RESEARCH ARTICLE

Brain Perfusion Anomalies in Rapid Eye Movement Sleep Behavior Disorder with Mild Cognitive Impairment

Mélanie Vendette, MSc,[1,2] Jacques Montplaisir, MD, PhD,[1,3] Nadia Gosselin, PhD,[1,3] Jean-Paul Soucy, MD, MSc,[4,5] Ronald B. Postuma, MD, MSc,[6] Thien Thanh Dang-Vu, MD, PhD,[1,7] and Jean-François Gagnon, PhD[1,8*]

[1]*Center for Advanced Research in Sleep Medicine, Hôpital du Sacré-Coeur de Montréal, Quebec, Canada*
[2]*Department of Psychology, University of Montreal, Montreal, Quebec, Canada*
[3]*Department of Psychiatry, University of Montreal, Montreal, Quebec, Canada*
[4]*Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada*
[5]*Department of Nuclear Medicine, Centre Hospitalier de l'Université de Montreal, Montreal, Quebec, Canada*
[6]*Department of Neurology, Montreal General Hospital, Montreal, Quebec, Canada*
[7]*Cyclotron Research Centre, University of Liege, Liege, Belgium*
[8]*Department of Psychology, Université du Québec à Montréal, Montreal, Quebec, Canada*

ABSTRACT: Rapid eye movement (REM) sleep behavior disorder is an important risk factor for Parkinson's disease and dementia with Lewy bodies. Approximately 50% of patients with REM sleep behavior disorder have mild cognitive impairment. Our objective was to investigate brain perfusion changes associated with mild cognitive impairment in REM sleep behavior disorder. Twenty patients with REM sleep behavior disorder, including 10 patients with mild cognitive impairment and 10 patients without mild cognitive impairment, and 20 healthy controls underwent a complete neuropsychological assessment and single-photon emission computerized tomography using ^{99mc}Tc-Ethylene Cysteinate Dimer. Compared with controls, both REM sleep behavior disorder groups had hypoperfusion in the frontal regions. In addition, patients with REM sleep behavior disorder and mild cognitive impairment showed cortical hypoperfusion in the occipital, temporal, and parietal regions compared with controls and patients with REM sleep behavior disorder without mild cognitive impairment. Both REM sleep behavior disorder groups had hyperperfusion in the right hippocampus and parahippocampal gyri. However, patients with REM sleep behavior disorder and mild cognitive impairment showed more pronounced anomalies in the right hippocampus and had increased perfusion in the putamen and the left paracentral gyrus. This study showed specific patterns of posterior cortical hypoperfusion and hyperperfusion in some brain areas in patients with REM sleep behavior disorder and mild cognitive impairment, similar to those found in Parkinson's disease dementia and dementia with Lewy bodies. This suggests the presence of an identifiable neuroimaging marker of synucleinopathy in REM sleep behavior disorder with mild cognitive impairment.

Key Words: REM sleep behavior disorder; SPECT (regional cerebral blood flow); mild cognitive impairment; Lewy body dementia; Parkinson's disease

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by excessive muscle activity during REM sleep and the presence of abnormal motor behaviors associated with dream mentation. RBD is frequent in neurodegenerative diseases characterized by α-synuclein deposition such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB).[1] RBD is also a risk factor for synucleinopathies: 20 to 45% of patients with RBD develop a synucleinopathy within 5 years of the diagnosis of RBD.[2,3] Recently, we found that approximately 50% of RBD patients have mild cognitive impairment

Additional Supporting Information may be found in the online version of this article.

***Correspondence to:** Dr. Jean-François Gagnon, Centre d'Études Avancées en Médecine du Sommeil, Hôpital du Sacré-Coeur de Montréal, 5400 Boul. Gouin Ouest, Montréal, Québec, Canada H4J 1C5; gagnon.jean-françois.2@uqam.ca

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(MCI),[4] which is defined as cognitive decline greater than expected for an individual's age and education level with preserved activities of daily living.[5] MCI is recognized as a risk factor for dementia.[5]

Regional cerebral blood flow (rCBF) and glucose metabolism changes have also been identified during wakefulness in RBD.[6–9] Studies have found that RBD patients have hypoperfusion in several brain areas in the frontal, parietal, temporoparietal, and occipitoparietal lobes as well as in the cingulate gyrus, limbic structures, and cerebellum. Hyperperfusion has also been observed in the pons, putamen, and right hippocampus in RBD patients compared with healthy subjects. However, those studies did not look for the presence of MCI in their RBD population.

The aim of the present study was to compare rCBF distribution in RBD patients with MCI (RBD-MCI), RBD patients without MCI (RBD-NoMCI), and healthy subjects.

Patients and Methods

Subjects

Patients were recruited at the sleep disorders center of the Sacre-Coeur Hospital in Montréal. All participants were interviewed by a sleep specialist and underwent polysomnographic (PSG) recording to confirm the diagnosis of RBD.[10,11] At the time of the PSG recording, all patients had discontinued psychotropic medications for at least 2 weeks, including antidepressants and anxiolytics. Thus, none of the participants had drug-induced RBD. Twenty–eight PSG-confirmed RBD patients were recruited for this study. Participants first received a complete neuropsychological examination followed by a single-photon emission computerized tomography (SPECT) scan in the same week. Exclusion criteria were the presence of dementia diagnosed according to *Diagnostic and Statistical Manual* IV-TR criteria (DSM-IV-TR)[12] and on neuropsychological evaluation, a psychiatric condition according to the DSM-IV-TR, EEG abnormalities suggestive of epilepsy, sleep apnea syndrome (defined as an apnea index greater than 10 or a combined apnea-hypopnea index greater than 20 per hour of sleep), the presence of diabetes or unstable hypertension, or a history of head injury, brain tumor, stroke, or encephalitis. A complete neurological examination was performed by a neurologist specialized in movement disorders (R.B.P.) to exclude subjects with parkinsonism or other neurological disorders. A motor assessment was also performed according to Part III of the Unified Parkinson Disease Rating Scale.[13]

Eight patients were excluded from the study: 4 had sleep apnea syndrome, 3 had dementia, and 1 had bipolar disorder. Twenty PSG-confirmed RBD patients (10 RBD-MCI patients and 10 RBD-NoMCI patients) and 20 healthy subjects were included. Seventeen of the RBD patients and all controls had participated in a previous study.[7] The RBD-MCI group included 3 women; mean age, 68.47 ± 5.72 years; mean educational level, 10.20 ± 4.52 years; mean MMSE score, 28.43 ± 1.51. The RBD-NoMCI group included 5 women; mean age, 65.64 ± 8.22 years; mean educational level, 13.50 ± 4.72 years; mean MMSE score, 29.00 ± 1.15. The control group included 5 women; mean age, 67.35 ± 6.38 years; mean educational level, 14.45 ± 4.21 years; mean MMSE score, 29.53 ± 0.71. Details of demographic and clinical variables are presented in supplemental data (Table e-1). At the time of the SPECT scan, 1 RBD-MCI patient and 3 RBD-NoMCI patients were taking clonazepam, a medication used for the treatment of RBD. The protocol was approved by the Sacré-Coeur Hospital-Université de Montréal ethics committee, and all participants signed a consent form to participate.

Polysomnography

PSG recording included 2 EEG leads (C3-A2 and O2-A1), left and right electro-oculograms (EOG), and a chin electromyogram (EMG). Stages 1–4 of non-REM sleep were scored according to Rechtschaffen and Kales.[14] REM sleep and the presence of excessive muscle activity during REM sleep were scored based on a method recently developed in our laboratory for RBD.[10] Several PSG variables were considered including total sleep time, sleep efficiency (ie, total sleep time/total sleep period × 100), sleep latency (time from lights off to the first sign of sleep), and percentages of stages 1, 2, slow-wave sleep (stages 3 and 4), and REM sleep. Respiration was recorded using a nasal cannula and a thoracic strain gauge. Blood oxygen saturation was recorded by a transcutaneous finger pulse oximeter. PSG variables are presented in supplemental data (Table e-1).

Neuropsychological Asessment and MCI criteria

Global cognitive functioning was assessed with the Mini–Mental State Examination (MMSE).[15] Three main cognitive domains were assessed. Attention and executive functions were assessed by the Digit Span subtest from the Wechsler Adult Intelligence Scale, version III (WAIS-III; scaled score),[16] the Trail Making Test part B (time in seconds),[17] a modified version of the Stroop Color Word Test (part III—part I time in seconds and part III—part I number of errors),[18] the semantic verbal fluency test (animals, fruits/vegetables; number of words in 1 minute for each category), and the letter verbal fluency test (letters *P, F,* and *L*; number of words in 1 minute for each letter).[19] Episodic verbal learning and memory domain was assessed by the following 5 variables from the Rey Auditory

Verbal Learning Test (RAVLT)[20]: sum of trials 1–5, list B, immediate recall, delayed recall after 20 minutes, and recognition. Visuospatial abilities were assessed by the Copy of the Rey-O figure,[21] the Block Design subtest of the WAIS-III (scaled score),[16] and the Bells test (number of omissions).[22]

MCI diagnosis was determined at a consensus meeting between the neurologist (R.B.P.) and the neuropsychologist (J.F.G.) based on the following criteria[4,5]: (1) a subjective cognitive complaint on the structured interview; (2) objective evidence of cognitive decline, defined as any 2 scores in the same cognitive domain $\geq$1.5 standard deviations below the standardized mean; (3) preserved activities of daily living based on previous and actual capacities; and (4) cognitive deficits not better explained by medication use or another medical/psychiatric disorder.

SPECT Image Transformation and Data Analysis

SPECT scans were performed in the morning during wakefulness under resting condition following intravenous injection of ^{99mc}Tc-Ethylene Cysteinate Dimer (ECD). Thirty minutes after the intravenous administration, subjects were placed in a 3-headed SPECT scanner (PRISM system, Picker Co., Cleveland, OH). Forty projections by scanner head (120 in total) were obtained, at 40 seconds per projection, on a 128 $\times$ 128 matrix using a photopeak window and a lower-energy Compton scatter window. Reconstruction was performed with filtered back-projection using a Butterworth filter (order, 8; cutoff, 0.39 FWHM) following subtraction of 40% of the Compton window from the peak window for scatter correction. Attenuation correction was performed with a noniterative Chang algorithm using a coefficient of 0.15 cm^{-1}. Images were converted to the DICOM format and then transformed to the Analyze format for further processing.

SPECT data were processed with the Statistical Parametric Mapping program version 2 (SPM2) using Matlab (version 7.1). All studies were registered and spatially normalized to the SPM SPECT template, and the normalized studies were smoothed with a 14-mm FWHM filter. Global normalization was performed using proportional scaling and the global value was set at 50. Scans were normalized to the global CBF value (unitless). A gray-matter threshold of 1.0 was used to minimize the risk that findings indicating hyperperfusion were artifacts resulting from the global mean normalization.[23] A gray-matter mask defined from a magnetic resonance imaging (MRI) atlas (ICBM152) was applied.

Statistical Analysis

One-way analyses of variance were used to measure differences between the 3 groups in demographic, clinical, PSG, and neuropsychological variables. Post hoc analyses were performed with Tukey HSD tests. Nonparametric Kruskal–Wallis (or Mann–Whitney) tests were applied for variables not distributed normally. Statistical significance was set at $P < .05$. Between-group differences in rCBF distribution were measured with SPM2 software using a 2-sample t test. Note that the atlas used to spatially register all cases was based on HMPAO studies, whereas our subjects were studied with ECD. Biological, class-specific differences between subjects and the individuals used to generate the template are not the strongest determinants of between-group differences in brain perfusion. However, some impact of using a tracer-unmatched template for voxel-based comparisons cannot be excluded.[24] We investigated hypoperfusion and hyperperfusion in 3 between-group comparisons (ie, RBD-MCI vs. controls, RBD-NoMCI vs. controls, and RBD-MCI vs. RBD-NoMCI). A region was considered significantly different between groups at $P < .05$ (peak voxel level) after correcting for multiple comparisons on small volumes of interest (SVC; sphere, 15 mm). This correction limits the analysis to specifically hypothesized brain regions of interest[25] whose coordinates have been previously published (see Tables 2 and 3). The statistically significant differences in regional cerebral perfusion were overlaid on a MRI template from the Montreal Neurological Institute.

Results

Demographic, Clinical, and PSG Variables

No significant between-group differences were observed for demographic, clinical, or PSG variables (Table e-1), except for tonic REM sleep EMG activity ($H_2 = 22.93$; $P < .001$), where both RBD groups showed a higher percentage compared with controls.

Neuropsychological Assessment

The neuropsychological testing results are presented in Table 1. Compared with controls and RBD-NoMCI patients, RBD-MCI patients showed poorer performance on the Digit span, Trail Making Test part B, semantic and letter verbal fluency test, sum of trials 1–5 of the RAVLT, and the Copy of the Rey-O figure. RBD-MCI patients also showed poorer performance than controls on immediate recall on the RAVLT. No significant differences were observed between RBD-NoMCI patients and control subjects.

Regional Perfusion: Group Differences

Results on between-group differences in rCBF with regions significant at $P_{corrected} < .05$ are presented in Table 2 (hypoperfusion) and Table 3 (hyperperfusion). Other regions significant at $P_{uncorrected} < .01$ are presented in supplemental material Table e-2.

TABLE 1. Neuropsychological performance

	A (RBD-MCI)	B (RBD-NoMCI)	C (controls)	*P*	Post hoc significance
Digit span	7.10 ± 1.66	9.80 ± 1.55	10.20 ± 3.02	.007	[A<B[b]];[A<C[b]]
Trail Making Test part B (s)	173.90 ± 94.60	104.00 ± 47.71	92.05 ± 44.74	.005	[A>B[b]];[A>C[c]]
Stroop III–I (s)	88.33 ± 33.71	62.29 ± 25.87	61.83 ± 20.40	ns	ns
Stroop III–I (errors)[a]	5.50 ± 10.17	4.14 ± 4.20	1.94 ± 2.11	ns	ns
Verbal fluency semantic	25.67 ± 3.84	36.50 ± 10.65	35.13 ± 6.75	.007	[A<B[c]];[A<C[b]]
Verbal fluency letter	20.33 ± 6.89	34.10 ± 9.34	39.93 ± 10.10	.0001	[A<B[c]];[A<C[d]]
RAVLT sum of trials 1–5	34.70 ± 12.31	47.20 ± 5.73	47.30 ± 8.29	.002	[A<B[c]];[A<C[c]]
RAVLT list B	3.60 ± 1.43	5.00 ± 2.16	5.00 ± 1.84	ns	ns
RAVLT immediate recall	6.80 ± 2.49	9.30 ± 2.50	9.55 ± 3.05	.04	[A<C[b]]
RAVLT delayed recall	6.60 ± 3.50	10.40 ± 3.24	8.80 ± 3.58	ns	ns
RAVLT recognition	12.44 ± 2.19	13.50 ± 1.65	13.85 ± 1.04	ns	ns
Rey-O figure (copy)	25.95 ± 6.19	31.10 ± 2.51	31.48 ± 2.55	.002	[A<B[c]];[A<C[c]]
Block design	9.60 ± 3.00	10.60 ± 1.51	11.50 ± 3.59	ns	ns
Bells test (errors)[a]	2.50 ± 3.10	1.60 ± 1.58	2.00 ± 2.10	ns	ns

Mean ± standard deviation.
[a]Nonparametric (Kruskal–Wallis).
[b]$P < .05$.
[c]$P < .01$.
[d]$P < .001$.
Abbreviations: RBD, rapid eye movement sleep behavior disorder; RBD-MCI, RBD with mild cognitive impairment; RBD-NoMCI, RBD without MCI; RAVLT, Rey Auditory-Verbal Learning Test.

RBD-MCI Versus RBD-NoMCI

Compared with RBD-NoMCI patients, RBD-MCI patients showed significant relative hypoperfusion in the cortical posterior regions, including the occipital cunei (BA 18) and the superior temporal gyri (BA 22/42) bilaterally. Relative increased perfusion in the right hippocampus, bilateral putamen, and left paracentral region (BA 4/6) was also observed (Fig. 1).

RBD-MCI Versus Controls

Compared with controls, RBD-MCI patients showed significant relative hypoperfusion in the bilateral middle frontal gyri (BA 9). Significant cortical posterior hypoperfusion was also observed in both occipital cunei (BA 18), right superior occipital gyrus (BA19), left parieto-occipital (precuneus; BA 7), left inferior parietal lobule (angular gyrus; BA 39/40), and right

TABLE 2. Between-group differences in regional cerebral blood flow (hypoperfusion) significant at $P_{corrected} < .05$

			Voxel level				
					TAL Coordinates		
Structure	Side	BA	*t* Score	*Z* score	*X*	*Y*	*Z*
rCBF RBD-MCI < RBD-NoMCI							
Occipital gyrus (cuneus)[29]	R	18	3.02	2.58	8	−77	19
Occipital gyrus (cuneus)[29]	L	18	2.43	2.23	−14	−73	26
Superior temporal gyrus[31]	R	22/42	4.46	3.61	63	−32	11
Superior temporal gyrus[31]	L	22/42	2.59	2.62	−65	−31	9
rCBF RBD-MCI < controls							
Middle frontal gyrus[29]	R	9	3	2.77	24	33	32
Middle frontal gyrus[29]	L	9	2.56	2.41	−38	30	26
Occipital gyrus (cuneus)[29]	R	18	2.76	2.58	14	−63	18
Occipital gyrus (cuneus)[29]	L	18	2.85	2.65	−10	−75	13
Superior occipital gyrus[31]	R	19	2.4	2.27	42	−75	15
Parieto-occipital gyrus (precuneus)[31]	L	7	2.72	2.54	−34	−65	29
Inferior parietal lobule (angular)[41]	L	39/40	2.44	2.31	−51	−61	31
Superior temporal gyrus[31]	R	22	2.58	2.43	57	−50	15
rCBF RBD-NoMCI < controls							
Superior frontal gyrus[31]	R	10	4.02	3.54	22	49	3
Middle frontal gyrus[6]	R	47	2.94	2.72	38	34	19
Middle frontal gyrus[6]	L	47	3.45	3.12	−42	30	26

rCBF, regional cerebral blood flow; RBD, rapid eye movement sleep behavior disorder; RBD-MCI, RBD with mild cognitive impairment; RBD-NoMCI, RBD without MCI; BA, Brodmann area; TAL, Talairach coordinates; R, right; L, left.

TABLE 3. Between-group differences in regional cerebral blood flow (hyperperfusion) significant at $P_{corrected} < .05$

			Voxel level				
					TAL Coordinates		
Structure	Side	BA	*t* Score	*Z* score	*X*	*Y*	*Z*
rCBF RBD-MCI > RBD-NoMCI							
Hippocampus[6]	R		2.63	2.39	32	−12	−16
Putamen[6]	R		2.88	2.58	12	17	−8
Putamen[6]	L		3.08	2.73	−14	19	−9
Paracentral gyrus[38]	L	4/6	3.14	2.77	−18	−21	45
rCBF RBD-MCI > controls							
Hippocampus[6]	R		4.47	3.13	34	−16	−8
Parahippocampal gyrus[36]	R	36	3.97	3.5	40	−22	−12
Parahippocampal gyrus[36]	L	36	3.1	2.85	−42	−28	−10
Paracentral gyrus[41]	L	4/6	2.83	2.63	−22	−17	47
rCBF RBD-NoMCI > controls							
Hippocampus[6]	R		2.73	2.55	30	−16	−6
Parahippocampal gyrus[36]	R		3.54	3.19	42	−32	−14
Parahippocampal gyrus[36]	L		2.79	2.6	−40	−32	−12

rCBF, regional cerebral blood flow; RBD, rapid eye movement sleep behavior disorder; RBD-MCI, RBD with mild cognitive impairment; RBD-NoMCI, RBD without MCI; BA, Brodmann area; TAL, Talairach coordinates; R, right; L, left.

superior temporal gyrus (BA 22). Moreover, significant relative increased perfusion was observed in the right hippocampus, bilateral parahippocampal gyri, and left paracentral gyrus (4/6; Fig. 2).

RBD-NoMCI Versus Controls

Compared with controls, RBD-NoMCI patients showed significant relative hypoperfusion in the right superior frontal gyrus (BA 10) and both middle frontal gyri (BA 47). Significant relative hyperperfusion was also found in the right hippocampus and both parahippocampal gyri (Fig. e-1).

Discussion

The present study looked for specific abnormalities in rCBF in RBD-MCI patients compared with RBD-NoMCI patients and healthy subjects. Our main finding was decreased perfusion in the posterior cortical regions in RBD-MCI patients, mainly in the occipital, parietal, and temporal areas. Hypoperfusion and hypometabolism in these regions have been reported using SPECT and positron emission tomography (PET) in RBD.[6–9] However, these studies did not look for the presence of MCI in their RBD population. Similar posterior cortical hypoperfusion in occipito-parieto-temporal regions has been well described in PD patients with MCI, PD with dementia (PDD), and DLB.[26,27] Posterior occipital brain hypoperfusion has been identified as a hallmark of brain anomalies associated with PDD and DLB compared with Alzheimer's disease, in which more temporal hypoperfusion was observed.[28,29] Furthermore, posterior cortical dysfunction in PDD or DLB has also been frequently reported by studies using EEG, voxel-based morphometry, and diffusion tensor imaging.[30–32]

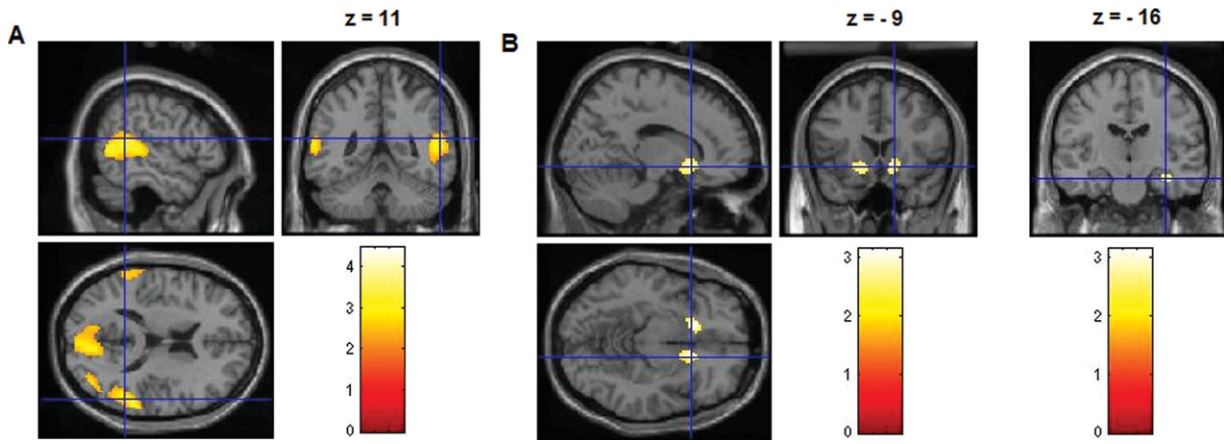

FIG. 1. Results of regional cerebral blood flow (rCBF) difference between rapid eye movement sleep behavior disorder (RBD) patients with mild cognitive impairment (RBD-MCI) and RBD patients without MCI (RBD-NoMCI). **A:** Brain areas in which rCBF is lower in RBD-MCI than in RBD-NoMCI patients. **B:** Brain areas in which rCBF is higher in RBD-MCI than in RBD-NoMCI patients.

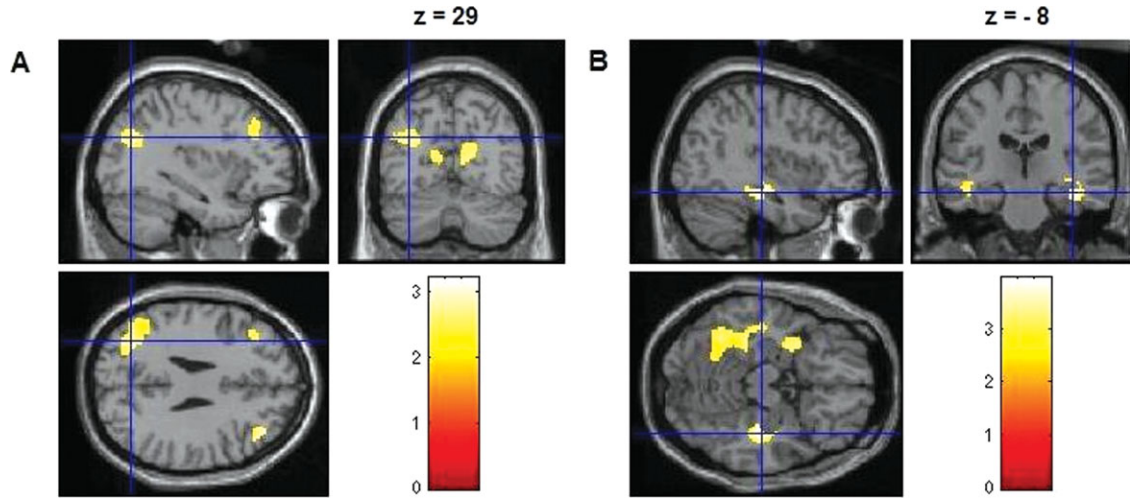

FIG. 2. Results of regional cerebral blood flow (rCBF) difference between rapid eye movement sleep behavior disorder (RBD) patients with mild cognitive impairment (RBD-MCI) and control subjects. **A:** Brain areas in which rCBF is lower in RBD-MCI patients than in controls. **B:** Brain areas in which rCBF is higher in RBD-MCI patients than in controls.

Overall, this suggests that RBD-MCI patients share a common pattern of rCBF anomalies with PDD and DLB. The posterior cortical hypoperfusion, particularly in occipital areas, found only in RBD-MCI, might signal that these patients are at risk of developing subsequent cognitive decline.

We found a frontal rCBF decrease in both RBD groups compared with healthy controls. These results suggest that the frontal lobe hypoperfusion found in RBD patients is relatively independent of cognitive status. Cognitively intact PD patients also demonstrated frontal hypoperfusion compared with healthy subjects.[33] This frontal hypoperfusion is consistent with the presence of reduced frontal lobe activity related to reduced dopaminergic input from the basal ganglia to this region.[34] Thus, the rCBF anomalies in the frontal lobes in RBD may be more related to preclinical PD and not necessarily to incipient dementia.

Increased perfusion in the right hippocampus and in the bilateral parahippocampal regions in both RBD groups relative to controls has been found. This is concordant with the results of previous SPECT studies in RBD.[6,7] Moreover, a voxel-based morphometry study of MRI in RBD found increased gray-matter density in the hippocampus.[35] Hippocampal hyperperfusion has been observed in the initial stage of PD[36] as well as in other neurodegenerative diseases.[37] It has been demonstrated that hippocampal activation may predict cognitive decline in MCI subjects.[38] Our results showed that RBD-MCI patients present a more pronounced increase in rCBF in the hippocampus, suggesting that this subgroup of RBD patients is at greater risk for cognitive deterioration. Another study using arterial spin-labeling perfusion with MRI found increased perfusion in the hippocampus and the putamen of MCI patients who progress toward neurodegenerative disease.[39]

Our results showed hyperperfusion in the putamen bilaterally in RBD-MCI patients compared with RBD-NoMCI patients. We also observed hyperperfusion in the left paracentral region in RBD-MCI patients compared with RBD-NoMCI patients and controls. Bilateral putamen hyperperfusion has been observed in PD and DLB.[36,40] Increased brain activity in the putamen in parkinsonism disease may result from the loss of dopaminergic innervation from the substantia nigra, which normally inhibits the striatum.[34] Increased metabolism in the paracentral cortical region is also present in PD, and it has been demonstrated that this paracentral hyperactivity progresses with the course of the disease.[41] In a recent PET study, it was shown that increased metabolism in the putamen and the paracentral areas may precede the onset of motor symptoms in PD.[42] Indeed, hyperperfusion in the putamen and the paracentral regions observed in RBD-MCI patients might be a preclinical sign of PD.

To conclude, the risk of developing PD or DLB in RBD has been estimated at 20%–45% within 5 years after RBD diagnosis. Approximately 50% of RBD patients have MCI, which is an important risk factor for dementia. No study to date has estimated the risk of developing dementia in RBD with MCI. However, our results show a pattern of rCBF anomalies in RBD with MCI that is different from RBD without MCI, with a distribution similar to that reported in PDD and DLB. Future prospective and longitudinal studies are needed to determine whether these rCBF markers predict conversion to PD or DLB in RBD.

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