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The functional brain connectome in isolated rapid eye movement sleep behavior disorder and Parkinson's disease

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ABSTRACT

Background: Isolated rapid-eye-movement behavior disorder (iRBD) often precedes the development of alpha-synucleinopathies such as Parkinson's disease (PD). Magnetic resonance imaging (MRI) studies have revealed structural brain alterations in iRBD partially resembling those observed in PD. However, relatively little is known about whole-brain functional brain alterations in iRBD. Here, we characterize the functional brain connectome of iRBD compared with PD patients and healthy controls (HC) using resting-state functional MRI (rs-fMRI).

Methods: Eighteen iRBD subjects (67.3 ± 6.6 years), 18 subjects with PD (65.4 ± 5.8 years), and 39 age- and sex-matched HC (64.4 ± 9.2 years) underwent rs-fMRI at 3 T. We applied a graph theoretical approach to analyze the brain functional connectome at the global and regional levels. Data were analyzed using both frequentist and Bayesian statistics.

Results: Global connectivity was largely preserved in iRBD and PD individuals. In contrast, both disease groups displayed altered local connectivity mainly in the motor network, temporal cortical regions including the limbic system, and the visual system. There were some group specific alterations, and connectivity changes were pronounced in PD individuals. Overall, however, there was a good agreement of the connectome changes observed in both disease groups.

Conclusions: This study provides evidence for widespread functional brain connectivity alterations in iRBD, including motor circuitry, despite normal motor function. Connectome alterations showed substantial resemblance with those observed in PD, underlining a close pathophysiological relationship of iRBD and PD.

1. Introduction

Isolated rapid-eye-movement (REM) sleep behavior disorder (iRBD) is characterized by a loss of muscle atonia during REM sleep, and dream-enactment behavior [1]. iRBD is a harbinger of alpha-synucleinopathies (ASYN) such as Parkinson's disease (PD), dementia with Lewy bodies, and multiple system atrophy. Epidemiological studies indicate that more than 70% of iRBD individuals develop an ASYN within 12 years [2].

Magnetic resonance imaging (MRI) has provided valuable insights on the interrelationship of iRBD and PD. Previous work has demonstrated that structural brain changes in iRBD overlap with those observed in PD [3–6]. iRBD subjects show reduced striatal dopaminergic integrity, exhibit network level metabolic brain changes, and display reduced striato-cortical connectivity comparable to that typically seen in PD [7–11]. More recently, resting state functional MRI (rs-fMRI) and graph theory have been employed to characterize the brain connectome in health and disease [12]. Graphs are comprised of anatomical regions

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Abbreviations

%ROPE	Percentage of data in the region of practical equivalence
(MDS)-UPDRS	(Movement disorder society)-Unified Parkinson's Disease Rating Scale
ANOVA	Analysis of variance
ASYN	Alpha-synucleinopathy
B-LM	Bayesian linear modelling
HC	Healthy control subjects
iRBD	Isolated rapid-eye-movement (REM) sleep behavior disorder
LEDD	Levodopa equivalent daily dose
MMSE	Mini-Mental state exam
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
PD	Parkinson's disease
pd	Probability of direction
PMC	Primary motor cortex
PPMI	Parkinson's Disease Progression Marker Initiative
PSC	Primary sensory cortex
rs-fMRI	Resting state functional MRI
SMA	Supplementary motor area

(nodes) and their links (edges). Neuronal networks display characteristic "small-world" properties [13], i.e. clustering of highly interconnected nodes (modules) that show sparse but direct interconnections with other modules of the global network, resulting in high overall efficiency [12]. Neurodegenerative diseases such as PD alter network properties and disrupt network efficiency [14,15]. Whereas a substantial body of literature has elaborated on hypothesis driven analyses of brain functional connectivity in iRBD, relatively few studies have used a hypothesis free approach to identify functional alterations at the network level and their relationship to PD pathology [16,17]. Here, we applied a graph-theoretical approach to characterize the brain connectome in iRBD in comparison with PD patients. We hypothesized that iRBD patients would exhibit functional brain changes comparable to those found in PD.

2. Material and methods

2.1. Subjects

Eighteen subjects with video-polysomnography confirmed iRBD (age mean ± standard deviation 67.3 ± 6.6 years, 2 female), 18 subjects with PD (65.4 ± 5.8 years, 9 female), and 39 age- and sex-matched healthy control subjects (HC) (64.4 ± 9.2 years, 11 female) with no prior neurological or psychiatric medical history were included in the final sample. Subjects were recruited from 2012 to 2020 through the movement disorder and sleep clinics of the universities of Aachen and Marburg, Germany. In addition, we retrieved MRI and demographical data of eligible iRBD subjects and HC from the Parkinson's Disease Progression Marker Initiative (PPMI) database (www.ppmi-info.org). The diagnoses of iRBD and PD were made according to established criteria [18,19]. The presence of motor signs suspicious of parkinsonism (defined as Unified Parkinson's Disease Rating Scale (UPDRS) [20] III score >5) in iRBD individuals and HC was an exclusion criterion. Two iRBD individuals were on low dose therapy with dopamine agonists, one for treatment of iRBD symptoms, and one for concomitant restless-legs-syndrome. There was no systematic screening for the presence of RBD symptoms in the PD cohort, and none of the PD patients underwent video-polysomnography. All subjects gave written informed consent prior to study participation. The study has been approved by the local ethics committees of the universities of Aachen (EK 231/09) and Marburg (AZ 89/12), respectively. The study was conducted in accordance with the Declaration of Helsinki.

2.2. Motor and cognitive assessments

All participants underwent motor and cognitive assessments using the UPDRS III and Montreal Cognitive Assessment (MoCA [21]). For 9 PD patients, no MoCA was available, and the Mini-Mental state exam (MMSE [22]) was used instead. MMSE scores were within the normal range (mean ± SD: 29 ± 1.2, range 27–30). Subjects undergoing MMSE were not included in statistical analyses of cognitive function to avoid combining MMSE and MoCA scores. iRBD subjects recruited from the PPMI database were assessed using the revised MDS-UPDRS III [23].

2.3. Imaging

All subjects underwent a structural T1-weighted scan and rs-fMRI utilizing echo-planar-imaging (EPI) at 3 T. PD subjects were scanned while on their regular dopaminergic medication. During the rs-fMRI scan, subjects were instructed to relax, to not think about something in particular, and to not fall asleep. Details on the scanning procedures of PPMI subjects are available at https://www.ppmi-info.org/study-design/researchdocuments-and-sops/. Participants recruited in Marburg were scanned on a Siemens 3 T TIM Trio (n = 14; 6 HC, 8 iRBD), individuals from Aachen were scanned on a Siemens 3 T TIM Trio (n = 19; 7 HC, 12 PD), or Siemens 3 T PRISMA (n = 26; 15 HC, 6 PD, 5 iRBD). Acquisition details are shown in Table S1.

2.4. Data processing

Processing of MRI data was done using a lab-made wrapper written in R 4.1 (R Foundation for Statistical Computing, Vienna, Austria) using FSL (https://fsl.fmrib.ox.ac.uk/) functions [24]. Pre-processing included skull stripping and motion correction. The anatomical data set was automatically segmented into probabilistic maps of white matter, gray matter, and cerebrospinal fluid. Masks for white matter and cerebrospinal fluid were binarized at a threshold of 0.95 probability for later use. Functional data, anatomical data, and the binarized masks were transformed into Montreal Neurological Institute (MNI) space applying linear followed by non-linear registration (FSL tools flirt and fnirt). We performed slice scan time correction and extracted nuisance variables. To this end, we extracted time courses of white matter and cerebrospinal fluid based on the previously generated binary masks and the mean global signal from the functional data. Movement parameters and their first and second derivatives were regressed out from the functional data. Next, regions obtained from a modified version of the AALv3.1 atlas [25,26] (see below for details) were projected onto the functional data and time courses were extracted, resulting in a $t \times 142$ matrix for each subject, where t is the number of volumes acquired. The subsequent analyses were performed in MNI space. For each region, the time course was extracted and band-pass filtered with 0.01 Hz and 0.15 Hz cut-offs and scaled to the z-distribution. The first three observations of these time courses were removed for all subjects to account for stabilization of the magnetic field. Additionally, we removed observations if total movement in one dimension exceeded 1.5 mm or 1.5°, and if volume-to-volume movement in all dimensions exceeded 1.5 mm (the brain was viewed as a sphere with a radius of 50 mm to compute the total movement). Subjects were excluded if there were more than three volumes exceeding 1.5 mm or 1.5° of movement in one dimension, or if there were more than 20 volumes or 10% of total volumes (whichever was smaller) where movement in all directions exceeded 1.5 mm. Finally, pairwise correlations between all regional time courses were calculated.

2.5. Atlas

Due to concerns that very small regions in the AAL 3.1 atlas may not be represented properly using functional data, we edited regions smaller than 10 functional voxels. Specifically, small thalamic nuclei were merged with neighboring regions as well as the substantia nigra with the ventral tegmental area (for details, please see Appendix in the supplemental material). Because meaningful merging with neighboring regions was not possible for the Raphé nucleus and locus coeruleus, the latter regions were not considered for analyses.

2.6. Graph construction and analysis

Each subject's correlation matrix was turned into a graph with nodes representing anatomical regions, and correlation coefficients the edge weights, respectively. For each subject, we identified the largest proportion of weakest edges that could be removed without causing the graph to disintegrate into several components. Based on these values, we first removed subjects with the lowest 2.5% of thresholds to avoid effects of low average connectivity [27]. The lowest remaining individual proportional threshold (0.254) was then applied to all other subjects.

To evaluate the connectome at a global level, we computed the following measures using the R packages tidygraph [28] and igraph [29]: mean distance (the average length of all shortest paths (geodesics)), diameter (the longest geodesic), and small-worldness (a coefficient indicating whether a graph follows a small-world topology, i.e. a network with high local transitivity and short mean distance). At the regional level, we computed degree (the total number of a node's connections), betweenness (the number of times geodesics traverse a node), triangles (the number of connections between neighbors), and Katz centrality (progressive degree with a penalty function).

2.7. Statistical analyses

Data analysis was performed using R 4.1 [30]. We applied analysis of variance (ANOVA) and the Chi-squared test for analyses of demographic data where appropriate. Significance was assumed for $p < 0.05$.

We applied a dual analytical approach to compare graph measures across groups, employing two variants of linear models, i.e. frequentist modelling and Bayesian linear modelling (B-LM), respectively. There are inherent limitations to p-value based null-hypothesis significance tests to determine the validity of observed effects [31]. Compared with null-hypothesis significance tests, B-LM is advantageous because it is more robust regarding unbalanced sample sizes, and is not affected by issues pertaining to multiple comparisons [32]. On the downside, B-LM requires a priori assumptions about the data being analyzed. We used the implementation from the rstanarm [33] package. The model used weakly informative Gaussian priors. For fitting, 4 Markov-chains with 2000 iterations each were used, with the first 1000 iterations for burn-in. From the posterior distribution, the percentage of data in the region of practical equivalence (%ROPE) as a measure of an effect's significance, and the probability of direction (pd, the proportion of parameter values in the posterior distribution having the same sign as the median) as a measure of an effect's existence, were calculated and used for inference [34]. In contrast to null-hypothesis significance tests, the interpretation of pd and %ROPE values is less categorical. The B-LM indicates the likely existence of effects for pd > 0.97, and more than negligible significance for %ROPE <97.5. Effects are considered to be stronger (probably significant) for %ROPE <2.5 [35]. We only reported results that were 1) significant as per the frequentist linear model ($p < 0.05$), and 2) showed pd > 0.97 and %ROPE <5 in pairwise group comparisons as analyzed by B-LM. Despite the rigorous UPDRS III score threshold applied in the iRBD cohort, we utilized the Spearman correlation coefficient to investigate the relationship of motor dysfunction with nodal graph measures in regions where at least one of the disease groups significantly differed from HC.

2.8. Data sharing

Due to legal reasons, data cannot be shared in a public repository, but may be made available upon reasonable request to the corresponding author.

3. Results

3.1. Demographics

There was no difference in age ($F(2, 89) = 1.917$, $p = 0.153$), gender ($\chi^2(2) = 2.70$, $p = 0.259$), or cognitive status as assessed by MoCA ($F(2, 63) = 1.262$, $p = 0.290$) across the three groups. Detailed demographics are displayed in Table 1.

3.2. Analysis of global graph measures

There was no difference of mean distance in either iRBD or PD patients compared with HC (iRBD $p = 0.406$, pd $= 0.799$, %ROPE $= 20.158$; PD $p = 0.269$, pd $= 0.863$, %ROPE $= 17$), or between iRBD and PD subjects ($p = 0.803$, pd $= 0.583$, %ROPE $= 23.921$), respectively. Similarly, diameter did not differ among groups (iRBD vs. HC $p = 0.182$, pd $= 0.917$, %ROPE $= 11.289$; PD vs. HC $p = 0.322$, pd $= 0.842$, %ROPE $= 18.868$; iRBD vs. PD $p = 0.768$, pd $= 0.610$, %ROPE $= 23.526$). There were reduced small-worldness properties in iRBD compared with HC ($p = 0.013$, pd $= 0.995$, %ROPE $= 0$) and in PD subjects compared with HC ($p = 0.031$, pd $= 0.982$, %ROPE $= 0.500$). Small-worldness did not differ between iRBD and PD groups ($p = 0.755$, pd $= 0.626$, %ROPE $= 22.395$).

Details of statistical analyses and descriptives of the global graph measures are provided in Table 2 and Table S2, respectively.

3.3. Analysis of nodal graph measures

We found increased values for at least one nodal measure in the iRBD group compared with HC in the left gyrus rectus, left paracentral lobule, and right lobules 4 and 5 (including the vermal portion) of the cerebellum. Lower values compared to HC were observed in the right primary motor cortex (PMC), right primary sensory cortex (PSC), right supplementary motor area (SMA), bilateral frontal cortices, wide-spread (meso)-temporal regions, (temporo)-occipital regions, left supramarginal gyrus, bilateral cingulate cortex (middle portion), right

Table 1
Demographics and clinical data of the study sample.

	HC	iRBD	PD
Subjects [n]	39	18	18
Gender Female/Male [n]	11/28	2/16	9/9
Location Aachen/Marburg/ PPMI [n]	22/6/11	5/8/5	18/0/0
Age [years]	64.4 ± 9.2; 64	67.3 ± 6.6; 68.5	65.4 ± 5.8; 64.7
UPDRS III	0.5 ± 1.1; 0	2.2 ± 1.6; 2	24.7 ± 15.5; 20
Hoehn & Yahr Stage	0 ± 0; 0	0 ± 0; 0	1.7 ± 0.8; 1.5
MoCA	28.3 ± 1.3; 29	27.6 ± 2; 28	28 ± 1.4; 28
Disease duration [years]	0 ± 0; 0	10.5 ± 15.7; 5	5.2 ± 3.6; 5.1
LEDD [mg]	0 ± 0; 0	2.8 ± 11.8; 0	935.8 ± 1843.7; 402.5

Values are displayed as mean ± standard deviation; median. There was one missing value for disease duration in iRBD which was omitted from these statistics.
HC: healthy controls; iRBD: isolated REM sleep behavior disorder; PD: Parkinson's disease; UPDRS: Unified Parkinson's disease rating scale; PPMI: Parkinson's progression markers initiative; MoCA: Montreal Cognitive Assessment; LEDD: levodopa equivalent daily dose; NA: not applicable. [1] MDS-UPDRS III was used in PPMI subjects.

Table 2
Group effects of global graph measures.

Measure	Comparison	B-LM Est	pd	%ROPE	p
Mean Distance	HC vs. PD	−0.001	0.863	17.000	0.269
	HC vs. iRBD	−0.001	0.799	20.158	0.406
	PD vs. iRBD	0.000	0.583	23.921	0.803
Diameter	HC vs. PD	−0.158	0.842	18.868	0.322
	HC vs. iRBD	−0.208	0.917	11.289	0.182
	PD vs. iRBD	−0.054	0.610	23.526	0.768
Small Worldness	HC vs. PD	−0.033	0.982	50.000	0.031
	HC vs. RBD	−0.039	0.995	0	0.013
	PD vs. iRBD	−0.006	0.626	22.395	0.755

Estimates of pairwise comparisons are displayed in relation to the first group shown in the comparison column. HC: healthy controls; iRBD: isolated REM sleep behavior disorder; PD: Parkinson's disease; B-LM Est: Estimate of the Bayesian linear model; pd: probability of direction; %ROPE: percentage of values in the region of practical equivalence.

putamen, right caudate, right thalamus, and vermal lobule 9. Inconsistent findings were found in the anterior cingulate cortex where a higher degree and betweenness, but lower Katz index were observed. Similarly, iRBD individuals showed a higher degree but lower triangles and Katz index in the anterior cingulate cortex compared with HC.

In the PD group, we found higher values compared with HC in the bilateral PMC, bilateral paracentral lobule, bilateral PSC, left cuneus, bilateral thalamus, and right lobules 4–6 of the cerebellum and right vermal lobe 6 of the cerebellum. Lower values compared with HC were identified in the PD cohort in the left inferior frontal gyrus, wide-spread (meso)-limbic regions including the bilateral amygdala and left hippocampus, (temporo)-occipital cortical regions, bilateral supramarginal gyrus, right putamen, and left crus I and right cerebellar lobule 8.

When comparing iRBD with PD individuals, we found higher values in the former group in the left rolandic operculum, left orbitofrontal cortex, right amygdala, bilateral occipital cortex, left angular gyrus, and left crus I of the cerebellum. Lower values in iRBD subjects were evident in the right PMC, right SMA, right paracentral lobule, right PSC, right superior frontal gyrus, and left thalamus. Heterogeneous differences between groups were observed in the cingulate cortex with lower values in the iRBD cohort in the left middle section, but higher values in its right anterior and posterior portion. All findings are summarized in Fig. 1 and Table S3. A graphical illustration of the anatomical distribution of nodal connectivity changes in the iRBD and PD groups is shown in Fig. 2.

We did not observe any significant correlations of nodal graph measures with UPDRS III scores in either iRBD or PD individuals ($p > .95$ after Bonferroni correction for multiple comparisons).

4. Discussion

Most studies exploring functional alterations of brain connectivity in iRBD have done so using either seed or region of interest based analyses [36–38], or explored connectivity changes within predefined networks related to motor and non-motor function, respectively [10,39]. Moreover, studies including combined samples of iRBD and PD patients are scarce [10,36]. This study utilized a data driven, hypothesis free, graph-theoretical approach to identify whole-brain functional connectome changes in a combined sample of iRBD and PD patients compared with HC. We found a deterioration of network connectivity in both iRBD and PD individuals compared with HC. In line with previous research studies, global network architecture remained largely intact [40–43], whereas pronounced changes of graph measures were observed at the regional level in both disease groups. There were differences between iRBD and PD groups, but the connectome changes observed in iRBD overall were remarkably similar to those observed in PD subjects.

iRBD and PD subjects exhibited connectivity alterations in major hubs of the motor network. Specifically, both groups showed reduced

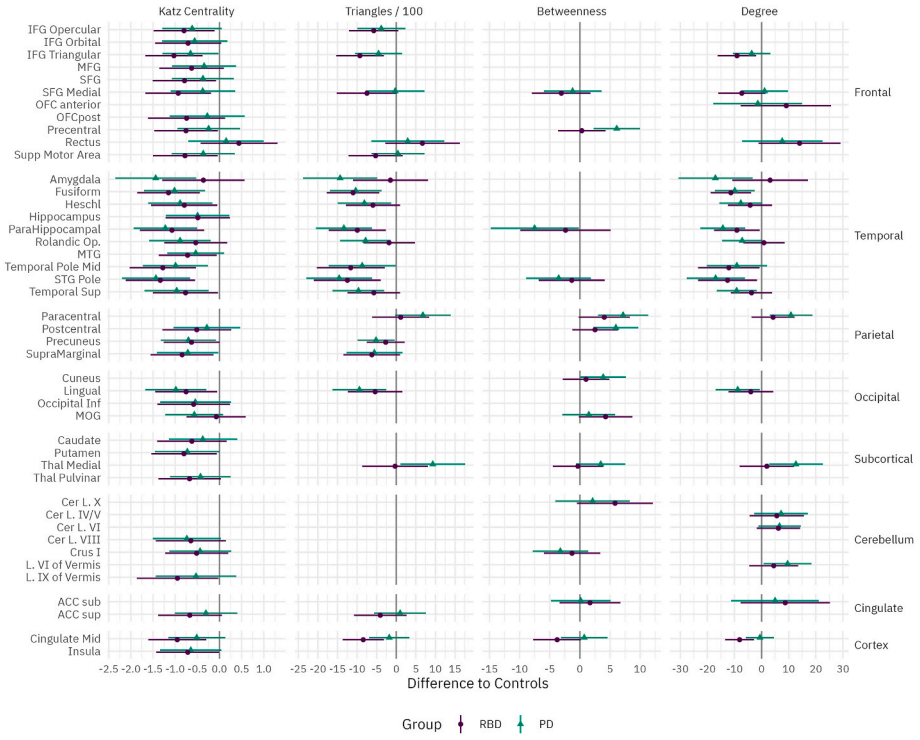

Fig. 1. Regions of altered connectivity in at least one patient group (iRBD or PD) compared with HC (vertical lines). Points indicate the estimated median difference in the Bayesian linear model (B-LM), error bars show the 89% credible interval. Values of paired regions were averaged, and triangle values were divided by 100 for clarity. iRBD: isolated REM sleep behavior disorder; PD: Parkinson's disease; IFG: inferior frontal gyrus; SFG: superior frontal gyrus; OFC: orbitofrontal gyrus; post: posterior; Supp: supplementary; Op: operculum; Inf: inferior; MTG: middle temporal gyrus; Mid: middle; STG: superior temporal gyrus; Sup: superior; MOG: middle occipital gyrus; Thal: thalamus; Cer: cerebellum; L: lobule; ACC sub: anterior cingulate cortex, subgenual part; ACC sup: anterior cingulate cortex, supracallosal part.

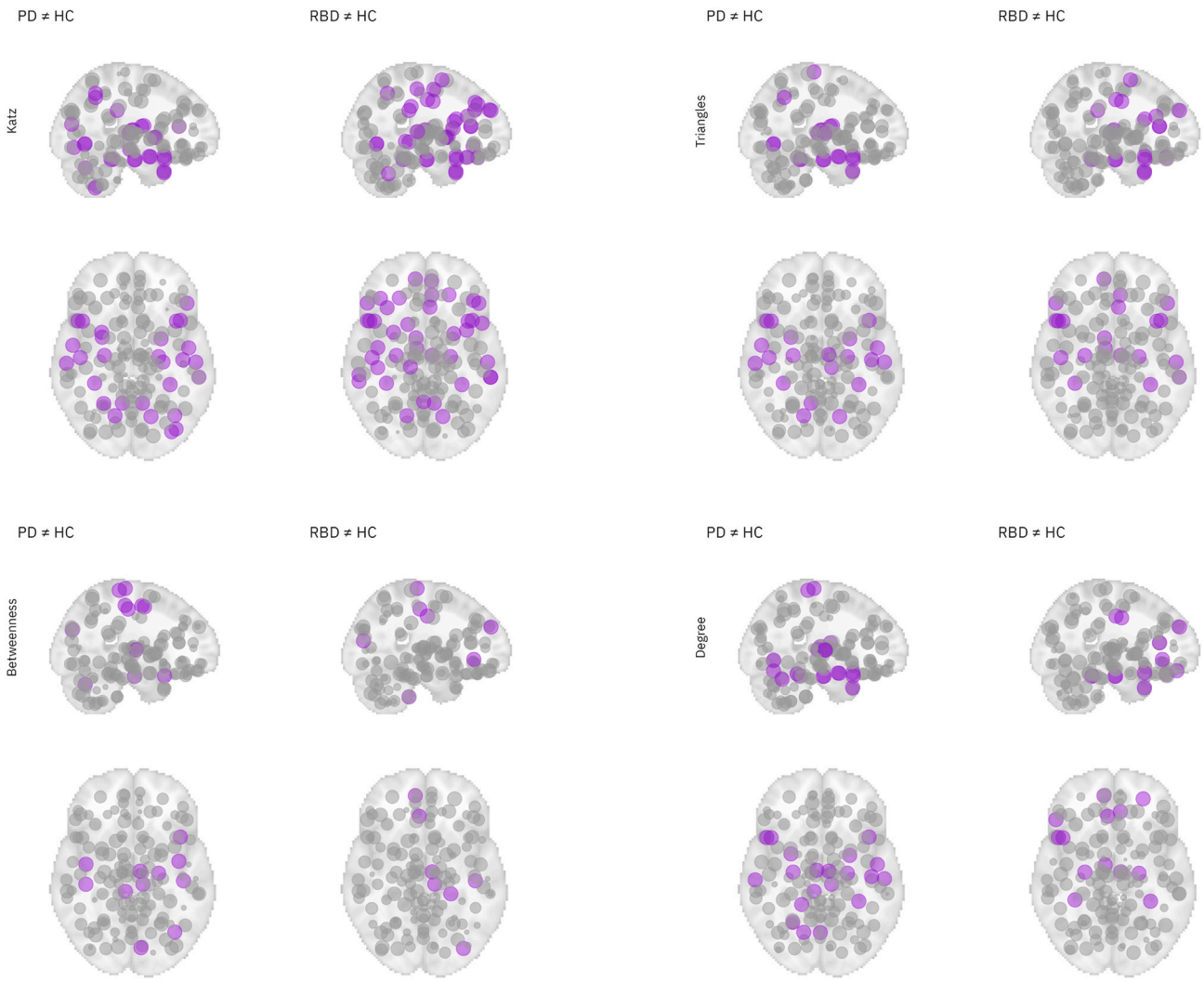

Fig. 2. Regional connectivity alterations in iRBD and PD patients compared with HC. Gray circles indicate all nodes comprising the graph, purple circles indicate nodes that showed altered connectivity between groups ($p < .05$, $pd > 0.97$, ROPE <5%). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

connectivity in the putamen and elevations of various connectivity measures in the motor cerebellum. That said, changes of motor network connectivity were not identical in both groups. PD patients exhibited increased connectivity in the PMC, PSC, and the thalamus. In contrast, iRBD individuals showed reduced connectivity in these regions and the SMA compared to both HC and PD subjects. Moreover, iRBD subjects showed connectivity changes in (orbito-)frontal regions that were not apparent in PD individuals. Altered functional connectivity in the motor network has been consistently reported in PD [44–47]. Specifically, fMRI studies have revealed that striatal dopaminergic depletion leads to reduced putamen-motor-cortical connectivity [48,49]. Of note, similar changes have been found in iRBD cohorts with normal or slightly reduced motor function [10,11,37]. That said, PD related changes in motor circuitry are complex, and earlier findings from graph-theoretical studies are conflicting. For example, some authors reported reduced connectivity in motor cortical regions including the PMC and SMA [15,41,47], whereas others found increased connectivity of these regions that have been suggested to be compensatory in nature [42]. Furthermore, hypermetabolism or hyperperfusion of the putamen have been reported in both iRBD and PD [50–53], which likely are compensatory in nature. We speculate that the reductions of the Katz index of the putamen in our analyses may constitute a graph-theoretical correlate of putamenal dopaminergic diminution. The increased connectivity observed in the PMC, PSC, and thalamus that were exclusive to the PD group suggest that these changes may be a compensatory consequence of motor symptom manifestation. The co-occurrence of reduced striatal and motor cortical connectivity but increased graph measures in the cerebellum in the iRBD group on the other hand may reflect both emerging nigro-striatal dopaminergic decline and incipient compensatory mechanisms.

Indeed, the cerebellum is increasingly recognized to contribute to PD pathophysiology [4,54,55]. Several studies have found cerebellar over-activation and increased connectivity of cerebello-cortical projections in PD [56]. Interestingly, comparable enforcement of cerebello-cortical connectivity has recently been reported in iRBD individuals with minor motor dysfunction [11,57]. In addition, others and we have found increased cerebellar volume in iRBD individuals [4,58]. Commonly, these changes have been interpreted as compensation for declining dopaminergic striatal integrity, but may also reflect abnormal activation caused by altered input from the basal ganglia [56]. That said, findings are equivocal, and others have reported cerebellar atrophy and reduced cerebellar blood flow in iRBD [59,60]. Along these lines, a recent large meta-analysis including more than 420 PD patients reported hypo-activation of the sensorimotor network, including the cerebellum, during motor activation [54]. We found increased connectivity measures in the motor cerebellum in both disease groups, supporting the

hypothesis of compensatory cerebellar over-activation. We also identified cerebellar regions that displayed reduced connectivity in the iRBD and PD cohorts, respectively. That being said, these regions (Crus I and vermal lobule 9) are not commonly associated with general motor function [61].

Wide-spread reductions of connectivity measures were found in (meso)temporal cortices in both iRBD and PD cohorts. Temporal lobe atrophy and altered connectivity of the mesolimbic system have been reported in PD [42,62]. These changes have been associated with cognitive impairment and autonomic dysfunction, and may be related to dopaminergic deficiency [62–64]. However, temporal lobe changes have been shown to occur early in the disease course and do not necessitate the presence of cognitive impairment [65,66]. Similarly, atrophy and altered activation of the limbic system and temporal cortex have been found in iRBD [4,16,67]. As with PD, these alterations have been linked to cognitive impairment [16,67]. Of note, subjects included in our study were cognitively intact, suggesting that cognitive dysfunction is not a prerequisite for functional temporal lobe changes in iRBD.

Lastly, both groups showed reduced connectivity measures in regions associated with visual processing. Occipital hypometabolism has commonly been associated with iRBD, whereas it remains unclear if this finding is a feature of iRBD *per se* or indicative of subsequent cognitive decline [9,52,68,69]. Similarly, occipital cortical structural and functional alterations have been found in PD cohorts [43,70,71]. Similar to alterations in the temporal cortex, these changes have been reported to correlate with cognitive performance but have also been identified in cognitively intact PD cohorts [43,70,71].

Overall, the connectome changes observed were pronounced and more wide-spread in the PD cohort compared with iRBD subjects. Importantly, there were group specific connectivity alterations. For example, iRBD subjects showed decreased connectivity in frontal regions compared with both HC and PD individuals. Moreover, PD patients displayed a marked reduction of connectivity in the amygdala that was not apparent in iRBD subjects, whereas the latter group showed exclusive connectivity alterations in the cingulate cortex. That said, even though significance was not achieved at all nodes in both disease groups, the direction of the deviation of regional graph measures from HC still was largely homogenous, further underlining the similarity of connectome changes observed in iRBD and PD [72].

Of note, we did not observe a correlation of UPDRS III scores and regional graph measures in iRBD or PD subjects at any of the nodes where at least one of the disease groups significantly differed from HC. Given the fact that we only included iRBD subjects with UPDRS III scores $\leq$5 this may not be surprising and suggests that the complex network changes observed were not a mere reflection of motor dysfunction.

We believe it is a strength of our study that we applied a complimentary approach to interrogate the imaging data. We applied frequentist null-hypothesis significance testing, which is commonly employed for graph theory analysis of functional imaging data [15,41,42]. The latter method applies clearly defined significance thresholds and does not require making assumptions about the data. That said, p-values calculated from this type of analysis sometimes are interpreted in too formulaic ways [31]. In contrast, Bayesian methods are not hampered by this limitation, but demand more time and resources to compute, require making assumptions about the data, and are more difficult to interpret. There was an overall good agreement between both methods, supporting the validity of our findings and suggesting that we did not overemphasize small effect sizes. Another strength is the careful selection of iRBD individuals. Diagnoses were confirmed by video-polysomnography, and we excluded all subjects that showed subtle parkinsonian features. Moreover, groups did not differ in terms of cognitive status, minimizing potential effects of disturbed cognition on our findings [16,73].

There are limitations to our work. The sample size was limited, and the disease groups were heterogeneous in terms of disease duration and severity. Moreover, the study design was cross-sectional, MRI was obtained on different scanners, and we do not know if and when iRBD individuals will develop PD. Thus, our findings have to be interpreted with caution, and to replicate our results in more homogeneous cohorts is desirable. Furthermore, the presence of iRBD was not assessed in the PD cohort. Several studies have reported distinct brain connectivity changes in PD individuals with concurrent iRBD compared to those without [74,75]. Specifically, PD-RBD + individuals have been found to exhibit an increase of regional homogeneity in the left cerebellum, the right middle occipital region and the left middle temporal region, and decreased regional homogeneity in the left middle frontal region [76]. Others have reported reduced motor cortical activity and more widespread activity changes in the limbic system in PD-RBD + compared with PD-RBD - patients [74,75]. Indeed, there is mounting evidence that the spreading of alpha-synuclein depositions follows different trajectories in PD (i.e. body first vs. brain first subtypes) [77]. Along these lines, a recently published multimodal imaging study proposed that PD patients who developed iRBD before motor onset belong to the body first PD subtype [77]. Even though no functional MRI data was presented, body first and brain first PD subjects differed substantially in terms of striatal dopaminergic integrity, cardiac sympathetic imaging, and neuromelanin imaging of the locus coeruleus. Most likely, a dichotomization of PD into subtypes will never reflect the full spectrum of PD pathology [78], but it appears reasonable to assume that PD-iRBD + differs in many aspects from PD-iRBD -. Lastly, PD patients were scanned on their regular dopaminergic medication. It is well known that dopaminergic treatment partially restores abnormal brain activity in the PD brain [40,49,79]. Thus, dopaminergic treatment may have obscured some brain alterations in the PD group and may have led to an underestimation of effect sizes.

5. Conclusion

In summary, we found widespread alterations of the brain functional connectome in iRBD patients with normal motor function that showed substantial concordance with those observed in PD patients. Our study provides further evidence for a close pathophysiological relationship of iRBD and PD and suggest dynamic brain changes that may reflect both neurodegenerative and adaptive processes in an iRBD-PD spectrum.

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CRediT authorship contribution statement

Florian Holtbernd: Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Conceptualization. **Christian Hohenfeld:** Writing – review & editing, Formal analysis, Conceptualization. **Wolfgang H. Oertel:** Writing – review & editing, Resources, Investigation. **Susanne Knake:** Writing – review & editing, Investigation. **Elisabeth Sittig:** Writing – review & editing, Project administration, Investigation. **Sandro Romanzetti:** Writing – review & editing, Methodology, Investigation. **Anna Heidbreder:** Writing – review & editing, Resources. **Jennifer Michels:** Writing – review & editing, Investigation. **Imis Dogan:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Jörg B. Schulz:** Writing – review & editing, Resources. **Johannes Schiefer:** Writing – review & editing, Resources. **Annette Janzen:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Kathrin Reetz:** Writing – review & editing, Supervision, Resources, Project

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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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Appendix A. Supplementary data

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