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Association of Nucleus Basalis of Meynert Functional Connectivity and Cognition in Idiopathic Rapid-Eye-Movement Sleep Behavior Disorder

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Background and Purpose Cognitive impairments are common in isolated rapid-eye-movement sleep behavior disorder (iRBD), in which the cholinergic system may play an important role. This study aimed to characterize the cortical cholinergic activity using resting-state functional connectivity (FC) of the nucleus basalis of Meynert (NBM) according to the cognitive status of iRBD patients.

Methods In this cross-sectional study, 33 patients with polysomnography-confirmed iRBD and 20 controls underwent neuropsychological evaluations and resting-state functional magnetic resonance imaging. Thirteen of the iRBD patients had mild cognitive impairment (iRBD-MCI), and the others were age-matched patients with normal cognition (iRBD-NC). The seed-to-voxel NBM–cortical FC was compared among the patients with iRBD-MCI, patients with iRBD-NC, and controls. Correlations between average values of significant clusters and cognitive function scores were calculated in the patients with iRBD.

Results There were group differences in the FC of the NBM with the left lateral occipital cortex and lingual gyrus (adjusted for age, sex, and education level). The strength of FC was lower in the iRBD-MCI group than in the iRBD-NC and control groups (each post-hoc $p<0.001$). The average NBM–lateral occipital cortex FC was positively correlated with the memory-domain score in iRBD patients.

Conclusions The results obtained in this study support that cortical cholinergic activity is impaired in iRBD patients with MCI. FC between NBM and posterior regions may play a central role in the cognitive function of these patients.

Keywords REM sleep behavior disorder; functional brain imaging; nucleus basalis of Meynert; cognitive function; mild cognitive impairment.

INTRODUCTION

Cognitive impairments are common in patients with isolated rapid-eye-movement sleep behavior disorder (iRBD).[1] Up to half of iRBD patients have mild cognitive impairment (MCI), and deficits in attention, executive function, episodic memory, and visuospatial function.[1] The vast majority of iRBD patients progress to develop alpha synucleinopathies, especially dementia with Lewy bodies (DLB) and Parkinson's disease (PD).[2] Unlike parkinsonism-first converters, phenoconverters who develop dementia initially show impaired cognitive function at baseline.[3]

The cholinergic system plays an essential role in various aspects of cognitive function, such as memory and attention. Loss of cholinergic neurotransmission in the cerebral cortex has been suggested as a hallmark of Alzheimer's disease (AD), which is known as the

cholinergic hypothesis,[4] and it is also evident in MCI patients before the onset of dementia.[5] Cortical cholinergic activity also known plays a central role in cognitive function in PD or DLB.[6,7]

The cholinergic system might play essential roles in cognition in patients with iRBD. A transcranial magnetic stimulation study using short-latency afferent inhibition of the motor cortex suggested that cognitive dysfunction in iRBD is related to widespread central cholinergic disruption.[8] A recent ^{11}C-donepezil positron-emission tomography (PET) study showed reduced cortical acetylcholinesterase activity (suggesting cholinergic dysfunction) in rapid-eye-movement sleep behavior disorder (RBD), with the reductions being more extensive in those with cognitive impairment (Montreal Cognitive Assessment [MoCA] score <26).[9] The cholinergic system may be altered to a greater extent in iRBD patients with MCI than in those without MCI.

The nucleus basalis of Meynert (NBM), located in the basal forebrain, is a primary source of cholinergic projections to the neocortex. Extranigral Lewy bodies are present in the NBM in the early stage of PD,[10] with loss of basal forebrain cholinergic neurons.[11] Moreover, a recent study found microglial activation, suggesting that neuroinflammation in the substantia innominata is associated with reduced cholinergic activity in iRBD.[12] Therefore, NBM alterations may affect cognitive function in iRBD patients.

Functional magnetic resonance imaging (fMRI) of the NBM has been used to measure its resting-state functional connectivity (FC) in evaluations of the basal forebrain cholinergic system.[13] Resting-state NBM FC was identified as a useful biomarker of cholinergic dysfunction in MCI patients and as a predictor of their cognitive outcome after cholinesterase inhibitor treatment.[14] A recent study of nondemented PD patients showed that reductions of FC and structural connectivity of basal forebrain cholinergic nuclei were associated with cognitive impairment.[15]

We hypothesized that resting-state NBM FC representing cortical cholinergic activity is altered in iRBD patients with MCI. This study was therefore designed to compare NBM FC between iRBD patients with MCI and age- and sex-matched iRBD patients without MCI and controls in order to identify its association with cognitive performance in these populations.

METHODS

Participants

This cross-sectional study enrolled consecutive polysomnography (PSG)-confirmed iRBD patients who visited the Sleep Clinic of Seoul National University Hospital. RBD diagnoses were based on ICSD-3 (third edition of the International Classification of Sleep Disorders) criteria.[16] Patients with 1) a neurodegenerative disease or another neurological disorder, 2) a severe medical illness, or 3) moderate-to-severe obstructive sleep apnea with an apnea-hypopnea index of >20/hr were excluded.

MCI was diagnosed based on the following Level II category of PD-MCI criteria[17]: 1) expression of a subjective cognitive complaint by the patient or caregiver in a structured interview, 2) an objective cognitive decline (>1 standard deviation below the standardized mean in two or more cognitive domains), 3) preserved activities of daily living, and 4) cognitive deficits not suitably explained by medication use or other medical/psychiatric disorders. The iRBD patients were divided into two groups based on their cognitive status: 1) iRBD patients with MCI (iRBD-MCI) and 2) age-matched patients with normal cognition (iRBD-NC). All of those with MCI had an overall Clinical Dementia Rating index[18] of 0.5.

Controls were age- and sex-matched healthy volunteers. Questionnaires and clinical interviews were applied to screen for any sleep, neurological, or psychological diseases. Those with cognitive decline were excluded from this study, defined as a score of <26 on the Mini-Mental Status Examination in the Korean version of the CERAD assessment packet (MMSE-KC) or of <24 on the MoCA-K.

Demographics and the scores on the Korean version of the Scale for Outcomes in Parkinson's Disease−Autonomic (K-SCOPA-AUT)[19] and on an RBD questionnaire (Korean version of the Rapid Eye Movement Sleep Behavior Disorder Questionnaire−Hong Kong [RBDQ-KR])[20] were reviewed for each participant. The Movement Disorder Society−sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score[21] was assessed for patients with RBD.

This study was approved by the Institutional Review Board of Seoul National University Hospital and Kyung Hee University Hospital at Gangdong (IRB Nos. 1702-150-835 and 2020-05-022, respectively). Written informed consent to participate was obtained from all participants.

Neuropsychological assessment

Global cognitive function was evaluated using the MoCA-K.[22] The Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) was used to evaluate cognitive function in detail. The CERAD-K includes 12 tests: the verbal fluency test (animal category), the 15-item Boston Naming Test, the MMSE-K, word list (WL) memory, WL recall, WL recognition, constructional praxis, constructional recall, the Trail-Making Test (TMT), the Stroop word test, and the Stroop color test.[23] The age-, sex-, and ed-

ucation-adjusted z-score[24] of each test is presented.

Image acquisition and preprocessing

We used a 3-tesla Siemens Biograph fMRI scanner (Siemens Healthcare, Erlangen, Germany) with the same protocol that was used in our previous study.[25] Prior to performing scanning, the participant was instructed to close their eyes and relax, but not to fall asleep. Acquired images were inspected by a radiologist for any technical problems during acquisition and for structural lesions.

The first 10 resting-state fMRI scans were excluded due to magnetic field saturation, and the subsequent images were processed using Statistical Parametric Mapping (SPM) software (version 12, Wellcome Department of Cognitive Neurology, London, UK) and the CONN-fMRI FC toolbox (version 19c, https://www.nitrc.org/projects/conn[26]), as in our previous study.[25] The default preprocessing pipeline involving the CONN toolbox was used to preprocess the remaining 170 functional images. Those with excessive head motion (translation >2.5 mm or rotation >2.5° in any direction) were excluded from the analysis.

Seed region of interest

The region of interest (ROI) of the NBM was based on stereotaxic probabilistic maps of the Ch4 cell groups in the basal forebrain,[27] which were obtained from the SPM Anatomy Toolbox[28] (version 2.2c) (Supplementary Fig. 1 in the online-only Data Supplement). Probabilistic maps were created from the histological analysis of 10 postmortem human brains, which describes the anatomic probability of the ROI in the Montreal Neurological Institute reference anatomic space.[29] A mask was created by combining the probability masks, resampling to functional space, and applying thresholding at a >40% probability, as in a previous study.[30]

Seed-to-voxel FC analysis

Second-level seed-to-voxel analysis was preformed to measure NBM–cortical FC using the Harvard-Oxford atlas in the CONN toolbox[26] after the preprocessing step. The temporal correlations between the blood oxygen level dependent signals of the NBM and other voxels in the whole brain were computed using Pearson's bivariate correlation analyses. One-way analysis of variance with a generalized linear model was used to evaluate differences in the FC patterns between the groups using age, sex, and education level as covariates. Significant clusters were identified based on a criterion of $p<0.05$ for the familywise-error-corrected probability.

Statistical analyses

The Kruskal-Wallis test was used to evaluate differences in demographics and cognitive measures between the three groups (iRBD-MCI, iRBD-NC, and controls), with Mann-Whitney U tests used for post-hoc analysis. Chi-square tests were used to analyze categorical data. Pearson correlation coefficients were calculated to assess the association between aberrant NBM–cortical FC and cognitive performance in iRBD patients regardless of the MCI status. The significance cutoff was set to 0.05, and the Bonferroni-corrected p-value was used for post-hoc and correlation analyses. SPSS (version 22.0; IBM Corp., Armonk, NY, USA) was used for statistical analyses.

Table 1. Demographics and clinical characteristics of the study subjects

Characteristic	Controls (n=20)	iRBD-NC (n=20)	iRBD-MCI (n=13)	p*	Post-hoc analysis (p<0.017)
Age (yr)	68.1±3.4	70.6±3.6	69.6±8.9	0.166	
Sex, male	11 (55.0)	12 (60.0)	7 (53.8)	0.925	
BMI (kg/m^2)	22.8±2.5	23.1±2.6	24.7±3.1	0.121	
Education level (yr)	14.1±2.3	11.8±4.4	12.7±3.0	0.191	
iRBD duration (yr)	n.a.	6.5±3.1	8.5±3.0	0.061	
MDS-UPDRS motor score	n.a.	2.1±2.3	1.8±2.2	0.521	
RBDQ-KR score	4.1±2.8	38.5±17.9	46.1±23.1	<0.001	MCI=NC>C
K-SCOPA-AUT					
Total score	6.5±5.0	12.9±7.9	14.9±8.2	0.002	MCI=NC>C
GI subscore	1.4±1.8	4.3±3.0	4.3±2.6	0.001	MCI=NC>C
Urinary subscore	3.0±2.0	5.0±3.1	6.4±3.7	0.005	MCI>C

Data are mean±standard-deviation or number (percentage) values.
*Analysis of covariance; independent t-test for iRBD duration and MDS-UPDRS motor score.
BMI, body mass index; C, controls; GI, gastrointestinal; iRBD, isolated rapid-eye-movement sleep behavior disorder; K-SCOPA-AUT, Korean version of the Scales for Outcomes in Parkinson's Disease–Autonomic; MCI, mild cognitive impairment; MDS-UPDRS, Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale; n.a., not applicable; NC, normal cognition; RBDQ-KR, Korean version of the Rapid Eye Movement Sleep Behavior Disorder Questionnaire–Hong Kong.

Table 2. Neuropsychological performance of the study subjects

	Controls (*n*=20)	iRBD-NC (*n*=20)	iRBD-MCI (*n*=13)	*p*	Post-hoc analysis (*p*<0.017)
MoCA-K score	27.4±1.2	27.6±2.0	24.2±2.7	0.001	MCI<NC=C
CERAD-K z-score					
Verbal fluency	0.31±1.01	0.29±1.00	-0.41±0.75	0.083	
Boston Naming Test score	0.82±0.60	0.93±0.61	0.47±0.53	0.092	
MMSE-K score	0.80±0.50	0.58±0.50	0.24±0.56	0.023	MCI<C
WL memory z-score	0.33±1.08	0.69±0.60	-0.41±0.80	0.003	MCI<NC
WL recall z-score	0.16±1.10	0.27±0.89	-1.04±0.67	<0.001	MCI<NC=C
WL recognition z-score	0.39±0.49	0.18±0.55	-1.22±1.24	<0.001	MCI<NC=C
Constructional praxis score	0.44±0.34	0.54±0.47	0.17±1.12	0.408	
Constructional recall score	0.90±0.49	0.59±0.84	-0.15±1.01	0.008	MCI<C
TMT-A score	1.23±0.37	1.09±0.41	0.85±0.47	0.023	MCI<C
TMT-B score	0.78±1.23	0.84±1.00	-0.32±1.55	0.103	
Stroop word test score	0.67±0.72	0.88±0.86	0.16±0.91	0.041	
Stroop color test score	0.57±0.78	0.32±0.94	-0.31±0.60	0.010	MCI<C

Data are mean±standard-deviation values.
C, controls; CERAD-K, Korean version of the Consortium to Establish a Registry for Alzheimer's Disease; iRBD, isolated rapid-eye-movement sleep behavior disorder; MCI, mild cognitive impairment; MMSE-K, Korean version of the Mini-Mental State Examination; MoCA-K, Korean version of the Montreal Cognitive Assessment; NC, normal cognition; TMT, Trail-Making Test; WL, word list.

RESULTS

Patient characteristics

Data from 13 iRBD-MCI patients, 20 age-matched iRBD-NC patients, and 20 age- and sex-matched controls were analyzed. Twenty of the patients (12 iRBD-NC and 8 iRBD-MCI) and 15 of the controls also participated in our previous study.[25] The disease duration tended to be longer (p=0.061) in the patients with MCI than in those with NC. The RBDQ-KR and SCOPA-AUT total scores were higher in those with iRBD than in controls regardless of the MCI status (Table 1). The MDS-UPDRS motor score and the video PSG results were similar in the two groups (Supplementary Table 1 in the online-only Data Supplement).

Neuropsychological assessment

The MoCA-K score was lower in patients with iRBD-MCI than in the controls and the iRBD-NC patients (each post-hoc p=0.001). CERAD-K z-scores were lower in the patients with iRBD-MCI than in controls and iRBD-NC patients for WL recall (each post-hoc p<0.001) and WL recognition (post-hoc p<0.001 and p=0.002, respectively). The z-scores for MMSE-K (post-hoc p=0.007), constructional recall (post-hoc p=0.003), TMT-A (post-hoc p=0.008), and Stroop color test (post-hoc p=0.003) were lower for iRBD-MCI than for controls. WL memory (post-hoc p<0.001) scores were lower for iRBD-MCI than for iRBD-NC (Table 2).

NBM–cortical FC changes in patients with iRBD-MCI

NBM FC differed among the three groups within the two clusters in the occipital regions (left lateral occipital cortex and bilateral lingual gyrus) after adjusting for age, sex, and education level (Fig. 1A, Table 3). The strength of NBM FC was lower in the iRBD-MCI group than in the control group (each post-hoc p<0.001) and the iRBD-NC group (each post-hoc p<0.001). FC was similar in the iRBD-NC patients and controls (Fig. 1B).

Cognitive correlates of NBM–occipital cortex FC in patients with iRBD-MCI

We evaluated the correlations between the strength of NBM–cortical FC and the MoCA-K score or CERAD-K z-score in all patients with iRBD. A positive correlation was observed between the strength of NBM FC in the two regions and the z-scores for WL memory (r=0.492 and p=0.004 for left lateral occipital cortex; r=0.570 and p=0.001 for lingual gyrus) and WL recognition (r=0.449 and p=0.009, and r=0.527 and p=0.002, respectively). Positive correlations were also found between the NBM–left occipital cortex FC and MoCA-K score (r=0.521, p=0.002) and WL recall z-score (r=0.619, p< 0.001) (Fig. 2).

DISCUSSION

To elucidate the cholinergic mechanism of cognitive impairment in iRBD, we investigated the detailed cognitive function and resting-state FC with respect to the NBM seed in

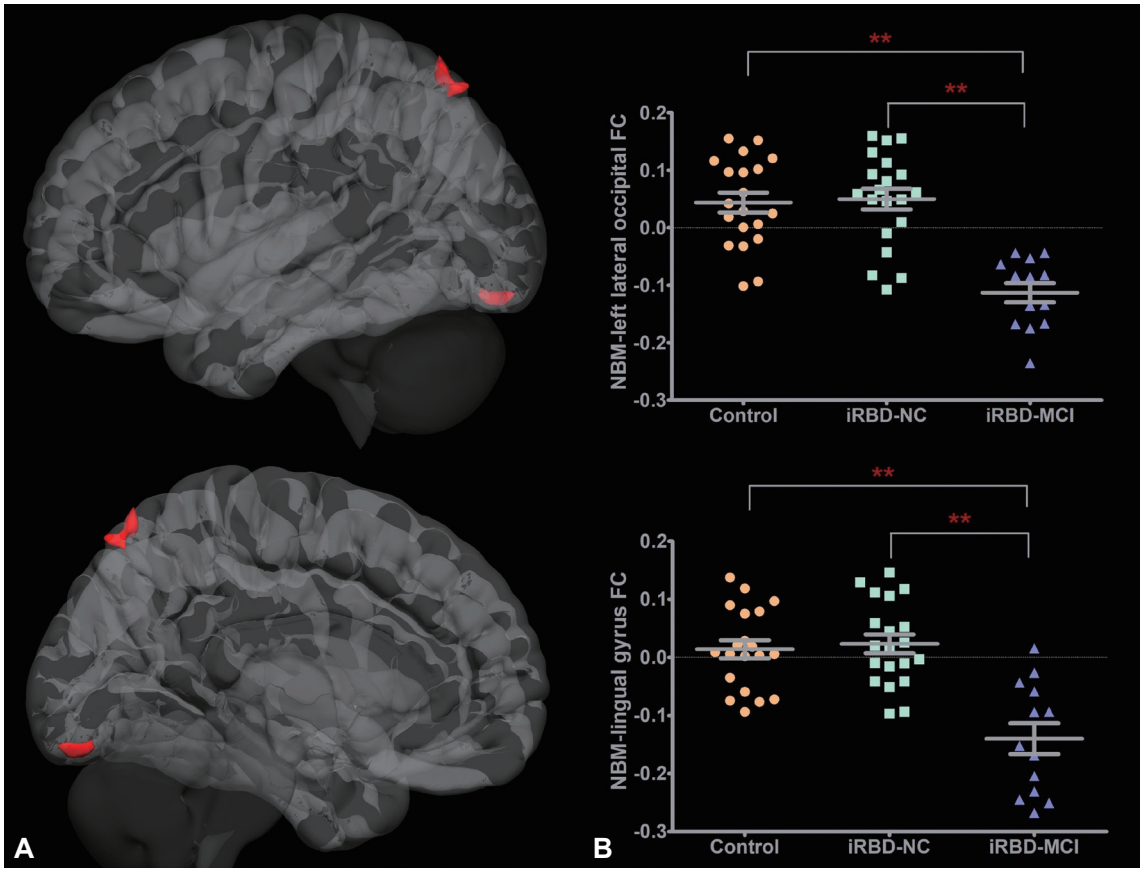

Fig. 1. Altered nucleus basalis of Meynert (NBM)–cortical functional connectivity (FC) in isolated rapid-eye-movement sleep behavior disorder (iRBD) patients with mild cognitive impairment (MCI) (iRBD-MCI), iRBD patients with normal cognition (NC) (iRBD-NC), and controls. A: Statistical maps of the regions where FC with the right NBM differed significantly different among the three groups. B: Average FC values of the NBM to the left lateral occipital cortex and the bilateral lingual gyrus among controls, iRBD-NC patients, and iRBD-MCI patients. $^{**}p<0.01$, post-hoc Bonferroni test.

Table 3. Between-group differences in right nucleus basalis of Meynert functional connectivity (seed-to-voxel connectivity adjusted for age, sex, and education level)

Coordinates (MNI)			Peak region	Cluster size	Peak *p* (uncorr)	Size *p* (FWE)
x	y	z				
-10	-78	+56	Left lateral occipital cortex	135	0.000004	0.000058
+10	-90	-12	Lingual gyrus	94	0.000013	0.001176

FWE, familywise-error-corrected value; MNI, Montreal Neurological Institute reference anatomic space; uncorr, uncorrected value.

patients with iRBD. The FC between the NBM and occipital regions—including the left lateral occipital cortex and bilateral lingual gyrus—was lower in patients with iRBD-MCI than in the controls and the iRBD-NC patients. Positive correlations were found between the strength of NBM FC and the MoCA-K score and the WL memory, WL recall, and WL recognition z-scores in patients with iRBD.

Our study supports that cholinergic dysfunction plays a role in cognitive impairment in iRBD. The cholinergic system is reportedly associated with both cognitive impairment and RBD, because the cholinergic brainstem structure including the pedunculopontine and laterodorsal tegmental nuclei are involved in the pathogenesis of RBD. RBD was found to be associated with cholinergic degeneration in patients with PD. PET studies with radiotracers specific for acetylcholine transporters[31] or acetylcholinesterase[9] showed altered cerebral cholinergic activity in iRBD. The cholinergic and dopaminergic systems play central roles in cognition in synucleinopathies, according to the so-called dual-syndrome hypothesis.[7]

The occipital regions are associated with cognitive decline in PD and DLB. The posterior–anterior gradient of the cortical cholinergic deficit has been reported to be related to cognitive function in PD. PD patients without dementia showed a decrease in vesicular acetylcholine transporter uptake only in the parietal and occipital lobes, whereas those

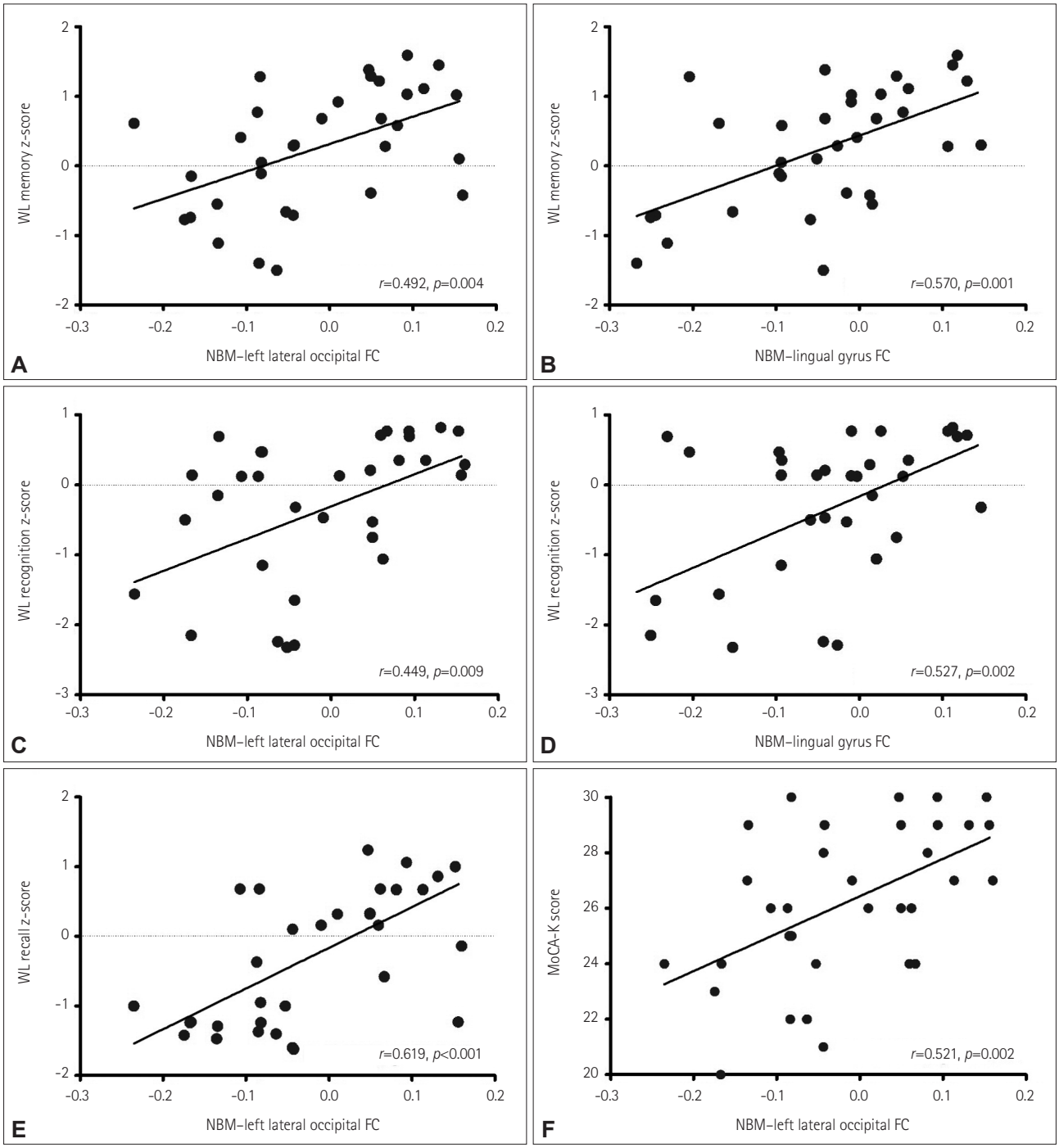

Fig. 2. Correlations of the average functional connectivity (FC) values of the nucleus basalis of Meynert (NBM) to the left lateral occipital cortex and lingual gyrus with cognitive performance in patients with isolated rapid-eye-movement sleep behavior disorder (iRBD). A and B: Correlations of the word list (WL) memory z-score with NBM–left lateral occipital cortex FC (A) and NBM–lingual gyrus FC (B). C and D: Correlations of the WL recognition z-score and NBM–left lateral occipital cortex FC (C) and NBM–lingual gyrus FC (D). E and F: Correlations of the NBM–left occipital cortex FC with the WL recall z-score (E) and MoCA-K (Korean version of the Montreal Cognitive Assessment) score (F).

with dementia showed extensive decreases across the entire cerebral cortex.[32] Another PET study found that PD patients in the early stage had reduced cholinergic function, particularly in the medial occipital cortex, which was more widespread in both PD dementia and DLB.[33] The NBM intermediate subregion is known to have projections to occipital regions, and patients with early PD show greater deficits in this subregion.[11] A recent study showed that NBM–occipi-

tal cortex and NBM–lingual gyrus connectivities are more specific to DLB than to PD dementia.[34] Moreover, NBM–occipital cortex FC in Lewy body dementia patients differed from those in patients with AD and controls.[35] The results of the present study suggest that MCI in iRBD shares common FC changes involving occipital regions, as in other synucleinopathies.

Occipital regions are known to be associated with cognitive decline in iRBD. A topographical analysis of cortical cholinergic denervation using ^{11}C-donepezil PET revealed greater denervation involving the occipital cortex in patients with iRBD,[9] which supports the findings of our study. Functional connectome analysis using network-based statistics also revealed that corticocortical FC was weaker in the posterior regions associated with mental processing speed.[36] We previously reported that enhanced thalamo-occipital FC in iRBD was associated with cognitive function.[25] The pedunculopontine nucleus is involved in rapid-eye-movement sleep generation, and it directly projects to the forebrain cholinergic system and indirectly projects to thalamocortical projections.[6] Increased thalamo-occipital FC may represent functional compensation for cholinergic deficits involving the occipital regions. Moreover, longitudinal neuroimaging studies have suggested that occipital regions are associated with progression to neurodegenerative disorders in iRBD.[37]

The strength of NBM–left lateral occipital cortex FC and NBM–lingual gyrus FC was associated with memory tasks—including WL memory, WL recall, and WL recognition performance—in patients with iRBD but not with TMT-A or Stroop color test scores. Episodic memory may be more closely involved with cholinergic function than executive function and attention.[38] The lateral occipital cortex reacts to object shape and processes higher-level shape information.[39] Damage to the left lateral occipital cortex can result in pure alexia, which suggests that the regions play a role in reading and recognizing characters.[40] The lingual gyrus is associated with the process of semantic relatedness. One structural MRI study suggested that the lingual gyrus volume is an important neural marker of long-term visual memory storage.[41]

The present study is the first to evaluate the significance of the cholinergic system on cognitive impairment in patients with iRBD. However, it involved a single center and only a small number of patients with MCI, which means that the results might not be generalizable. Moreover, its cross-sectional design may mean that its results are not representative of ongoing neurodegenerative processes associated with alpha-synucleinopathy. The cross-sectional design further means that the altered NBM FC observed might not have been causally related to cognitive impairment in iRBD. Moreover it may be related to age-related amyloid pathology, not to prodromal Lewy body dementia. Although the controls were extensively screened for sleep and cognitive disorders, they did not undergo PSG.

In conclusion, this study suggests that reduced cortical cholinergic activity plays a central role in cognitive impairment in iRBD. FC changes might be useful as biomarkers of cognitive decline. Future longitudinal studies involving larger numbers of patients are needed to elucidate the causality of FC changes and cognitive decline in iRBD patients.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.5.562.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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