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Disruption of posterior brain functional connectivity and its relation to cognitive impairment in idiopathic REM sleep behavior disorder

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ABSTRACT

Background: Resting-state functional MRI has been proposed as a new biomarker of prodromal neurodegenerative disorders, but it has been poorly investigated in the idiopathic form of rapid-eye-movement sleep behavior disorder (IRBD), a clinical harbinger of subsequent synucleinopathy. Particularly, a complex-network approach has not been tested to study brain functional connectivity in IRBD patients.
Objectives: The aim of the current work is to characterize resting-state functional connectivity in IRBD patients using a complex-network approach and to determine its possible relation to cognitive impairment.
Method: Twenty patients with IRBD and 27 matched healthy controls (HC) underwent resting-state functional MRI with a 3T scanner and a comprehensive neuropsychological battery. The functional connectome was studied using threshold-free network-based statistics. Global and local network parameters were calculated based on graph theory and compared between groups. Head motion, age and sex were introduced as covariates in all analyses.
Results: IRBD patients showed reduced cortico-cortical functional connectivity strength in comparison with HC in edges located in posterior regions ($p < 0.05$, FWE corrected). This regional pattern was also shown in an independent analysis comprising posterior areas where a decreased connectivity in 51 edges was found, whereas no significant results were detected when an anterior network was considered ($p < 0.05$, FWE corrected). In the posterior network, the left superior parietal lobule had reduced centrality in IRBD. Functional connectivity strength between left inferior temporal lobe and right superior parietal lobule positively correlated with mental processing speed in IRBD ($r = .633$; $p = .003$). No significant correlations were found in the HC group.
Conclusion: : Our findings support the presence of disrupted posterior functional brain connectivity of IRBD patients similar to that found in synucleinopathies. Moreover, connectivity reductions in IRBD were associated with lower performance in mental processing speed domain.

1. Introduction

Rapid-eye-movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by dream-enacting behaviors, such as shouting, punching, and falling out of bed, related to unpleasant dreams and loss of normal REM-sleep muscle atonia (Schenck and Mahowald, 2002).

The idiopathic form of RBD (IRBD) has been reported as one of the strongest prodromal biomarkers for alfa-synucleinopathies (Berg et al., 2015), namely Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (Iranzo et al., 2014; Mahlknecht et al., 2015). A recent multicenter follow-up Postuma et al. (2019) found that the overall conversion rate from IRBD to an overt neurodegenerative condition was 6.3% per year, with 73.5% converting after a 12-year follow-up. In this setting, there is a need to detect potential new biomarkers of prodromal neurodegeneration in this

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preclinical stage. Since MRI is a non-invasive and widely available technique that could be used for this purpose, there is a growing interest to better characterize brain changes in IRBD patients.

Brain structure in IRBD has previously been studied by means of voxel-based morphometry, cortical thickness and diffusion-tensor imaging, suggesting changes in both cortical (Campabadal et al., 2019; Hanyu et al., 2012; Park et al., 2018; Pereira et al., 2019; Rahayel et al., 2018b, 2018a, 2015; Unger et al., 2010) and subcortical (Ellmore et al., 2010; Hanyu et al., 2012; Park et al., 2018; Rahayel et al., 2018b, 2018a; Scherfler et al., 2011; Unger et al., 2010) structures. Regarding resting-state functional MRI (rs-fMRI), a prior work, using a seed-based approach focused on the substantia nigra, identified altered nigrostriatal and nigrocortical connectivity (Ellmore et al., 2013). Furthermore, a subsequent study found altered basal ganglia connectivity similar to that found in PD patients when using a pre-established template of basal ganglia network (Rolinski et al., 2016). Taking these prior results into account, rs-fMRI has been proposed as a new biomarker of prodromal neurodegeneration in PD (Postuma, 2016).

Network-based statistics (NBS) and graph-derived metrics allow studying the brain as a complex network, characterizing the dynamic interactions between different brain regions (Telesford et al., 2011). These techniques have been used before to detect brain functional connectivity abnormalities in PD (see Hohenfeld et al., 2018 for review) and DLB (Peraza et al., 2015). Nevertheless, as far as we know, there is no previous literature in IRBD studying rs-fMRI following the functional connectome approach. Bearing in mind the findings in alfa-synucleinopathies, we aimed to characterize brain functional connectivity in IRBD using graph theory analyses and to determine its possible relation to cognitive dysfunctions. We hypothesize that in comparison with healthy subjects, patients will show a reduction in brain functional connectivity, similar to that found in PD and DLB, and that this will be associated with cognitive impairment.

2. Method

2.1. Participants

Twenty patients with IRBD without cognitive or motor complaints at the time of diagnosis, and at the time of the current study, were recruited from our sleep unit. Diagnosis of IRBD required a history of dream-enacting behaviors, video-polysomnographic demonstration of REM sleep without atonia, and absence of other neurological diseases (Boeve, 2010; Iranzo et al., 2006). All patients underwent a full-night polysomnography that demonstrated increased electromyographic activity during REM sleep associated with abnormal disruptive motor behaviors. At the time of the current study, fifteen patients were taking benzodiazepines to reduce RBD symptomatology. Twenty-seven healthy subjects without cognitive, motor, or sleep complaints were recruited from the Institut de l'Envelliment (Barcelona, Spain).

Exclusion criteria consisted of [1] presence of psychiatric and/or neurologic comorbidity, [2] MMSE score <25, [3] claustrophobia, [4] MRI artifacts, [5] pathological MRI findings other than mild white matter hyperintensities, and [6] no evidence in healthy controls (HC) of sleep disorders or mild cognitive impairment by detailed clinical history.

The study was approved by the Ethics Committee of the University of Barcelona (IRB00003099) and Hospital Clinic (HCB/2014/0224). All subjects provided written informed consent to participate after full explanation of the procedures involved.

2.2. Neuropsychological and Clinical Assessment

Participants were evaluated with a comprehensive neuropsychological battery. Expected z scores adjusted for age, sex, and education for each test and each subject were calculated based on a multiple regression analysis performed in the HC group (Aarsland et al., 2009). Five cognitive domains were obtained using the combination of two neuropsychological tests for each one (computed as the mean of the expected z scores): [1] attention domain, including Digit Span Forward and Backward (WAIS); [2] memory domain, the total learning recall (sum of correct responses from trial I to trial V) and recognition (true recognition after 20 min) from the Rey's Auditory Verbal Learning Test; [3] visuospatial and visuoperceptual (VS/VP) domain, calculated with Benton Facial Recognition and Clock Copying Test; [4] executive function domain, with Stroop Interference and phonemic fluency (words beginning with the letter “p” in 1 min); and [5] mental processing speed domain, using the Symbol Digits Modalities Test-Oral version (SDMT) and Stroop Color test.

Presence of motor symptoms was evaluated using the International Parkinson and Movement Disorders Society Unified Parkinson's Disease Rating Scale motor section (MDS-UPDRS-III). Neurological examination based on the MDS-UPDRS-III frequently disclosed mild parkinsonian signs, that were, however, not sufficient to diagnose Parkinsonism according to standard criteria. (Postuma et al., 2015)

The Beck Depression Inventory II (BDI) (Beck et al., 1996), Starkstein's Apathy Scale (SAS) (Starkstein et al., 1992), and the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) were used to asses neuropsychiatric symptomatology.

2.3. MRI Acquisition and Preprocessing

MRI data were acquired with a 3T scanner (MAGNETOM Trio, Siemens, Germany). The scanning protocol included high-resolution 3-dimensional T1-weighted images acquired in the sagittal plane (TR = 2300ms, TE = 2.98ms, TI = 900ms, 240 slices, FOV = 256mm; 1mm isotropic voxel), an axial FLAIR sequence (TR = 9000ms, TE = 96ms) and a resting-state 10-min-long functional gradient-echo echo-planar imaging sequence (240 T2$*$ weighted images, TR = 2.5s, TE = 28 ms, flip angle = 80°, slice thickness = 3mm, FOV = 240mm). Subjects were instructed to keep their eyes closed, not to fall asleep, and not to think anything in particular

2.4. Resting-State Images

Basic functional image preprocessing, using AFNI tools, included: discarding the first five volumes to allow magnetization stabilization, despiking, motion correction, grand-mean scaling, linear detrending, and temporal filtering (maintaining frequencies above 0.01 Hz).

2.5. Noise Correction and Head Motion

Regarding head motion parameters, an exclusion cut-off was established for mean interframe head motion at $\geq$0.3mm translation or 0.3° rotation; and for maximum interframe head motion at $\geq$1mm translation or 1° rotation. We excluded one HC due to excessive head movement. In order to remove the effects of head motion and other non-neural sources of signal variation from the functional data, we used an Independent Component Analysis based strategy for Automatic Removal of Motion Artifacts (ICA-AROMA) (Pruim et al., 2015). ICA-AROMA decomposes the data via ICA and automatically identifies which of these components are related to head motion, by using four robust and standardized features. As quality control measure to assess the efficacy of ICA-AROMA in reducing relationship between signal variation and motion, we performed correlations between framewise head displacement (Power et al., 2012) and overall signal variation (defined as the voxel-wise root mean square intensity difference between subsequent time points) after regressing the ICA-AROMA components. These two measures should not correlate significantly because signal change should not be explained by head motion.

2.6. Characterization of brain functional connectivity

In order to test for intergroup differences in interregional connectivity between IRBD and HC, we used Threshold-free network-based statistics (TFNBS) (Baggio et al., 2018), which performs statistical inference on brain graphs. This approach combines network-based statistics (Zalesky et al., 2010), frequently used for statistical analysis of brain graphs, and threshold-free cluster enhancement, a common method in voxel-wise statistical inference (Smith and Nichols, 2009). One of the main characteristics of TFNBS is that it allows generating edge-wise significance values that can be used to select relevant connectivity features. The 246 regions defined in the Brainnetome Atlas (https://atlas.brainnetome.org/bnatlas.html) (Supplementary material 1) were used for the characterization of global functional connectivity (Fan et al., 2016). Head motion, age and sex were introduced as covariates in all analyses.

2.7. Graph theory computation

The analysis of brain functional connectivity was complemented with topological information derived from graph theory, allowing a description of global (whole-brain) and local (nodal) properties of the network (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). The Brain Connectivity Toolbox (BCT) was used to extract the topological parameters, including global and local clustering coefficient, global and local node degree, “small-worldness”, path length, local efficiency and betweenness centrality (See Rubinov and Sporns, 2010 for detailed definitions and calculations of the graph metrics included in this work). Head motion, age and sex were introduced as covariates in all analyses. Given that graph metrics were computed using nine density thresholds (maintaining the 5% to 25% strongest edges, at intervals of 2.5%), only those results consistently found in more than one are reported.

2.8. Statistical analyses

Statistical analyses of demographic and clinical data were carried out using the statistical package SPSS-24 (2016; Armonk, NY: IBM Corp.). Inter-group comparisons for neuropsychological domains adjusted for age, sex and years of education were performed using Mann-Whitney's U test. Pearson's chi-squared test was applied to assess group differences in categorical variables. Spearman's correlations were used to study the association between clinical and imaging variables. Differences between HC and IRBD in connectivity measures were tested with the general lineal model using in-house MATLAB scripts. Statistical significance was established using Monte Carlo simulations with 10,000 permutations. Two-tailed p-values were calculated as the proportion of values in the null distribution more extreme than those observed in the actual model.

3. Results

3.1. Sociodemographic, clinical and neuropsychological data

Table 1 shows the sociodemographic and clinical characteristics of the groups. No significant intergroup differences were observed for age, sex and years of education. Inter-group comparisons showed IRBD patients had significant greater scores in NPI (U = 398.0; p = .001), and lower performance in the memory (U = 134.0; p = .008), VS/VP (U = 121.0; p = .006) and mental processing speed (U = 130.0; p = .017) domains. (Table 2).

3.2. Functional connectivity and network graph metrics

Table 1 summarizes head motion parameters. Despite not significant at a p < .05 threshold, mean interframe head rotation was higher in the IRBD group (U = 339.0; p = .080); this measure was therefore introduced as a covariate in the analyses that included functional resting-state data.

Table 1
Sociodemographic, clinical and head motion comparison between HC and IRBD.

	HC (n = 27)	IRBD (n = 20)	Test stat/p
Sociodemographic and clinical data			
Age (years)	66.5 (13.0)	71.0 (10.0)	343.5/.113
Education (years)	10.0 (8.0)	10.0 (7.0)	257.0/.779
Sex (male/female)	(13/14)	(14/6)	2.24/.134
Neuropsychiatric Inventory	1.0 (4.0)	4.0 (7.0)	**398.0/.001**
Beck Depression Inventory II	5.0 (8.0)	7.0 (10.0)	286.5/.242
Starkstein's Apathy Scale	8.0 (5.0)	12.0 (9.0)	299.5/.141
IRBD duration (years)	-	2.0 (5.0)	-
MDS-UPDRS-III	-	2.0 (4.0)	-
Mean interframe head motion			
Rotation (degrees)	.026 (.017)	.037 (.024)	339.0/.080
Translation (mm)	.088 (.106)	.104 (.118)	329.0/.126
Maximum interframe head motion			
Rotation (degrees)	.178 (.157)	.181 (.172)	283.0/.610
Translation (mm)	.431 (.252)	.382 (.210)	252.0/.859

Abbreviations: HC, healthy controls; IRBD, idiopathic rapid eye movement sleep behavior disorder; MDS-UPDRS-III, Movement Disorder Society Unified Parkinson's Disease Rating Scale motor section. Data are presented as median (interquartile range) for continuous variables or frequencies for categorical ones. Group differences between HC and IRBD were tested using Mann-Whitney's U test. Pearson's chi-square' was applied to assess differences in categorical variables.

Table 2
Group comparison of cognitive domains

Cognitive domains	HC (n = 25)	IRBD (n = 20)	Test stat/ p
Attention	−.232 (.87)	−.272 (.77)	285.0/.424
Memory	.532 (.64)	−.081 (1.39)	134.0/.008
Visuospatial/Visuoperceptual	.345 (.88)	−.529 (1.33)	121.0/.006
Executive functions	−.212 (.91)	−.346 (.64)	193.0/.392
Mental processing speed	−.164 (.87)	−.433 (1.0)	130.0/.017

Abbreviations: HC, healthy controls; IRBD, idiopathic rapid eye movement sleep behavior disorder. Data are presented as median (interquartile range) of the Z scores adjusted for age, years of education and sex. Group differences in cognitive domains were tested using Mann-Whitney's U test.

Fig. 1 shows the six connections with significantly reduced functional connectivity strength in IRBD when compared with HC in the whole-brain analysis ($p < 0.05$, FWE corrected). All connections were found to be cortico-cortical tracts, with a posterior distribution and a left hemispheric predominance. To better study this regional pattern, we performed a supplementary analysis focusing on brain posterior connectivity. To this end, we selected 58 out of the 246 regions extracted from the Brainnetome Atlas, including cuneus, fusiform, superior occipital gyrus, occipital pole, precuneus, inferior parietal and superior parietal subregions. Additionaly, in order to have a control network, we also studied brain anterior connectivity with 68 regions including superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, orbital gyrus, precentral gyrus and paracentral lobule (Supplementary material 1). As shown in Fig. 2 and Supplementary material 2, intergroup-comparison of the posterior network showed reduced connectivity in 51 connections in IRBD ($p < 0.05$, FWE corrected), whereas no group effect was found for the anterior network.

No significant intergroup differences were found in global graph parameters in any network threshold. At the node-level, reduced centrality was observed in IRBD patients compared with HC in the left superior parietal region (specifically, in SPL_L_5_2) in 4 out of 9 thresholds in the posterior network. Results were controlled by age, sex and head motion (Fig. 2D).

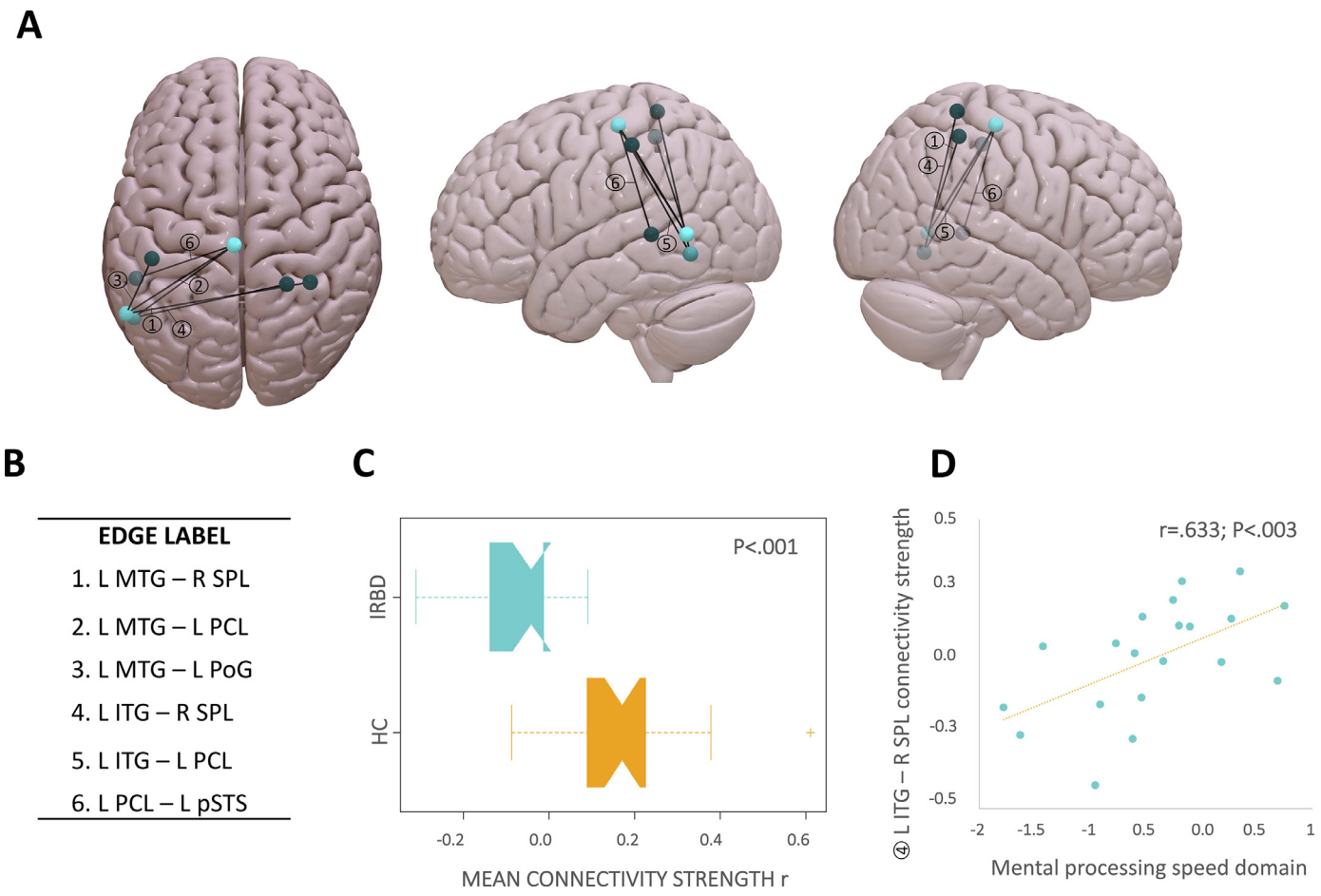

Figure 1. Comparison between idiopathic REM sleep behavior disorder (IRBD) patients and healthy controls (HC) using threshold-free network-based statistics. A. Schematic representation of the reduced functional connectivity strength in IRBD patients compared with HC in the whole-brain analysis consisting of six edges found to be significantly different between groups ($p < 0.05$, family-wise error corrected). Lighter colors represent nodes connected to a greater number of altered connections. Numbers correspond to the edge label (see panel B). B. Labels of the altered edges shown in panel A. Regions were defined based on the Brainnetome Atlas (see Supplementary material 1). Panel C shows the mean connectivity strength distribution (computed for each subject individually) of the six significant connections according to group. D. Significant correlation was found only between the mental processing speed domain and left ITL - right SPL functional connectivity strength (see edge number 4 in brain maps) in IRBD patients. Age, sex and head motion were entered as covariates. Abbreviations: HC, healthy controls; IRBD, idiopathic REM-sleep behavior disorder; ITG, inferior temporal gyrus; L, left; MTG, middle temporal gyrus; PCL, paracentral lobule; PoG, postcentral gyrus; pSTS, posterior superior temporal sulcus; R, right; r, connectivity strength (Pearson's correlation coefficient); SPL, superior parietal lobule. Brain plots were created with Surf Ice (https://www.nitrc.org/projects/surfice/).

3.3. Correlation of cognitive parameters with functional connectivity

The mean strength of those edges that showed reduced functional connectivity in the whole-brain analysis (Fig. 1A, 1B) was correlated with the cognitive domains that were impaired in IRBD (Table 2). A positive correlation was found only between the mental processing speed domain and left ITL - right SPL functional connectivity strength in IRBD patients (r = .633; p = .003) (Fig. 1D). No significant correlations were found in the HC group.

4. Discussion

As far as we know, this is the first work investigating resting-state functional connectivity in a sample of IRBD patients using complex network analyses. Our data suggest that in comparison with healthy subjects, IRBD patients had reduced resting-state functional connectivity with a predominant posterior distribution. Furthermore, this reduction was associated with cognitive impairment in IRBD patients.

The whole-brain analysis showed reduced posterior cortico-cortical functional connectivity strength in IRBD patients compared with a group of healthy subjects in six edges. Particularly, the left middle temporal gyrus had reduced functional connectivity with left paracentral lobule, left post central gyrus and right superior parietal lobule. Disrupted connectivity was also found between left inferior temporal gyrus and left paracentral lobule, between left paracentral lobule and left posterior superior temporal sulcus, and also between left inferior temporal gyrus and right superior parietal lobule. In summary, our results showed a connectivity alteration pattern involving associative regions of the temporal and parietal lobes that are known to support complex cognitive functions. To better characterize this posterior-predominant pattern, further independent analyses were performed for anterior and posterior networks. Whereas no significant results were found in the anterior network, posterior complex network characterization showed abnormal connectivity patterns in IRBD with a brain functional connectivity reduction in 51 edges. Although the greater number of significantly altered nodes may be due in part to the lower number of comparisons included in the posterior analysis, the same method was used to analyze the anterior network, yielding no significant results.

As stated in the introduction, only two published studies focused on rs-fMRI data in IRBD, one using an ad hoc developed template (Rolinski et al., 2016) and another performed with a seed-to-seed

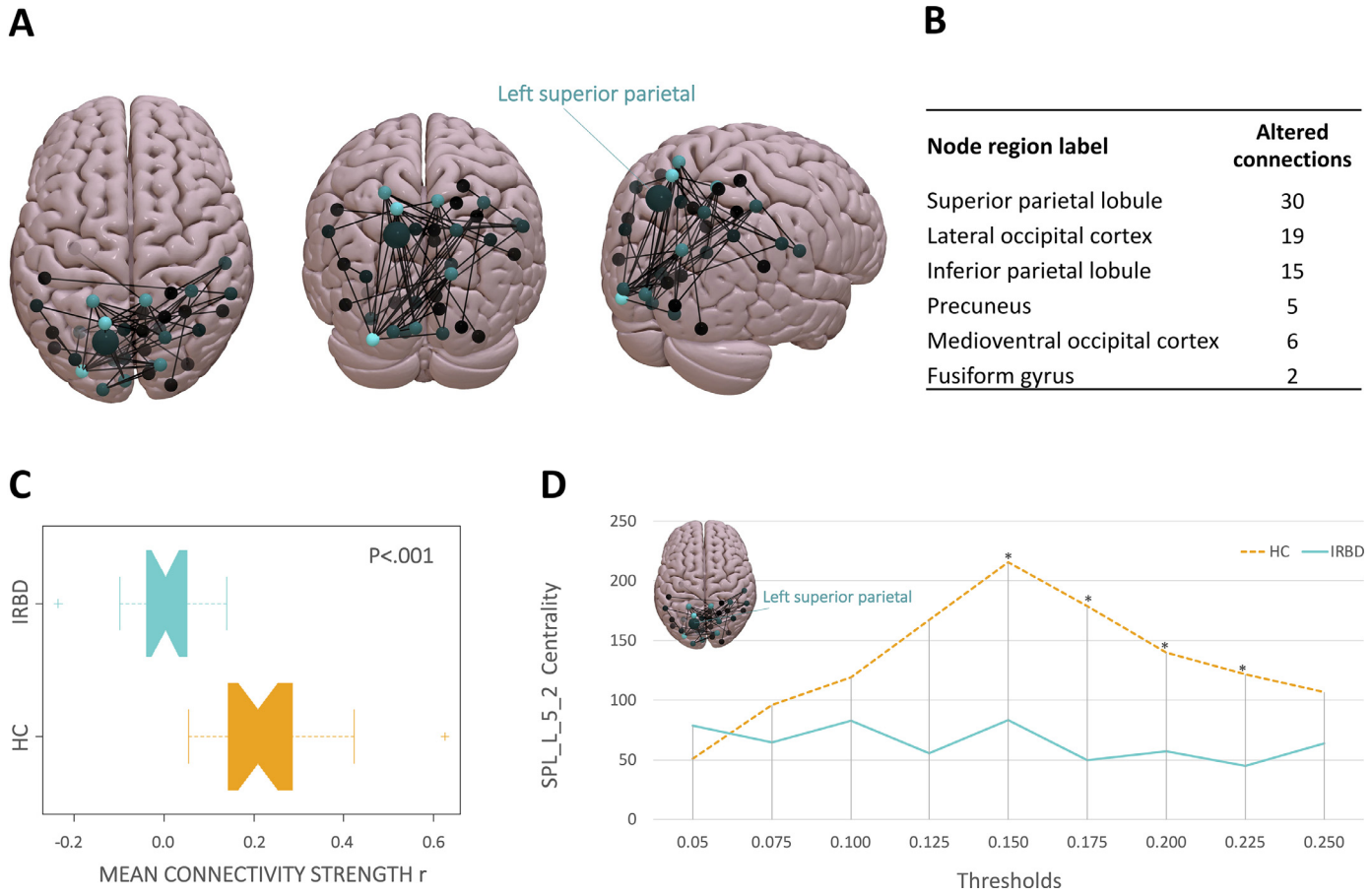

Figure 2. Comparison between idiopathic REM sleep behavior disorder (IRBD) patients and healthy controls (HC) using threshold-free network-based statistics in posterior regions. A. Schematic representation of the reduced functional connectivity strength in IRBD patients compared with HC in the posterior network consisting of 51 edges considered significantly different between groups ($p < 0.05$, family-wise error corrected). Lighter colors represent nodes connected to a greater number of altered connections. The larger sphere represents SPL_L_5_2 (see Supplementary material 1) which showed reduced centrality in IRBD patients. B. Nodes with number of altered edges connected to them. Panel C shows the mean connectivity strength distribution (computed for each subject individually) of the 51 significant connections according to group. Panel D. shows centrality reduction in the left superior parietal in IRBD patients compared with HC. SPL_L_5_2 node centrality (vertical axis) as a function of sparsity thresholds (horizontal axis) for HC and IRBD subgroups. *Indicates significant differences between HC and IRBD. Age, sex and head motion were entered as covariates. Abbreviations: HC, healthy controls; IRBD, idiopathic form of REM-sleep behavior disorder; r, mean connectivity strength of all significant edges (Pearson's correlation coefficient). Brain plots were created with Surf Ice (https://www.nitrc.org/projects/surfice/).

approach (Ellmore et al., 2013). Both works found altered basal ganglia functional connectivity in these patients. Interestingly, our results demonstrated that when a whole-brain analysis is conducted, reduced cortico-cortical connectivity is also identified. Brain functional connectivity in IRBD should be further addressed with longitudinal cohorts inspecting whether possible involvement of cortical and subcortical structures change with disease progression.

Functional disruption of the parietal cortex in IRBD agrees with previously studies reporting structural decrements in cortical thickness of this region (Rahayel et al., 2018b, 2015; Campabadal et al., 2019). Thus, both structural and functional MRI studies point out a cortical involvement in IRBD congruent with its prodromal symptom of alpha-synucleinopathies. In PD, the posterior atrophy is mainly seen in patients with mild cognitive impairment (Segura et al., 2014). Although our patients did not have cognitive complaints at the time of the study, compared to controls they showed impairment in memory, visuospatial/visuoperceptual and speed of mental processing domains. This neuropsychological pattern is consistent with previous literature where IRBD patients without cognitive complaints and without parkinsonism frequently showed abnormalities when neuropsychological batteries were undergoing (Campabadal et al., 2019; Fantini et al., 2011; Ferini-Strambi et al., 2004; Massicotte-Marquez et al., 2008; Terzaghi et al., 2013, 2008; Vendette et al., 2012).

In the current study, we found evidence of the potential role of altered brain functional connectivity in cognitive impairment. In particular, a positive correlation between mental processing speed and temporo-parietal functional connectivity was found in the IRBD group, but not in healthy controls. It is interesting to note that mental processing speed domain was calculated using the Stroop Color and SDMT-oral version, tests that are known to have a strong posterior cortical component (Forn et al., 2009; Garcia-Diaz et al., 2018a, 2018b; Lezak, 2012). Specifically, and in line with our results, SDMT has been found to be associated with cortical atrophy in temporo-parietal regions in PD patients (Garcia-Diaz et al., 2018a). It could be speculated that the relationship among these tests and the loss of co-activation between right superior parietal and left inferior temporal regions could be reflecting integration abnormalities between the right dorsal-stream, required for visuospatial processing, and regions of the left ventral-stream, that may be involved in visuo-verbal decodification required in both tasks. Such findings could be underling specific vulnerability of long-distance connections in IRBD patients. In this sense, further research is needed to elucidate possible changes in the organization and topology of white matter tracts in IRBD. Finally, it is worth noting that only mental speed processing domain significantly correlated with brain functional connectivity. It can be speculated that SDMT and Stroop Color Word test require not only mental speed processing, but

also integration of attention, visuospatial, and visuoperceptual functions, possibly making them more sensitive tests when it comes to find brain dysfunctions in IRBD patients.

Results obtained in global graph parameters were less outstanding than those obtained using the TFNBS approach (Baggio et al., 2018). No group effect was found in global graph parameters in any network. We only found decreased centrality for a node located in the left superior parietal lobule. This result is consistent with a prior work with DLB patients where decreased centrality in this same region, among others, was found (Peraza et al., 2015). Neuropathological explanations for this regional centrality reduction in IRBD remain speculative at this point but could include disease-specific regional preferences of Lewy body pathology that have been evidenced previously (Hansen et al., 2019). It is worth noting that our results highlighted brain connectivity reduction with left-hemispheric predominance in IRBD patients. This finding is in line with prior studies showing left asymmetries in motor symptoms and in nigrostriatal function in right-handed PD patients (Barrett et al., 2011; Scherfler et al., 2012; Uitti et al., 2005). Interestingly, in keeping with these works in our IRBD sample eighteen out of twenty patients were right-handed (90%). Based on this, it could be hypothesized that functional brain connectivity has an asymmetric vulnerability at premotor stages that might be related to hemispheric dominance.

Some limitations to the present study should be pointed out. Firstly, IRBD sample is relatively small; thus, we cannot assume that the set of functional connections identified in our study would generalize to other datasets. Future multicenter studies should be carried out to replicate our findings. Secondly, some patients were evaluated under the influence of benzodiazepines. Mainly brain functional connectivity increases (Kiviniemi et al., 2005; Pflanz et al., 2015) have been reported in response to benzodiazepines administration. Unfortunately, our sample does not allow us to study differences between medicated and non-medicated patients. Thirdly, another possible limitation of our work is that, despite the inclusion of a variety of tests in the main cognitive domains defined in recent guidelines (Litvan et al., 2012), we used MMSE instead of MoCa, a less sensitive cognitive screening test in alfa-synucleopathies.

5. Conclusion

In the current work, our results indicate that modelling the brain as a functional connectome is a useful approach to detect changes in the organization of brain functional connectivity in IRBD, as a clinical model of PD and DLB prodrome. Overall, our findings support the presence of disrupted posterior functional connectivity in IRBD patients, suggesting a posterior pattern that is in line with previous literature in DLB and PD. In addition, connectivity reductions between the left inferior temporal lobe and the right superior parietal lobule were associated with lower performance in speed of processing domain in IRBD patients.

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Author Contributions

CJ contributed in the design of the study. AC, AA, and CU contributed to the analysis of the data and AC, BS, CJ, MS, AA, CU, HB, CG, JS, YC, and AI contributed to the interpretation of the data. AC and CJ contributed to the draft of the article. AC, BS, CJ, MS, AA, CU, HB, CG, JS, YC, NB, and AI revised the manuscript critically for important intellectual content and approved the final version of the manuscript.

Declaration of Competing Interest

The authors report no conflicts of interest relevant to this study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2019.102138.

References

Aarsland, D., Bronnick, K., Larsen, J.P., Tysnes, O.B., Alves, G., Norwegian ParkWest Study Group, 2009. Cognitive impairment in incident, untreated Parkinson disease: The Norwegian ParkWest Study. Neurology 72, 1121–1126. https://doi.org/10.1212/01.wnl.0000338632.00552.cb.

Baggio, H.C., Abos, A., Segura, B., Campabadal, A., Garcia-Diaz, A., Uribe, C., Compta, Y., Marti, M.J., Valldeoriola, F., Junque, C., 2018. Statistical inference in brain graphs using threshold-free network-based statistics. Hum. Brain Mapp. 39. https://doi.org/10.1002/hbm.24007.

Barrett, M.J., Wylie, S.A., Harrison, M.B., Wooten, G.F., 2011. Handedness and motor symptom asymmetry in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 82, 1122–1124. https://doi.org/10.1136/jnnp.2010.209783.

Beck, A, Steer, R, B, G., 1996. Manual for the Beck Depression Inventory-II. Psychological Corporation, San Antonio, Texas.

Berg, D., Postuma, R.B., Adler, C.H., Bloem, B.R., Chan, P., Dubois, B., Gasser, T., Goetz, C.G., Halliday, G., Joseph, L., Lang, A.E., Liepelt-Scarfone, I., Litvan, I., Marek, K., Obeso, J., Oertel, W., Olanow, C.W., Poewe, W., Stern, M., Deuschl, G., 2015. MDS research criteria for prodromal Parkinson's disease. Mov. Disord. 30, 1600–1611. https://doi.org/10.1002/mds.26431.

Boeve, B.F., 2010. REM Sleep Behavior Disorder: Updated Review of the Core Features, the RBD-Neurodegenerative Disease Association, Evolving Concepts, Controversies, and Future Directions. Ann. N. Y. Acad. Sci. 15–54. https://doi.org/10.1111/j.1749-6632.2009.05115.x.REM.

Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10, 186–198. https://doi.org/10.1038/nrn2575.

Campabadal, A., Segura, B., Junque, C., Serradell, M., Abos, A., Uribe, C., Baggio, H.C., Gaig, C., Santamaria, J., Compta, Y., Bargallo, N., Iranzo, A., 2019. Cortical Gray Matter and Hippocampal Atrophy in Idiopathic Rapid Eye Movement Sleep Behavior Disorder. Front. Neurol. 10, 1–9. https://doi.org/10.3389/fneur.2019.00312.

Cummings, J.L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D.A., Gornbein, J., 1994. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 44, 2308–2314.

Ellmore, T.M., Castriotta, R.J., Hendley, K.L., Aalbers, B.M., Furr-Stimming, E., Hood, A.J., Suescun, J., Beurlot, M.R., Hendley, R.T., Schiess, M.C., 2013. Altered nigrostriatal and nigrocortical functional connectivity in rapid eye movement sleep behavior disorder. Sleep 36, 1885–1892. https://doi.org/10.5665/sleep.3222.

Ellmore, T.M., Hood, A.J., Castriotta, R.J., Stimming, E.F., Bick, R.J., Schiess, M.C., 2010. Reduced volume of the putamen in REM sleep behavior disorder patients. Park. Relat. Disord. 16, 645–649. https://doi.org/10.1016/j.parkreldis.2010.08.014.

Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., Laird, A.R., Fox, P.T., Eickhoff, S.B., Yu, C., Jiang, T., 2016. The Human Brainnetome Atlas: A New Brain Atlas Based on Connectional Architecture. Cereb. Cortex 26, 3508–3526. https://doi.org/10.1093/cercor/bhw157.

Fantini, M.L., Farini, E., Ortelli, P., Zucconi, M., Manconi, M., Cappa, S., Ferini-Strambi, L., 2011. Longitudinal study of cognitive function in idiopathic REM sleep behavior disorder. Sleep 34, 619–625. https://doi.org/10.1093/sleep/34.5.619.

Ferini-Strambi, L., Di Gioia, M.R., Castronovo, V., Oldani, A., Zucconi, M., Cappa, S.F., 2004. Neuropsychological assessment in idiopathic REM sleep behavior disorder (RBD): does the idiopathic form of RBD really exist? Neurology 62, 41–45.

Forn, C., Belloch, V., Bustamante, J.C., Garbin, G., Parcet-Ibars, M.À., Sanjuan, A., Ventura, N., Ávila, C., 2009. A Symbol Digit Modalities Test version suitable for functional MRI studies. Neurosci. Lett. 456, 11–14. https://doi.org/10.1016/j.neulet.2009.03.081.

Garcia-Diaz, A.I., Segura, B., Baggio, H.C., Marti, M.J., Valldeoriola, F., Compta, Y., Bargallo, N., Uribe, C., Campabadal, A., Abos, A., Junque, C., 2018a. Structural Brain Correlations of Visuospatial and Visuoperceptual Tests in Parkinson's Disease. J. Int. Neuropsychol. Soc. 24. https://doi.org/10.1017/S1355617717000583.

Garcia-Diaz, A.I., Segura, B., Baggio, H.C., Uribe, C., Campabadal, A., Abos, A., Marti, M.J., Valldeoriola, F., Compta, Y., Bargallo, N., Junque, C., 2018b. Cortical thinning correlates of changes in visuospatial and visuoperceptual performance in Parkinson's disease: A 4-year follow-up. Park. Relat. Disord. 46. https://doi.org/10.1016/j.parkreldis.2017.11.003.

Hansen, D., Ling, H., Lashley, T., Holton, J.L., Warner, T.T., 2019. Review: Clinical, neuropathological and genetic features of Lewy body dementias. Neuropathol. Appl. Neurobiol. 1–20. https://doi.org/10.1111/nan.12554.

Hanyu, H., Inoue, Y., Sakurai, H., Kanetaka, H., Nakamura, M., Miyamoto, T., Sasai, T., Iwamoto, T., 2012. Voxel-based magnetic resonance imaging study of structural brain changes in patients with idiopathic REM sleep behavior disorder. Parkinsonism Relat. Disord. 18, 136–139. https://doi.org/10.1016/j.parkreldis.2011.08.023.

Hohenfeld, C., Werner, C.J., Reetz, K., 2018. Resting-state connectivity in neurodegenerative disorders: Is there potential for an imaging biomarker? NeuroImage Clin. 18, 849–870. https://doi.org/10.1016/j.nicl.2018.03.013.

Iranzo, A., Fernández-Arcos, A., Tolosa, E., Serradell, M., Molinuevo, J.L., Valldeoriola, F., Gelpi, E., Vilaseca, I., Sánchez-Valle, R., Lladó, A., Gaig, C., Santamaría, J., 2014. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: Study in 174 patients. PLoS One 9. https://doi.org/10.1371/journal.pone.0089741.

Iranzo, A., Molinuevo, J.L., Santamaría, J., Serradell, M., Martí, M.J., Valldeoriola, F., Tolosa, E., 2006. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. Lancet Neurol. 5, 572–577. https://doi.org/10.1016/S1474-4422(06)70476-8.

Kiviniemi, V.J., Haanpää, H., Kantola, J.H., Jauhiainen, J., Vainionpää, V., Alahuhta, S., Tervonen, O., 2005. Midazolam sedation increases fluctuation and synchrony of the resting brain BOLD signal. Magn. Reson. Imaging 23, 531–537. https://doi.org/10.1016/j.mri.2005.02.009.

Lezak, M.D., 2012. Neuropsychological assessment. Oxford University Press.

Litvan, I., Goldman, J.G., Troster, A.I., Schmand, B.A., Weintraub, D., Petersen, R.C., Mollenhauer, B., Adler, C.H., Marder, K., Williams-Gray, C.H., Aarsland, D., Kulisevsky, J., Rodriguez-Oroz, M.C., Burn, D.J., Barker, R.A., Emre, M., 2012. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov. Disord. 27, 349–356. https://doi.org/10.1002/mds.24893.

Mahlknecht, P., Iranzo, A., Högl, B., Frauscher, B., Müller, C., Santamaría, J., Tolosa, E., Serradell, M., Mitterling, T., Gschliesser, V., Goebel, G., Brugger, F., Scherfler, C., Poewe, W., Seppi, K., 2015. Olfactory dysfunction predicts early transition to a Lewy body disease in idiopathic RBD. Neurology 84, 654–658. https://doi.org/10.1212/WNL.0000000000001265.

Massicotte-Marquez, J., Décary, A., Gagnon, J.-F., Vendette, M., Mathieu, A., Postuma, R.B., Carrier, J., Montplaisir, J., Petersen, R.C., 2008. Executive dysfunction and memory impairment in idiopathic REM sleep behavior disorder. Neurology 70, 1250–1257. https://doi.org/10.1212/01.wnl.0000286943.79593.a6.

Park, K.M., Lee, H.J., Lee, B.I., Kim, S.E., 2018. Alterations of the brain network in idiopathic rapid eye movement sleep behavior disorder: structural connectivity analysis. Sleep Breath 23, 587–593. https://doi.org/10.1007/s11325-018-1737-0.

Peraza, L.R., Taylor, J.P., Kaiser, M., 2015. Divergent brain functional network alterations in dementia with Lewy bodies and Alzheimer's disease. Neurobiol. Aging 36, 2458–2467. https://doi.org/10.1016/j.neurobiolaging.2015.05.015.

Pereira, J.B., Weintraub, D., Chahine, L., Aarsland, D., Hansson, O., Westman, E., 2019. Cortical thinning in patients with REM sleep behavior disorder is associated with clinical progression. npj Park. Dis. 3 (5), 7. https://doi.org/10.1038/s41531-019-0079-3.

Pflanz, C.P., Pringle, A., Filippini, N., Warren, M., Gottwald, J., Cowen, P.J., Harmer, C.J., 2015. Effects of seven-day diazepam administration on resting-state functional connectivity in healthy volunteers: A randomized, double-blind study. Psychopharmacology (Berl) 232, 2139–2147. https://doi.org/10.1007/s00213-014-3844-3.

Postuma, R.B., 2016. Resting state MRI: a new marker of prodromal neurodegeneration? Brain 139, 2106–2108. https://doi.org/10.1093/brain/aww131.

Postuma, R.B., Berg, D., Stern, M., Poewe, W., Marek, K., Litvan, I., 2015. CME MDS Clinical Diagnostic Criteria for Parkinson ' s Disease Centrality of Motor Syndrome — Parkinsonism and PD Criteria Benchmark — The Expert Examination 30. 10.1002/mds.26424.

Postuma, R.B., Iranzo, A., Hu, M., Högl, B., Boeve, B.F., Manni, R., Oertel, W.H., Arnulf, I., Ferini-Strambi, L., Puligheddu, M., Antelmi, E., Cochen De Cock, V., Arnaldi, D., Mollenhauer, B., Videnovic, A., Sonka, K., Jung, K.Y., Kunz, D., Dauvilliers, Y., Provini, F., Lewis, S.J., Buskova, J., Pavlova, M., Heidbreder, A., Montplaisir, J.Y., Santamaria, J., Barber, T.R., Stefani, A., Louis, S.E.K., Terzaghi, M., Janzen, A., Leu-Semenescu, S., Plazzi, G., Nobili, F., Sixel-Doering, F., Dusek, P., Bes, F., Cortelli, P., Ehgoetz Martens, K., Gagnon, J.F., Gaig, C., Zucconi, M., Trenkwalder, C., Gan-Or, Z., Lo, C., Rolinski, M., Mahlknecht, P., Holzknecht, E., Boeve, A.R., Teigen, L.N., Toscano, G., Mayer, G., Morbelli, S., Dawson, B., Pelletier, A., 2019. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: A multicentre study. Brain 142, 744–759. https://doi.org/10.1093/brain/awz030.

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59, 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018.

Pruim, R.H.R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J.K., Beckmann, C.F., 2015. ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. Neuroimage 112, 267–277. https://doi.org/10.1016/j.neuroimage.2015.02.064.

Rahayel, S., Montplaisir, J., Monchi, O., Bedetti, C., Postuma, R.B., Brambati, S., Carrier, J., Joubert, S., Latreille, V., Jubault, T., Gagnon, J.F., 2015. Patterns of cortical thinning in idiopathic rapid eye movement sleep behavior disorder. Mov. Disord. 30, 680–687. https://doi.org/10.1002/mds.25820.

Rahayel, S., Postuma, R.B., Montplaisir, J., Bedetti, C., Brambati, S., Carrier, J., Monchi, O., Bourgouin, P.A., Gaubert, M., Gagnon, J.F., 2018a. Abnormal Gray Matter Shape, Thickness, and Volume in the Motor Cortico-Subcortical Loop in Idiopathic Rapid Eye Movement Sleep Behavior Disorder: Association with Clinical and Motor Features. Cereb. Cortex 28, 658–671. https://doi.org/10.1093/cercor/bhx137.

Rahayel, S., Postuma, R.B., Montplaisir, J., Génier Marchand, D., Escudier, F., Gaubert, M., Bourgouin, P.-A., Carrier, J., Monchi, O., Joubert, S., Blanc, F., Gagnon, J.-F., 2018b. Cortical and subcortical gray matter bases of cognitive deficits in REM sleep behavior disorder. Neurology 90, e1759–e1770. https://doi.org/10.1016/S0306-4522(99)00316-4.

Rolinski, M., Griffanti, L., Piccini, P., Roussakis, A.A., Szewczyk-krolikowski, K., Menke, R.A., Quinnell, T., Zaiwalla, Z., Klein, J.C., Mackay, C.E., Hu, M.T.M., 2016. Basal ganglia dysfunction in idiopathic REM sleep behaviour disorder parallels that in early Parkinson ' s disease. Brain 2224–2234. https://doi.org/10.1093/aww131.

Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: Uses and interpretations. Neuroimage 52, 1059–1069. https://doi.org/10.1016/J.NEUROIMAGE.2009.10.003.

Schenck, C.H., Mahowald, M.W., 2002. REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP. Sleep 25, 120–138.

Scherfler, C., Frauscher, B., Schocke, M., Iranzo, A., Gschliesser, V., Seppi, K., Santamaria, J., Tolosa, E., Högl, B., Poewe, W., 2011. White and gray matter abnormalities in idiopathic rapid eye movement sleep behavior disorder: A diffusion-tensor imaging and voxel-based morphometry study. Ann. Neurol. 69, 400–407. https://doi.org/10.1002/ana.22245.

Scherfler, C., Seppi, K., Mair, K.J., Donnemiller, E., Virgolini, I., Wenning, G.K., Poewe, W., 2012. Left hemispheric predominance of nigrostriatal dysfunction in Parkinson's disease. Brain 135, 3348–3354. https://doi.org/10.1093/brain/aws253.

Segura, B., Baggio, H.C., Marti, M.J., Valldeoriola, F., Compta, Y., Garcia-Diaz, A.I., Vendrell, P., Bargallo, N., Tolosa, E., Junque, C., 2014. Cortical thinning associated with mild cognitive impairment in Parkinson's disease. Mov. Disord. 29, 1495–1503. https://doi.org/10.1002/mds.25982.

Smith, S.M., Nichols, T.E., 2009. Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 44, 83–98. https://doi.org/10.1016/j.neuroimage.2008.03.061.

Starkstein, S.E., Mayberg, H.S., Preziosi, T.J., Andrezejewski, P., Leiguarda, R., Robinson, R.G., 1992. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J. Neuropsychiatry Clin. Neurosci. 4, 134–139. https://doi.org/10.1176/jnp.4.2.134.

Telesford, Q.K., Simpson, S.L., Burdette, J.H., Hayasaka, S., Laurienti, P.J., 2011. The Brain as a Complex System: Using Network Science as a Tool for Understanding the Brain. Brain Connect. 1, 295–308. https://doi.org/10.1089/brain.2011.0055.

Terzaghi, M., Sinforiani, E., Zucchella, C., Zambrelli, E., Pasotti, C., Rustioni, V., Manni, R., 2008. Cognitive performance in REM sleep behaviour disorder: a possible early marker of neurodegenerative disease? Sleep. Med. 9, 343–351. https://doi.org/10.1016/j.sleep.2007.06.013.

Terzaghi, M., Zucchella, C., Rustioni, V., Sinforiani, E., Manni, R., 2013. Cognitive Performances and Mild Cognitive Impairment in Idiopathic Rapid Eye Movement Sleep Behavior Disorder: Results of a Longitudinal Follow-Up Study. Sleep 36, 1527–1532. https://doi.org/10.5665/sleep.3050.

Uitti, R.J., Baba, Y., Whaley, N.R., Wszolek, Z.K., Putzke, J.D., 2005. Parkinson disease: Handedness predicts asymmetry. Neurology 64, 1925–1930. https://doi.org/10.1212/01.WNL.0000163993.82388.C8.

Unger, M.M., Belke, M., Menzler, K., Heverhagen, J.T., Keil, B., Stiasny-Kolster, K., Rosenow, F., Diederich, N.J., Mayer, G., Möller, J.C., Oertel, W.H., Knake, S., 2010. Diffusion tensor imaging in idiopathic REM sleep behavior disorder reveals microstructural changes in the brainstem, substantia nigra, olfactory region, and other brain regions. Sleep 33, 767–773. https://doi.org/10.1093/sleep/33.6.767.

Vendette, M., Montplaisir, J., Gosselin, N., Soucy, J.-P., Postuma, R.B., Dang-Vu, T.T., Gagnon, J.-F., 2012. Brain perfusion anomalies in rapid eye movement sleep behavior disorder with mild cognitive impairment. Mov. Disord. 27, 1255–1261. https://doi.org/10.1002/mds.25034.

Zalesky, A., Fornito, A., Bullmore, E.T., 2010. Network-based statistic: Identifying differences in brain networks. Neuroimage 53, 1197–1207. https://doi.org/10.1016/j.neuroimage.2010.06.041.