

# Brain Metabolism Related to Mild Cognitive Impairment and Phenoconversion in Patients With Isolated REM Sleep Behavior Disorder

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## Abstract

### Background and Objectives

Mild cognitive impairment (MCI) in isolated REM sleep behavior disorder (iRBD) is a risk factor for subsequent neurodegeneration. We aimed to identify brain metabolism and functional connectivity changes related to MCI in patients with iRBD and the neuroimaging markers' predictive value for phenoconversion.

### Methods

This is a prospective cohort study of patients with iRBD with a mean follow-up of  $4.2 \pm 2.6$  years. At baseline, patients with iRBD and age- and sex-matched healthy controls (HCs) underwent  $^{18}\text{F}$ -fluorodeoxyglucose (FDG)-PET and resting-state fMRI scans and a comprehensive neuropsychological test battery. Voxel-wise group comparisons for FDG-PET data were performed using a general linear model. Seed-based connectivity maps were computed using brain regions showing significant hypometabolism associated with MCI in patients with iRBD and compared between groups. A Cox regression analysis was applied to investigate the association between brain metabolism and risk of phenoconversion.

### Results

Forty patients with iRBD, including 21 with MCI (iRBD-MCI) and 19 with normal cognition (iRBD-NC), and 24 HCs were included in the study. The iRBD-MCI group revealed relative hypometabolism in the inferior parietal lobule, lateral and medial occipital, and middle and inferior temporal cortex bilaterally compared with HC and the iRBD-NC group. In seed-based connectivity analyses, the iRBD-MCI group exhibited decreased functional connectivity of the left angular gyrus with the occipital cortex. Of 40 patients with iRBD, 12 patients converted to Parkinson disease (PD) or dementia with Lewy bodies (DLB). Hypometabolism of the occipital pole (hazard ratio [95% CI] 6.652 [1.387–31.987]), medial occipital (4.450 [1.143–17.327]), and precuneus (3.635 [1.009–13.093]) was associated with higher phenoconversion rate to PD/DLB.

### Discussion

MCI in iRBD is related to functional and metabolic changes in broad brain areas, particularly the occipital and parietal areas. Moreover, hypometabolism in these brain regions was a predictor of phenoconversion to PD or DLB. Evaluation of cognitive function and neuroimaging characteristics could be useful for risk stratification in patients with iRBD.

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## Glossary

**AD** = Alzheimer disease; **ChEI** = cholinesterase inhibitor; **CIS** = cingulate island sign; **COWAT** = Controlled Oral Word Association Test; **CWST** = Color–Word Stroop Test; **DLB** = dementia with Lewy bodies; **dnPDRBD-RP** = de novo Parkinson disease with prolonged REM sleep behavior disorder symptoms before developing parkinsonism; **FDG** = <sup>18</sup>F-fluorodeoxyglucose; **FWE** = family-wise error; **FWHM** = full width at half maximum; **GLM** = general linear model; **HC** = healthy control; **HR** = hazard ratio; **iRBD** = isolated REM sleep behavior disorder; **K-BNT** = Korean version of the Boston Naming Test; **LB** = Lewy bodies; **MCI** = mild cognitive impairment; **MDS** = Movement Disorder Society; **MDS-UPDRS** = Movement Disorder Society–sponsored revision of the Unified Parkinson’s Disease Rating Scale; **MMSE** = Mini-Mental State Examination; **MNI** = Montreal Neurological Institute; **MPS** = mild parkinsonian signs; **MSA** = multiple system atrophy; **NC** = normal cognition; **PD** = Parkinson disease; **RBD** = REM sleep behavior disorder; **RBD RP** = REM sleep behavior disorder–related brain metabolic pattern; **RCFT** = Rey-Osterrieth Complex Figure Test; **ROI** = region of interest; **SVLT** = Seoul Verbal Learning Test; **TFCE** = threshold-free cluster enhancement; **TMT** = Trail-Making Test.

Isolated REM sleep behavior disorder (iRBD), a parasomnia manifested by vivid dreams associated with simple or complex motor behavior during REM sleep, has been recognized as a prodromal condition of Parkinson disease (PD) and dementia with Lewy bodies (DLBs).<sup>1</sup> A recent meta-analysis identified that the average phenoconversion rate in patients with REM sleep behavior disorder (RBD) to a defined neurodegenerative disease, such as PD, DLB, or multiple system atrophy (MSA), was 31.95% after a mean follow-up of  $4.75 \pm 2.43$  years. The majority of patients with iRBD converted to PD (43%) or DLB (25%). The phenoconversion risk increased with time; the estimated risk was 96.6% after 14 years of follow-up.<sup>2</sup> Similarly, in a previous study of our cohort of patients with iRBD, we found a phenoconversion rate of 27.3% to PD, DLB, or MSA at a mean follow-up of 3 years, and the phenoconversion rate estimated using the Kaplan-Meier method was 35.5% at 5 years.<sup>3</sup>

Studies on cognition in patients with iRBD identified impairments in multiple cognitive domains, such as attention, executive function, episodic memory, and visuospatial abilities,<sup>4,5</sup> and a high prevalence of mild cognitive impairment (MCI), from 32% to 50%.<sup>6,7</sup> Moreover, long-term follow-up studies found that >90% of patients with RBD who later developed DLB had MCI at baseline.<sup>8,9</sup> In patients with PD, the coexistence of RBD, MCI, and orthostatic hypotension strongly predicted the future development of dementia.<sup>10</sup> Thus, understanding the underlying pathomechanisms of the cognitive impairment in patients with iRBD is important for predicting phenoconversion to PD or DLB.

Several studies have explored brain changes in patients with iRBD associated with their cognitive impairment. Patients with iRBD with MCI had cortical thinning in the anterior and posterior temporal lobe, lateral occipital cortex, medial frontal cortex, and cingulate cortex and contraction in the putamen and thalamus compared with those without MCI.<sup>11</sup> In a previous study using brain perfusion SPECT, relative hypoperfusion in the medial occipital cortex and superior temporal gyrus and relative hyperperfusion in the hippocampus and putamen were found in the patients with iRBD with MCI.<sup>12</sup>

Among various neuroimaging biomarkers, <sup>18</sup>F-fluorodeoxyglucose (FDG)–PET, as an indicator of synaptic dysfunction,<sup>13</sup> has become an essential part of the diagnostic workup for neurodegenerative disorders. An abnormal brain network from FDG-PET imaging, known as PD-related metabolic pattern, could differentiate patients with PD from healthy controls and its expression was correlated with clinical disease severity.<sup>14</sup> In patients with DLB, occipital hypometabolism pattern with or without relative preservation of posterior cingulate metabolism to precuneus and cuneus (the cingulate island sign [CIS]) is a supportive biomarker for diagnosis.<sup>15</sup> The CIS has been particularly effective in discriminating patients with DLB from those with Alzheimer disease (AD).<sup>16</sup> Recently, we found that relative hypometabolism in the occipital area persisted during the follow-up period in patients with iRBD who later developed DLB.<sup>17</sup> Also, cognitive deterioration in patients with iRBD was correlated with expression of the metabolic pattern derived from patients with de novo PD with prolonged RBD symptoms before developing parkinsonism (dnPDRBD-RP),<sup>5</sup> characterized by relative hypometabolism in the occipital and precuneus cortex and relative hypermetabolism in the thalamus and putamen/globus pallidus.<sup>18</sup> These results suggest that there are specific metabolic changes that reflect prodromal features of PD before motor symptoms appear in patients with iRBD. However, as a risk factor for the subsequent development of PD or DLB, little work has been done on the association between brain metabolic changes and MCI in patients with iRBD. A recent study found hypometabolism in the cuneus/precuneus in patients with iRBD with MCI compared with those without, but there were no longitudinal data to evaluate the predictive value of hypometabolism for phenoconversion.<sup>19</sup>

We aimed to identify brain metabolism changes related to MCI in patients with iRBD and to evaluate the predictive value of the metabolism for phenoconversion to PD or DLB. Moreover, using resting-state fMRI, we explored the disruption of intrinsic functional connectivity of the brain regions showing metabolic changes in patients with iRBD with MCI. This multimodal approach may help us better understand the neuropathologic mechanisms of MCI in patients with iRBD. We hypothesized that patients with iRBD with MCI would reveal relatively reduced brain metabolic and functional connectivity changes

mainly in the posterior cortical region, as shown in patients with PD or DLB,<sup>14,15</sup> and this regional hypometabolism would associate with a risk of phenoconversion.

## Methods

### Participants

Forty consecutive patients with iRBD who visited the neurology clinic at the Seoul National University Boramae Medical Center between 2013 and 2019 were prospectively enrolled in this study. Diagnosis of iRBD was based on the criteria of the International Classification of Sleep Disorders, second edition (ICSD-II)<sup>20</sup> and confirmed by video-polysomnography. All patients underwent thorough neurologic evaluations for any signs of neurologic disease and were evaluated for parkinsonian symptoms using the Movement Disorder Society (MDS)–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Exclusion criteria were psychiatric or neurologic comorbidity, moderate to severe obstructive sleep apnea, and pathologic MRI findings other than mild white matter hyperintensities. We followed up the patients every 3–4 months to check for any changes in motor, nonmotor, or cognitive symptoms. Phenoconversion to PD, DLB, or MSA was diagnosed according to the MDS PD criteria,<sup>21</sup> Fourth Consensus Criteria of the DLB Consortium,<sup>15</sup> and Second Consensus Statement on MSA, respectively.<sup>22</sup> Age- and sex-matched healthy controls (HCs) (n = 24) who were free of any neurologic or psychiatric diseases were also enrolled during the study period.

All participants underwent the Seoul Neuropsychological Screening Battery at baseline.<sup>23</sup> We evaluated cognitive performance as follows: (1) Mini-Mental State Examination (MMSE); (2) attention and working memory: Trail-Making Test (TMT) A, digit span, and Color–Word Stroop Test (CWST); (3) executive function: TMT B and Controlled Oral Word Association Test (COWAT)—semantic and phonemic; (4) memory: Seoul Verbal Learning Test (SVLT)—immediate recall, delayed recall, and recognition; (5) visuospatial function: Rey-Osterrieth Complex Figure Test (RCFT)—copy; (6) language: Korean version of the Boston Naming Test (K-BNT). The performance on each test was expressed as a z score based on the age- and education level–adjusted normative performance data. MCI diagnosis was based on the level I category of diagnostic criteria of PD-MCI according to the recommendations by the MDS Task Force.<sup>24</sup> Impairment on each neuropsychological test was determined by z score <−1.5. We divided patients into 2 groups, patients with iRBD with MCI (iRBD-MCI) and those with normal cognition (iRBD-NC). Patients in the iRBD-MCI group can be classified as probable MCI with Lewy bodies (LB) according to the research criteria provided by McKeith and colleagues.<sup>25</sup>

### Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by the institutional review board of Boramae Medical Center (16-2013-101, 10-2021-105).

All participants provided written informed consent according to the Declaration of Helsinki.

### FDG-PET Preprocessing

FDG-PET scans were obtained using a PET/CT scanner (Gemini TF64, Philips Healthcare) at baseline. Detailed imaging protocols are described in the eMethods, [links.lww.com/WNL/B967](https://links.lww.com/WNL/B967).

FDG-PET data were processed with SPM12 (Statistical Parametric Mapping 12) running on MATLAB R2019b (MathWorks).

Each scan was spatially normalized to the dementia FDG-PET template<sup>26</sup> and then smoothed using an isotropic Gaussian kernel with 8-mm full width at half maximum (FWHM). Global mean scaling was applied to each image to account for between-subject uptake variability.

### Resting-State fMRI Preprocessing

A subset of participants was scanned using a Philips Achieva 3T MRI scanner (Philips Medical Systems) at baseline. Detailed imaging protocols are described in the eMethods ([links.lww.com/WNL/B967](https://links.lww.com/WNL/B967)). The first 10 volumes of the functional image were discarded to allow signal stabilization and adaptation to the scanning environment. A first preprocessing step of the remaining 170 volumes was carried out using SPM12 including slice-time correction, realignment, and unwarping. Spatial registration from functional images to T1-weighted anatomical volumes was conducted using boundary-based registration in FSL 6.0 (FMRIB software library v6.0; [fmrib.ox.ac.uk/fsl/](https://fmrib.ox.ac.uk/fsl/)) and linear and nonlinear transformations to standard Montreal Neurological Institute (MNI) template were performed using the advanced normalization tools software package.<sup>27</sup> Images were spatially resampled to a voxel size of 2 × 2 × 2 mm<sup>3</sup> and underwent spatial smoothing using a 6-mm FWHM. Denoising was performed using the Conn toolbox (version 20.b).<sup>28</sup> The signal from white matter and CSF estimated using a CompCor method<sup>29</sup> and 6 motion parameters and their first-order derivatives were regressed from the functional data. Volumes with a composite subject motion threshold of >0.5 mm or a global signal threshold of z > 3 were flagged and included as regressors in the first-level analysis. One patient with iRBD with less than 5 minutes of data remaining after scrubbing was excluded from the analysis. The residual blood oxygenation level–dependent time series were temporally bandpass filtered (0.008–0.1 Hz) and linearly detrended.

To assess how brain metabolism changes are associated with functional connectivity, the regions showing significant metabolic changes in the iRBD-MCI group compared with the iRBD-NC group were selected as seed regions (10-mm cubes around the peak coordinates). Seed-based connectivity maps were computed as the Fisher-transformed bivariate correlation coefficients between the mean time course of each seed

**Table 1** Demographic and Clinical Characteristics of Participants at Baseline

	Healthy controls	iRBD-NC	iRBD-MCI	<i>p</i> Value
<b>FDG-PET</b>				
<b>N</b>	24	19	21	
<b>Age, y</b>	69.5 ± 4.3 (58–78)	69.1 ± 5.2 (62–78)	70.5 ± 5.8 (58–80)	0.645
<b>Sex, F:M</b>	17:7	9:10	10:11	0.190
<b>Education, y</b>	11.1 ± 3.4 (5–18)	9.4 ± 5.2 (0–16)	8.7 ± 4.9 (1–18)	0.213
<b>MMSE</b>	28.5 ± 1.5 (24–30)	27.7 ± 2.1 (23–30)	26.6 ± 2.5 (23–30)	0.017 <sup>a</sup>
<b>RBD duration, y</b>		5.8 ± 4.9 (1–23)	4.0 ± 2.6 (1–10)	0.164
<b>MDS-UPDRS-I</b>		7.3 ± 4.0 (0–14)	9.7 ± 6.9 (2–29)	0.199
<b>MDS-UPDRS-II</b>		2.7 ± 3.2 (0–12)	5.3 ± 4.5 (0–17)	0.047
<b>MDS-UPDRS-III</b>		3.9 ± 3.2 (0–13)	8.3 ± 5.5 (0–18.5)	0.004
<b>MPS</b>		4 (21.1)	9 (42.9)	0.141
<b>fMRI</b>				
<b>N</b>	12	12	13	
<b>Age, y</b>	68.1 ± 4.9 (58–75)	69.3 ± 4.7 (63–76)	70.5 ± 6.1 (58–78)	0.540
<b>Sex, F:M</b>	17:7	9:10	10:11	0.311
<b>Education, y</b>	9.1 ± 3.5 (5–14)	10.5 ± 4.9 (0–16)	9.9 ± 5.7 (1–18)	0.811
<b>MMSE</b>	28.3 ± 1.9 (24–30)	28.3 ± 1.6 (26–30)	27.5 ± 2.2 (23–30)	0.426
<b>RBD duration, y</b>		5.2 ± 3.1 (1–10)	3.9 ± 3.0 (1–10)	0.318
<b>MDS-UPDRS-I</b>		7.1 ± 4.0 (0–12)	6.9 ± 3.5 (2–12)	0.915
<b>MDS-UPDRS-II</b>		2.3 ± 2.4 (0–8)	3.2 ± 2.8 (0–10)	0.395
<b>MDS-UPDRS-III</b>		3.2 ± 2.3 (0–6.5)	6.9 ± 4.5 (2–17)	0.018
<b>MPS</b>		1 (8.3)	5 (38.5)	0.078

Abbreviations: iRBD = isolated REM sleep behavior disorder; MCI = mild cognitive impairment; MDS-UPDRS = Movement Disorder Society–sponsored revision of the Unified Parkinson’s Disease Rating Scale; MMSE = Mini-Mental State Examination; MPS = mild parkinsonian signs; NC = normal cognition. Values are n (%) or mean ± SD (range).

<sup>a</sup> Healthy controls vs iRBD-MCI; *p* = 0.013.

region and the time course of all other voxels using the Conn toolbox.

### Statistical Analysis

Differences in demographic and clinical data between groups were analyzed with 1-way analysis of variance with the Tukey post hoc test, Mann-Whitney *U* test, and  $\chi^2$  test as appropriate. Voxel-wise group comparisons for FDG-PET data were performed using a general linear model (GLM) with age as a covariate of no interest (threshold-free cluster enhancement [TFCE] family-wise error [FWE] corrected; *p* < 0.05). Duration of disease was included as an additional covariate for comparisons between iRBD groups. Correlation analyses between cognitive performances and brain metabolic patterns were performed in patients with iRBD with adjustment for age and duration of disease. We inclusively masked the correlation analyses with a result map of the comparison between the

iRBD-MCI and iRBD-NC groups to focus exclusively on brain regions showing metabolic changes in the iRBD-MCI group (*p* < 0.05, FWE corrected at the cluster level; height threshold, *p* < 0.001). In addition to voxel-wise group comparisons of FDG-PET, the CIS was quantified by calculating the ratio between the mean value in the posterior cingulate gyrus region of interest (ROI) and the mean value in the precuneus plus cuneus ROI. The ROIs were defined using the Harvard-Oxford atlas. The CIS ratio compared groups using the GLM with adjustment for age and duration of disease as appropriate. Group comparisons of the functional connectivity maps were analyzed in the same manner as FDG-PET data analyses using the GLM (TFCE FWE-corrected, *p* < 0.05/17 maps = 0.003).

The association of brain glucose metabolism and cognitive function with phenoconversion in patients with iRBD was evaluated using a Cox regression analysis. For brain glucose



**Table 2** Results of Baseline Neuropsychological Tests

	Healthy controls	iRBD-NC	iRBD-MCI	<i>p</i> Value <sup>a</sup>
<b>Attention and working memory</b>				
TMT-A	-0.07 ± 0.41	0.25 ± 0.66	-1.66 ± 3.69	0.001 <sup>f</sup>
Digit span	-0.47 ± 0.69	-0.31 ± 0.57	0.34 ± 0.71	0.009 <sup>d</sup>
CWST	-0.17 ± 0.90	-0.26 ± 0.84	-1.28 ± 1.01	0.003 <sup>b,e</sup>
<b>Executive function</b>				
TMT-B	0.52 ± 0.23	-0.78 ± 3.60	-2.37 ± 2.02	<0.001 <sup>c,f</sup>
COWAT, semantic	-0.23 ± 0.91	0.19 ± 1.13	-0.61 ± 0.90	0.100
COWAT, phonemic	-0.43 ± 0.73	-0.27 ± 0.71	-1.03 ± 0.81	0.009 <sup>e</sup>
<b>Memory</b>				
SVLT, immediate recall	0.65 ± 0.94	0.24 ± 0.85	-0.58 ± 0.81	0.001 <sup>d</sup>
SVLT, delayed recall	0.43 ± 0.85	-0.20 ± 0.89	-1.12 ± 1.10	0.001 <sup>c,e</sup>
SVLT, recognition	0.83 ± 0.66	0.34 ± 0.71	-0.55 ± 1.01	<0.001 <sup>c,d</sup>
<b>Visuospatial function</b>				
RCFT	-0.92 ± 1.05	-0.88 ± 1.06	-1.98 ± 1.76	0.095
<b>Language</b>				
K-BNT	0.50 ± 0.56	0.17 ± 0.97	-0.32 ± 1.23	0.161

Abbreviations: COWAT = Controlled Oral Word Association Test; CWST = Color-Word Stroop Test; iRBD = isolated REM sleep behavior disorder; K-BNT = Korean version of the Boston Naming Test; MCI = mild cognitive impairment; NC = normal cognition; TMT = Trail-Making Test; SVLT = Seoul Verbal Learning Test; RCFT = Rey-Osterrieth Complex Figure Test.

Values are mean ± SD.

<sup>a</sup> Kruskal-Wallis test followed by Mann-Whitney *U* test using Bonferroni correction; *p* < 0.016 was considered significant (*p* = 0.05/3).

<sup>b</sup> Healthy controls vs iRBD-MCI; *p* < 0.01.

<sup>c</sup> Healthy controls vs iRBD-MCI; *p* ≤ 0.001.

<sup>d</sup> iRBD-no MCI vs iRBD-MCI; *p* < 0.01.

<sup>e</sup> iRBD-no MCI vs iRBD-MCI; *p* ≤ 0.005.

<sup>f</sup> iRBD-no MCI vs iRBD-MCI; *p* = 0.001.

metabolism, mean FDG uptake within the clusters showing significant hypometabolism in the iRBD-MCI group compared with the iRBD-NC group was extracted from each participant. The clusters were divided into anatomical structures using the Harvard-Oxford atlas. Patients with iRBD were subsequently dichotomized at 1 SD below the mean of HC for each significant structure and at 1 SD above the mean of HC for the CIS ratio. For cognitive function, the presence of MCI and scores of each neuropsychological test were included as a predictor in a separate analysis. In addition, we evaluated the effect of motor signs on a risk of phenoconversion using the presence of mild parkinsonian signs (MPS) or MDS-UPDRS-III scores as a predictor. MPS was defined as MDS-UPDRS-III score >6 excluding postural and action tremor.<sup>30</sup> The hazard ratios were adjusted for age and disease duration. The analyses were carried out with SPSS 26.0 (IBM Corp.).

### Data Availability

Upon reasonable request for research purposes, data generated and analyzed during this study are available from the corresponding authors.

## Results

### Baseline Characteristics

The demographic and clinical characteristics of the participants are presented in Table 1. Among 40 patients with iRBD, 21 patients were classified as having MCI (52.5%). There were no differences in age, sex, or years of education among HC, iRBD-MCI, and iRBD-NC groups. Between iRBD groups, there was no difference in duration of disease, but the iRBD-MCI group had significantly higher MDS-UPDRS-III scores than the iRBD-NC group. None of the patients had experienced fluctuating cognition with pronounced variations in alertness and attention or visual hallucination at baseline. There were no patients with iRBD who were treated with cholinesterase inhibitors (ChEIs). In neuropsychological tests, the iRBD-MCI group revealed significantly lower performance in attention and working memory, executive function, and memory than HC and the iRBD-NC group. The iRBD-NC group revealed no significant differences in any tests compared with HC. The results of neuropsychological testing are presented in Table 2.

**Table 3** Brain Regions Showing Hypermetabolism in the iRBD-MCI Group Compared With the iRBD-NC Group and HC

Brain region	BA	Peak coordinates			$p_{\text{FWE-corr}}$	TFCE	Cluster size (voxels)
		x	y	z			
<b>iRBD-NC &gt; iRBD-MCI</b>							
L angular gyrus	39	-52	-52	24	0.002	1,930.74	9,710
L lateral occipital, superior division	19/39	-52	-70	16	0.002	1,924.44	
L precuneus	7/31	-6	-54	16	0.002	1,916.18	
L lateral occipital, inferior division	19	-42	-80	8	0.004	1,702.57	
R occipital pole	17	10	-102	-8	0.004	1,680.82	
L middle temporal gyrus, temporooccipital part	21/22	-64	-46	4	0.005	1,630.53	
L intracalcarine cortex	17	-4	-74	10	0.006	1,569.23	
L inferior temporal gyrus, posterior division	20	-62	-44	-16	0.006	1,565.34	
R intracalcarine cortex	17	12	-78	10	0.008	1,502.88	
L occipital pole	17	-8	-98	4	0.008	1,502.42	
R angular gyrus	39	54	-60	30	0.006	1,579.57	3,963
R lateral occipital cortex, inferior division	19/39	54	-68	12	0.006	1,571.92	
R middle temporal gyrus, posterior division	21	66	-38	-14	0.008	1,495.56	
R middle temporal gyrus, temporooccipital part	37	62	-54	0	0.012	1,378.79	
L frontal pole	10/46	-16	50	20	0.022	1,213.49	1,316
R frontal pole	10	42	40	-10	0.027	1,160.15	500
R inferior frontal gyrus, pars opercularis	44/45	56	20	8	0.028	1,145.78	248
<b>HC &gt; iRBD-MCI</b>							
R occipital pole	17/18	8	-102	2	0.001	2,492.59	18,676
R lateral occipital cortex, inferior division	18/19	40	-84	-18	0.001	2,289.11	
L occipital pole	17/18	-4	-98	-6	0.002	2,242.39	
L precuneus	18	-10	-60	10	0.002	2,173.92	
R intracalcarine cortex	17	12	-78	10	0.002	2,172.70	
L lateral occipital cortex, inferior division	19	-48	-76	8	0.005	1,856.68	
L lateral occipital cortex, superior division	19	-46	-74	18	0.006	1,749.86	
R middle temporal gyrus, temporooccipital part	21	68	-42	-4	0.009	1,610.49	
R angular gyrus		56	-54	24	0.004	1,923.12	

Abbreviations: BA = Brodmann area; FWE = family-wise error; HC = healthy controls; iRBD = isolated REM sleep behavior disorder; MCI = mild cognitive impairment; NC = normal cognition; TFCE = threshold-free cluster enhancement.

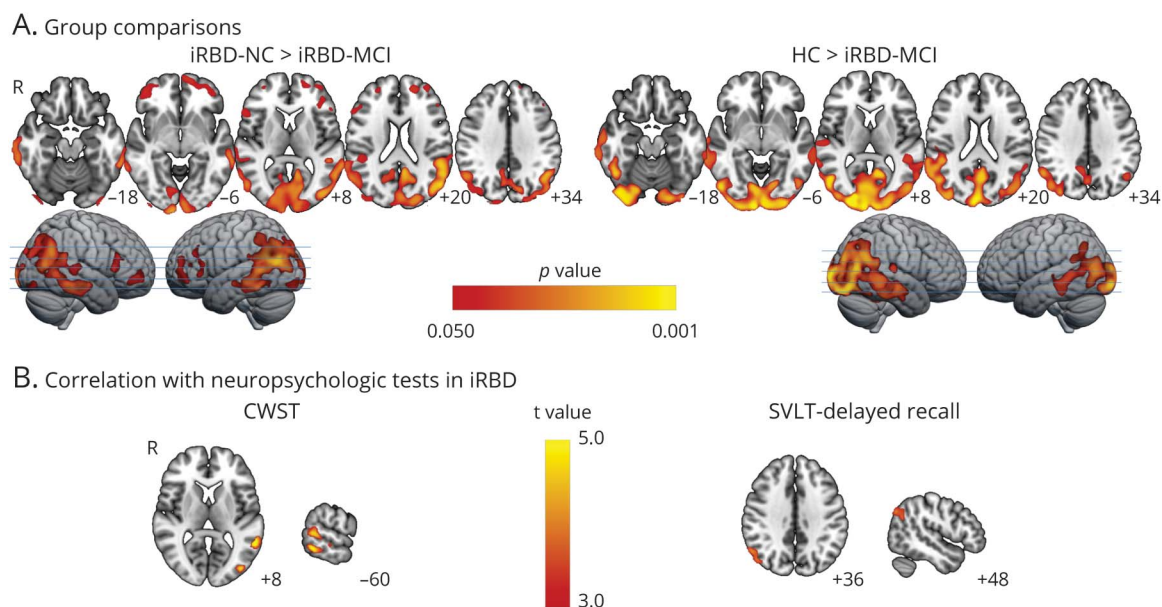
### Brain Metabolic Changes

The iRBD-MCI group revealed relative hypometabolism in the bilateral inferior parietal lobule, lateral and medial occipital cortex, precuneus, and middle and inferior temporal cortex compared with HC and the iRBD-NC group. Moreover, the iRBD-MCI group showed frontal pole hypometabolism compared with the iRBD-NC group. However, there was no significant difference in brain metabolism between HC and the iRBD-NC group (Table 3 and Figure 1A). The mean CIS ratios were  $0.871 \pm 0.031$  (HC),  $0.881 \pm$

$0.044$  (iRBD-NC), and  $0.890 \pm 0.028$  (iRBD-MCI), and there were no differences among the 3 groups ( $F_{2,60} = 2.135$ ,  $p = 0.127$ ).

For the correlation analyses with neuropsychological performance in patients with iRBD, we found significant positive correlation of CWST scores with the left temporo-occipital region ( $x = -56$ ,  $y = -50$ ,  $z = 8$ ; T value = 5.82) and those of SVLT delayed recall scores with the right angular gyrus ( $x = 54$ ,  $y = -60$ ,  $z = 36$ ; T value = 4.08) (Figure 1B).

**Figure 1** Brain Glucose Metabolism in Patients With iRBD Associated With Their Cognitive Function



(A) The isolated REM sleep behavior disorder (iRBD)-mild cognitive impairment (MCI) group revealed relative hypometabolism in the bilateral inferior parietal lobule, lateral and medial occipital, precuneus, and middle and inferior temporal cortex compared with the iRBD-normal cognition (NC) group and healthy controls (HC). (B) In patients with iRBD, the left temporo-occipital region showed positive correlation with Color-Word Stroop Test (CWST) and the right angular gyrus showed positive correlation with Seoul Verbal Learning Test (SVLT) delayed recall.

## Functional Connectivity Changes

Seventeen seed regions were defined in the brain areas showing significant hypometabolism in the iRBD-MCI group compared with the iRBD-NC group. The iRBD-MCI group exhibited reduced functional connectivity of the left angular gyrus with the bilateral lingual gyrus (MNI coordinates: left:  $x = -18$ ,  $y = -56$ ,  $z = 4$ ; right:  $22$ ,  $-56$ ,  $8$ ;  $p_{\text{FWE-corr}} = 0.001$ ), superior part of the bilateral lateral occipital cortex (left:  $-28$ ,  $-80$ ,  $26$ ,  $p_{\text{FWE-corr}} = 0.001$ ; right:  $28$ ,  $-80$ ,  $22$ ,  $p_{\text{FWE-corr}} = 0.002$ ), and inferior part of the left lateral occipital cortex ( $-40$ ,  $-80$ ,  $-18$ ,  $p_{\text{FWE-corr}} < 0.001$ ) compared with HC (Figure 2). When we compared the functional connectivity between the iRBD-NC and iRBD-MCI groups and between the iRBD-NC group and HC, there were no significant group differences in seed regions.

## Prediction of Disease Conversion

During  $4.2 \pm 2.6$  years of follow-up, 5 patients in the iRBD-NC group (1 DLB, 3 PD, 1 MSA) and 7 patients in the iRBD-MCI group (3 DLB, 4 PD) developed PD, DLB, or MSA. Between the phenoconverters and nonphenoconverters, there were no differences in their baseline demographic and clinical characteristics (Table 4). During follow-ups and before phenoconversion, 2 patients in the iRBD-MCI group were prescribed ChEIs. One patient developed PD 1 year after the start of ChEI use and the other one has maintained the diagnosis of iRBD with MCI. No patient in the iRBD-NC group was treated with ChEIs.

Cox regression analyses were performed after excluding data of a patient who converted to MSA. MCI per se did not predict phenoconversion to PD/DLB (hazard ratio [HR]

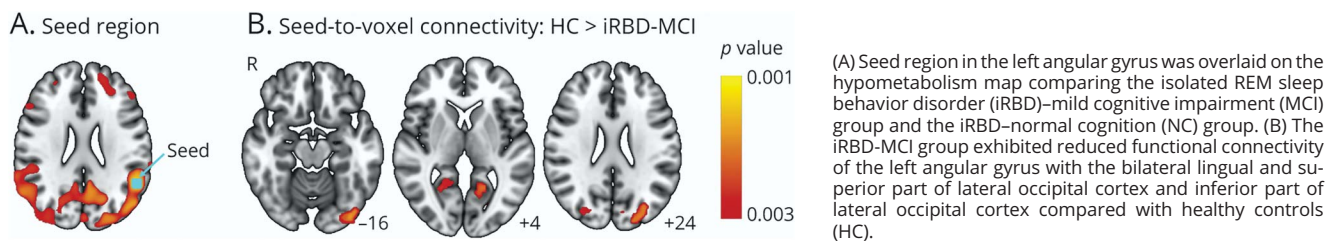
[95% CI] 1.529 [0.401–5.828],  $p = 0.534$ ). However, hypometabolism in the occipital pole (HR [95% CI] 6.652 [1.387–31.987],  $p = 0.018$ ), medial occipital (HR [95% CI] 4.450 [1.143–17.327],  $p = 0.031$ ), and precuneus (HR [95% CI] 3.635 [1.009–13.093],  $p = 0.048$ ) was associated with a higher risk of phenoconversion (Figure 3). Among the 4 phenoconverters in the iRBD-NC group, the DLB phenoconverter and 1 PD phenoconverter exhibited hypometabolism at the baseline examination in all 3 brain regions described above. Among the remaining 2 PD phenoconverters, 1 had hypometabolism in the medial occipital cortex and occipital pole, but the other showed average metabolism above the cutpoint in all 3 regions.

The CIS ratio (HR [95% CI] 1.858 [0.541–6.382],  $p = 0.325$ ), MPS (HR [95% CI] 1.533 [0.411–5.708],  $p = 0.525$ ), and the MDS-UPDRS-III score (HR [95% CI] 1.102 [0.980–1.238],  $p = 0.103$ ) did not reveal the association with higher phenoconversion rate to PD/DLB. None of the neuropsychological tests predicted phenoconversion (eTable 1, [links.lww.com/WNL/B967](https://links.lww.com/WNL/B967)).

## Discussion

The current study investigated the brain metabolic and functional connectivity changes associated with MCI in patients with iRBD. The iRBD-MCI group revealed hypometabolism in the lateral and medial occipital, middle and inferior temporal cortex, precuneus, and inferior parietal lobule compared with HC and the iRBD-NC group.

**Figure 2** Group Differences in Functional Connectivity of the Left Angular Gyrus



Decreased metabolism was also found in the frontal pole in the iRBD-MCI group compared with the iRBD-NC group. When we evaluated the functional connectivity of the brain regions showing hypometabolism in the iRBD-MCI group, functional connectivities of the left inferior parietal lobule with the bilateral medial occipital and left lateral occipital cortex were decreased in the iRBD-MCI group compared with HC. During the follow-up, 11 out of 40 patients with iRBD developed PD or DLB. The baseline brain metabolism in the medial occipital cortex, occipital pole, and precuneus predicted phenoconversion to PD/DLB in patients with iRBD.

Previous FDG-PET studies have consistently identified a specific RBD-related brain metabolic pattern (RBDRP), which was represented by relative metabolic decreases in the middle and lateral occipital, parietal, and temporal cortex and relative metabolic increases in the brainstem, cerebellum, sensory-motor cortex and hippocampus.<sup>18</sup> The relative posterior brain hypometabolism in our iRBD-MCI group considerably overlapped with the RBDRP, but we also found hypometabolism in the prefrontal area and no relative hypermetabolism in this group. On the other hand, the iRBD-NC group revealed no significant metabolic changes compared with HC. Consistent with our findings, a recent study evaluated metabolic differences among 3 groups—HC, patients with iRBD with normal cognition, and patients with iRBD with MCI—as in the present study, reporting that the iRBD with MCI group showed relative hypometabolism in the occipital, temporal, and parietal areas but patients with iRBD with normal cognition did not show any differences with the same statistical level when compared with HC.<sup>19</sup> The hypometabolism pattern in the iRBD-MCI group was distinct from regions of RBDRP and the iRBD-NC group did not reveal any different metabolism compared with HC. Therefore, we suggest that MCI in iRBD represents a different phenotype or a more progressed disease stage than iRBD-NC. Indeed, the iRBD-MCI group revealed higher MDS-UPDRS-III scores compared with the iRBD-NC group in the current study.

The hypometabolism pattern in the iRBD-MCI group is similar to patterns of metabolic changes in patients with DLB<sup>31,32</sup> as well as patients at the prodromal stages of

DLB,<sup>33,34</sup> which is characterized by medial and lateral occipital cortex hypometabolism with temporoparietal and frontal cortex hypometabolism. The DLB-related hypometabolism pattern can differentiate patients with DLB from those with AD, PD,<sup>32</sup> or other atypical parkinsonisms including corticobasal degeneration, MSA, and progressive supranuclear palsy.<sup>31</sup> A study showed that patients with PD exhibiting the DLB-related hypometabolism pattern were associated with an increased risk of developing dementia during the subsequent disease course.<sup>35</sup> Moreover, patients with PD who had MCI before developing parkinsonism exhibited relative hypometabolism in the bilateral posterior temporo-parieto-occipital area. Among them, patients who later developed dementia exhibited hypometabolism in the posterior parieto-occipital association cortex more often than those who did not

**Table 4** Baseline Characteristics of iRBD Converters and Nonconverters

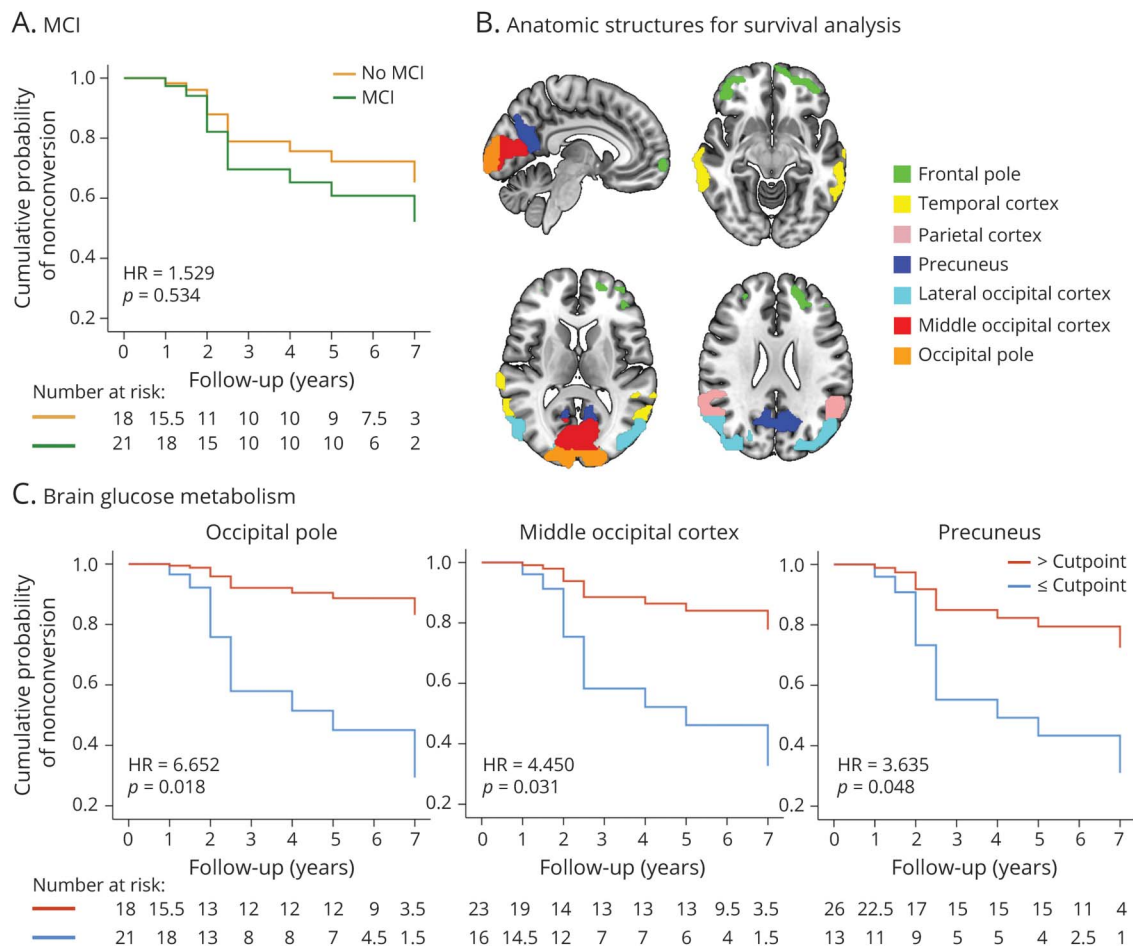
	Nonphenoconverters	Phenoconverters	<i>p</i> Value
<b>N</b>	28	12	
<b>Age, y</b>	69.0 ± 5.8	71.8 ± 4.4	0.152
<b>Sex, F:M</b>	15:13	4:8	0.311
<b>Education, y</b>	9.1 ± 5.3	8.8 ± 4.4	0.822
<b>MMSE</b>	27.1 ± 2.4	27.2 ± 2.2	0.942
<b>RBD duration, y</b>	5.3 ± 4.5	4.0 ± 2.2	0.363
<b>MDS-UPDRS-I</b>	8.4 ± 6.5	8.8 ± 3.7	0.841
<b>MDS-UPDRS-II</b>	4.0 ± 4.4	4.3 ± 3.5	0.862
<b>MDS-UPDRS-III</b>	5.6 ± 4.9	7.7 ± 5.2	0.238
<b>MPS</b>	9 (32.1)	4 (33.3)	0.941
<b>MCI</b>	14 (50.0)	7 (58.3)	0.736
<b>Follow-up, y<sup>a</sup></b>	4.6 ± 2.7	2.9 ± 1.7	0.019

Abbreviations: iRBD = isolated REM sleep behavior disorder; MCI = mild cognitive impairment; MDS-UPDRS = Movement Disorder Society–sponsored revision of the Unified Parkinson’s Disease Rating Scale; MMSE = Mini-Mental State Examination; RBD = REM sleep behavior disorder. Values are n (%) or mean ± SD.

<sup>a</sup> Time of last assessment for nonphenoconverters and conversion time for phenoconverters.



**Figure 3** Survival Curves of Phenoconversion to Parkinson Disease or Dementia With Lewy Bodies



(A) Mild cognitive impairment (MCI)–normal cognition (NC) was not associated with phenoconversion to Parkinson disease (PD)/dementia with Lewy bodies (DLB). (B) Mean FDG uptake within the clusters showing significant hypometabolism in the isolated REM sleep behavior disorder (iRBD)–MCI group compared with the iRBD–NC group was extracted from each participant. The clusters were divided into anatomical structures using the Harvard-Oxford atlas. (C) Baseline glucose metabolism in the occipital pole, medial occipital, and precuneus predicted phenoconversion to PD/DLB after adjusting for age and duration of iRBD. The cutpoint was defined as the 1 SD value of the mean  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) uptake in HC. HR = hazard ratio.

at an individual level.<sup>36</sup> These results support our observations that the metabolic changes in the iRBD–MCI group mainly characterized by hypometabolism in posterior parietal and occipital regions are associated with phenoconversion to PD/DLB.

We found that mean FDG uptake values in the medial occipital cortex, occipital pole, and precuneus are related to a high risk of phenoconversion to PD/DLB. Moreover, those brain regions already showed hypometabolism at baseline in patients who belonged to the iRBD–NC group, but later developed PD/DLB. Previous studies have consistently demonstrated that occipital hypometabolism is a robust marker for differential diagnosis between DLB and AD.<sup>32,37</sup> The hypometabolism in occipital areas also differentiated patients with MCI due to DLB from those due to AD, which suggest that the metabolic decrease could be present at a very early stage of disease.<sup>37</sup> Moreover, in a case study, patients with

probable RBD who developed DLB revealed hypometabolism in the occipital lobe and parieto-temporal cortex at baseline.<sup>38</sup> In patients with PD, incident dementia was heralded by posterior cortical hypometabolism, mainly in the occipital region.<sup>39</sup> Recently, our group reported that dnPDRBD–RP predicted cognitive decline in patients with iRBD.<sup>5</sup> The dnPDRBD–RP showed a relative metabolic decrease in the parietal and occipital cortex and precuneus, highlighting the importance of hypometabolism in posterior brain regions predicting disease progression in patients with iRBD. On the other hand, although MCI and MPS have been suggested as important predictive markers for phenoconversion to PD/DLB in patients with iRBD,<sup>40</sup> neither of them significantly associated with higher phenoconversion rate in the current study. Our relatively small sample size and short follow-up time might be associated with this inconsistency. Alternatively, many of our patients with iRBD have some degree of action tremors, which might attenuate the significance of

MDS-UPDRS-III scores. We might need to apply objective motor testing to define MPS more clearly. These results suggest that the hypometabolism patterns on FDG-PET imaging might be more sensitive or earlier markers of phenoconversion than clinically defined MCI or MPS in patients with iRBD.

Occipital hypometabolism is a distinctive pattern in patients with DLB compared with those with AD as mentioned above, while the metabolic reduction in the temporoparietal regions and precuneus represents a typical AD-related metabolic pattern.<sup>41</sup> Autopsy-confirmed AD and DLB cases showed hypometabolism in the temporoparietal and frontal association cortex in common, but only patients with DLB revealed occipital hypometabolism. Principal component analysis of regional glucose metabolism in patients with DLB revealed that the occipital hypometabolism was independent of the temporoparietal cortex or frontal cortex hypometabolism. Moreover, MMSE scores correlated with temporal, parietal, and frontal metabolic reduction, but not with occipital metabolic reduction.<sup>42</sup> Similarly, we found that patients with iRBD revealed positive correlations between cognitive performances and metabolism in the parietal and temporo-occipital cortex but not in the occipital regions. These results suggest that the occipital hypometabolism in the iRBD-MCI group may have distinct neural bases from hypometabolism in temporal and parietal regions. Neuropathologic explanation for the bases of hypometabolism may be speculative at this point, but several studies of patients with PD or DLB shed light on that matter. LB-related pathology in the occipital cortex was associated with a high risk of dementia in patients with PD or non-AD type dementia, such as DLB or corticobasal syndrome.<sup>43</sup> On the other hand, a recent amyloid imaging study in patients with DLB, PD, or PD dementia identified increased amyloid deposition in temporal, parietal, and occipital areas compared with HC, and the occipital and parietal amyloid deposition was associated with striatal dopamine depletion and a shorter latency to dementia from onset of motor symptoms, respectively.<sup>44</sup> These findings suggest that in terms of cognitive decline in patients with iRBD, the occipital hypometabolism could be more directly associated with LB-related pathology predicting future dementia, while the parieto-temporal hypometabolism might be associated with promoting disease progression. AD pathology frequently coexists with LB pathology in varying degrees, and associates with more aggressive disease course and more pronounced cognitive dysfunction in patients with PD/DLB.<sup>45</sup> Future pathologic or biomarker studies with longitudinal follow-up could elucidate the underlying mechanisms of brain metabolic alterations and the interaction between LB and AD pathologies on phenoconversion in patients with iRBD.

Although the CIS is supposed to be highly specific for differentiating DLB from AD,<sup>16</sup> we observed no differences in CIS ratios between the iRBD-MCI and iRBD-NC groups and no associations between the CIS ratios and phenoconversion

to PD/DLB. Because RBD is acknowledged as a core clinical feature of DLB and occurs typically before the onset of dementia or parkinsonism,<sup>24</sup> some patients in the iRBD-NC group might have CIS despite the absence of MCI. In the present study, CIS ratios did not reveal a difference with HC. Therefore, it also could be possible that the CIS is not evident in the prodromal stage of DLB. Because we could not analyze parkinsonism first and dementia first phenoconverters separately in Cox regression analyses, the predictive value of CIS ratio might be underestimated in our sample. On the other hand, 1 patient in the iRBD-MCI group who was treated with ChEIs has maintained the diagnosis, which suggest that we cannot ignore the possibility that ChEI treatment might be associated with delaying phenoconversion in patients with iRBD. These results of the current study suggest that a future large prospective cohort study will be needed to clarify how the CIS and the use of ChEIs relate to phenoconversion in patients with iRBD.

Using resting-state functional connectivity analysis, we found that MCI in patients with iRBD is related to disruption of the functional connectivity between the angular gyrus and occipital cortex, in addition to metabolic changes in these brain regions. This result is consistent with previous functional neuroimaging studies showing functional disruption of posterior brain regions related to cognitive dysfunction in patients with iRBD. In whole-brain functional connectivity analysis using network-based statistics, patients with iRBD revealed reduced cortico-cortical functional connectivity strength in posterior regions compared with HC, and this reduction was correlated with mental processing speed.<sup>46</sup> In seed-based approaches, functional connectivity of the left thalamus to the occipital cortex was increased in patients with iRBD compared with HC and the increased connectivity was associated with the word recognition score.<sup>47</sup> Moreover, in patients with PD, functional connectivity of brain posterior parts, prominently parietal and occipital cortex, was decreased compared with HC and the decrease in functional connectivity revealed correlation with cognitive decline.<sup>48</sup> We suggest that MCI in patients with iRBD is associated with both hypometabolism and functional disconnection of posterior brain regions and these changes may have a critical role in phenoconversion to PD/DLB.

There are several limitations to the current study. Phenoconversion in patients with iRBD was not analyzed separately by dementia first or parkinsonism first conversion because of the limited number of converted participants in the study. Although PD and DLB are distinct entities, they share similar neuropathologic and clinical characteristics.<sup>49</sup> We suggest that the occipital and precuneus hypometabolism might be a shared biomarker of phenoconversion in patients with iRBD independent of motor or dementia first. We evaluated cognitive function and brain metabolism at 1 time point in the current study, but their longitudinal changes throughout the disease course might be more associated with later development of PD/DLB.<sup>9,17</sup> To better understand the

underlying pathophysiology of neurodegeneration in iRBD, we should investigate longitudinal changes of cognitive function and brain metabolism over time and explore the relationship between them. The diagnosis of PD/DLB was not confirmed at autopsy. However, we adopted standardized clinical diagnostic criteria, which showed high specificity in an autopsy validation study.<sup>50</sup> The presence of cognitive fluctuations was based on the patients' and caregivers' reports in this study. Although this might not affect our analyses significantly, the objective evaluation of cognitive fluctuation will be allowed to further stratification of phenoconversion risk in patients with iRBD.

Cognitive impairment in patients with iRBD was related to functional and metabolic changes in posterior brain areas, particularly occipital and parietal areas. Moreover, hypo-metabolism in these brain regions was a predictor of phenoconversion. iRBD is a heterogeneous condition with a different phenoconversion diagnosis and a wide range of time to phenoconversion.<sup>40</sup> Evaluation of cognitive function and neuroimaging characteristics in patients with iRBD could be essential for monitoring phenoconversion and risk stratification for interventional trials in the future.

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## Disclosure

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## Appendix (continued)

Name	Location	Contribution
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