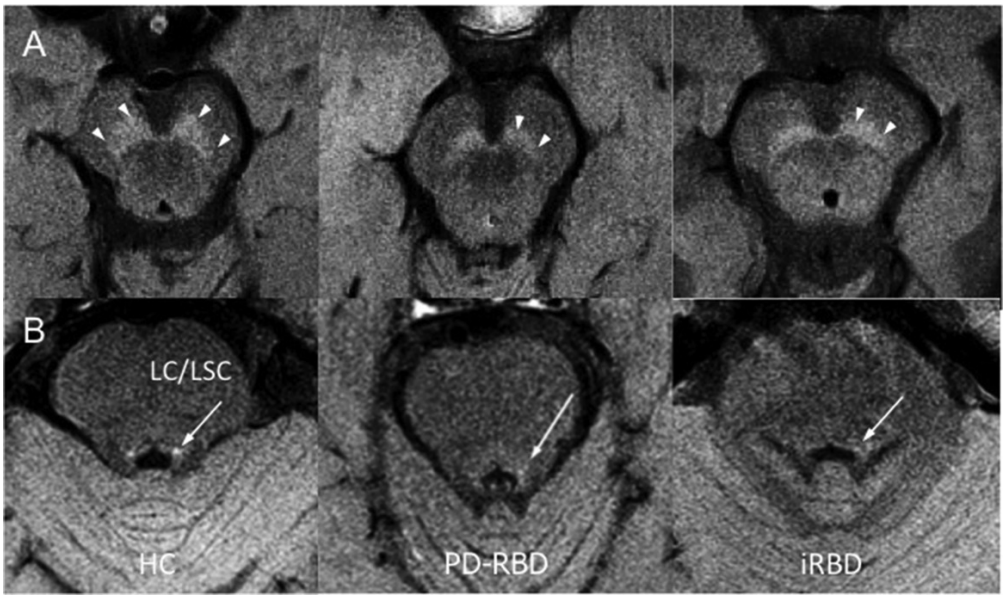
Figure 2: The upper panel displays striatal [^{18}F]DOPA uptake in an iRBD patient (right) and a healthy control (left). Note the reduced red intensity in the iRBD patient compared to the control, reflecting lower AADC availability within the striatum. The lower panel shows the [^{11}C]PK11195 binding within the substantia nigra in a patient with iRBD (right) and a healthy control (left). Note the increased red intensity for the iRBD patient relative to the control, which indicates greater microglial activation in the substantia nigra (Stokholm et al., 2017).

Neuroimaging iRBD and PD patients with RBD

Reprinted from The Lancet, 16, Stokholm GM, Iranzo A, Østergaard K, Serradell M, Otto M, Svendsen KB, Garrido A, Vilas D, Borghammer P, Santamaria J, Møller A, Gaig C, Brooks DJ, Tolosa D, and Pavese N, Assessment of neuroinflammation in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a case-control study, 789-796, Copyright (2017), with permission from Elsevier.

Figure 3: These axial images were acquired using a high-resolution spin echo T1-weighted MRI sequence. The upper panel (A) displays neuromelanin imaging of the substantia nigra while the lower panel displays the locus coeruleus/subcoeruleus area (LC/LSC) in a healthy control (HC), PD patient with RBD (PD-RBD), and a patient with iRBD, respectively. The normal substantia nigra (arrowheads) and the locus area (arrows) are visible with high signal intensity. There is a decreasing signal intensity and size of the substantia nigra and locus area going from HC to iRBD to PD-RBD (Lehericy et al., 2017).

Reproduced from Movement Disorders, 32, Lehericy S, Vaillancourt DE, Seppi K, Monchi O, Rektorova I, Antonini A, McKeown MJ, Masellis M, Berg D, Rowe JB, Lewis SJG, Williams-Gray CH, Tessitore A, Siebner HR, and International Parkinson and Movement Disorder Society (IPMDS)-Neuroimaging Study Group, The Role of High-Field Magnetic Resonance Imaging in Parkinsonian Disorders: Pushing the Boundaries Forward, 510-525, (2017). Licensed under the CC by 4.0 (https://creativecommons.org/licenses/by/4.0/).



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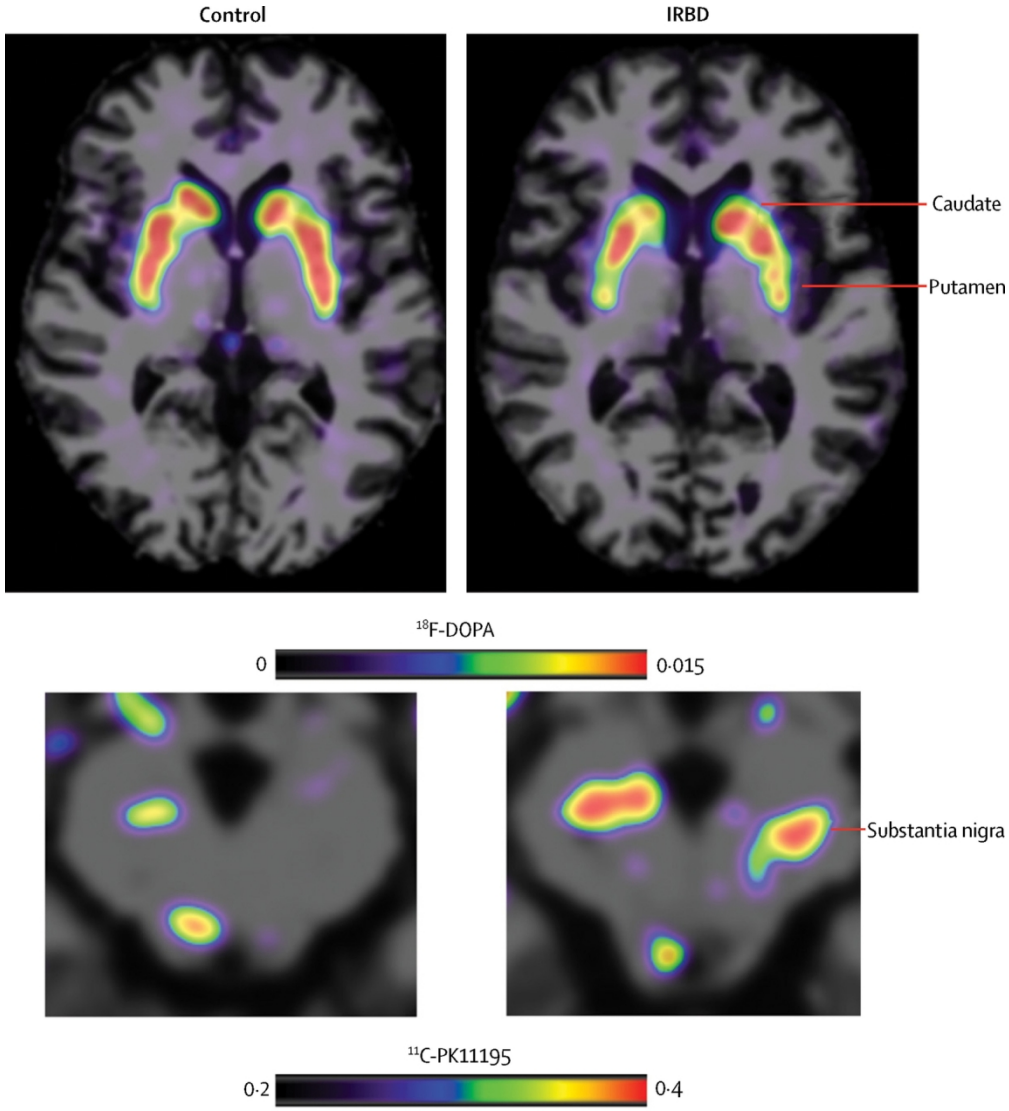

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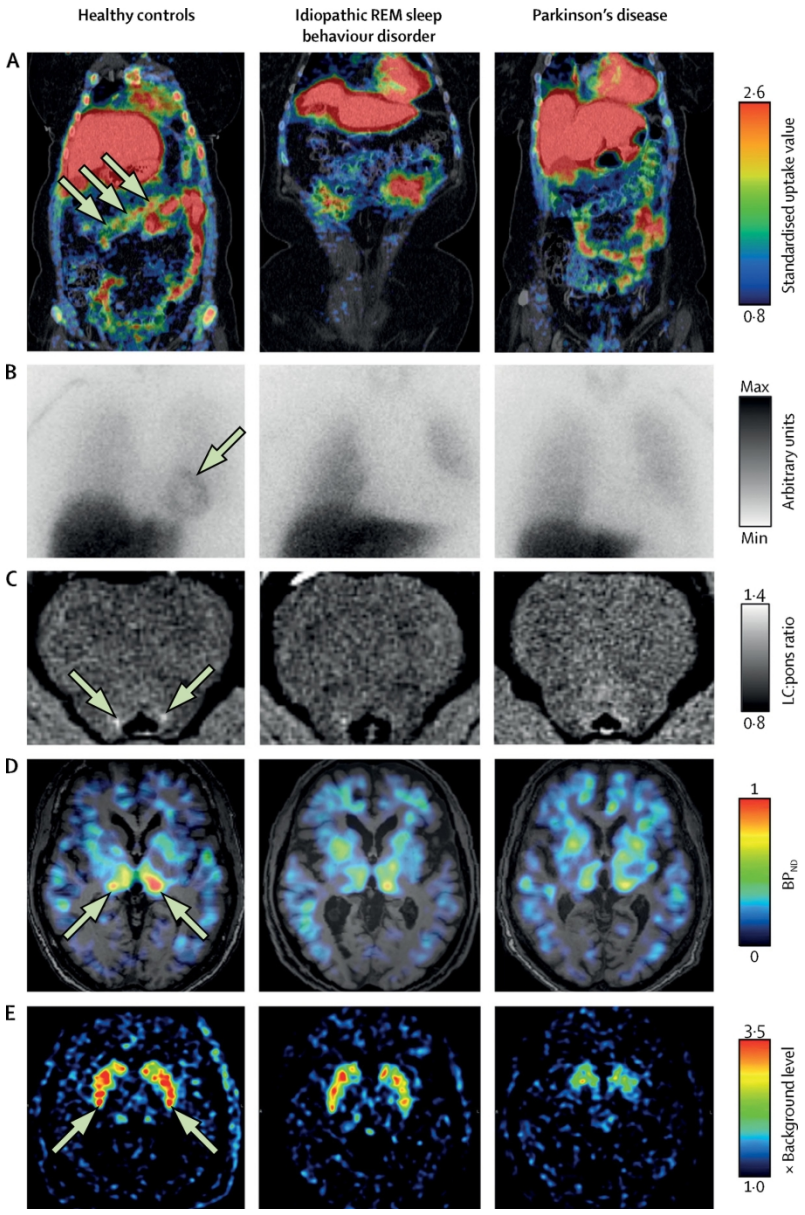

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