



Narrow doorways alter brain connectivity and step patterns in isolated REM sleep behaviour disorder

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ABSTRACT

Background: Motor impairments in those with isolated REM sleep behaviour disorder (iRBD) significantly increases the likelihood of developing Lewy body disease (e.g. Parkinson's disease and Dementia with Lewy Bodies).

Objective: This study sought to explore the prodromal process of neurodegeneration by examining the neural signature underlying motor deficits in iRBD patients.

Methods: A virtual reality (VR) gait paradigm (which has previously been shown to elicit adaptive changes in gait performance whilst navigating doorways in Parkinson's Disease - PD) was paired with fMRI to investigate whether iRBD patients demonstrated worsened motor performance and altered connectivity across frontoparietal, motor and basal ganglia networks compared to healthy controls. Forty participants (23 iRBD and 17 healthy controls) completed the virtual reality gait task whilst in the MRI scanner, and an additional cohort of 19 Early PD patients completed the behavioural virtual reality gait task.

Results: As predicted, iRBD patients demonstrated slower and more variable stepping compared to healthy control participants and demonstrated an exaggerated response when navigating narrow compared to wide doorways, a phenomenon characteristically seen in PD. The iRBD patients also demonstrated less BOLD signal change in the left posterior putamen and right mesencephalic locomotor region, as well as reduced functional connectivity between the frontoparietal network and the motor network, when navigating narrow versus wide doorways compared to healthy control participants.

Conclusions: Taken together, this study demonstrates that iRBD patients have altered task-related brain connectivity, which may represent the neural underpinnings of early motor impairments that are evident in iRBD.

1. Introduction

Rapid Eye Movement REM sleep behaviour disorder (RBD) is characterised by a loss of muscle atonia during REM sleep and the acting out of one's dreams (Boeve et al., 2007; Postuma et al., 2012). Isolated REM sleep behaviour disorder (iRBD) patients are at very high risk of developing Parkinson's Disease (PD) or Dementia with Lewy Bodies (DLB), with reported overall phenoconversion rates of 6.25% per year and the risk of phenoconversion after 12 years rising to a striking 73.5% (Postuma et al., 2019). Thus, studying this cohort provides a unique

opportunity to learn about the prodromal phase of neurodegeneration that precedes clinical diagnosis.

A recent multi-centre study has confirmed that quantitative motor testing is the strongest single predictor of phenoconversion to PD or LBD (Postuma et al., 2019; Postuma et al., 2012). In addition, a recent study has confirmed that iRBD have subtle gait abnormalities (e.g. slower gait patterns that are more variable and more asymmetric) compared to age-matched controls (McDade et al., 2013; Ehgoetz Martens et al., 2019; Ehgoetz Martens et al., 2020). Evidence from resting state functional MRI has suggested that there are measurable abnormalities in the

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connectivity within the basal ganglia in patients with iRBD compared to healthy controls (Rolinski et al., 2016). Moreover, structural gray matter abnormalities in the motor cortico-subcortical loop have also been detected in iRBD patients (Rahayel et al., 2018; Rahayel et al., 2018), and shown to be associated with early motor deficits (such as slower finger tapping) (Rahayel et al., 2018). Likewise, alternations in functional connectivity between the motor network and basal ganglia have also been noted in patients with iRBD compared to healthy controls during a dual-task virtual walking paradigm (Ehgoetz Martens et al., 2020). Indeed, these changes in brain dynamics resemble those seen in PD. Thus, a compelling next step would be to examine the neural mechanisms underlying motor abnormalities in patients with iRBD compared to healthy controls.

Here we examined the prodromal process of neurodegeneration by investigating the neural signature underlying motor deficits in iRBD patients by utilizing a previously validated virtual reality gait paradigm that has been shown to elicit specific changes in step time variability while walking through doorways in PD patients compared to healthy controls (Matar et al., 2014; Matar et al., 2019). Impaired pace, rhythmicity and variability is a signature of parkinsonian gait, which is known to be exacerbated when walking through doorways, especially when narrow since the width of a door requires scaling of motor outputs (Cowie et al., 2010; Almeida and Lebold, 2010). This work has shown that navigating narrow doorways has a more pronounced effect on speed and greater step variability in PD patients compared to healthy controls. Thus, navigating doorways of differing widths represents a unique paradigm to examine and potentially draw out early differences between iRBD patients and healthy controls. To probe for any neural signatures associated with the navigation of doorways of different widths in patients with iRBD compared to controls, we contrasted BOLD activity and functional connectivity during periods when participants walked through narrow compared to wide doorways during a well-established virtual reality gait paradigm performed inside the MRI scanner.

2. Materials and methods

2.1. Participants

Twenty-three iRBD patients confirmed using diagnostic polysomnography, and seventeen healthy control participants were recruited from the participant database at the Parkinson's Disease

Table 1
Demographic details of study participants.

	Controls (n = 17)	iRBD (n = 23)	Early PD (n = 16)	p-value (comparing HC & iRBD)
Age	65.5 (8.2)	66.9 (7.2)	62.3 (11.4)	0.56
Sex	9M	19M	12M; 2F	0.04*
Years of Education	14 (3.4)	13.7 (2.5)	13.7 (4.4)	0.75
MMSE	29.3 (1)	29 (1.1)	28.9 (1.5)	0.32
MoCA	27.8 (1.6)	27.3 (2.2)	28.1 (2.4)	0.41
HADS	4.3 (3.5)	6.6 (7.3)	7.3 (5.6)	0.23
BDI	2.0 (2.5)	3 (5.4)	4.2 (4.6)	0.58
SCOPA-S	3.2 (2.7)	3.2 (2.9)	3.9 (3.4)	0.99
Nocturnal SCOPA-S	1.7 (1.6)	2.6 (3.1)	3.3 (2.9)	0.39
Daytime SCOPA-S	2.1 (1.1)	8.4 (3.3)	3.5 (2.8)	<0.001*
Total RBDQ	4.8 (2.7)	7.3 (5.9)	6.9 (4.3)	0.18
ESS Total			19.5 (11)	
MDS-UPDRS-III				

Abbreviations: MMSE: Mini Mental State Exam; MoCA: Montreal Cognitive Assessment; HADS: Hospital Anxiety and Depression Scale; BDI: Beck Depression Inventory; SCOPA-S: SCOPA-Sleep; RBDQ: REM Sleep Behaviour Disorder Questionnaire; EES: Epworth Sleepiness Scale.

Research Centre at the Brain and Mind Centre in Sydney, Australia (see Table 1 for participant demographics). Participants underwent a neurological assessment by a neurologist and movement disorder specialist (SJGL), and did not satisfy diagnostic criteria for PD, DLB or MSA (McKeith et al., 2017; Berg et al., 2018; Gilman et al., 2008). Additionally, a clinical motor assessment using the Unified Parkinson's Disease Rating Scale (Goetz et al., 2008) was also performed on every participant. All elements of the MDS-UPDRS-III were included as part of the initial neurological assessment. Cognition was assessed using the Mini Mental State Examination as well as the Montreal Cognitive Assessment (Gill et al., 2008). All healthy control and iRBD participants which took part in this study, were also part of a larger ongoing cohort study which has been published on previously (Ehgoetz Martens et al., 2020). Additionally, a supplementary Parkinson's cohort (n = 16) who were less than five years from diagnosis, also performed the behavioural virtual gait paradigm in their 'on' dopaminergic state. This group was included to illustrate the similarity in behaviour while navigating narrow compared to wide doorways between the iRBD and early PD patients. The current study received ethical approval from the University of Sydney Human Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

2.2. Protocol

All participants completed a virtual reality gait paradigm while lying supine in the MRI scanner (Fig. 1. As per previous work (Shine et al., 2013; Shine et al., 2013; Matar et al., 2013), foot pedals were positioned at the participants' feet and they were instructed to tap the pedals in a comfortable rhythm to navigate forward through the virtual reality environment, which consisted of a straight corridor with wide and narrow doorways. Walking and stopping in the virtual environment were initiated by simple and complex cue words that were briefly displayed on the screen (for further details please refer to (Shine et al., 2013; Shine et al., 2013; Matar et al., 2013). Before scanning, all participants were familiarized with the task.

Footsteps were collected by recording the timing of each sequential pedal depression. From this output, the modal footstep latency (i.e. step time) and variability (i.e. coefficient of variation of step time) were calculated for epochs in which the participants navigated through wide and narrow doorways by extracting timing information from six consecutive steps (i.e. three steps prior to the door and three steps after walking through the door). These event times were also extracted, modelled and contrasted to further examine differences in BOLD responses and functional connectivity between iRBD and healthy control participants in this task.

2.3. Imaging

A General Electric 3 T MRI was used to obtain T2*-weighted echo planar functional images that were acquired in sequential order with repetition time = 3 s, echo time = 32 ms, flip angle = 90 degrees, 40 axial slices covering the whole brain, field of view = 250 mm, slice spacing = 0 mm and raw voxel size = 3.9 mm × 3.9 mm × 4 mm thick. High-resolution 3D T1-weighted anatomical images with voxel size = 0.4x0.4x0.9 mm were obtained for co-registration with functional scans.

Statistical Parametric Mapping Software (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK, <http://www.fil.ion.ucl.ac.uk/spm/software/>) was used for image pre-processing, according to the SPM 12 standard pipeline. Functional scans were: (i) manually realigned along the anterior-posterior commissure; (ii) slice time corrected to the median (21st) slice in each repetition time; (iii) realigned to create a mean realigned image (measures representing 6 degrees of rigid head movements were calculated for later use in the correction of minor head movements); (iv) unwarped to deal with residual movement related variance induced by the susceptibility-by-movement interaction effects;



Fig. 1. Study protocol. Left - Participants had the foot pedals placed comfortably at their feet while lying in the MRI scanner; Middle - Display of the virtual reality paradigm while approaching a wide doorway; Right - Display of the virtual reality paradigm while approaching a narrow doorway.

(v) spatially normalized using the T1-weighted image to improve segmentation accuracy; (vi) co-registered and estimated; and (vii) smoothed using an 8-mm full-width at half maximum isotropic Gaussian kernel. Spatial normalization was then manually checked for quality assurance.

Multiple precautions were taken to ensure head motion was fully accounted for: (i) all subjects were instructed to minimize head motion by only moving the ankles to depress the foot pedals, carefully keeping the legs and hips (and hence, the torso and head) stationary; (ii) cushions were placed inside the head coil to ensure optimal performance with the least amount of head motion; (iii) following data collection, trials with >3 mm or 3 degrees of scan-to-scan movement were considered a-priori exclusion criterion; (iv) *ArtRepair* was used to analyse each trial and applied the interpolation method to correct for large amounts of global drift or scan-to-scan head movement >1.5 mm; and (v) six motion and nuisance regressors were regressed out of each participants' extracted time series. Finally, it was verified that there were no differences in framewise displacement between healthy controls (1.8 ± 0.2) and iRBD patients (2.4 ± 0.4 ; $t = 1.13$, $p = 0.27$).

2.4. Regions of Interest

For the neuroimaging analysis, key subcortical and cortical regions of interest (ROI) across the motor and frontoparietal networks were pre-

Table 2
Regions of Interest from the functional imaging analysis.

	Left			Right		
	x	y	z	x	y	z
M1	-8	-31	60	8	-31	60
preSMA	-9	6	53	9	6	53
PMd	-30	-4	58	30	-4	58
supOFC	-12	41	-16	12	41	-16
CBM	-27	-58	-25	27	-58	-25
ACC	-8	50	11	8	50	11
DLPFC	-45	11	34	45	11	34
PPC	-52	-49	47	52	-49	47
Thal	-8.5	-12	14	8.5	12	14
STN	-11	-14	-7	13	-14	-7
DCP	-28	1	3	28	1	3
PP	-26	-8	8	26	-8	8
DRP	-25	8	6	25	8	6
VRP	-20	12	-3	20	12	-3
DC	-13	15	9	13	15	9
VSSs	-10	15	0	10	15	0
VSi	-9	9	-8	9	9	8
CLR	0	-49	-20	0	-49	-20
MLR	-4	-30	-18	4	-30	-18

Abbreviations: M1: primary motor cortex; preSMA: pre-supplementary motor area; PMd: dorsal premotor cortex; supOFC: superior orbital frontal cortex; CBM: cerebellum; ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; PPC: posterior parietal cortex; Thal: thalamus; STN: subthalamic nucleus; DCP: dorsal caudal putamen; PP: posterior putamen; DRP: dorsal rostral putamen; VRP: ventral rostral putamen; DC: dorsal caudate; VSSs: superior ventral striatum; VSi: inferior ventral striatum; CLR: cerebellar locomotor region; MLR: mesencephalic locomotor region.

defined as seeds for the functional connectivity analyses (see Table 2). These ROIs were selected based on previous work that has investigated a similar virtual reality gait task and related step time variability in healthy older adults and people with PD (Gilat et al., 2017). In keeping with previous work, we separated the striatum into 7 distinct ROIs of 2 mm spheres (Bell et al., 2015). Cortical 8 mm spheres and subcortical 2 mm spheres were centered on MNI coordinates from these previous studies.

3. Statistical analyses

3.1. Virtual reality gait behaviour

To examine behavioural differences between iRBD patients and healthy control participants during the virtual reality gait task, mixed repeated measures ANOVAs (condition: wide, narrow \times group: iRBD, HC) were carried out for step time and step time variability. Separate mixed repeated measures ANOVAs (condition: wide, narrow \times group: iRBD, PD) were carried out to confirm the similarity in behaviour while navigating narrow compared to wide doorways between the iRBD and Early PD patients. The alpha significance level was set to $p < 0.05$.

3.2. Event-related BOLD signal analysis

To contrast walking through narrow versus wide doorways, we extracted the onset time and duration for epochs including three steps before and three steps after crossing either a narrow or wide doorway from the virtual reality output. To investigate brain regions that had greater or less BOLD response while navigating narrow compared to wide doorways, a first level general linear model was implemented in SPM12 for each participant, contrasting epochs of narrow doorways to wide doorways (narrow $>$ wide) using an event-related approach. The data was modelled according to a canonical hemodynamic response function. At the second level, multi-subject analysis was computed on the mean contrast after sex was regressed out.

3.3. Functional connectivity analysis

A seed-based functional connectivity analysis was conducted to analyse functional connectivity across the 37 pre-defined regions using the Marsbar toolbox. Time series data were extracted from the first level general linear model for each of the 37 ROIs. Functional connectivity analyses were performed by fitting the BOLD signal from the narrow versus wide doorway contrast to the general linear model and then using the multiplication of temporal derivatives metric (Shine et al., 2015) to compute the average correlation between regions over time. Sex was regressed out of the functional connectivity contrast. Non-parametric permutation testing (5000 iterations) was performed to correct for multiple comparisons (Nichols and Holmes, 2002) and identified results that were more extreme than the 2.5th and 97.5th percentile of the permutation distribution ($p < 0.05$). Additionally, a strict family wise error (FWE) correction was also carried out by obtaining that maximum value across all the ROIs for each permutation, and counting the number of times the uncorrected value was more extreme than the 2.5th and

97.5th percentile of the max distribution.

To further examine how the task-based neural signature related to changes in gait variability within the iRBD group when walking through the narrow compared to wide doorways, we correlated the raw functional connectivity matrix to the difference in gait variability (i.e. step time variability) between narrow and wide doorways. We then applied nonparametric permutation testing to correct for multiple comparisons as described above.

4. Results

4.1. Virtual reality gait behaviour

The iRBD participants demonstrated a longer (i.e., slower) step time overall compared to controls ($F(1,38) = 11.55$, $p = 0.002$) and all participants demonstrated an effect of condition ($F(1,38) = 5.25$, $p = 0.028$), such that participants increased their step time while walking through the narrow compared to wide doorway. In addition, there was a significant interaction between condition and group ($F(1,38) = 4.46$, $p = 0.041$), which revealed that iRBD patients had an exaggerated response to the narrow doorway (Fig. 2A). Notably, there were no significant group differences between iRBD and Early Parkinson's patients ($F(1,37) = 0.15$, $p = 0.7$) when comparing foot step latency while navigating narrow and wide doorways.

All participants demonstrated greater step time variability while navigating narrow doorways compared to wide ($F(1,38) = 7.2$, $p = 0.011$). However, iRBD participants demonstrated worse variability compared to control participants in both doorway conditions ($F(1,38) = 7.02$, $p = 0.012$). There was a trend toward an interaction between

condition and group ($F(1,38) = 3.71$, $p = 0.062$), such that the narrow doorways seemed to exaggerate stepping variability more in the iRBD cohort compared to the healthy controls (Fig. 2B). Indeed, a priori planned comparisons confirmed that iRBD patients did demonstrate significantly greater step-to-step variability while navigating through the narrow doorways compared to healthy controls ($p = 0.003$) but were only marginally different from healthy controls when navigating wide doorways ($p = 0.05$). There was also no main effect of group between the Early Parkinson's and iRBD groups step time variability ($F(1,37) = 0.38$, $p = 0.54$), however a significant condition \times group interaction ($F(1,37) = 7.23$, $p = 0.011$) revealed that iRBD patients showed a significant increase in step time variability when navigating narrow compared to wide doorways ($p = 0.005$), while Early PD patients (in their 'on' state) demonstrated high levels of variability across both doorway sizes ($p = 0.22$).

4.2. Event-related BOLD signal changes

After regressing sex and correcting for multiple comparisons using a parametric null model hypothesis test (Nichols and Holmes, 2002), greater BOLD signal change in the right mesencephalic locomotor region was found while navigating narrow doorways compared to wide doorways in the healthy control participants compared to iRBD patients ($p = 0.029$; corrected for multiple comparisons; did not survive strict FWE correction). While both iRBD and healthy control participants also demonstrated greater BOLD signal in the left posterior putamen while navigating narrow doorways compared to wide doorways, healthy controls demonstrated a greater change from wide to narrow doorways compared to iRBD patients ($p = 0.024$; corrected for multiple

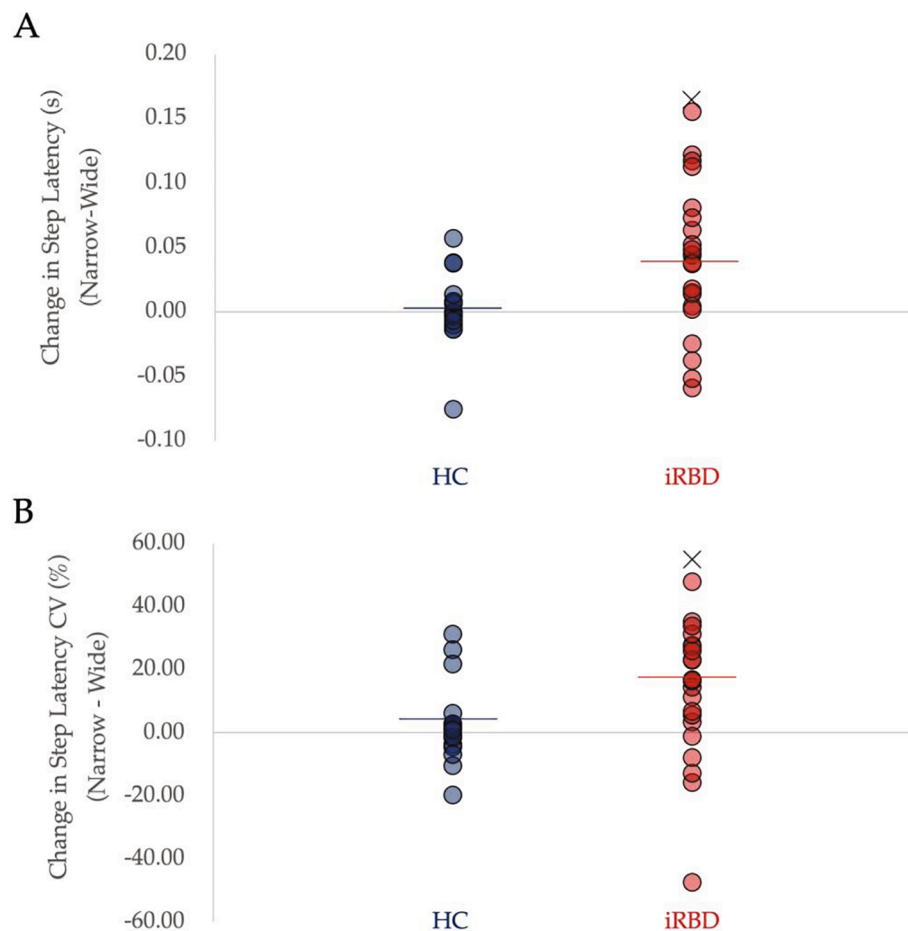


Fig. 2. iRBD patients demonstrated slower (A) and more variable (B) walking behaviour compared to healthy controls, particularly when navigating through a narrow doorway. Note that the 'x' denotes an outlier rescaled to two standard deviations from the mean. Removal of this outlier did not change the findings reported.

comparisons; did not survive strict FWE correction) (see supplementary figure). Both these group differences survived multiple comparison corrections with non-parametric null model, although they did not survive the strict FWE correction when using the max values of the distribution across all the ROIs.

4.3. Mean effect of doorways on functional connectivity in healthy participants

To understand the functional connectivity required to navigate a narrow compared to a wide doorway in a healthy brain, we examined the mean functional connectivity in healthy control participants for this contrast. It is important to emphasize that we are not reporting significant findings here, instead we report a mean connectivity map thresholded to show connections which exceeded a moderate correlation ($z > 0.25$) to aid in the interpretation of differences between healthy controls and iRBD patients (i.e. not for statistical inference). While navigating narrow compared to wide doorways, healthy control participants demonstrated increased connectivity between the cerebellar locomotor region and left mesencephalic locomotor region, increased connectivity between the left and right mesencephalic locomotor region, as well as increased connectivity between the left mesencephalic locomotor region and the left dorsal lateral prefrontal cortex (See Fig. 3A). In contrast, reduced interhemispheric connectivity between the left and right thalamus, the left and right superior orbital frontal cortex as well as between the left and right ventral superior and inferior striatum was observed in healthy control participants while navigating narrow compared to wide doorways. Finally, reduced connectivity was also found between bilateral thalamus and (i) the left dorsal caudate, and (ii) the cerebellar locomotor region.

4.4. iRBD versus healthy participants

To understand the group differences in functional connectivity required to navigate a narrow compared to a wide doorway (narrow > wide), we examined the contrast in functional connectivity (narrow > wide) between groups. While navigating narrow compared to wide doorways, iRBD patients had significantly reduced functional connectivity in the cortex, between frontoparietal and motor regions, compared to controls. Whereas iRBD patients showed significantly greater subcortical connectivity within the basal ganglia and between fronto-striatal regions (Fig. 3B). More specifically, iRBD patients showed significantly less functional connectivity (i.e. reduced coupling) than controls within the frontoparietal network (i.e. bilateral dorsal lateral

prefrontal cortex and left posterior parietal cortex, as well as right posterior parietal cortex and right dorsal lateral prefrontal cortex). The fronto-parietal network was also significantly less functionally connected to the motor network (i.e. left dorsal lateral prefrontal cortex and left pre-supplementary motor area; left dorsal lateral prefrontal cortex and left primary motor cortex; right dorsal lateral prefrontal cortex and right premotor cortex; and left posterior parietal cortex and bilateral premotor cortex as well as left pre-supplementary area) in iRBD patients compared to healthy controls while navigating narrow versus wide doorways. These findings remained significant after regressing sex and permutation testing, however, most did not survive when the strict FWE correction was applied. The only result that survived the strict FWE correction was that iRBD patients showed reduced functional connectivity between the left dorsolateral prefrontal cortex and the left posterior parietal cortex compared to controls.

Subcortically, iRBD patients had significantly greater functional connectivity (i.e. increased coupling) between the bilateral dorsal caudate and the right inferior ventral striatum. Significantly greater functional connectivity was also seen in iRBD patients between the right inferior ventral striatum and the left pre-supplementary motor area as well as the anterior cingulate cortex (bilaterally) compared to healthy controls. Finally, the functional connectivity between the left pre-supplementary motor area and left thalamus was significantly greater in iRBD patients compared to controls. These findings remained significant after regressing sex and permutation testing, however, did not survive when the strict FWE correction was applied.

Note that the cerebellar locomotor region was significantly less functionally connected to the mesencephalic locomotor region (bilaterally) in iRBD patients compared to healthy controls during the task, however this did not remain significant after regressing sex.

4.5. Relationship between functional connectivity and gait variability within iRBD patients

To further understand the relationship between brain functional connectivity and changes in gait variability seen in iRBD patients in response to doorway width, we correlated the raw functional connectivity matrix to the difference in gait variability (i.e. step time variability) between narrow and wide doorways, and then applied permutation testing to adjust for multiple comparisons (Fig. 4). We found a positive relationship between the change in step time variability and the functional connectivity: (1) between the bilateral anterior cingulate cortex and the left dorsolateral prefrontal cortex (L: $p = 0.028$; R: $p = 0.039$) as well as bilateral cerebellum ($p < 0.01$), (Postuma et al., 2012)

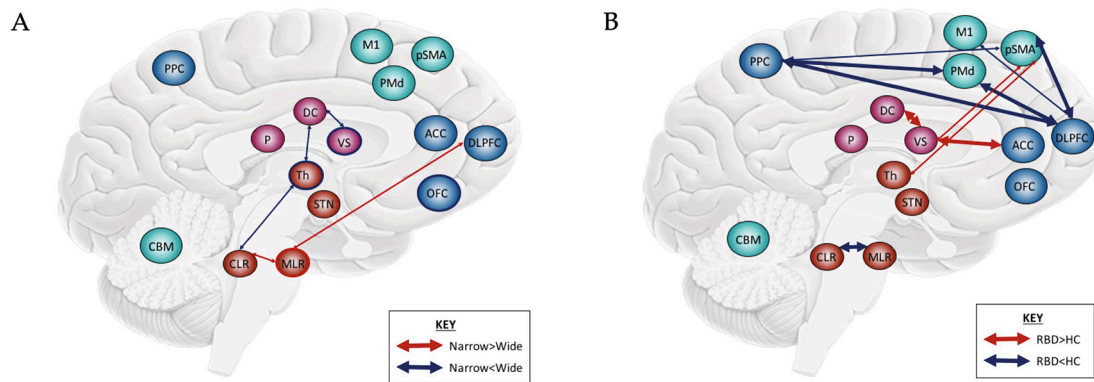


Fig. 3. (A) displays the mean connectivity within healthy control participants when navigating narrow compared to wide doors; (B) displays the schematic group differences between iRBD patients and healthy controls for the narrow vs wide contrast. Note the weight of the line indicates the strength of the correlation. Abbreviations: M1: primary motor cortex; preSMA: pre-supplementary motor area; PMd: dorsal premotor cortex; supOFC: superior orbital frontal cortex; CBM: cerebellum; ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; PPC: posterior parietal cortex; P: posterior putamen; DRP: dorsal rostral putamen; VRP: ventral rostral putamen; DC: dorsal caudate; VS: superior ventral striatum; VS: inferior ventral striatum; CLR: cerebellar locomotor region; MLR: mesencephalic locomotor region.

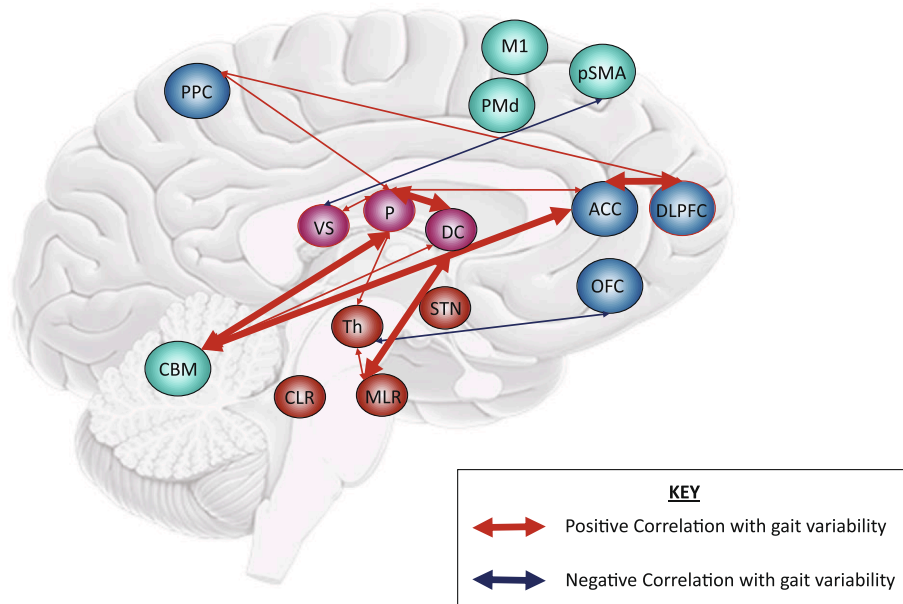


Fig. 4. Illustration of the significant relationships between the brain functional connectivity signature and the change in gait variability (i.e. step time variability) in iRBD patients. Abbreviations: M1: primary motor cortex; preSMA: pre-supplementary motor area; PMd: dorsal premotor cortex; supOFC: superior orbital frontal cortex; CBM: cerebellum; ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; PPC: posterior parietal cortex; Thal: thalamus; STN: subthalamic nucleus; DCP: dorsal caudal putamen; PP: posterior putamen; DRP: dorsal rostral putamen; VRP: ventral rostral putamen; DC: dorsal caudate; VS: superior ventral striatum; VSi: inferior ventral striatum; CLR: cerebellar locomotor region; MLR: mesencephalic locomotor region.

between the left and right dorsolateral prefrontal cortex ($p = 0.028$), (Postuma et al., 2019) between right posterior parietal cortex to the bilateral dorsolateral prefrontal cortex (L: $p = 0.046$; R: $p = 0.001$), (Postuma et al., 2012) between the left posterior parietal cortex and the left dorsal caudal putamen ($p = 0.038$) as well as left dorsal rostral putamen ($p = 0.007$), (McDade et al., 2013) between the bilateral cerebellum and the right dorsal rostral putamen (L: $p = 0.005$; R: $p = 0.003$) as well as between the left cerebellum and the left posterior putamen ($p = 0.035$), right dorsal caudal putamen ($p = 0.048$), and right dorsal caudate ($p = 0.012$), (Ehgoetz Martens et al., 2019) between the bilateral mesencephalic locomotor region and the right dorsal caudate (L: $p = 0.025$; R: $p = 0.04$) as well as the left mesencephalic locomotor region and the left dorsal caudate ($p = 0.023$), and finally (Ehgoetz Martens et al., 2020) between the right mesencephalic locomotor region and right thalamus ($p = 0.019$). We also found a positive relationship between the change in step time variability and the functional connectivity (Boeve et al., 2007) within the dorsal putamen sub-regions, (Postuma et al., 2012) within the ventral striatum, as well as (Postuma et al., 2019) between the dorsal putamen and the dorsal caudate, and (Postuma et al., 2012) between the dorsal putamen and the ventral striatum (see supplementary data for the sub-region p-values). Finally, a negative relationship was found between the change in step time variability and functional connectivity was found between (Boeve et al., 2007) the right thalamus and right superior orbitofrontal cortex ($p = 0.043$), and (Postuma et al., 2012) the left pre-supplementary motor area and the right inferior ventral striatum ($p = 0.039$).

5. Discussion

Here, we report reduced functional connectivity between the frontoparietal and motor networks in iRBD patients that corresponds to a distinct Parkinson-like motor pattern of reduced speed and increased stepping variability while navigating narrow (compared to wide) doorways in a virtual reality paradigm. The emergence of this neural signature in patients with iRBD may reflect mechanisms of early neurodegeneration and be a viable target for future preventative therapeutic strategies.

5.1. Narrow doorways exaggerate motor impairments in iRBD

We confirm that iRBD patients had significantly greater motor impairments than healthy controls (Postuma et al., 2012; McDade et al., 2013; Ehgoetz Martens et al., 2019), and present novel data on difficulties navigating narrow doorways during the virtual reality gait task. Furthermore, our results resembled gait behaviours characteristically seen in Parkinson's patients (Matar et al., 2014; Cowie et al., 2010; Almeida and Lebold, 2010; Cowie et al., 2012; Matar et al., 2019). It is also noteworthy that iRBD patients are more likely to go on to develop the 'Postural Instability and Gait Disordered' subtype of PD (Kumru et al., 2007), which is typically the group of PD patients (i.e. Freezers) who exemplify this exaggerated locomotor response when crossing doorways (Matar et al., 2014; Almeida and Lebold, 2010; Cowie et al., 2012; Matar et al., 2019). In fact, recent work by Matar and colleagues (2019) showed that footstep latency while navigating doorways was significantly slower in the OFF state compared ON state in PD Freezers (Matar et al., 2019).

5.2. Neural signature of motor impairment in iRBD patients

In addition to finding measurable behavioural differences that distinguished iRBD patients from healthy controls, we also observed task-based functional impairments in both BOLD signal changes and network connectivity in iRBD patients allowing a neural signature to be determined for these early motor deficits. Specifically, iRBD patients demonstrated less BOLD signal change compared to healthy controls in the left posterior putamen, as well as little change in the mesencephalic locomotor region while walking through narrow versus wide doorways compared to healthy control participants. This observation may indicate early functional impairments in subcortical regions that are critical for planning, coordinating and controlling locomotion (Garcia-Rill et al., 1983; Jahn et al., 2008; Tattersall et al., 2014). Although there is a complex interplay between the network of neurons within the mesencephalic locomotor region (MLR), there are extensive connections with the basal ganglia (e.g. the MLR receives strong inhibitory inputs from both the globus pallidus internus and substantia nigra) (Takakusaki

et al., 2003). Therefore, the interaction between the basal ganglia and mesencephalic locomotor region observed in this study might explain slower and more variable gait in iRBD patients, especially since recent work has shown a robust relationship between gait speed and activity within different nuclei within the mesencephalic locomotor region (i.e. cuneiform and pedunculopontine nucleus) (Caggiano et al., 2018). Furthermore, this notion was supported by the correlational results which showed that greater change in gait variability within the iRBD patients when navigating the narrow compared to the wide doorway was associated increased functional connectivity between the mesencephalic locomotor region and the dorsal caudate.

Recent findings comparing Freezers who navigated narrow and wide doorways in their ON and OFF dopaminergic state showed that the degree of footstep latency when passing through doorways was positively correlated with increased functional connectivity between the pre-supplementary motor area (pSMA) and the subthalamic nucleus (STN) in the OFF state (relative to the ON state) (Matar et al., 2019). Whilst the current study did not find any group differences in the connectivity between the pSMA and STN, task-based functional connectivity was increased between the pSMA and ventral striatum as well as the thalamus in iRBD patients compared to controls during narrow versus wide doorway walking. Additionally, task-based connectivity between the pSMA and the ventral striatum was negatively associated with changes in gait variability when navigating the narrow compared to the wide doorway in the iRBD group. These findings may reflect more generalized impairment in networks subserving early motor deficits rather than mechanisms underlying freezing of gait which typically present in the advanced stages of disease.

Recent research using PET imaging during complex gait showed that both young and middle aged adults increased metabolic activity in frontoparietal regions (Mitchell et al., 2019). The authors note the importance of these regions for implementing visuomotor control of complex gait as well as integrating external visual information with internal movement-related goals, highlighting the crucial role of the cognitive control network for goal-oriented behaviour during complex gait (Mitchell et al., 2019). In the current study, when navigating narrow doorways, healthy controls demonstrated greater connectivity between bilateral mesencephalic locomotor regions, as well as between these locomotor regions and the dorsal lateral prefrontal cortex, in support of the notion of a greater need for top-down control of adaptive locomotion compared to navigating through the wide doorway. However, when iRBD patients were compared to healthy controls (in the narrow vs wide doorway contrast), iRBD patients displayed significantly reduced connectivity within the frontoparietal network as well as between the frontoparietal network and the motor network. One explanation for impaired motor performance while navigating narrow doorways might be reflected in the inability of iRBD patient to engage adequate top-down control of their movement to properly interact with their motor network and regulate adaptive locomotion. Navigating doorways of different sizes could also trigger alternative motor plans associated with postural and gait adjustments, which results in additional demands on higher cognitive centers to resolve the conflict of competing motor programs that encode adjustments in timing and possibly rely on top down control to achieve adaptive locomotion (Matar et al., 2019). Therefore, a failure to coordinate communication between frontoparietal and motor networks might provide another explanation for impaired motor control in iRBD patients during more complex tasks. In support of this, we found that increased connectivity within the cognitive control network was associated with greater change in step time variability in iRBD patients. Interestingly, another study by Mitchell and colleagues has shown a relationship between gait impairments and activation in the dorsal lateral prefrontal cortex in Freezers during a complex gait task (Mitchell et al., 2019). Overall, their findings suggested that Freezers may have alternate control mechanisms to regulate complex gait which are mediated by prefrontal and supplementary motor area regions (Mitchell et al., 2019). Further work is needed to

determine when these alternate (or compensatory) mechanisms develop during the disease progression, as our current findings suggest that even in the prodromal stage of disease compensatory mechanisms for complex gait control are observable.

An alternative explanation could be that iRBD patients already display impairments in sensorimotor integration (a common early impairment in Parkinson's disease) (Patel et al., 2014). A recent study by Mitchell and colleagues (2019) has shown that metabolic changes associated with aging are suggestive of declining central sensorimotor processing when investigated using PET imaging during complex walking (Mitchell et al., 2019). Furthermore, activity of neurons in the mesencephalic locomotor region, namely the PPN, have been shown to be modulated by passive limb movement, a manipulation that provides proprioceptive inputs to the PPN (Tattersall et al., 2014), and recent work has suggested that the PPN plays a key role in integrating sensory-motor information from many brain structures (Caggiano et al., 2018). Likewise, visual information about doorway size may not be properly integrated with locomotor control processes, reflected through the reduced connectivity between the posterior parietal and premotor cortices. Previous work in cats, show that lesions to the posterior parietal cortex leads to an inability to modify walking patterns on the basis of visual input (Drew et al., 2008). Furthermore, Cowie and colleagues proposed that the posterior parietal cortex is important for processing visual inputs (external visuospatial cues and associated affordances) used to adjust basic locomotor patterns, and thus this area is sometimes thought of as a key connector of the visual system to the pre-motor system (Cowie et al., 2010), which may offer another interpretation for these findings.

Previous resting state fMRI work has shown that iRBD patients have significantly reduced coactivation within the basal ganglia network at rest (similar to Parkinson's) compared to healthy controls (Rolinski et al., 2016). Thus, a somewhat unexpected finding was that iRBD demonstrated greater connectivity between the dorsal caudate and ventral striatum as well as between the ventral striatum and the frontal cortex while navigating narrow versus wide doorways compared to healthy controls. Furthermore, we found that in the iRBD group, greater connectivity within the striatum was positively associated with changes in gait variability when navigating narrow compared to wide doorways. We postulate that this finding might reflect similar degeneration within the basal ganglia that was shown in Rolinski's study (2016) at rest, such that the basal ganglia lose their segregated circuitry during a task as well. It has been put forward that degeneration commences in the dorsal posterior putamen and progresses toward the dorsal caudate in Parkinson's disease (Rolinski et al., 2016). Thus, the pattern of connectivity that is observed in this study may reflect compensation from other intact striatal nuclei (e.g. ventral striatum and dorsal caudate), attempting to overcome impaired processing of incoming information from the cortex in the putamen, in an effort to correct ongoing movement plans. This may also mark yet another common feature associated with Parkinson's disease, whereby the basal ganglia are unable to achieve functionally segregated loops and instead moves toward very integrated networks (Kim et al., 2017; Nieuwhof and Helmich, 2017).

It is important to acknowledge some limitations of this work. First, there was a significant difference in sex proportion between isolated RBD and control participants, reflecting the predominance of isolated RBD in males. While sex differences in overground gait characteristics are well-known, there is little evidence to suggest that sex influences performance on the virtual reality gait paradigm. This is because height and stride length, for example, do not impact tapping of the foot pedals in the same way as normal overground walking. Nonetheless, we did regress sex out of all our models which compared groups and reported the findings that remained significant after accounting for sex differences. Second, the Early PD participants performed the behavioural virtual reality gait task in their ON dopaminergic state which may have masked the severity of motor deficits present. Future research should directly compare the neural signature of Early PD and iRBD patients,

both in their OFF dopaminergic state, to better understand the extent to which iRBD demonstrate similar brain network alterations as those with Early PD. Third, our study opted for an ROI analysis which were selected regions based on previous relevant findings (Ehgoetz Martens et al., 2020; Gilat et al., 2017; Matar et al., 2019; Ehgoetz Martens et al., 2018), however this limited ROI set that were selected and used in our analysis may have also limited our findings. Despite our small clinical sample size, we attempted to correct for FWE with a strict correction, however few of the results survived when this was applied. It is important to interpret these results with caution and also acknowledge that this strict correction may have inflated Type 2 errors leading to incorrect acceptance of false negatives. Nonetheless, this unique paradigm offers a sensitive method for detecting subtle motor impairments early in the prodromal stage of neurodegeneration. Future research is needed to determine whether a short trial of the behavioural virtual reality gait paradigm is sensitive to longitudinal changes in iRBD and whether it is a useful predictor of phenoconversion.

6. Conclusion

In conclusion, this study presents novel evidence that iRBD patients have altered task-related brain connectivity, which may underlie early motor impairments that rely on sensorimotor integration and/or facilitate adaptive locomotion. We also highlight a number of clinical behavioural patterns that whilst characteristically observed in PD were also present in iRBD, a cohort which represents a prodromal stage of neurodegeneration. In addition to casting light on the neural correlates of motor impairments in iRBD patients, we also postulate that subtle gait impairments may originate prior to Parkinson's disease onset. This paradigm offers a sensitive method for detecting subtle motor impairments early in the prodromal stage of neurodegeneration and may be useful for targeted prodromal interventions to prevent severe gait impairments, falls and future development of freezing of gait, all of which represent a major burden to healthcare and to the patient's independence and well-being.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author roles

Research Project: A. Conception (KEM, SJGL), B. Organisation (KEM, EM), C. Execution (KEM, EM, JRP); Statistical Analysis: A. Design (KEM), B. Execution (KEM, JMS), C. Review and Critique (JMS, EM, GMH, SJGL); Manuscript: A. Writing of the first draft (KEM), B. Review and Critique (EM, JRP, JMS, SJGL, RRG, GMH).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2022.102958>.

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