

RESEARCH ARTICLE

Altered Intra- and Inter-Network Resting-State Functional Connectivity is Associated with Neuropsychological Functioning and Clinical Symptoms in Patients with Isolated Rapid Eye Movement Sleep Behavior Disorder

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ABSTRACT: Background: Isolated rapid-eye movement (REM) sleep behavior disorder (iRBD) is characterized by abnormal behaviors in REM sleep and is considered as a prodromal symptom of alpha-synucleinopathies. Resting-state functional magnetic resonance imaging (rsfMRI) studies have unveiled altered functional connectivity (rsFC) in patients with iRBD. However, the associations between intra- and inter-network rsFC with clinical symptoms and neuropsychological functioning in iRBD remain unclear.

Objective: To characterize intra- and inter-network rsFC in iRBD patients using a data-driven approach and to assess its associations with clinical features and cognitive functioning.

Methods: Forty-two patients with iRBD and 45 healthy controls (HC) underwent rsfMRI and comprehensive neuropsychological testing. Resting-state networks were characterized using independent component analyses. Group differences in intra- and inter-network rsFC and

their associations with clinical and neuropsychological data were studied. A threshold of corrected $P < 0.05$ was used in all the analyses.

Results: iRBD patients displayed lower intra-network rsFC within basal ganglia, visual, sensorimotor, and cerebellar networks, relative to HC. Mean rsFC strength within the basal ganglia network positively correlated with processing speed and negatively with the non-motor symptoms in iRBD patients. Reduced inter-network rsFC between sensorimotor and visual medial networks was observed in iRBD patients, which was associated with global cognitive status.

Conclusions: iRBD is characterized by both reductions in intra-network rsFC in cortical and subcortical networks and inter-network dysconnectivity between sensorimotor and visual networks. Abnormalities in intra- and inter-network rsFC are associated with cognitive performance and non-motor symptoms, suggesting the utility of both rsFC measures as imaging markers in prodromal alpha-synucleinopathies. © 2025 The

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Key Words: isolated REM sleep behavior disorder; neuroimaging; neuropsychology; prodromal alpha-synucleinopathies; resting-state functional connectivity

Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by the loss of REM-sleep skeletal muscle atonia and vivid dreams, frequently leading to dream-enacting behaviors and falling out of bed.¹ RBD is caused by dysfunction of the lower brainstem structures that maintain muscle atonia during REM sleep.² In the last decades, isolated RBD (iRBD) has been recognized as a core prodromal symptom of alpha-synucleinopathies, that can be present up to 20 years before diagnosis.^{3,4} In fact, the risk for conversion in a 14-year follow-up exceeds 96%, with most iRBD patients converting to Parkinson's disease (PD) and dementia with Lewy bodies (DLB).⁵ Since magnetic resonance imaging (MRI) has allowed characterization of structural and functional brain alterations in most neurodegenerative diseases, its application in iRBD is warranted to identify brain changes in early stages of neurodegeneration.^{6,7}

Resting-state functional MRI (rsfMRI) examines the correlation of low-frequency spontaneous fluctuations occurring in remote brain regions, known as resting-state functional connectivity (rsFC).⁸ (rsfMRI) has allowed detection of abnormalities in rsFC in the alpha-synucleinopathies^{9–12} and has been proposed as a suitable biomarker of prodromal neurodegeneration.^{12,13} Previous rsfMRI studies in iRBD have focused on predetermined regions or *seeds* known to be affected in PD,^{6,7} mainly the basal ganglia (BG), showing that altered intrinsic connectivity in these structures is present already in early stages.^{14–17} Decreased BG rsFC with cortical^{15–20} and subcortical structures^{17,18,21} has also been reported in iRBD. Whereas seed-based studies are useful to test specific research questions, they may overlook potential contributions of other brain regions outside of the specified circuitry to brain dynamics.²²

Data-driven approaches, such as independent component analyses (ICA), or complex-network approaches, are exploratory methodologies that do not necessitate a priori specification of a particular seed region, thereby allowing the study of whole-brain rsFC. In this line, one study from our group used a complex-network approach to investigate whole-brain connectivity and detected reduced posterior cortico-cortical rsFC in iRBD patients.²³ Another study used ICA to investigate four resting-state networks (rsNs) of interest and showed decreased intra-network rsFC in sensorimotor, BG, and executive-control networks.²⁴ However, to our

knowledge, inter-network rsFC has not yet been studied in iRBD.

Cognitive dysfunction has been reported in patients with iRBD, showing heterogeneity in the cognitive domains affected – mainly involving memory, executive, and visuospatial functions – and in the severity of these alterations.²⁵ A few studies in iRBD have found relationships between rsFC measures and clinical or neuropsychological data.^{17,23,26,27} Decreased parieto-temporal rsFC has been shown to correlate with low processing speed²³ and reduced cortico-striatal rsFC to be associated with attentional-executive deficits in iRBD.¹⁷ Research with larger sample sizes has shown that rsFC strength between the posterior insula and the precuneus positively correlated with general cognition as assessed with the Montreal Cognitive Assessment (MoCA),²⁸ whereas other authors have not found associations between rsFC and neuropsychological functioning.²⁴ Remarkably, the studies including larger samples estimated general cognitive functioning based on screening instruments and not through comprehensive neuropsychological assessments. Research including extensive neuropsychological profiling is needed to characterize the potential associations between rsFC and clinical deficits in iRBD.

In this study, we aimed to characterize intra- and inter-network rsFC in patients with iRBD using a data-driven approach and to evaluate its associations with clinical features and cognitive functioning as assessed in a comprehensive neuropsychological battery. We hypothesized that iRBD patients show intra- and inter-network alterations in rsNs similar to those reported in manifest PD and DLB and that these would be associated with clinical symptoms and cognitive performance.

Methods

Participants

Participants were prospectively recruited from the Sleep Unit of the Neurology Service, at the Hospital Clínic de Barcelona, Catalonia, Spain. The total sample comprised 121 participants, 67 video-polysomnography-confirmed (v-PSG) iRBD patients, and 54 healthy controls (HC).

The inclusion criteria for iRBD patients were: (1) v-PSG demonstrating REM sleep without atonia and dream-enacting behaviors, (2) absence of overt motor complaints at recruitment, (3) unremarkable neurological

examination, and (4) no temporal association between the estimated RBD onset and the introduction or withdrawal of a medication.^{4,29} HC participants were recruited through community channels.

The exclusion criteria for all participants were: (1) presence of dementia according to the Movement Disorder Society criteria,^{30,31} (2) Mini-Mental State Examination (MMSE) scores below 25,³² (3) claustrophobia, (4) MRI artifacts or pathological findings, (5) excessive movement during resting-state sequence acquisition, (6) severe psychiatric or neurological comorbidities, and (7) scaled score below 7 in the Vocabulary subtest of the Wechsler Adult Intelligence Scale 4th edition (WAIS-IV), an estimator of premorbid intellectual functioning. HC-specific exclusion criteria included self-reported RBD symptomology.

This study was approved by the Bioethics Committee of the University of Barcelona (IRB00003099) and conducted according to the Declaration of Helsinki and other relevant regulations. All participants signed informed written consent following explanation of the procedures.

Clinical and Neuropsychological Assessment

Demographic and clinical information was collected for all participants. Global cognitive status was assessed using the MMSE³² Spanish version. iRBD patients' clinical features were registered from our database and interviews, including iRBD diagnosis date – when v-PSG was performed, interval between diagnosis and rsfMRI, current treatments – including prescribed medications, and motor signs assessed using Part III of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III).³³ Neuropsychiatric and non-motor symptoms were assessed through the Cummings Neuropsychiatric Inventory (NPI),³⁴ Beck Depression Inventory³⁵ (BDI-II), Starkstein's Apathy Scale³⁶ (AS), and Non-Motor Symptoms Questionnaire³⁷ (NMS).

All participants underwent a comprehensive neuropsychological assessment based on the proposed diagnostic criteria for mild cognitive impairment (MCI) in PD:³⁸ (1) attention and working memory, including Digits Span – Forward and Backward (WAIS-IV) and Trail Making Test, Part A³⁹ (TMT-A); (2) memory, including Rey's Auditory Verbal Learning Test (RAVLT) – total and delayed recall score, and Warrington Recognition Memory for Faces; (3) executive functioning (EF), assessed with semantic (animals) and phonemic (letter “P”) fluencies, and Stroop Word-Color Test; (4) visuospatial and visuoperceptual (VS/VP) abilities, assessed with the Benton's Judgment of Line Orientation (BJLO), the Clock Copying Test and the short version of the Benton's Facial Recognition Test (BFRT); (5) processing speed, assessed with the Symbol Digit

Modalities Test (SDMT)-oral version and Stroop Word Test; and (6) language, including Boston Naming Test (BNT) and Similarities (WAIS-IV). The Part B of the Trail Making Test³⁹ (TMT-B) was administered but was not included in any cognitive domain due to some participants lacking data for the test. Manual dexterity with the dominant and non-dominant hand was assessed using the Grooved Pegboard Test (GPT). Color discrimination was assessed with the Farnsworth-Munsell 100-Hue Test (FM-100).⁴⁰ The Spanish version of the University of Pennsylvania Smell Identification Test, 40 items (UPSIT-40)⁴¹ was used to assess odor identification. Expected Z-scores adjusted for age, sex, and years of education were calculated for each participant on each cognitive test, based on a multiple regression analysis performed in the HC group.^{9,42,43}

MRI Acquisition and Preprocessing

MRI data were acquired with a 3-T scanner (MAGNETOM Prisma, Siemens, Germany), at the Centre de Diagnòstic per la Imatge of the Hospital Clínic de Barcelona (Catalonia, Spain). The scanning protocol included high-resolution three-dimensional T1-weighted images acquired in the sagittal plane (TR = 2400 ms, TE = 2.22 ms, TI = 1000 ms, 208 slices, FOV = 256 mm; 1 mm isotropic voxel) and a resting-state 10-min functional gradient-echo echo-planar (750 T2*-weighted volumes, TR = 800 ms, TE = 37 ms, flip angle = 52°, slice thickness = 2 mm, FOV = 208 mm).

Resting-State Processing

fMRI data was pre-processed with the fMRIPrep tool (<https://fmriprep.org/en/stable/>). Nuisance regression, detrending, standardization of the temporal signal, and bandpass filtering (using high-pass and low-pass cut-offs of 0.009 and 0.1 Hz, respectively) were performed using *clean_img* function from Nilearn package (<https://nilearn.github.io/stable/index.html>). Smoothing was performed using FSL (FWHM = 6).

Head motion parameters during rsfMRI were extracted. Exclusion cut-off were established for mean interframe head motion at ≥ 0.3 mm translation or 0.3° rotation; and for maximum interframe head motion at ≥ 1 mm translation or 1° rotation. We excluded 5 HC and 3 iRBD patients due to excessive MRI acquisition movement. No intergroup differences in head motion parameters were found (Table S1).

Data-Driven Connectivity Analyses

Group ICA

FSL-MELODIC⁴⁴ with the temporal concatenation option with predetermined dimensionality of 50 was used. Thirty-four independent component networks (ICNs) were selected as rsNs (Fig. S1) based on

descriptions available from reference studies⁴⁵ and the remaining 16 ICs were identified as sources of noise.

Intra-Network rsFC Analyses

To study intergroup differences in rsNs, all group ICN maps were fed into a dual-regression analysis,⁴⁶ including age and sex as covariates. Intergroup connectivity analyses were performed using a voxelwise general lineal model with 5000 permutations. Threshold-free cluster enhancement (TCFE) was used to correct for multiple comparisons. Only clusters larger than 30 voxels after TFCE were considered significant.

Subject's rsFC values were extracted for each significant rsN resulting from intergroup comparisons, as the mean network strength for each subject within the group-defined thresholded network ($Z = 3$).

Inter-Network rsFC Analyses

Between-group differences in inter-network rsFC were analyzed using the FSLNets package (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets>) in MATLAB (The MathWorks, Natick, MA, USA). Subject-specific timeseries for all 34 ICNs were obtained from the first stage of the dual regression and were used as input for FSLNets. *Nets_clean* was used to regress identified noise components. Inter-network connectivity patterns of HC and iRBD patients were compared based on the full correlation matrix, applying 5000 permutations.

Only family-wise error (FWE)-corrected P -values < 0.05 were considered significant.

Statistical Analyses

Demographic and clinical data were analyzed with R Statistical Software (v4.3.1, R Core Team 2023). Intergroup differences in categorical variables were analyzed through Pearson's chi-squared test, whereas continuous variables were tested using Student's t -test and Mann-Whitney test. Analyses of covariance were used to examine between-group differences in cognitive variables using the *lm()* function, with age, sex, and years of education as covariates. Pearson's and Spearman's correlations, depending on normality, were performed only between rsFC strength and non-imaging variables showing significant inter-group differences, to avoid multiple comparisons. Statistical significance was set at $P < 0.05$.

Results

Demographic and Clinical Analyses

The final sample consisted of 42 patients with iRBD and 45 HC. Twenty-three iRBD patients and 9 HC were excluded from the recruited sample based on exclusion criteria (see flowchart in Fig. S2).

There were significant differences between groups in age, sex, and years of education (Table 1). Specifically, the iRBD group had higher age, greater presence of

TABLE 1 Demographic and clinical characteristics of healthy controls and isolated rapid eye movement behavior disorder groups

Characteristic	HC (n = 45)	iRBD (n = 42)	Test stats	P-value
Age, years, mean (SD)	63.96 (8.65)	69.55 (7.46)	-3.233^t	0.003
Sex, n, male (%)	18 (39.02)	34 (80.95)	13.497^{χ^2}	<0.001
Education, years, mean (SD)	14.69 (4.45)	11.95 (4.64)	2.800^t	0.008
Education level, n, elementary (%)	10 (22.22)	17 (40.48)	2.583^{χ^2}	0.108
MMSE, mean (SD)	29.26 (0.99)	28.5 (1.15)	1343.5^U	<0.001
Vocabulary (WAIS-IV), mean (SD)	38.17 (7.32) [†]	34.17 (7.95)	-1.664^t	0.100
NPI, mean (SD)	2.44 (4.42)	10.95 (13.43)	386^U	<0.001
BDI, mean (SD)	3.9 (5.28)	7.08 (6.81)	523^U	0.012
AS, mean (SD)	7.41 (4.33)	12.95 (6.36)	386.5^U	<0.001
NMS, mean (SD)	3.51 (2.47)	6.85 (4.15)	405.5^U	<0.001
MDS-UPDRS-III, mean (SD)	—	1.41 (1.82)	—	—
Age at iRBD diagnosis, years (SD)	—	66.51 (6.21)	—	—
RBD duration, years (SD)	—	3.89 (4.51)	—	—

Note: χ^2 Chi-square test, ^tStudent's t -test, and ^UMann-Whitney U-test were used. All P -values are false discovery rate (FDR)-corrected. [†]Vocabulary was available for 41 HC. Abbreviations: HC, healthy controls; iRBD, isolated rapid eye movement (REM) behavior disorder; SD, standard deviation; MMSE, Mini-Mental State Examination; WAIS-IV, Wechsler Adult Intelligence Scale 4th edition; NPI, Cumming's Neuropsychiatric Inventory; BDI, Beck's Depression Inventory; AS, Starkstein's Apathy Scale; NMS, Non-Motor Symptoms Questionnaire; MDS-UPDRS-III, Movement Disorder Society-Unified Parkinson's Disease Rating Scale-Part III. Bilateral p

males, and lower years of education. Therefore, these variables were included as covariates in subsequent between-group analyses for cognitive data. Patients with iRBD showed lower scores in global cognition as assessed with MMSE, and significantly higher scores in questionnaires assessing neuropsychiatric and non-motor symptoms, depression, and apathy relative to HC (see Table S2 for relevant comorbidities and pharmacological treatments; see group scores on non-motor subdomains in Table S3 and Fig. S3).

Intra-Network Connectivity: Group Comparisons with Dual Regression

Significant intergroup differences were observed in rsNs, with the iRBD group showing lower rsFC in brain regions belonging to visual (VIS) medial and lateral networks, sensorimotor (SMN), cerebellar (CerN), and basal ganglia (BGN) networks (see Fig. 1 and Table 2 for detailed information).

In the VIS lateral network, lower rsFC was observed bilaterally in lateral occipital cortices and inferotemporal regions, comprising the bilateral lingual and fusiform gyrus, hippocampus, and parahippocampal

regions. Decreased rsFC was found between the VIS lateral network and the bilateral thalamus.

In the VIS medial network, iRBD showed reduced rsFC in the left lingual and fusiform gyri, left intracalcarine cortex, and bilaterally in the lateral occipital cortex, precuneal, and cuneal regions.

The iRBD group displayed lower rsFC in SMN relative to HC, in an area that extended bilaterally over the precentral and postcentral gyrus, including the supplementary motor area, the superior parietal lobe, and the right precuneus. A second SMN (SMN II) spreading laterally was identified, and reduced rsFC was also observed in iRBD compared with HC lateralized to the left hemisphere (Left-SMN), comprising both the pre- and post-central gyrus of this hemisphere.

In the BGN, iRBD patients showed reduced rsFC in the bilateral putamen, the thalami, and the right caudate. iRBD patients also displayed lower rsFC in the CerN, comprising left crus I and right crus II.

Patients with iRBD did not show increased rsFC relative to HC in any of the rsNs.

Dual-regression analyses results incorporating years of education as a covariate are reported in Table S4. Significant intergroup differences remain in visual

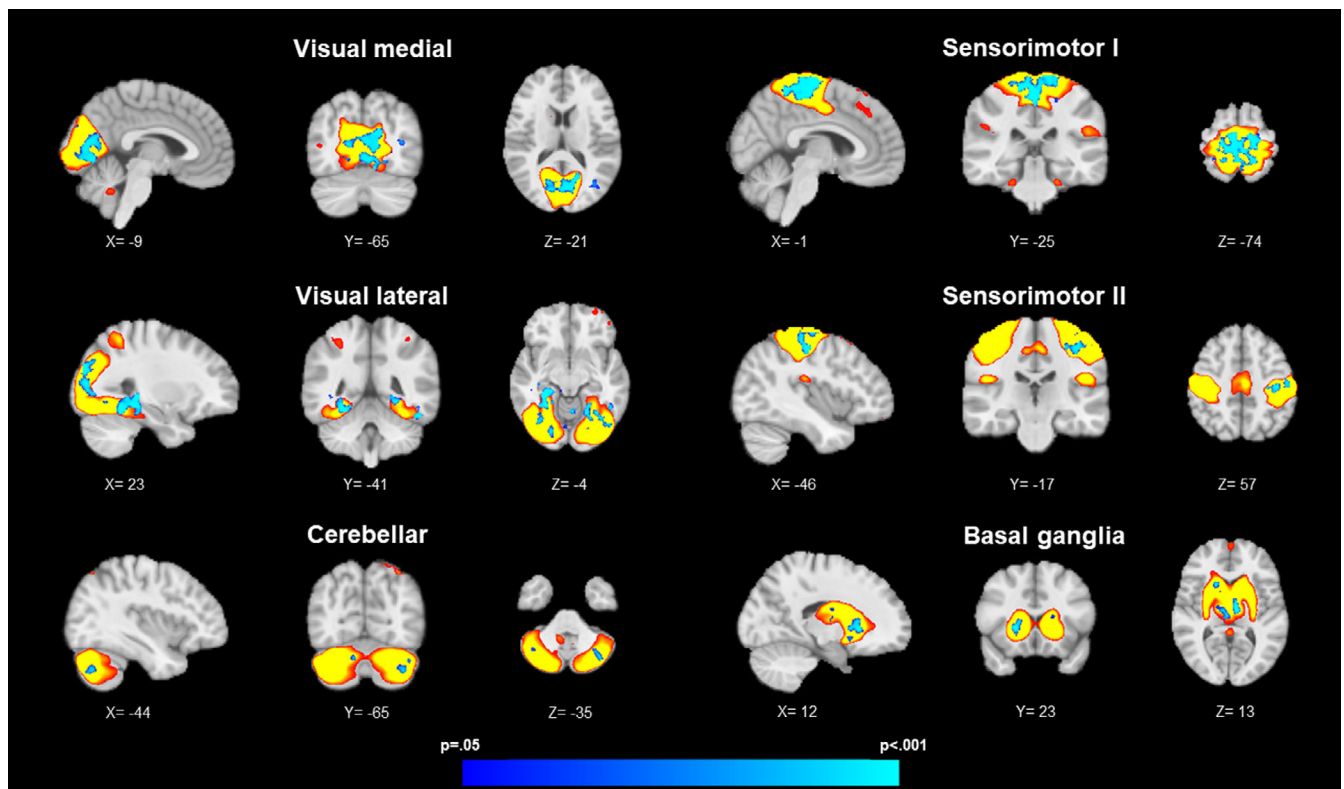


FIG. 1. Intra-network functional connectivity differences between healthy controls (HC) and patients with isolated rapid eye movement (REM) behavior disorder (iRBD). Group-level maps obtained from dual-regression analyses ($P < 0.05$, threshold-free cluster enhancement [TFCE] corrected). Network maps derived from independent component analyses (ICA) are shown in red-yellow on the standard Montreal Neurological Institute (MNI) T1 template. Blue areas within each component reflect lower intrinsic connectivity in iRBD relative to HC. The left hemisphere is displayed on the right side of coronal and axial views. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Clusters of significant intergroup differences in intra-network functional connectivity

rsNs	Regions	MNI152 coordinates of maximum (x, y, z)	Cluster voxels	Peak TFCE-corrected <i>P</i> -value
VIS lateral	Left inferior temporal gyrus, temporal occipital fusiform cortex	−48, −46, −22	1670	0.002
	Right temporal occipital fusiform cortex	27, −50, −16	958	<0.001
	Right lateral occipital cortex, occipital pole	37, −86, 13	912	<0.001
	Left lateral occipital cortex	−26, −86, 23	157	0.013
	Left thalamus	−6, −26, 3	128	0.011
	Left lateral occipital cortex, fusiform gyrus	−20, −90, −2	54	0.009
VIS medial	Left lingual gyrus, intracalcarine cortex	−4, −74, −2	1880	0.002
	Left lateral occipital cortex	−38, −70, 13	93	0.017
	Right cuneal cortex, right occipital pole	11, −86, 29	79	0.029
SMN I	Right precentral gyrus, supplementary motor area	5, −16, 67	2389	<0.001
	Right angular gyrus, right lateral occipital cortex	53, −58, 29	30	0.024
SMN II	Left precentral gyrus, left postcentral gyrus	−40, −20, 49	368	0.002
BGN	Right putamen, right caudate	19, 17, 1	200	0.001
	Left thalamus	−8, −14, 9	200	0.001
	Right thalamus	7, −14, 3	116	0.009
	Left putamen	−28, 5, 0	61	0.014
CerN	Left crus I	−44, −62, −28	164	0.005
	Left crus I	−18, −80, −22	115	0.001
	Right crus II	39, −60, −46	49	0.012

Note: Results correspond to healthy controls (HC) > isolated rapid eye movement (REM) behavior disorder (iRBD) contrast. Regions were identified based on the Harvard-Oxford Cortical and Subcortical Structural atlases (<https://fsl.fmrib.ox.ac.uk/fsl/docs/#/other/datasets>).

Abbreviations: rsNs, resting-state networks; MNI, Montreal Neurological Institute; TFCE, threshold-free cluster enhancement; VIS, visual network; SMN, sensorimotor network; BGN, basal ganglia network; CerN, cerebellar network.

lateral, medial, and sensorimotor networks, to a lesser extent relative to the originally reported results.

Inter-Network Connectivity Analyses: Group Comparisons with FSLNets

Inter-network connectivity analyses yielded significant intergroup differences in rsFC between the SMN I (IC29) and the VIS medial network (IC15) (Fig. 2B.), such that iRBD patients showed decreased SMN-VIS medial rsFC relative to HC.

Clinical and Neuropsychological Assessments

Due to 4 HC lacking complete neuropsychological data, cognition analyses were performed on the 42 iRBD patients and 41 HC. Patients with iRBD showed low performance relative to HC in UPSIT-40, SDMT, and GPT – with both dominant and non-dominant hands (Table 3). A tendency towards a significant intergroup difference was observed for semantic fluency and Stroop Word Tests. TMT-B data were only

available for 37 iRBD patients and 40 HC. No intergroup differences were found in this test. Only intergroup differences in the SDMT and UPSIT-40 remained significant after false discovery rate (FDR) correction.

Significant intergroup differences were observed at a domain-level, with iRBD patients showing decreased performance in VS/VP, EF, and processing speed domains relative to HC (Table S5). Only between-group differences in processing speed survived FDR-correction.

Associations between Intra- and Inter-Network rsFC, Clinical Features, and Cognitive Functioning

A significant negative association was observed between BGN mean rsFC strength and NMS ($\rho = -0.355$, $P = 0.025$) (Fig. 2A.). No significant correlations were found between mean rsFC strength of

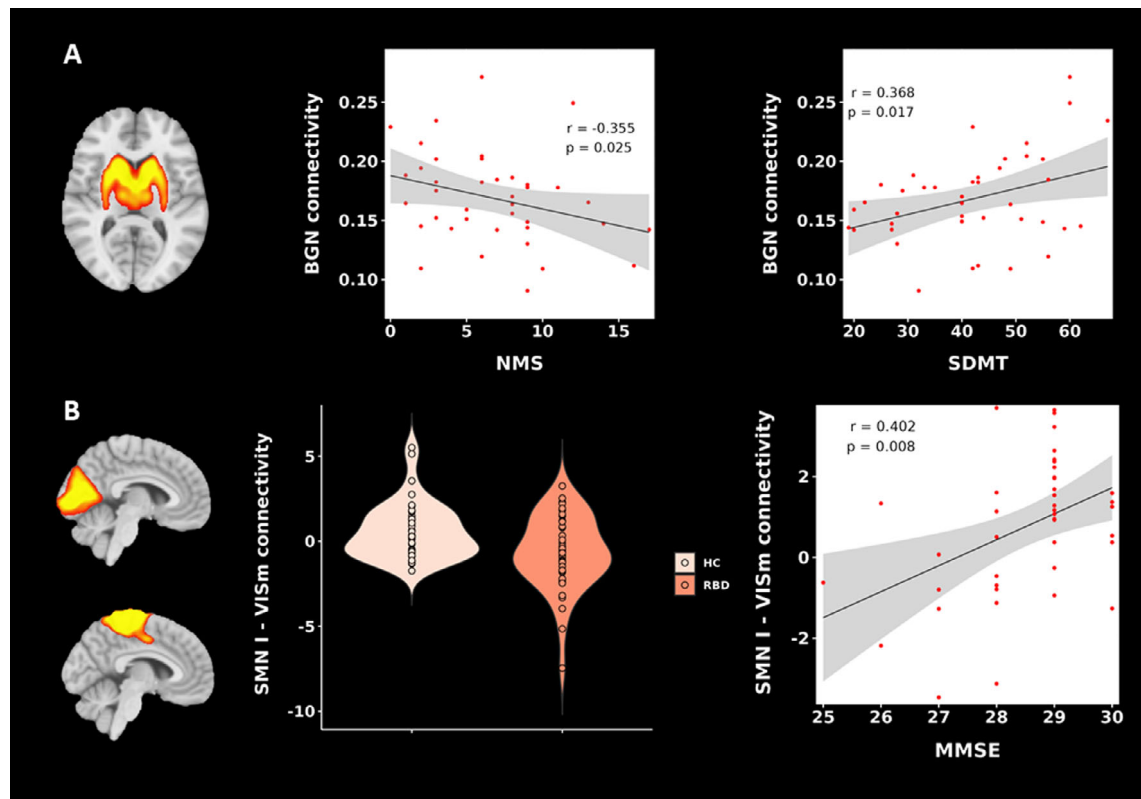


FIG. 2. Associations between functional connectivity strength, clinical, and cognitive variables in isolated rapid eye movement (REM) behavior disorder (iRBD) patients. (A) Correlations between functional connectivity strength of the basal ganglia network, non-motor symptoms and Symbol-Digit Modality Test-oral version (SDMT) scores. (B) Inter-network functional connectivity inter-group differences (z-scores) and correlation with Mini-Mental State Examination (MMSE) scores in the iRBD group. Abbreviations: BGN, basal ganglia network; r , correlation coefficient; NMS, non-motor symptoms; SDMT, Symbol-Digit Modality Test-oral version; SMN I, sensorimotor network I; VISm, visual medial network; MMSE, Mini-Mental State Examination. Graphs were obtained using the package ggplot2 (Wickham, 2016). [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/mds.30126)]

any rsN and other clinical variables, or years of education.

A significant positive association was found between BGN mean rsFC strength and SDMT scores ($r = 0.368$, $P = 0.017$) (Fig. 2A).

Inter-network rsFC between SMN and VIS medial network showed a significant positive correlation with MMSE scores ($r = 0.403$, $P = 0.008$) (Fig. 2B).

No significant associations were found between intra- or inter-network rsFC and clinical or neuropsychological variables in HC.

Discussion

The results of the present study show that both intra- and inter-network rsFC alterations are already present in early stages of synucleinopathies and are associated with clinical symptoms and neuropsychological performance. In our study, iRBD patients displayed intra-network rsFC alterations in visual, sensorimotor, basal ganglia, and cerebellar networks. Decreased intra-network BGN rsFC was associated with higher non-motor symptomatology and slower processing speed. Our

study also evidenced lower inter-network connectivity between SMN and VIS networks in iRBD, which was associated with general cognitive status.

In this study we have used a data-driven approach to study rsFC in iRBD patients and found decreased intrinsic connectivity in motor and non-motor rsNs. Regarding motor networks, alterations in BGN and SMN have been consistently reported in iRBD patients in studies using both seed¹⁶ and data-driven methods.²⁴ Using the same data-driven procedure as in the present study, but focusing only on four networks of interest, Wakasugi et al. (2021) reported low rsFC within the BGN and SMN.²⁴ In our study, we did not limit our analyses to any particular network and we found reduced rsFC in both networks, which extended beyond unilateral regions reported by Wakasugi et al., affecting the right caudate, bilateral putamen, and thalamic nuclei in the BGN, and bilateral superior parietal lobes, supplementary motor areas, and right precuneus in the SMN. Overall, BGN and SMN alterations in our iRBD group are in line with consistently reported dysfunction in these networks in alpha-synucleinopathies.^{10,47} Particularly, it has been suggested that SMN decoupling is a prominent rsFC alteration

TABLE 3 Intergroup differences neuropsychological tests

Domains	Tests	HC (n = 41)	iRBD (n = 42)	Statistics	P-value
Attention and working memory	Digit Span Forward	5.88 (1.17)	5.24 (1.19)	3.046	0.085
	Digit Span Backward	4.49 (0.98)	4.14 (1.22)	0.341	0.561
	Trail Making Test, Part A	37.59 (16.06)	47.21 (19.57)	0.757	0.387
Memory	RAVLT, Total	47.98 (9.88)	39.21 (10.43)	0.808	0.372
	RAVLT, Delayed Recall	10.49 (3.05)	7.81 (3.42)	1.521	0.221
	Warrington Recognition Memory for Faces	41.85 (4.26)	39.74 (6.57)	1.158	0.285
Executive functions	Semantic Fluency (animals)	23.56 (4.38)	19.4 (5.36)	3.978	0.050
	Phonemic Fluency (p)	16.46 (4.81)	13.45 (4.78)	1.077	0.303
	Stroop Test, Word-Color	38.07 (8.73)	31.9 (10.54)	0.221	0.640
Visuospatial and visuo-perceptual abilities	Clock Copying Test	14.54 (0.64)	14.02 (1.05)	3.252	0.372
	BJLO	24.66 (3.9)	23 (5.66)	0.806	0.372
	BFRT	23.22 (1.92)	22.26 (2.38)	0.753	0.388
Processing speed	SDMT	53.63 (9.97)	41.74 (12.79)	8.986	0.004*
	Stroop, Word	99.44 (15.77)	88.76 (15.76)	3.632	0.060
Language	Boston Naming Test	14.17 (1.07)	13.81 (0.94)	0.003	0.960
	Similarities (WAIS-IV)	23.34 (4.75)	19.62 (5.23)	1.568	0.214
Manual dexterity	GPT, dominant hand	81.5 (16.88)	98.34 (33.1)	7.186	0.009
	GPT, non-dominant hand	94.04 (25.15)	113.76 (40.94)	5.046	0.028
Color perception	Farnsworth-Munsell 100 Hue Test, total error score	136.61 (53.47)	177.03 (98.53)	0.387	0.536
Olfactory perception	UPSIT-40	30.28 (5.11)	19.6 (6.29)	41.435	<0.001*

Note: Data are presented as means and standard deviations. Group differences in cognitive tests were tested using ANCOVA analyses using sex, age, and years of education as covariates. Non-adjusted *P*-values are presented. Asterisks indicate those contrasts that survived false discovery rate (FDR)-correction for multiple comparisons.

Abbreviations: HC, healthy controls; iRBD, isolated rapid eye movement (REM) sleep behavior disorder; RAVLT, Rey Auditory Verbal Learning Test; BJLO, Benton's Judgment of Line Orientation Test; BFRT, Benton's Facial Recognition Test; SDMT, Symbol-Digit Modality Test-Oral Version; WAIS-IV, Wechsler Adult Intelligence Scale 4th edition; GPT, Grooved Pegboard Test; UPSIT-40, University of Pennsylvania Smell Identification Test, 40 items.

in PD.^{48,49} Whereas altered BGN rsFC in iRBD could be explained based on the physiopathological process underlying nigrostriatal neurodegeneration, SMN hypoconnectivity observed in our study may not be attributed to synuclein deposition in somatosensory cortical regions, expected to ensue in later stages of neurodegeneration. In turn, altered SMN rsFC has been proposed to arise as a downstream consequence of pathology in other regions and neurotransmitter nuclei.⁵⁰ Prior research has pointed towards the posterior putamen as a structure with a key role in SMN modulation, due to its prominent connections to somatosensory cortical regions and to being predominantly affected by dopaminergic denervation following nigrostriatal degeneration.^{15,49,51–53} Indeed, dopaminergic medication in PD has been shown to mainly modulate putaminal rsFC⁵² and to normalize alterations in both intra- and inter-network SMN rsFC.^{50,54,55} However, whereas it could be argued that

SMN alterations observed in this study could be at least partially explained by the concomitant striatal rsFC dysfunction, which affects the bilateral putamen, the results of our inter-network analyses fail to show an association between BGN and SMN.

Patients with iRBD exhibited decreased rsFC in medial and lateral visual networks, which extended beyond medial and lateral occipital regions and affected medial parietal cortices, cuneus, precuneus, inferotemporal regions, hippocampal, and parahippocampal structures. These findings align with prior reports of altered posterior rsFC in studies using complex-network approaches in rsfMRI data^{23,27,56} and with metabolic studies demonstrating occipital hypometabolism in iRBD.^{57,58} It is worth noting that occipital hypometabolism is considered a hallmark feature of DLB and a risk factor for dementia in PD.^{20,59,60} However, increased occipital rsFC and hypermetabolism have also been reported in

iRBD^{14,59,61} in the same large-scale networks in which DLB patients exhibit hypometabolism. This has been interpreted as a compensatory response to early synucleinopathy-related changes in posterior regions, which will show connectivity decreases as the neurodegenerative process advances.⁵⁹

The cerebellum has often been overlooked in rsfMRI studies in RBD and PD,¹⁰ although its role in the pathophysiological mechanisms of the disease has been increasingly recognized, with studies reporting both increases^{19,56,62,63} and decreases^{21,48,64} in rsFC. Increased cerebellar rsFC both in iRBD and PD¹¹ has been interpreted as a compensatory mechanism triggered by dopaminergic dysfunction⁵⁵ or altered BG input due to pathophysiological processes.^{56,65,66} In contrast, decreased intra- and inter-network cerebellar rsFC has been reported in DLB.⁶³ In this study, iRBD patients exhibited decreased cerebellar rsFC relative to HC. The lack of correlation between cerebellar rsFC and clinical measures warrants further investigation into the role of the cerebellum in prodromal alpha-synucleinopathies.

Inter-network analyses evidenced altered rsFC between the SMN and VIS medial cortical network. These findings align with recent research in PD patients in OFF state using the same inter-network approach as in this study, and reporting SMN connectivity alterations mainly between visual and motor networks.⁵⁰ In this line, research using a connectome approach shows that the greatest inter-network rsFC changes in PD involve SMN and visual cortical networks, with a relatively small BGN contribution.⁴⁸ Interestingly, a recent study showed that SMN -visual network dysconnectivity strongly correlated with MDS-UPDRS-III scores in PD patients.⁶⁷ Altogether, prior research supports that impaired integration between brain networks characterizes PD and is associated with clinical symptoms.⁹ To our knowledge, our study is the first to use an inter-network approach to demonstrate that, added to abnormal intra-network connectivity, altered sensorimotor integration is already present in iRBD. In this study, SMN-VIS connectivity correlated with scores in a general cognition instrument, suggesting its potential as a biomarker of cognitive decline in prodromal synucleinopathies.

Non-motor symptoms, such as cognitive decline and neuropsychiatric alterations, have been systematically reported in iRBD patients and can be present up to 20 years before clinical diagnosis of PD and DLB.⁶⁸ However, the association between non-motor symptoms and rsFC in iRBD remains unclear. We have found that reduced BGN rsFC is associated with greater non-motor symptomatology and reduced processing speed, as assessed with the oral version of the SDMT. Our findings, showing that slowness in information processing was the most prominent cognitive alteration

in our sample of iRBD, support prior evidence suggesting that processing speed is already impaired in early stages of alpha-synucleinopathies.^{23,69–73} Regarding its rsFC correlates, decreased processing speed has been associated with altered temporo-parietal rsFC in iRBD²³ and with dopamine transporter availability in striatal regions in de novo PD patients.⁷⁴ Thus, the SDMT could be sensitive to early brain rsFC alterations in iRBD, which supports its inclusion in the clinical practice in iRBD.

Besides decreased processing speed, we report evidence suggestive of decline in EF and VS/VP domains, which are considered hallmarks of the cognitive profile of iRBD patients.^{69,75–78} In this line, studies converge that executive dysfunction is present in iRBD patients up to 10 years before phenoconversion and is considered as a strong marker of dementia in these patients.^{70,76,79,80} However, interpreting EF alterations in iRBD requires caution. EF is an umbrella term used to represent a heterogeneous construct that subsumes multiple cognitive functions.⁸¹ This is particularly relevant in iRBD research, in which the classification of neuropsychological tests in this cognitive domain has not been consistent across iRBD studies.⁸² In our study, we report subtle EF alterations in iRBD patients, which do not remain significant after correction for multiple comparisons. A plausible explanation is that, in contrast to prior studies, we do not include within this domain tests assessing processing speed, which has been shown to account for the largest intergroup differences within EF.⁷⁰

The main study limitation regards the demographic differences between our study groups. Although these differences were statistically controlled for in the analyses, further studies using matched samples are needed to corroborate our findings. It is noteworthy that only two-thirds of the originally recruited iRBD sample complied with the strict inclusion and exclusion criteria to study the associations between rsFC and clinical symptoms in a well-characterized patient sample without overt cognitive and motor complaints. However, this characterization comes at the cost of loss of generalizability of findings, which must be replicated in other cohorts. Moreover, although self-reported iRBD symptomatology was used to exclude HC participants, the lack of vPSG examination in this group precludes definite exclusion of HC exhibiting subtle forms of the disorder. It must be remarked that our patients were not asked to refrain from taking any prescribed medications during the time of the study. This is particularly relevant for medications that may potentially influence rsFC, such as clonazepam, commonly prescribed for RBD symptomatology, and some antidepressants, prescribed for psychiatric symptoms. Whereas this could entail a limitation, it obeys the objective of studying rsFC in an ecological setting, where the impact of the

disorder is evaluated under real-world conditions. Several strengths of the study should be noted. First, we report rsFC alterations in a relatively large sample size compared with prior rsfMRI studies addressing cognitive functioning, considering the application of strict inclusion and exclusion criteria. Only vPSG-confirmed iRBD participants were enrolled in the study and all participants underwent a comprehensive neuropsychological assessment based on gold-standard recommendations, including measures of non-motor features, such as neuropsychiatric symptomology and olfactory functioning. Finally, whereas most rsFC studies in iRBD have focused on regions or networks of interest, we used a data-driven network approach to characterize intra- and inter-network connectivity in iRBD.

Conclusions

In summary, iRBD is associated with extensive intra-network rsFC alterations – mainly affecting sensorimotor, striatal, and visual networks – which are associated with non-motor symptoms, and decoupling between sensorimotor and visual medial networks, related to global cognition. Overall, our results suggest that not only posterior intra-network but also inter-network dysconnectivity is a feature of iRBD, supporting its potential as a biomarker for early-stage neurodegeneration. Particularly, decreased processing speed correlates with low striatal connectivity in iRBD patients, which warrants its systematic assessment in neuropsychological research of prodromal alpha-synucleinopathies. ■

Author Roles: (1) Research Project: A. Conception, B. Design, C. Data Collection; (2) Statistical Analysis: A. Design, B. Data Analysis, C. Review and Critique; (3) Manuscript Preparation: A. Data Interpretation and Writing of the First Draft, B. Contributed to the Final Draft, C. Review and Critique; D. Approval.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

The data are not publicly available due to privacy or ethical restrictions.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.