Cortical and subcortical gray matter bases of cognitive deficits in REM sleep behavior disorder

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Abstract

Objective

To investigate cortical and subcortical gray matter abnormalities underlying cognitive impairment in patients with REM sleep behavior disorder (RBD) with or without mild cognitive impairment (MCI).

Methods

Fifty-two patients with RBD, including 17 patients with MCI, were recruited and compared to 41 controls. All participants underwent extensive clinical assessments, neuropsychological examination, and 3-tesla MRI acquisition of T1 anatomical images. Vertex-based cortical analyses of volume, thickness, and surface area were performed to investigate cortical abnormalities between groups, whereas vertex-based shape analysis was performed to investigate subcortical structure surfaces. Correlations were performed to investigate associations between cortical and subcortical metrics, cognitive domains, and other markers of neurodegeneration (color discrimination, olfaction, and autonomic measures).

Results

Patients with MCI had cortical thinning in the frontal, cingulate, temporal, and occipital cortices, and abnormal surface contraction in the lenticular nucleus and thalamus. Patients without MCI had cortical thinning restricted to the frontal cortex. Lower patient performance in cognitive domains was associated with cortical and subcortical abnormalities. Moreover, impaired performance on olfaction, color discrimination, and autonomic measures was associated with thinning in the occipital lobe.

Conclusions

Cortical and subcortical gray matter abnormalities are associated with cognitive status in patients with RBD, with more extensive patterns in patients with MCI. Our results highlight the importance of distinguishing between subgroups of patients with RBD according to cognitive status in order to better understand the neurodegenerative process in this population.

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Glossary

AUC = area under the curve; **DLB** = dementia with Lewy bodies; **FM-100** = Farnsworth-Munsell 100; **MCI** = mild cognitive impairment; **MNI** = Montreal Neurological Institute; **PD** = Parkinson disease; **RBD** = REM sleep behavior disorder; **ROC** = receiver operating characteristic; **UPSIT** = University of Pennsylvania Smell Identification Test.

REM sleep behavior disorder (RBD) is characterized by abnormal motor manifestations during REM sleep.¹ Patients with idiopathic RBD are at high risk of development toward synucleinopathies.² From 33% to 50% of patients with RBD present with mild cognitive impairment (MCI),^{3,4} the majority of whom will develop dementia with Lewy bodies (DLB).⁵ Color discrimination deficits, anosmia, and dysautonomia are also markers of neurodegeneration found in RBD.⁶

Gray matter volume abnormalities have been studied in RBD, with inconsistent results.^{7–11} Vertex-based analyses of cortical volume, thickness, and surface area provide an alternative to volumetric measurements for detecting submillimeter cortical differences.¹² In RBD, studies using these techniques have revealed extensive patterns of cortical thinning in the frontal, lingual, and fusiform cortices.^{10,11} Abnormal contraction in the pallidum and putamen has also been identified in patients with RBD using vertex-based shape analysis.¹¹ The cortical and subcortical gray matter bases of cognitive, perceptual (olfaction and color discrimination), and autonomic deficits remain to be investigated in RBD.

In this study, we investigated cortical volume, thickness, surface area, and subcortical surface between RBD patients with MCI, RBD patients without MCI, and controls. We also assessed the sensitivity and specificity of cortical abnormalities to determine which cluster provided the best discrimination between RBD patients with MCI and the 2 other groups. Moreover, we examined associations between the structural metrics and cognitive, perceptual, and autonomic performance in patients with RBD.

Methods

Participants

Since July 2008, 59 patients with polysomnography-confirmed RBD were recruited and underwent neuropsychological, neurologic, and MRI examinations. All patients were enrolled at the Center for Advanced Research in Sleep Medicine of the CIUSSS-NÎM-Hôpital du Sacré-Coeur de Montréal and met diagnostic criteria for RBD according to the *International Classification of Sleep Disorders, Third Edition*.^{1,13} Patients underwent a neurologic examination by a movement disorders specialist (R.B.P.),⁶ and those with parkinsonism or dementia were excluded.^{14,15} Patients with a history of stroke, head trauma, brain injury, unstable hypertension or diabetes, chronic obstructive pulmonary disease, claustrophobia, EEG abnormalities suggesting epilepsy, encephalitis, or any other

neurologic disorders, or with artifacts on brain scans were excluded. Forty-one controls were recruited at the Center for Advanced Research in Sleep Medicine of the CIUSSS-NÎM-Hôpital du Sacré-Coeur de Montréal. They were selected from the general population through newspaper advertisements or by word of mouth. They underwent neuropsychological assessment to rule out MCI and were subject to the same exclusion criteria as patients with RBD.

Standard protocol approvals, registrations, and patient consents

Research protocols were approved by a university hospital ethics committee and all participants gave their informed consent to participate.

Neuropsychological assessment

MCI was diagnosed using the following criteria: (1) evidence of subjective cognitive complaints by the patient, the spouse, or an informant during semistructured interview or using the Cognitive Failures Questionnaire¹⁶; (2) evidence of objective cognitive impairment through a neuropsychological assessment, with impaired performance defined as a score at least 1.5 SD below the standardized mean on at least 2 tasks within a single cognitive domain, in one (single-domain MCI) or more (multiple-domain MCI) cognitive domains; (3) preservation of daily living functioning; (4) absence of dementia; and (5) cognitive deficits not solely explained by medication or other medical conditions.^{4,5} Three cognitive domains were assessed: attention and executive functions, learning and memory, and visuospatial abilities.^{4,5} Attention and executive functions were assessed using the Digit Span subtest (Wechsler Adult Intelligence Scale–III); Trail Making Test, Part B; Stroop Color Word Test III-I contrast score; verbal semantic fluency; and verbal phonemic fluency. Episodic verbal learning and memory were assessed using the Rey Auditory Verbal Learning Test (sum of trials 1–5, list B, immediate recall, delayed recall, and recognition). Visuospatial abilities were assessed using the Rey-Osterrieth Complex Figure (copy), Bells test, and Block Design subtest (Wechsler Adult Intelligence Scale–III). The list of cognitive tests and the normative data used have been published previously.^{4,5}

Color discrimination, olfaction, and autonomic functions

Color discrimination testing was conducted in all patients using the Farnsworth-Munsell 100 (FM-100) Hue Test.¹⁷ The error score was calculated, corresponding to the degree of deviation from correct placement, where a higher FM-100 score indicated worse performance. Olfactory testing was conducted using the University of Pennsylvania Smell

Identification Test (UPSIT), and scores were normalized according to published age and sex norms.¹⁸ Blood pressure was measured manually in supine position and after standing for 1 minute, and systolic blood pressure drop was calculated by subtracting supine from the standing measure.⁶

MRI

MRI data acquisition

MRI measurements were obtained on a 3T Siemens TrioTIM MR scanner (Siemens, Erlangen, Germany) and a 12-channel head matrix coil at the Unité de Neuroimagerie Fonctionnelle of the Institut universitaire de gériatrie de Montréal (unf-montreal.ca). High-resolution T1-weighted images were acquired using a magnetization-prepared rapid acquisition with gradient-echo sequence with the following parameters: repetition time 2.3 seconds, echo time 2.91 milliseconds, inversion time 900 milliseconds, 9-degree flip angle, 160 slices, 256 × 240 mm field of view, 256 × 240 matrix resolution (voxel size: 1 × 1 × 1 mm³), and 240 Hz/Px bandwidth.

Processing for cortical surface analysis

Cortical reconstruction was performed with FreeSurfer (version 5.3.0).^{19,20} This processing includes removal of nonbrain tissue, Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures, intensity normalization, and cortical reconstruction.^{19,20} Cortical thickness and volume maps were smoothed using a 15-mm full-width at half-maximum gaussian smoothing kernel and cortical surface area maps with a 20-mm smoothing kernel. Different smoothing filter sizes were used to increase the sensitivity for each structural metric, because a filter that is optimal for one metric may not be applicable to another.²¹

Processing for subcortical surface analysis

Subcortical structures, namely, the left and right nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, and thalamus, were segmented using FSL-FIRST.²² Surface analyses were conducted using rigid alignment in MNI (Montreal Neurological Institute) space to normalize for brain size. All steps were quality-controlled to ensure optimized image processing.

Statistical analysis

Demographic and clinical variables

Statistical analyses were conducted using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY). Between-group differences for continuous variables were investigated using one-way analysis of variance or Kruskal-Wallis *H* test, and pairwise differences with Student *t* tests and Mann-Whitney *U* tests. Between-group differences for categorical variables were investigated using the Freeman-Halton extension of the Fisher exact probability test and χ^2 tests for pairwise comparisons. Raw cognitive scores were standardized according to normative data to obtain *z* scores,

which were then averaged to compute 3 composite scores for each cognitive domain.

Cortical volume, thickness, and surface area analyses

Cortical thickness, surface area, and volume at each vertex of the cortical surface were compared between groups using general linear modeling. Cortical thickness, surface area, and volume were modeled individually as a function of group by controlling for the effects of age, sex, and education. For cortical volume and surface area, total intracranial volume was added as a covariate because of its relationship to both volume and surface area but not to thickness.²³ Results were considered significant at *p* < 0.05 using Monte Carlo simulation.

Subcortical surface analysis

Subcortical surface analysis was conducted at each vertex using general linear modeling, with the effects of age, sex, and education regressed out from between-group comparisons. Total intracranial volume was not included as a covariate because the analysis was performed in MNI152 standard space. Models were tested in FSL-Randomise using non-parametric permutation tests (5,000 permutations).²⁴ Threshold-free cluster enhancement was used to avoid arbitrary selection of cluster thresholds, and results were considered significant at *p* < 0.05 corrected for family-wise error.²⁵

Sensitivity and specificity of structural abnormalities

Receiver operating characteristic (ROC) curves were performed to determine the brain regions that enabled optimal detection of MCI in patients with RBD (and of RBD-MCI vs controls). Each cluster that showed a significant between-group difference was projected back into each participant's native space, and mean thickness was extracted for each cluster. ROC curves were then used to assess area under the curve (AUC), sensitivity, specificity, positive predictive value, negative predictive value, and percentage of diagnostic effectiveness for each cluster. The optimal value for each cluster that best discriminated between subgroups was determined as the maximum accuracy value calculated by the Youden Index (*y* = sensitivity + specificity – 1).²⁶

Correlation analyses

Vertex-wise correlation analyses were conducted in patients with RBD between gray matter metrics (cortical thickness, cortical surface area, cortical volume, and subcortical surface) and clinical measures (cognitive domains, color discrimination, olfaction, and systolic blood pressure drop). Age, education, and sex were used as covariates, and total intracranial volume was added for correlations with surface area and volume.²³ Correlation analyses with subcortical surface were performed in MNI152 standard space. Patients were pooled together in the statistical model to increase the variability. Results were considered significant when corrected for multiple comparisons using a Monte Carlo simulation *p* value of <0.05.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

Demographic, clinical, and neuropsychological data

Of the 59 patients with RBD who were recruited, 7 were excluded because of parkinsonism at baseline (6 patients) or abnormal scan (one patient), leaving a total of 52 patients with RBD (table 1), of whom 17 (33%) were classified as RBD with MCI and 35 as RBD without MCI. There were no significant between-group differences in age, sex, education, handedness, RBD duration, REM sleep EMG activity, Unified Parkinson's Disease Rating Scale, Part III total score, or UPSIT score. RBD patients with MCI scored significantly lower on the Montreal Cognitive Assessment compared to

RBD patients without MCI and controls, and had lower FM-100 performance and composite cognitive scores vs RBD patients without MCI. Patients with MCI also had greater systolic blood pressure drop compared to patients without MCI. In RBD patients with MCI, 65% (11/17) had the single-domain subtype and 35% (6/17) had the multiple-domain subtype.

Cortical thickness, surface area, and volume analyses

RBD patients with MCI vs RBD patients without MCI

RBD patients with MCI exhibited a more extensive pattern of cortical thinning compared to RBD patients without MCI in the left anterior and posterior temporal lobe, the insula, the occipital cortex, the left medial superior frontal and anterior and posterior cingulate cortices, and the right temporal, superior frontal, posterior cingulate, and insular cortices (table 2, figure 1A). RBD patients with

Table 1 Demographic and clinical characteristics of participants

Variable	RBD	RBD with MCI	RBD without MCI	Controls	<i>p</i> Value ^a	Post hoc tests
Age, y	65.5 (6.6)	67.9 (4.4)	64.4 (7.2)	63.2 (8.2)	NS ^b	
Men, n (%)	42 (81)	12 (71)	30 (86)	25 (61)	NS ^c	
Education, y	13.5 (3.7)	12.1 (3.8)	14.2 (3.5)	14.6 (4.1)	NS ^b	
Handedness, % right-handed	96	100	94	98	NS ^c	
RBD duration, symptom onset, y	11.7 (11.9)	12.6 (13.3)	11.2 (11.3)	—	NS ^d	
RBD duration, PSG diagnosis, y	1.6 (2.2)	1.6 (2.1)	1.6 (2.2)	—	NS ^d	
Tonic activity during REM sleep, %	44.2 (28.0)	49.0 (31.0)	41.9 (26.6)	—	NS ^e	
Phasic activity during REM sleep, %	35.8 (14.4)	32.3 (13.4)	37.5 (14.7)	—	NS ^e	
UPDRS-III, total	4.2 (3.5)	5.5 (4.9)	3.5 (2.5)	—	NS ^d	
MoCA score, /30	26.1 (2.8)	24.0 (3.2)	27.0 (2.0)	27.9 (1.4)	<0.001 ^e	RBD with MCI < controls, RBD without MCI (<i>p</i> < 0.001) ^d
FM-100 Hue Test ^f	134.5 (55.7)	164.7 (48.5)	121.1 (54.0)	—	0.010 ^g	
UPSIT, % expected for age and sex	74.3 (28.5)	64.1 (28.6)	79.3 (27.6)	—	NS ^g	
Systolic blood pressure drop, mm Hg	11.2 (13.6)	18.4 (16.3)	7.7 (10.8)	—	0.007 ^g	
Cognitive composite z scores						
Attention and executive functions	−0.02 (0.66)	−0.59 (0.62)	0.28 (0.48)	—	<0.001 ^g	
Learning and memory	−0.02 (0.79)	−0.63 (0.65)	0.31 (0.67)	—	<0.001 ^g	
Visuospatial abilities	−0.007 (0.69)	−0.45 (0.84)	0.23 (0.50)	—	0.002 ^g	

Abbreviations: FM-100 = Farnsworth-Munsell 100; MCI = mild cognitive impairment; MoCA = Montreal Cognitive Assessment; NS = not significant; PSG = polysomnography; RBD = REM sleep behavior disorder; UPDRS-III = Unified Parkinson's Disease Rating Scale, Part III; UPSIT = University of Pennsylvania Smell Identification Test.

Data are shown as mean (SD).

^a RBD with MCI compared to RBD without MCI compared to controls.

^b Analysis of variance.

^c Fisher-Freeman-Halton exact test for contingency.

^d Mann-Whitney *U* test.

^e Kruskal-Wallis *H* test.

^f Higher scores represent lower performance (i.e., increased degree of deviation from correct placement of colored discs).

^g Student *t* test.

Table 2 Results of vertex-based cortical analyses

Cortical metric	Region with cortical abnormalities	Hemisphere	Cluster size, mm ²	No. of vertices	Talairach coordinates			−log ₁₀ p value
					x	y	z	
RBD with MCI < RBD without MCI								
Thickness	Anterior temporal lobe including entorhinal cortex and insula	Left	6,697.08	14,438	−52.3	0.5	−24.9	4.527
	Middle temporal cortex	Right	1,527.79	2,763	61.8	−18.7	−15.5	3.747
	Posterior temporal lobe including fusiform, lingual, and lateral occipital cortex	Left	3,813.46	5,425	−58.8	−45.4	−3.2	3.529
	Medial superior frontal and posterior cingulate cortex	Right	1,871.47	4,205	4.7	−20.6	37.2	3.312
	Medial superior frontal and anterior and posterior cingulate cortex	Left	1,569.01	3,717	−11.7	17.3	28.8	2.841
	Superior temporal cortex and insula	Right	2,144.36	5,146	55.6	−16.9	−1.7	2.535
RBD with MCI < controls								
Thickness	Superior medial frontal and cingulate cortex	Right	4,101.36	8,876	5.5	25.1	−6.0	4.233
	Anterior temporal lobe including the entorhinal cortex, insula, and inferior/middle frontal cortex	Left	6,981.42	14,159	−27.3	0.6	−26.2	4.175
	Superior medial frontal, paracentral, and posterior cingulate cortex	Left	3,576.85	7,679	−9.9	−19.5	36.0	4.094
	Anterior temporal lobe and insula	Right	3,651.97	7,285	60.9	−16.1	−16.7	3.411
	Posterior temporal lobe and fusiform cortex	Left	2,060.51	3,262	−59.8	−44.8	−2.9	2.748
Volume ^a	Precentral and postcentral cortex	Left	2,095.41	4,734	−58.8	−8.6	31.3	2.464
RBD without MCI < controls								
Thickness	Precentral and paracentral cortex	Right	1,722.65	4,173	38.6	−13.3	56.4	5.213
	Superior medial frontal and paracentral cortex	Left	2,103.28	4,359	−7.9	−15.7	45.7	3.778

Abbreviations: MCI = mild cognitive impairment; RBD = REM sleep behavior disorder.

Results are corrected with Monte Carlo simulation at $p < 0.05$ with age, sex, and education as covariates for thickness analysis. Total intracranial volume was also added as a covariate for volume analyses.

^a Significant using a unilateral test (RBD with MCI < controls).

MCI did not show cortical thickening. No differences were found between groups in cortical volume or surface area.

RBD patients with MCI vs controls

RBD patients with MCI had cortical thinning in the left anterior temporal lobe, including the entorhinal cortex, insula, and inferior and middle frontal cortices, in the left superior medial frontal, paracentral, and posterior cingulate cortices, and in the left posterior temporal lobe and fusiform cortex (table 2, figure 1B). On the right side, RBD patients with MCI showed cortical thinning in the superior medial frontal and cingulate cortices and in the anterior temporal lobe and insula. Looking at where RBD patients with MCI

showed decreased cortical volume vs controls, significant reduction was found in the precentral and postcentral cortices (table 2, figure 1D). No increases in cortical thickness or volume were found in RBD patients with MCI. No difference was found between groups in cortical surface area.

RBD patients without MCI vs controls

RBD patients without MCI presented cortical thinning in the left superior medial frontal and paracentral cortices and in the right precentral and paracentral cortices (table 2, figure 1C). RBD patients without MCI did not show cortical thickening. No differences were found between groups in cortical volume or surface area.

Figure 1 Results of cortical and subcortical analyses between groups

Cortical and subcortical abnormalities in RBD patients with MCI, RBD patients without MCI, and controls. RBD patients with MCI showed thinning compared to RBD patients without MCI in the bilateral temporal, frontal, and cingulate cortices, with involvement of the occipital cortex on the left side (A). RBD patients with MCI also had thinning compared to controls in the bilateral temporal, frontal, and cingulate cortices (B). RBD patients without MCI showed thinning compared to controls in the left medial frontal cortex and right precentral and paracentral cortices (C). Decreased cortical volume was also found in RBD patients with MCI compared to controls in the left sensorimotor cortex (D). The color bar indicates the logarithmic scale of p values ($-\log_{10}$) for between-group differences, with red-yellow areas representing reductions in the first compared to the last group in the contrast (corrected with Monte Carlo simulation at $p < 0.05$ with age, sex, and education as covariates as well as total intracranial volume for cortical volume analysis). Compared to RBD patients without MCI, RBD patients with MCI showed abnormal contraction in the left putamen and thalamus (E). RBD patients with MCI also had abnormal contraction compared to controls in the bilateral putamen and thalamus and the left pallidum (F). No differences in subcortical surface were found between RBD patients without MCI and controls. Red areas represent clusters with abnormal surface contraction between groups (corrected for family-wise error at $p < 0.05$ with age, sex, and education as covariates). MCI = mild cognitive impairment; RBD = REM sleep behavior disorder.

Subcortical surface analyses

RBD patients with MCI vs RBD patients without MCI

Compared to RBD patients without MCI, RBD patients with MCI showed abnormal surface contraction in the left putamen and thalamus (table 3, figure 1E). No surface expansion was found in RBD patients with MCI.

RBD patients with MCI vs controls

RBD patients with MCI had abnormal surface contraction in the bilateral putamen and thalamus and in the left pallidum (table 3, figure 1F). No surface expansion was found in RBD patients with MCI.

RBD patients without MCI vs controls

There were no significant between-group differences in subcortical surfaces.

ROC curves

ROC curves were applied to clusters with abnormal thickness that differed between patients with and patients without MCI. The cluster that best discriminated MCI in patients with RBD was the right middle temporal cortex, with an AUC of 0.79 (95% confidence interval: 0.65–0.94) using the optimal cutoff

thickness value of 2.70 mm (table 4). However, clusters located strictly in the frontal and cingulate cortices did not discriminate significantly between groups.

ROC curves were also applied to clusters with abnormal thickness between RBD patients with MCI and controls (considered as normal thickness) (table 4). All clusters allowed discrimination between groups. The cluster with the highest AUC was in the left anterior temporal cortex (and posterior insula), with an AUC of 0.91 (95% confidence interval: 0.83–0.996) using the optimal cutoff thickness of 2.66 mm.

Correlation analyses

Cognitive domains

Lower performance in attention and executive functions was associated with thinning in the frontal (medial superior, dorsolateral paracentral, sensorimotor), temporal (fusiform, lingual), and occipital (cuneus) cortices (table 5, figure 2A). Lower performance in learning and memory was associated with cortical thinning in the temporal (pole, anterior superior, posterior lingual and fusiform), insular, and occipital (cuneus) cortices (table 5, figure 2A) and with greater surface

Table 3 Results of vertex-based subcortical analyses

Structure with abnormal contraction	Hemisphere	No. of vertices	MNI152 coordinates		
			x	y	z
RBD with MCI < RBD without MCI					
Thalamus	Left	1,115	105	96	67
Putamen	Left	109	122	120	68
RBD with MCI < controls					
Pallidum	Left	837	110	117	65
Putamen	Left	1,435	107	136	59
Thalamus	Right	1,724	75	135	60
	Left	844	105	96	67
	Right	408	75	96	68
	Right	169	76	99	86

Abbreviations: MCI = mild cognitive impairment; MNI = Montreal Neurological Institute; RBD = REM sleep behavior disorder.

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expansion in the right hippocampus (table e-1, links.lww.com/WNL/A441; figure 2D). Lower performance in visuospatial abilities was associated with thinning in the frontal (medial superior, paracentral, and widespread areas of the prefrontal cortex), temporal (middle temporal, posterior lingual and fusiform), insular, parietal (precuneus), and occipital (cuneus and lateral occipital) cortices (table 5, figure 2A). Lower performance in visuospatial abilities also correlated with reduced cortical volume in the right lateral occipital cortex (table 5, figure 2B) and with greater surface expansion in the right hippocampus (table e-1, figure 2D).

Olfaction, color discrimination, and autonomic functions

Lower performance on the FM-100 Hue Test was associated with cortical thinning in the right cuneus (figure 2A, table 5). Lower performance on the FM-100 also correlated with increased cortical surface area in the right cuneus (figure 2C, table 5) and with abnormal surface expansion in the right hippocampus (figure 2D; table e-1, links.lww.com/WNL/A441). Lower performance on the UPSIT correlated with thinning in the left and right lateral occipital cortices and right cuneus (figure 2A, table 5). Higher systolic blood pressure drop was associated with cortical thinning in the left lateral occipital and inferior parietal cortices and in right superior, middle, and inferior temporal cortices (figure 2A, table 5).

Discussion

In this study, RBD patients with MCI had cortical thinning in the frontal, cingulate, temporal, and occipital cortices and shape contraction in the lenticular nucleus (putamen and pallidum) and thalamus. RBD patients without MCI showed cortical thinning in the frontal cortex only. Thinning in the

anterior temporal lobe and middle temporal cortex best differentiated RBD patients with MCI from controls and from RBD patients without MCI, respectively. Poorer cognitive performance was associated with thinning in several cortical regions and with hippocampal shape abnormalities. All other markers of neurodegeneration in RBD, such as color discrimination deficits, anosmia, and dysautonomia, shared cortical thinning in the occipital lobe. Our results highlight the importance of distinguishing between subgroups of patients with RBD according to cognitive status.

Extensive frontal, fusiform, and lingual thinning has been reported previously in RBD, regardless of cognitive status.^{10,11} Here, we found that both RBD patients with and without MCI shared frontal thinning, but only patients with MCI had thinning in the fusiform and lingual cortices. The thinning extent in the frontal cortices in RBD patients with MCI was wider and included the cingulate, temporal, and occipital cortices. Thinning in the right middle temporal cortex showed the best diagnostic accuracy to detect MCI in RBD, suggesting that this region has an important role in the cognitive deficits found in these patients. The anterior temporal cortices are also the regions that best discriminated patients with RBD from MCI and controls, making them promising potential prodromal biomarkers of DLB. Abnormalities in gray matter volume have also been reported in RBD.^{7–11,27} Here, we found that only RBD patients with MCI had decreased cortical volume, located in the sensorimotor cortex, which is in line with previous findings.¹¹ Our cortical findings also concur with the abnormal patterns of regional cerebral blood flow and EEG slowing during wakefulness found in RBD patients with MCI vs without MCI.^{28,29} In the subcortical structures, abnormal volume and surface contraction in RBD as a whole group have been reported in the hippocampus, pallidum, and putamen.^{7,11,27} Here, the subcortical shape results revealed

Table 4 Receiver operating characteristic curves for discriminating the presence of MCI

	Hemisphere	Cutoff value ^a	Sensitivity	Specificity	PPV	NPV	Diagnostic effectiveness ^b	AUC (95% CI); <i>p</i>
RBD with MCI vs RBD without MCI								
Middle temporal cortex	Right	2.70	82.4	74.3	60.9	89.7	76.9	0.794 (0.649–0.939); 0.001 ^c
Anterior temporal lobe including entorhinal cortex and insula	Left	2.65	82.4	68.6	56.0	88.9	73.1	0.769 (0.615–0.923); 0.002 ^c
Superior temporal cortex and insula	Right	2.43	76.5	65.7	52.0	85.2	69.2	0.716 (0.555–0.877); 0.012 ^c
Posterior temporal lobe including fusiform, lingual, and lateral occipital cortex	Left	2.33	82.4	60.0	50.0	87.5	67.3	0.700 (0.550–0.850); 0.020 ^c
Medial superior frontal and anterior and posterior cingulate cortex	Left	2.52	76.5	48.6	41.9	81.0	57.7	0.632 (0.456–0.807); 0.126
Medial superior frontal and posterior cingulate cortex	Right	2.46	29.4	94.3	71.4	73.3	73.1	0.597 (0.422–0.772); 0.262
RBD with MCI vs controls								
Anterior temporal lobe including entorhinal cortex, insula, and inferior/middle frontal cortex	Left	2.66	76.5	95.1	86.7	90.7	78.8	0.910 (0.825–0.996); <0.001 ^c
Anterior temporal lobe and insula	Right	2.61	58.8	100.0	100.0	85.4	87.9	0.858 (0.723–0.993); <0.001 ^c
Superior medial frontal, paracentral, and posterior cingulate cortex	Left	2.39	47.1	97.6	88.9	81.6	82.8	0.789 (0.640–0.938); 0.001 ^c
Superior medial frontal and cingulate cortex	Right	2.48	41.2	97.6	87.5	80.0	81.0	0.745 (0.587–0.902); 0.004 ^c
Posterior temporal lobe and fusiform cortex	Left	2.66	29.4	92.7	62.5	76.0	74.1	0.750 (0.612–0.888); 0.003 ^c

Abbreviations: AUC = area under the curve; CI = confidence interval; MCI = mild cognitive impairment; NPV = negative predictive value; PPV = positive predictive value; RBD = REM sleep behavior disorder.

^a Maximum accuracy value according to the Youden Index. Values are given in millimeters.

^b Percentage of correctly classified patients among all patients.

^c Significant AUCs.

that only RBD patients with MCI had abnormal contraction in the pallidum, putamen, and thalamus. This is consistent with findings of abnormal cerebral blood flow in the basal ganglia in RBD patients with MCI vs without MCI.²⁸ This suggests that cognitive deficits in patients with RBD arise from both cortical and subcortical abnormalities that disrupt proper regulation of the cortico-subcortical loops. Our study supports the importance of distinguishing between cognitive subtypes when studying neurodegeneration processes in patients with RBD.

In Parkinson disease (PD), cortical thinning was found in several regions,^{30,31} including the sensorimotor cortex,³¹ and

involving the frontal, temporal, parietal, and occipital cortices in the presence of MCI.³⁰ Subcortical shape abnormalities have also been reported in the striatum, pallidum, and thalamus in PD.^{32–35} Thalamic and striatal shape are independent predictors of dementia in PD with MCI.³⁶ In DLB, cortical thinning was extensive in the parietal and occipital cortices as well as the frontal, insular, cingulate, and temporal cortices.³⁷ Abnormal subcortical shape has also been reported in the hippocampus and thalamus in DLB.^{38,39} In RBD patients with MCI, we found very similar thickness abnormalities to those in DLB, although restricted to the frontal, insular, cingulate, and temporal cortices. Extension of these abnormalities to more posterior regions may signal transition toward DLB.

Table 5 Results of cortical correlation analyses in patients

Region with significant correlation	Hemisphere	Cluster size, mm ²	No. of vertices	Talairach coordinates			−log ₁₀ p value
				x	y	z	
Attention and executive functions							
Cortical thickness							
Fusiform, lingual, and lateral occipital	Left	3,669.37	4,964	−27.3	−79.6	−5.0	3.883
Postcentral, precentral, and paracentral	Left	1,980.61	4,662	−11.9	−35.7	70.3	3.807
Cuneus	Right	2,710.70	3,849	27.6	−62.0	27.4	2.765
Superior frontal extending to paracentral and postcentral	Right	4,225.20	9,612	10.2	−30.3	68.9	2.692
Learning and memory							
Cortical thickness							
Posterior temporal and lingual	Left	3,764.41	5,463	−38.3	−52.6	−14.0	4.224
Insula and anterior temporal	Left	4,573.79	8,767	−36.3	−5.1	−35.4	3.938
Cuneus	Right	1,425.13	1,902	11.5	−84.5	18.8	3.628
Visuospatial abilities							
Cortical thickness							
Fusiform and lingual	Left	3,169.18	4,425	−19.9	−73.4	−2.4	4.675
Superior frontal including pars orbitalis and insula	Left	4,295.90	7,410	−15.4	49.2	27.7	3.858
Pars opercularis, insula, and transverse temporal	Left	2,476.05	5,913	−39.4	−24.9	−0.8	3.473
Anterior portion of the middle temporal	Left	1,589.72	2,444	−57.2	−5.0	−22.2	3.439
Lingual and fusiform	Right	1,531.08	2,025	34.6	−47.9	−5.6	3.195
Cuneus	Right	3,038.83	4,308	34.6	−47.9	−5.6	3.195
Precuneus, paracentral, and superior frontal	Right	3,430.86	7,497	9.1	−44.0	42.0	3.083
Lateral occipital	Left	2,279.38	3,504	−26.7	−85.1	10.1	3.007
Superior and middle temporal	Right	1,429.10	2,592	49.8	−14.5	−7.5	2.980
Middle frontal	Left	1,425.78	2,622	−40.6	26.9	23.1	2.840
Cortical volume							
Lateral occipital	Right	1,641.23	2,414	40.6	−68.4	4.3	2.768
Color discrimination (FM-100 Hue Test)							
Cortical thickness							
Cuneus	Right	1,754.85	2,454	7.6	−83.8	20.4	−5.021
Cortical surface area							
Cuneus	Right	1,916.90	2,978	18.9	−66.1	17.5	3.731
Olfactory function (UPSIT)							
Cortical thickness							
Lateral occipital	Left	1,675.35	2,392	−38.3	−75.6	10.9	3.721
Lateral occipital and cuneus	Right	3,101.77	4,379	7.1	−84.6	19.6	5.224

Continued

Table 5 Results of cortical correlation analyses in patients (*continued*)

Region with significant correlation	Hemisphere	Cluster size, mm ²	No. of vertices	Talairach coordinates			−log ₁₀ <i>p</i> value
				x	y	z	
Systolic blood pressure drop							
Cortical thickness							
Lateral occipital and inferior parietal	Left	3,458.94	5,207	−29.1	−80.8	8.1	−2.961
Superior, middle, and inferior temporal	Right	1,540.45	2,576	55.5	−43.7	−6.6	−3.597

Abbreviations: FM-100 = Farnsworth-Munsell 100; UPSIT = University of Pennsylvania Smell Identification Test.

Abbreviations: FM-100 = Farnsworth-Munsell 100; UPSIT = University of Pennsylvania Smell Identification Test.

The patterns of structural impairment in patients with RBD can be interpreted 2-fold. First, recent longitudinal results by our group showed that having MCI increased the risk of developing DLB vs PD in patients with RBD,⁵ suggesting that RBD patients with or without MCI have distinct patterns of cortical and subcortical abnormalities. In the present study, only patients with MCI presented substantive subcortical abnormalities as well as extended cortical thinning. In contrast, patients without MCI had a limited pattern of cortical thinning restricted to the motor regions of the frontal lobe. Second, although both RBD subgroups showed no significant differences in age or disease duration, RBD patients with MCI may have had more advanced disease severity, in which case the cortical abnormalities found in RBD patients without MCI would represent very early prodromal structural abnormalities. Indeed, RBD patients without MCI are also at risk of developing MCI.⁴⁰ Longitudinal follow-up on these patients would be crucial to better understand the patterns of structural impairment that predict the development of neurodegenerative disease in these patients.

Lower performance in attention and executive functions was associated with frontal, fusiform, lingual, and occipital thinning in RBD, which concurs with the association between abnormal executive functioning in PD and thinner superior frontal cortex and cuneus.^{30,31} Lower performance in episodic verbal learning and memory in RBD was associated with temporal and occipital thinning, also found in PD in the fusiform and occipital cortices.^{41–43} Lower performance in visuospatial abilities in RBD was associated with widespread cortical thinning in the frontal, temporal, parietal, and occipital cortices, similar to that found in PD.^{30,41} We found that color discrimination impairment correlated with cortical thinning and increased surface area in the cuneus, a region functionally activated during chromatic stimulation.⁴⁴ The interplay between decreased cortical thickness and increased surface area in one region has also been reported in PD.⁴³ Impaired color discrimination in RBD is related to increased risk of developing neurodegenerative disease and to abnormal blood flow in the middle occipital gyrus.^{45,46} In PD, color discrimination deficits are associated with cognitive impairment and white matter alterations, including in the occipital portion of the fronto-occipital fasciculus.⁴⁷

Anosmia was associated with occipital thinning, corroborating similar findings on brain perfusion in RBD.⁴⁵ Increased systolic blood pressure drop was also associated with abnormal thickness in the occipital and middle temporal cortices, the latter in the same location as the region that best discriminated MCI in patients. Thus, most of the cognitive, perceptual, and autonomic markers of neurodegeneration in RBD are associated with abnormal occipital thickness, suggesting that this region has a central role in the conversion of patients with RBD through synucleinopathy. Future studies should more closely investigate structural and functional abnormalities in this region in patients with RBD. On the subcortical level, lower performance in learning and memory, visuospatial abilities, and color discrimination correlated with higher surface expansion in the hippocampus, which is supported by findings of increased hippocampal local volume and hypoperfusion that is more prominent in the presence of MCI and that predicts progression toward neurodegenerative disorders.^{7,28,48} Although the mechanisms underpinning these relationships remain to be elucidated, evidence from amnesic patients with MCI showed that hippocampal overactivation correlated with impaired memory performance, future cognitive decline, and greater cortical thinning.⁴⁹ This increased hippocampal activation may actually be an early marker of neuronal dysfunction. However, whether this stems from pathologic processes affecting neuronal or nonneuronal cells, synaptic architecture, neuronal morphology, vascular changes, or changes in signaling pathways remains to be determined.

Some study limitations should be mentioned. There are currently no standard diagnostic criteria for MCI in patients with RBD. We used a 3-domain solution to diagnose MCI in RBD,⁴ which effectively detected brain abnormalities between patients with or without MCI in this population.^{28,29} However a 5-domain solution was proposed for MCI diagnosis in patients with PD.⁵⁰ Therefore, we also diagnosed our patients with RBD using a 5-domain solution and found that none of them changed groups, suggesting that in this particular case, the results would not be influenced by the choice of a 3- or 5-domain solution for MCI. However, because 6 of our patients with RBD lacked certain neuropsychological abilities required for a proper 5-domain diagnosis of MCI (e.g., language abilities), we used the 3-domain criteria. Another limitation is the lack of follow-up,

Figure 2 Correlation analyses

Cortical and subcortical abnormalities are associated with composite cognitive scores, color discrimination, olfaction, and autonomic functions in patients with RBD. Cortical thinning was associated with lower performance in attention and executive functions, learning and memory, visuospatial abilities, color discrimination, and olfaction, as well as with increased systolic blood pressure drop (A). Note that higher Farnsworth-Munsell 100 Hue Test scores correspond to lower color discrimination performance. Decreased cortical volume was associated with lower performance in visuospatial abilities (B). Increased cortical surface area was associated with lower performance in color discrimination (C). The color bar shows the logarithmic scale of p values ($-\log_{10}$) for correlation analyses, with red-yellow areas representing positive association and blue areas representing negative association in patients with RBD (corrected with Monte Carlo simulation at $p < 0.05$ with age, sex, and education as covariates as well as total intracranial volume for cortical volume and surface area analyses). Subcortical surface abnormalities in the right hippocampus are associated with composite cognitive scores and color discrimination impairment in patients with RBD (D). Red areas correspond to negative correlations and blue areas to positive correlations. Analyses were conducted in the MNI (Montreal Neurological Institute) space, and results are corrected at $p < 0.05$ with age, sex, and education as covariates. RBD = REM sleep behavior disorder.

which would inform on the cortical abnormalities that may act as harbingers of progression toward neurodegenerative disorders.

Author contributions

Shady Rahayel: study concept and design, data acquisition, analysis and interpretation, manuscript drafting. Ronald B. Postuma: study concept and design, data acquisition, funding, manuscript revision for content. Jacques Montplaisir: study concept and design, data acquisition, funding,

manuscript revision for content. Daphné Génier Marchand: data acquisition, manuscript revision for content. Frédérique Escudier: data acquisition, manuscript revision for content. Malo Gaubert: data analysis and interpretation, manuscript revision for content. Pierre-Alexandre Bourgouin: data acquisition, manuscript revision for content. Julie Carrier: data acquisition, manuscript revision for content. Oury Monchi: data acquisition, manuscript revision for content. Sven Joubert: study design, manuscript revision for content. Frédéric

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Disclosure

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Cortical and subcortical gray matter bases of cognitive deficits in REM sleep behavior disorder

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Study question

How do patients with REM sleep behavior disorder (RBD) and comorbid mild cognitive impairment (MCI) differ from those without comorbid MCI in terms of cortical and subcortical gray matter abnormalities?

Summary answer

Patients with comorbid MCI exhibit more extensive cortical and subcortical gray matter abnormalities.

What is known and what this paper adds

Cortical thinning and subcortical atrophy occur in patients with RBD, but the relationship between these abnormalities and cognitive function remains undetermined. This study provides evidence that the extent of thinning and subcortical atrophy is related to the presence or absence of comorbid MCI.

Participants and setting

Beginning in July 2008, this study recruited 52 patients with RBD and 41 healthy controls without MCI. The participants were recruited through Montreal's Center for Advanced Research in Sleep Medicine and were free of stroke, head or brain injury, and EEG abnormalities suggestive of neurologic disorders. All patients with RBD were idiopathic and thus did not present with dementia or Parkinson disease.

Design, size, and duration

The presence or absence of MCI was determined through a neuropsychological assessment that included a battery of cognitive function tests. The participants underwent high-resolution T1-weighted MRI scans, and vertex-based analyses of the resulting data were used to detect cortical and subcortical abnormalities.

Primary outcomes

The primary outcomes were differences in cortical and subcortical abnormalities between the patients with RBD who had comorbid MCI and those who did not. These differences were assessed through general linear modeling.

Main results and the role of chance

Among the patients with RBD, 17 (33%) had comorbid MCI. Compared to patients with RBD without comorbid MCI, those with comorbid MCI had more extensive cortical thinning

Figure Cortical thinning in patients with RBD and comorbid MCI vs cortical thinning in those without comorbid MCI

and exhibited abnormal surface contraction in the left putamen and thalamus. A 2.66-mm cut-off thickness in the left anterior temporal cortex identified patients with comorbid MCI compared to controls with an area under the curve of 0.91 (76.5% sensitivity and 95.1% specificity, $p < 0.001$).

Bias, confounding, and other reasons for caution

No standard diagnostic criteria for comorbid MCI in patients with RBD exist. This study involved no follow-up evaluations; therefore, it remains unclear whether cortical and subcortical abnormalities can predict neurodegenerative progression.

Generalizability to other populations

Recruitment of study participants through a referral center might have biased the sample towards patients with severe clinical presentations.

Study funding/potential competing interests

This study was funded by the Canadian and Québécois governments and the W. Garfield Weston Foundation. Dr. Postuma and Dr. Montplaisir report receiving personal compensation from pharmaceutical companies. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.