Cortical connectivity of cholinergic basal forebrain in Parkinson's disease with mild cognitive impairment

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Background: Cholinergic basal forebrain (BF) pathology is a hallmark of Parkinson's disease (PD) with mild cognitive impairment (PD-MCI). Assessment of functional connectivity (FC) of different cholinergic BF nuclei may deepen the understanding of PD-MCI pathogenesis.

Methods: Seed-based FC analysis was performed with bilateral medial septal nucleus, the nucleus of the vertical limb of the diagonal band, nucleus of the horizontal limb of the diagonal band (Ch1-3), and the nucleus basalis of Meynert (NBM/Ch4) to explore the BF functional alterations in different frequency bands. Correlations between FC values of abnormal regions and scores of cognitive domains and depression in the PD group were also assessed.

Results: For the right Ch4, in the conventional frequency band, the PD-MCI group exhibited lower FC values in the right middle cingulate and paracingulate gyri, middle frontal gyrus, left inferior parietal gyrus, and superior frontal gyrus compared with healthy controls (HC), and in the left calcarine fissure and surrounding cortex compared with PD with normal cognition (PD-NC). For the slow 4 subbands, the PD-MCI group showed significantly lower FC values in the left putamen, middle frontal gyrus, right middle frontal gyrus, and precuneus compared with HC, and in right middle frontal gyrus cingulate and paracingulate gyri compared with the PD-NC group. For the slow 5 subbands, the PD-MCI group showed increased FC values in the right calcarine fissure and surrounding cortex, and left cerebellum. For the left Ch1-3, FC values in the right middle cingulate and paracingulate gyri were lower in patients with PD-MCI than in the PD-NC group in slow 4 subbands. Furthermore, altered FC values in the cortical regions for Ch4 seed were possibly correlated with depression and different cognitive domain scores.

Conclusions: The study identified an imbalanced association between different cholinergic BF nuclei and cortical regions in patients with PD-MCI, and showed that FC changes are frequency-specific, which may provide new insights into functional alterations within the cholinergic system in cognitive impairment

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associated with PD.

Introduction

Cognitive impairment is the most common non-motor symptom of Parkinson's disease (PD) and is associated with severely reduced quality of life (1,2). PD with mild cognitive impairment (PD-MCI), the early-stage cognitive deficit of PD, is a known risk factor for PD with dementia (PDD). According to previous studies, more than 80% of patients with PD and 90% of patients with PD-MCI gradually develop PDD in the late stages (3). Therefore, early identification of cognitive impairment in PD may provide a window of time to intervene and delay the progression to PDD. However, the mechanism of cognitive impairment in PD is unclear, and it may be affected by multiple factors, such as Lewy body deposition, Alzheimer-type pathology, and dysfunction of neurotransmitter systems. The dual syndrome hypothesis states that cholinergic deficit probably leads to dementia in PD (4). Therefore, it is very important to explore the role of the dysfunction of cholinergic basal forebrain (BF) in patients with PD-MCI.

The BF contains cholinergic cell populations in the brain, which are the major source of cholinergic fibers to the hippocampus, amygdala, and cortex (5). The BF consists of 4 different subdivisions, namely, the medial septal nucleus (Ch1), the nucleus of the vertical limb of the diagonal band (Ch2), the nucleus of the horizontal limb of the diagonal band (Ch3), and the nucleus basalis of Meynert (NBM/Ch4) (6). Among these subdivisions, Ch4 provides most of the projections to the amygdala and several cortical regions, whereas the hippocampus receives projections from Ch1-2 and the olfactory bulb from Ch3 (5). Previous studies have shown that Ch4 is impaired specifically in PD (7), and that Ch4 atrophy correlates with cognitive impairment progression in PD (8,9). Moreover, decreased functional connection has been found between Ch3-4 and the cortex in PD (10). However, in PD-MCI, the change of functional connection between BF and its subdivisions, especially the Ch4, is still unknown. Previous studies have utilized bilateral Ch4 as a region of interest (ROI) to investigate functional connectivity (FC) (10). However,

impaired awareness in mild cognitive impairment (MCI) predicted [18F] fluorodeoxyglucose hypometabolism in the left BF but not in the right BF over a 24-month period (11), which may indicate the difference in the left and right BF in neurodegenerative diseases.

Moreover, previous studies have indicated that different frequency bands of neural activity in the brain can be used to reflect distinct physiological functions of brain activity (12,13). The low-frequency range has been subdivided into 4 subfrequency bands, among which gray matter (GM) signals are mainly concentrated on the slow 4 (0.027–0.073 Hz) and slow 5 (0.01–0.027 Hz) subbands. Recent studies have suggested frequency-specific FC changes in other neurological disorders and shown that FC in functional magnetic resonance imaging (fMRI) with specific frequency bands might provide sensitive information on pathophysiological mechanisms (14). Wang *et al.* found that patients with amnestic MCI showed decreased FC of their brain connectome in the frequency interval 0.031 to 0.063 Hz (15). The amplitude of low-frequency fluctuations in the inferior temporal gyrus and middle frontal gyrus in slow 4 was found to provide the highest classification accuracy in distinguishing patients with PD with freezing of gait from those with PD without freezing (16). However, little is known about FC of BF in patients with PD-MCI with different frequency bands. Therefore, we conducted resting-state functional magnetic resonance imaging (rs-fMRI) analyses in early-stage cognitive impairment of patients with PD, followed by seed-based analysis to explore the FC of BF and its subdivisions in each hemisphere. The following article is presented in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-582/rc).

Methods

Participants

In this retrospective study, to control for the potentially confounding effects of age and gender on FC, 66 patients

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┌─────────────────────────────────────────┐
│ 69 patients with PD and 37 healthy       │
│ controls were enrolled into this study   │
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              │
              │        ┌─────────────────────────────────┐
              │───────▶│ Clinical data of 3 healthy      │
              │        │ controls was incomplete         │
              │        └─────────────────────────────────┘
              ▼
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│ MRI scanning was performed in 69 patients│
│ with PD and 34 healthy controls          │
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              │        ┌─────────────────────────────────┐
              │───────▶│ 3 patients with PD and 1 healthy│
              │        │ control moved their heads during│
              │        │ MRI scanning                    │
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│ 66 patients with PD and 33 healthy       │
│ controls were used for fMRI analysis     │
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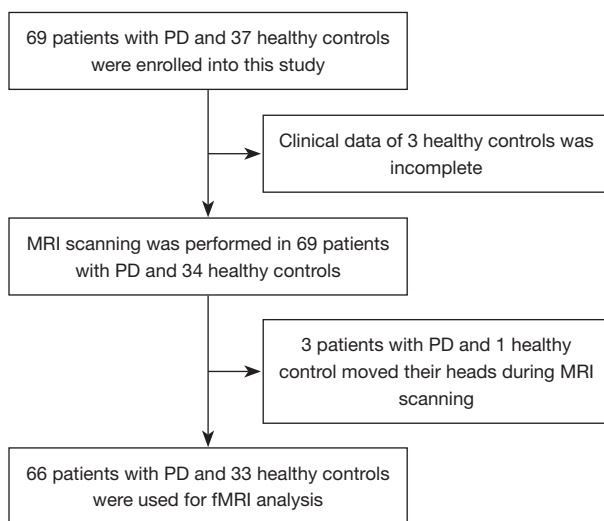
Figure 1 Flowchart of participants inclusion in this study. PD, Parkinson's disease; fMRI, functional magnetic resonance imaging.

with PD and 33 age- and sex-matched healthy controls (HC) were recruited from the outpatient and inpatient clinics of the Department of Guangdong Neuroscience Institute, Guangdong Provincial People's Hospital, between October 2017 and January 2020. The participant recruitment process flowchart is displayed in *Figure 1*. The same sample of patients and controls were analyzed in our previous study from the perspective of fractional amplitude of low-frequency fluctuation and degree centrality (17). The educational level of participants enrolled in this study was higher than primary school to control for the potentially confounding effect of years of education on cognitive assessment. All patients with PD enrolled in this study were clinically diagnosed according to the Queen Square Brain Bank criteria (18). In addition, the onset age of PD was over age 50 for all patients. The exclusion criteria were as follows: Hoehn and Yahr (H-Y) stage >3, Hamilton Anxiety Scale (HAMA) >29 points, Hamilton Depression Scale (HAMD) >35 points, use of acetylcholinesterase inhibitors drugs, other diagnosed neurological diseases, and tumors and dementia according to the Movement Disorders Society criteria (19). The levodopa equivalent dose of each patient with PD was calculated according to the formula: $LEED = $ levodopa dose + levodopa dose × 1/3 if on entacapone + piribedil (mg) + controlled release levodopa (mg) × 0.75 + pramipexole (mg) × 100 + selegiline (mg) × 10 + amantadine (mg). The Mini-Mental State Examination (MMSE) was used to assess the cognitive

function of participants, and only those whose MMSE scores were higher than the cut-off value of the Chinese version of the instrument were recruited as HC (20). All participants signed informed consent prior to the study, which was in accordance with the ethical standards of the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2018338H [R1]).

Clinical and neuropsychological evaluation

The Movement Disorder Society-sponsored Revision of the Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III) and H-Y scale were used to evaluate the severity of symptoms of patients with PD (21). The HAMA and HAMD were used for neurobehavioral assessment (22,23). Global cognitive function was evaluated using the MMSE and Montreal Cognitive Assessment (MoCA) (24). According to the Level II criteria of the MDS Task Force guidelines, participants with a score ≥1.5 standard deviation (SD) below the mean in at least 2 tests in 5 domains were identified as having PD-MCI (25). Executive functions were evaluated using the picture arrangement from the Wechsler Adult Intelligence Scale (WAIS-R) (26) and animal fluency test from the MoCA; memory was evaluated by immediate memory and logical memory tests from the Wechsler Memory Scale (WMS) (27); attention and working memory were evaluated using digit symbol and digit span tests from the WAIS-R; language was evaluated using the vocabulary and similarities subtests from the WAIS-R; visuospatial function was evaluated using block design and object assembly from the WAIS-R. Accordingly, 66 patients with PD were divided into 2 groups: 42 patients with PD with normal cognition (PD-NC) and 24 patients with PD with mild cognitive impairment (PD-MCI).

Neuroimaging

Magnetic resonance imaging (MRI) data acquisition and protocol

MRI data acquisition and postprocessing were conducted as described previously (17). Briefly, a 3.0 T scanner with an 8-channel head coil (Signa Excite HD; GE Healthcare, Milwaukee, WI, USA) was used to collect MRI data. To avoid pharmacological effects on neural activity, all patients with PD completed MRI scans in the morning during OFF state without taking antiparkinsonian medications for >12 h. High-resolution 3D T1-weighted images were

acquired with repetition time (TR) =8.4 ms, echo time (TE) =3.3 ms, matrix =256×256, flip angle =13°, slice thickness =1 mm, and voxel size =0.94 mm × 0.94 mm ×1 mm).

All participants were asked to keep their eyes open and rest quietly during rs-fMRI scanning. rs-fMRI was performed with gradient-echo echo planer imaging (GRE-EPI) sequence [TR: 2,000 ms, TE: 30 ms, field of view (FOV): 240×240 mm, matrix: 64×64, slice thickness: 4 mm, voxel size: 3.75 mm × 3.75 mm × 4 mm, interslice space: 1 mm, NEX:1, and time points: 186, 5,580 images, and 30 axial slices covering the entire brain were acquired]. Axial scans were parallel to the anterior-posterior commissure (AC-PC) line.

MRI data preprocessing

The rs-fMRI data analyses were carried out with SPM12 software (http://www.fil.ion.ucl.ac.uk/spm) and RESTplus Version 1.2 (http://www.restfmri.net/forum/RESTplusV1.2) on the Matlab 2014a platform as previously described (17). To eliminate the scanner noise, the first 10 time points were removed. Next, slice timing, realignment, and spatial normalization were performed when preprocessing the data. All individual structural images were coregistered to the mean functional image and then were segmented into GM, white matter (WM), and cerebrospinal fluid (CSF). The realigned functional images of all participants were normalized with DARTEL into the standard Montreal Neurological Institute space. The normalized functional images were sampled to 3 mm × 3 mm × 3 mm. After removing the linear trend, head motion parameters, WM signal, and CSF signal were regressed out as covariates. Band-pass filtering was performed to exact fMRI signals in conventional (0.01–0.08 Hz) and subfrequency bands, including slow 5 (0.01–0.027 Hz), and slow 4 (0.027–0.073 Hz). Time courses were filtered using a (0.01–0.08 Hz) band to reduce high-frequency noise and low-frequency drifts.

There are 5 subfrequency bands in the full frequency range (0–0.25 Hz): slow 2: 0.198–0.25 Hz, slow 3: 0.073–0.198 Hz, slow 4: 0.027–0.073 Hz, slow 5: 0.01–0.027 Hz, and slow 6: 0–0.01 Hz. In this study, frequency-specific FC changes were performed. Therefore, in addition to the conventional frequency band (0.01–0.08 Hz), the subfrequency bands (including slow 4 and slow 5) were finally chosen to be further investigated, because slow 2, slow 3, and slow 6 subbands were affected by WM signals, low-frequency drifting, and high-frequency physiological noise (18,19).

Seed-based FC analysis

We selected the 4 ROIs including bilateral Ch1-3 and Ch4 to investigate FC. The BF consists of magnocellular cholinergic cell complex and is divided histologically into Ch1, Ch2, Ch3, and Ch4 (2). The masks of bilateral Ch1-3 and Ch4 were identified using probabilistic anatomical map obtained from the SPM Anatomy Toolbox (27,28). The probabilistic anatomical map is based on microscopic delineations of postmortem human brain and has been made available (28). The bilateral Ch1-3 and Ch4 were created using the SPM Anatomy Toolbox. We used DPABI Version 4.0 toolkit (http://rfmri.org/dpabi) to analyze seed-based FC. An automated anatomical labeling (AAL) atlas, dividing the brain into 116 cortical and subcortical ROIs, was employed to define the brain areas (29). The mean time series across all voxels within ROIs were obtained for each participant and each seed. The correlation coefficients, which were acquired between the mean time series and the time series of each other voxels in the whole brain, were converted to z scores using Fisher's z transformation. The zFC maps were smoothed with a 4-mm FWHM isotropic Gaussian kernel. The value of each voxel throughout the whole brain represents the relative degree of FC with each seed.

The bilateral Ch1-3 and Ch4 volume was estimated using the same probabilistic anatomical map as previously described (30). Briefly, the brain was segmented into gray matter, WM, and CSF using the segmentation routine of the voxel-based morphometry (http://www.neuro.uni-jena.de/vbm/download/) and implemented in MATLAB R2018b (MathWorks, Natick, MA, USA). The segmented GM and WM were registered and normalized to Montreal Neurological Institute space using SPM's DARTEL algorithm. The bilateral Ch1-3 and Ch4 volumes were calculated and normalized with respect to total intracranial volume.

Statistical analysis

The software SPSS =25.0 (IBM Corp., Armonk, NY, USA) was used to perform statistical analyses. Normality of each clinical variable was tested using the Kolmogorov–Smirnov test. Then, age, bilateral Ch1-3, and Ch4 volume were compared using one-way analysis of variance (ANOVA); education, HAMA, HAMD, MMSE, and MoCA were compared using the Kruskal–Wallis H test; the Mann–Whitney U test was used to compare differences in duration of disease, LEDD, MDS-UPDRS-III, picture

arrangement, immediate memory, logical memory, digit symbol, vocabulary, similarities, block design, and object assembly test in PD-NC and PD-MCI; and the animal fluency test and digit span test were compared using the 2-sample t-test. Since the effects of head motion on FC were observed, mean framewise displacement (mFD) was calculated according to previous studies (31), and compared using the Kruskal–Wallis H test. The chi-square test was used to compare categorical variables.

To investigate differences in connectivity in these four ROIs among groups, 2-sample t-tests were performed using REST. If thresholds were given for each voxel, Monte Carlo simulations were used to define the random cluster size distribution. The resultant T-maps were thresholded using the Gaussian random field theory (GRF) correction (voxel $P<0.005$, cluster $P<0.05$) for multiple comparisons according to the distribution.

Correlations between FC and the clinical and neuropsychological evaluation were calculated. FC values (Z values) were extracted from regions that showed significant differences in connectivity to these four ROIs. Subsequently, to explore the relationship between the FC abnormalities and the functional impairments, Pearson correlation analysis was performed between FC within significant clusters and clinical variables in patients with PD-MCI and PD-NC, and multiple comparisons were adjusted for using the Bonferroni procedure with a factor of 28 to account for 2 groups of patients and 14 clinical variables ($P<0.002$). A corrected $P<0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics

There were no differences in age (F=1.06, P=0.35), sex (Fisher exact test, P=0.33), and education (H=4.04, P=0.13) among the PD-NC, PD-MCI, and HC group. MMSE (H=13.91, P<0.001), HAMA (H=18.85, P<0.001), and HAMD (H=24.76, P<0.001) were significantly different between the groups. No difference was found in the duration of disease (Z=–0.23, P=0.82), MDS-UPDRS-III (Z=–0.75, P=0.46), H-Y stage (P=0.48), and levodopa equivalent daily dose (Z=–0.27, P=0.79) between the PD-NC and PD-MCI groups (*Table 1*).

The mFD (P=0.18), as well as volume of bilateral Ch1-3 (left, P=0.70; right, P=0.30) and Ch4 (left, P=0.58; right, P=0.17) were not significantly different among HC, PD-NC, and PD-MCI groups. There was no difference in the

digit symbol test (Z=1.484, P=0.14) of the WAIS-R, which indicates no differences in attention and working memory between the PD-MCI and PD-NC, but the digit span test (t=–2.505, P=0.02) of the WAIS-R was worse in patients with PD-MCI compared with that of PD-NC. In addition, compared with PD-NC, patients with PD-MCI exhibited diminished executive function (picture arrangement, P<0.001; animal fluency test, P<0.001), memory (immediate memory, P<0.001; logical memory, P<0.001), language (vocabulary, P=0.03; similarities, P=0.002), and visuospatial function (block design, P=0.006; object assembly, P<0.001) (*Table 2*).

FC of each ROI in BF

In the conventional frequency band, we only found a significant difference in FC in the right Ch4 among groups (GRF corrected, voxel P<0.005, cluster P<0.05) (*Table 3, Figure 2*). The PD-MCI group exhibited decreased FC values in the right middle cingulate and paracingulate gyri, right middle frontal gyrus, left inferior parietal gyrus, and left superior frontal gyrus, whereas an increased FC value was observed in the right calcarine fissure and surrounding cortex when compared with the HC group. The PD-MCI group exhibited increased FC value in the left calcarine fissure and surrounding cortex, wheras there was an decreased FC value in the right middle frontal gyrus when compared with the PD-NC group. However, there was no difference in the right Ch4-FC between patients with PD-NC and HC. Moreover, FC values between the PD-NC, PD-MCI, and HC groups were not significantly different in the left Ch4, left Ch1-3, and right Ch1-3.

Regarding slow 4, for the right Ch4, compared with the HC group, the PD-MCI group showed significantly decreased FC values in the left putamen, right middle frontal gyrus, right precuneus, and left middle frontal gyrus, but an increased FC value in the right lingual gyrus, and the PD-NC group exhibited a decreased FC value in the right inferior temporal gyrus. The PD-MCI group exhibited lower FC values in the right middle frontal gyrus and the right middle cingulate and paracingulate gyri than the PD-NC group. Regarding the left Ch1-3, the FC values in the right middle cingulate and paracingulate gyri were lower in patients with PD-MCI compared with patients with PD-NC (*Table 3, Figure 3*).

Regarding slow 5, for the right Ch4, the PD-MCI group showed a higher FC value in the right calcarine fissure and surrounding cortex compared with PD-NC in the left

Table 1 Demographic and neuropsychological information

Variables	PD-NC	PD-MCI	HC	Z/F/H/χ^2	P value
Subjects	42	24	33		
Gender, females, n (%)	16 (38.10%)	7 (29.17%)	16 (48.48%)	2.22[b]	0.33
Age (years)	64.48 (6.87)	65.75 (6.03)	63.33 (5.31)	1.06[a]	0.35
Education	10.83 (3.33)	9.75 (3.47)	11.39 (3.15)	4.04[c]	0.13
HAMD	8.55 (9.05)	10.08 (7.60)	2.06 (2.08)	24.76[c]	<0.001
HAMA	7.33 (7.18)	9.13 (6.93)	2.85 (2.46)	18.85[c]	<0.001
MMSE	28.24 (1.89)	26.14 (2.88)	28.58 (1.50)	13.91[c]	<0.001
MoCA	23.26 (3.32)	18.58 (4.44)	26.21 (1.90)	40.88[c]	<0.001
Duration of disease	2.87 (2.19)	2.81 (2.33)	–	–0.23[d]	0.82
LEDD	182.38 (336.56)	147.08 (241.59)	–	–0.27[d]	0.79
MDS-UPDRS-III	31.17 (13.21)	34.25 (16.82)	–	–0.75[d]	0.46
H-Y stage	2.00 (0.52)	2.08 (0.64)	–	3.52[b]	0.48
Normalized volume of Ch1-3_L	0.07 (0.01)	0.06 (0.01)	0.06 (0.01)	0.36[a]	0.70
Normalized volume of Ch1-3_R	0.06 (0.01)	0.06 (0.01)	0.06 (0.01)	1.23[a]	0.30
Normalized volume of Ch4_L	0.10 (0.01)	0.09 (0.02)	0.09 (0.02)	0.55[a]	0.58
Normalized volume of Ch4_R	0.10 (0.01)	0.09 (0.02)	0.09 (0.02)	1.82[a]	0.17
mFD	0.12 (0.09)	0.14 (0.11)	0.16 (0.11)	3.39[c]	0.18

The data are shown as the mean (standard deviation). [a], one-way analysis of variance; [b], Pearson's chi-square (χ^2), [c], Kruskal-Wallis H test; [d], Mann–Whitney U test. PD-NC, Parkinson's disease with normal cognition; PD-MCI, Parkinson's disease with mild cognitive impairment; HC, healthy control; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; LEDD, levodopa equivalent daily dose; MDS-UPDRS-III, Part III of the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; H-Y, Hoehn and Yahr Scale; Ch1-3_L, left Ch1-3; Ch1-3_R, right Ch1-3; Ch4_L, left Ch4; Ch4_R, right Ch4; mFD, mean framewise displacement.

Table 2 Cognitive performance comparisons between the PD-NC and PC-MCI

Variables	PD-NC	PD-MCI	t/Z	P value
Picture arrangement	8.79 (2.13)	6.29 (2.33)	3.885[b]	<0.001
Animal fluency test	15.38 (2.87)	11.13 (4.05)	–4.978[a]	<0.001
Immediate memory	8.60 (2.93)	2.04 (2.82)	5.918[b]	<0.001
Logical memory	6.29 (2.83)	3.33 (1.17)	4.909[b]	<0.001
Digit symbol	7.19 (1.80)	6.42 (2.10)	1.484[b]	0.14
Digit span	10.55 (1.90)	9.33 (1.88)	–2.505[a]	0.02
Vocabulary	12.26 (2.62)	10.33 (3.47)	2.76[b]	0.03
Similarities	6.29 (2.83)	3.33 (1.17)	3.048[b]	0.002
Block design	8.31 (2.11)	6.58 (2.93)	2.760[b]	0.006
Object assembly	6.57 (2.41)	4.08 (2.02)	3.957[b]	<0.001

The data are shown as the mean (standard deviation). [a], two-sample *t*-tests; [b], Mann–Whitney U test. PD-NC, Parkinson's disease with normal cognition; PD-MCI, Parkinson's disease with mild cognitive impairment.

Table 3 Brain regions showing significant functional connectivity differences between patients with PD-MCI and patients with PD-NC and healthy controls

ROIs	Frequency bands	Contrast	Clusters No.	Number of voxel	Main brain regions	Peak MNI coordinate (x, y, z)	t value
Ch4_R	Conventional frequency band	PD-MCI *vs.* HC	1	130	Calcarine_R	15, −96, −6	4.0614
			2	132	Cingulum_Mid_R	3, −39, 36	−4.415
			3	172	Frontal_Mid_R	30, 30, 33	−5.3615
			4	59	Parietal_Inf_L	−48, −51, 36	−5.1066
			5	63	Frontal_Sup_L	−18, 36, 36	−4.0553
			6	99	Frontal_Sup_L	−18, 9, 60	−4.5736
		PD-MCI *vs.* PD-NC	1	144	Calcarine_L	0, −78, 6	4.4885
			2	94	Frontal_Mid_R	30, 42, 36	−4.5883
	Slow 4	PD-MCI *vs.* HC	1	64	Lingual_R	9, −60, 0	4.935
			2	55	Putamen_L	−21, −3, 12	−3.827
			3	208	Frontal_Mid_R	27, 42, 36	−4.6999
			4	58	Precuneus_R	3, −42, 45	−3.867
			5	124	Frontal_Mid_L	−18, 24, 48	−4.7368
		PD-NC *vs.* HC	1	77	Temporal_Inf_R	30, −24, −36	−4.4447
		PD-MCI *vs.* PD-NC	1	137	Frontal_Mid_R	30, 42, 36	−5.8167
			2	57	Cingulum_Mid_R	3, −15, 39	−4.4722
	Slow 5	PD-MCI *vs.* HC	1	243	Cerebellum_L	−9, −93, 21	4.9665
		PD-MCI *vs.* PD-NC	1	195	Calcarine_R	9, −93, −3	4.3561
Ch1-3_L	Slow 4	PD-MCI *vs.* PD-NC	1	151	Cingulum_Mid_R	9, −42, 36	−4.8412

All effects survived a voxel-wise statistical threshold (P<0.005) after GRF correction for multiple comparisons. *, main brain regions were located in white matter. PD-MCI, Parkinson's disease with mild cognitive impairment; PD-NC, Parkinson's disease with normal cognition; ROI, region of interest; MNI, Montreal Neurological Institute; HC, healthy control; R, right; L, left; Calcarine, calcarine fissure and surrounding cortex; Cingulum_Mid, middle cingulate and paracingulate gyri; Frontal_Mid, middle frontal gyrus; Parietal_Inf, inferior parietal, but supramarginal and angular gyri; Frontal_Sup, superior frontal gyrus; Lingual, lingual gyrus; Temporal_Inf, inferior temporal gyrus; GRF, Gaussian random field.

cerebellum when compared with HC (*Table 3*, *Figure 4*).

There was no difference in FC values among the three groups in the left Ch4 and right Ch1-3.

Correlation between FC and clinical variables

The correlations between clinical performance and FC values in significantly involved regions in PD-NC and PD-MCI group (*Figure 5*) were examined. Correlations between FC values and clinical performance were found in the right Ch4 rather than left Ch1-3 as per the seed-based analysis. HAMD scores of patients with PD-MCI were positively correlated with the FC values of the right middle cingulate and paracingulate gyri detected in the conventional frequency band (r=0.476, P=0.02). For global cognition, in patients with PD-MCI, MMSE scores were positively correlated with the FC values of the left calcarine fissure and surrounding cortex as detected in the conventional frequency band (r=0.435, P=0.03). Regarding executive function, the animal fluency test was positively correlated with the FC value in the right inferior temporal gyrus detected in patients with PD-NC in slow 4 (r=0.307, P=0.05). Regarding visuospatial functions, object assembly was negatively correlated with FC value in the right middle cingulate and paracingulate gyri in patients with PD-MCI in slow 4 (r=−0.406, P=0.05). Regarding memory function,
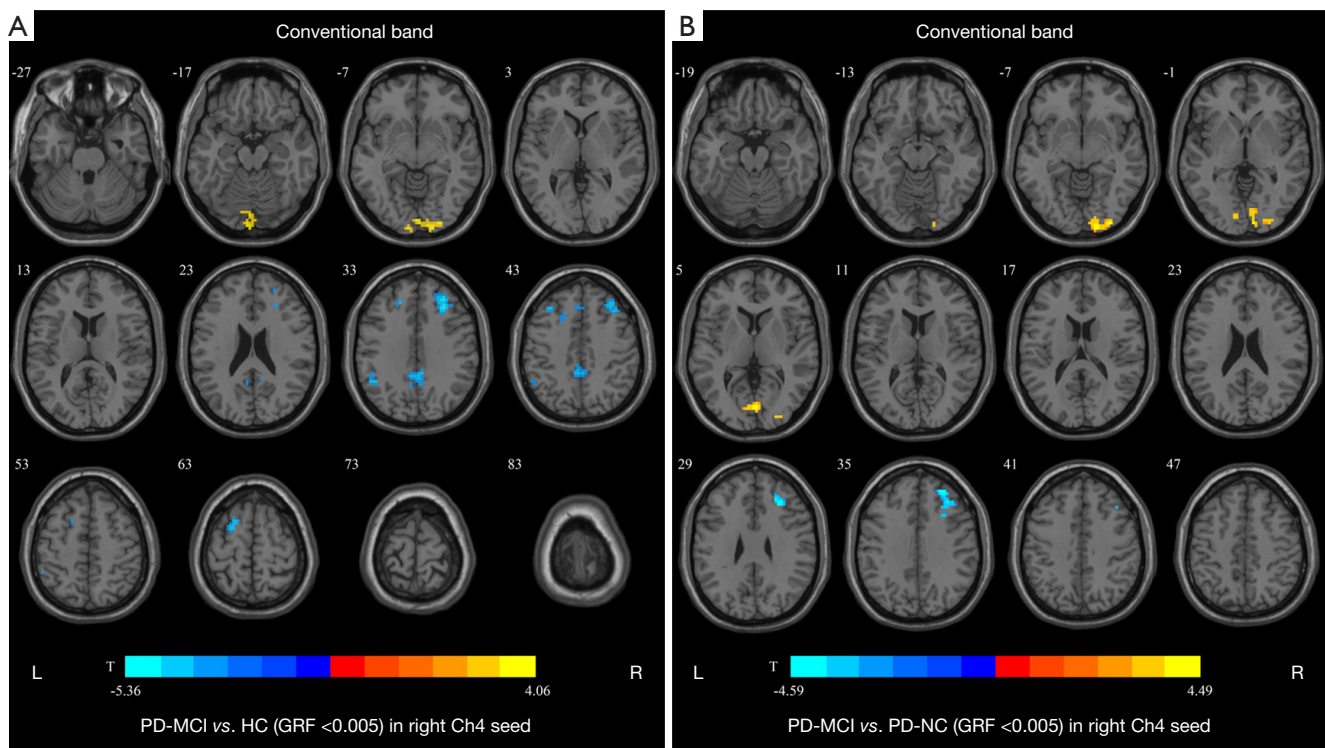
Figure 2 FC differences among the groups in conventional frequency band in the right Ch4 seed. The FC differences were compared using two sample *t*-tests (GRF corrected, voxel P<0.005, cluster P<0.05). (A) Regions showing decreased and increased FC in patients with PD-MCI between PD-MCI and HC. (B) Regions showing decreased and increased FC in patients with PD-MCI between PD-MCI and PD-NC. PD-MCI, Parkinson's disease with mild cognitive impairment; HC, healthy control; GRF, Gaussian random field; PD-NC, Parkinson's disease with normal cognition; FC, functional connectivity.

immediate memory test scores were negatively correlated with FC values in the left putamen detected in patients with PD-MCI in the slow 4 (r=–0.431, P=0.04), and logical memory test scores were positively correlated with FC values in the right middle frontal gyrus detected in patients with PD-NC in the slow 4 (r=0.397, P=0.009). Regarding language function, the vocabulary test was negatively correlated with the FC value in the right calcarine fissure and surrounding cortex detected in patients with PD-MCI in the slow 4 (r=–0.432, P=0.04). However, these correlations did not persist once multiple comparisons were adjusted for. No significant correlations were observed in Ch1-3 seed-based FC in significantly altered regions with other cognitive tests scores.

Discussion

Patients with PD with cognitive impairment presented evidence of abnormal FC in the BF. The findings of this

study indicated there was reduced FC between Ch4 and frontal, parietal, occipital cortex in patients with PD-MCI compared with patients with PD-NC and HC. Furthermore, changes in connectivity within the Ch4-cortical network possibly correlated with depression (HAMD), global cognition (MMSE), and executive, visuospatial, memory, and language function. Longitudinal studies are needed to explore whether connectivity changes in the cholinergic BF nuclei are closely associated with cognitive decline in non-demented PD.

Similar to our findings in patients with non-demented PD, previous studies have shown volumetric and FC changes between Ch4 and several related cortical and subcortical regions in patients with PDD (10,32). This is in line with previous postmortem histological studies, and some neuroimaging findings (7,33). Severely reduced cortical cholinergic activity and loss of Ch4 cholinergic neurons in PD and PDD have been reported by many studies (7,34). Overall, these changes indicate widespread
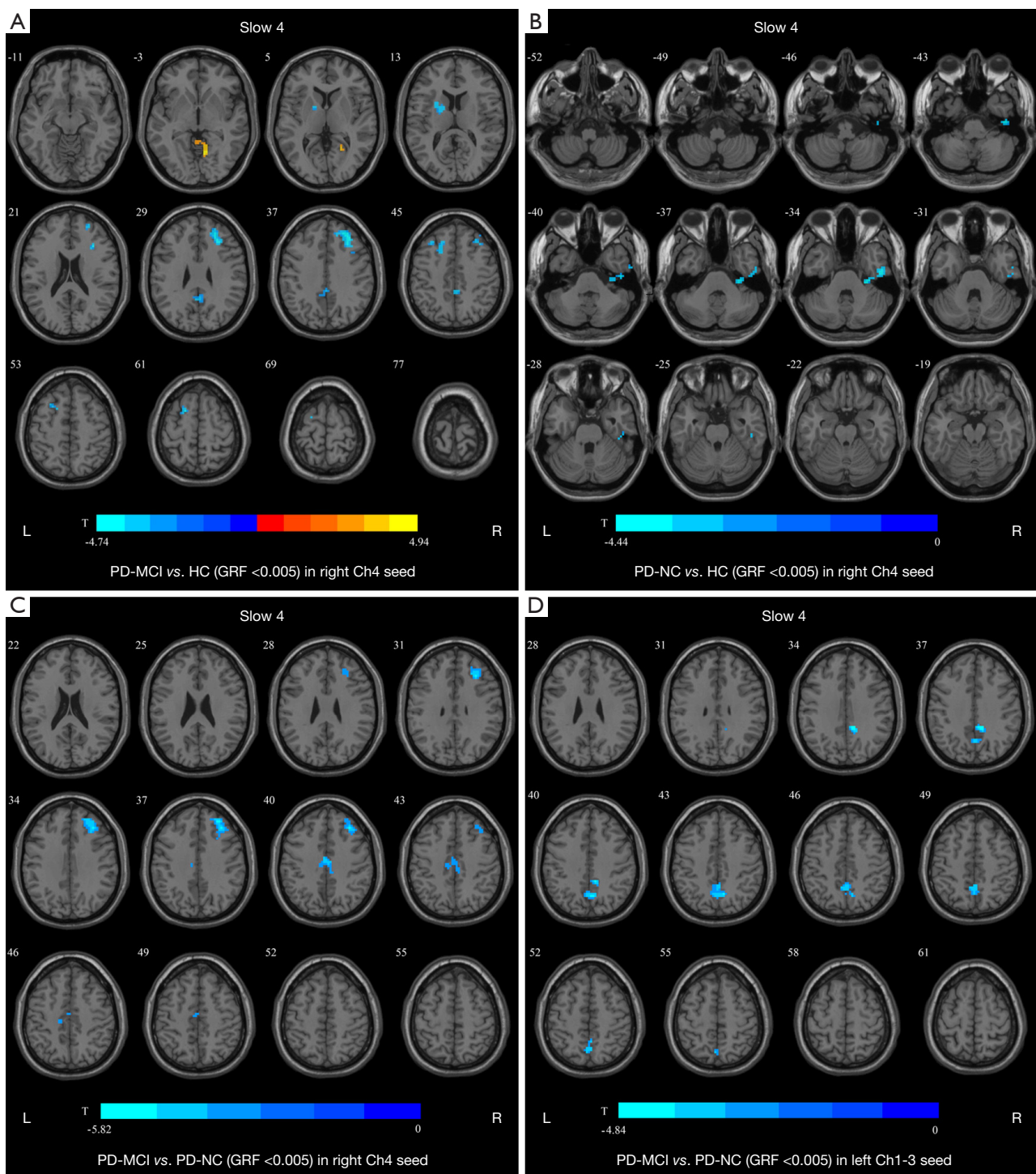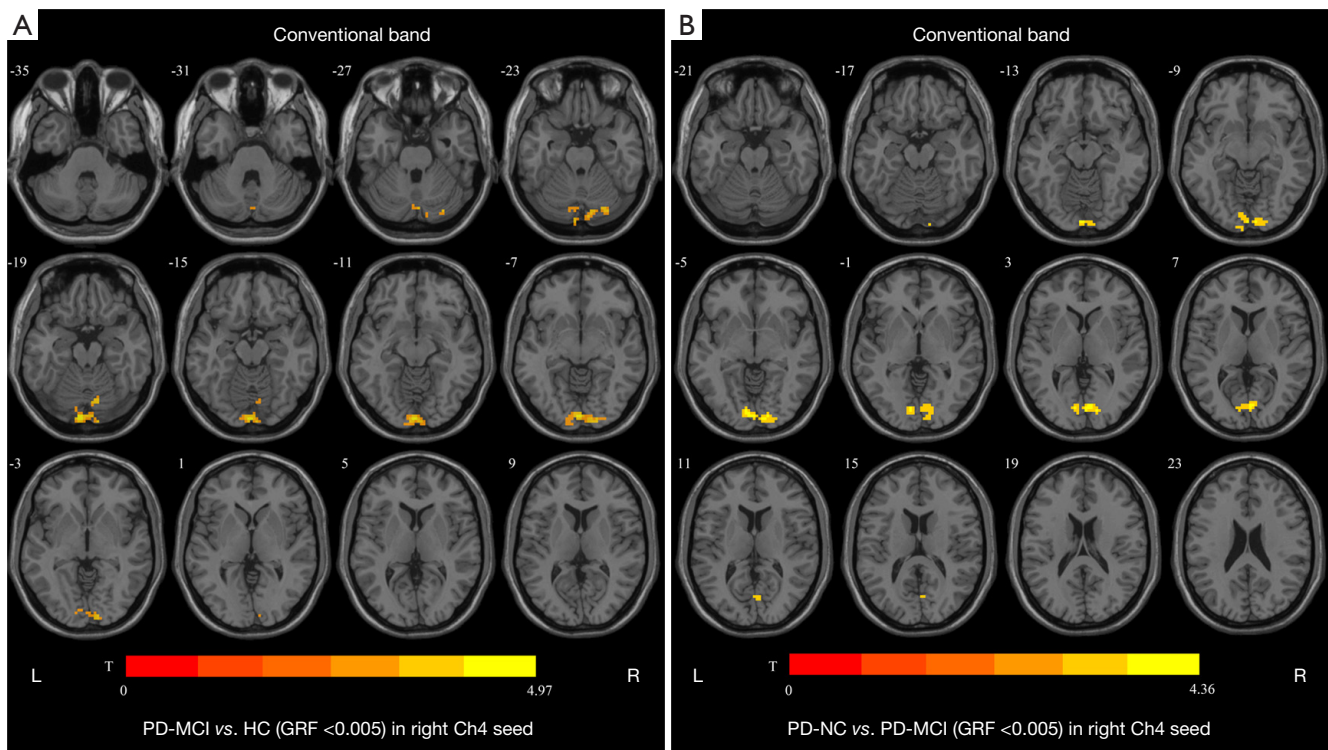
Figure 3 FC differences among the groups in slow 4. The FC differences were compared using two sample t-tests (GRF corrected, voxel P<0.005, cluster P<0.05). (A) Regions showing decreased and increased FC in patients with PD-MCI between PD-MCI and HC in the right Ch4 seed. (B) Regions showing decreased FC in PD-NC patients between PD-NC and HC in the right Ch4 seed. (C) Regions showing decreased FC in patients with PD-MCI between PD-MCI and PD-NC in the right Ch4 seed. (D) Regions showing decreased FC in patients with PD-MCI between PD-MCI and PD-NC in slow 4. PD-MCI, Parkinson's disease with mild cognitive impairment; HC, healthy control; GRF, Gaussian random field; PD-NC, Parkinson's disease with normal cognition; FC, functional connectivity.

Figure 4 FC differences among the groups in slow 5 in the right Ch4 seed. The FC differences were compared using two sample t-tests (GRF corrected, voxel P<0.005, cluster P<0.05). (A) Regions showing increased FC in patients with PD-MCI between PD-MCI and HC. (B) Regions showing increased FC in patients with PD-MCI between PD-MCI and PD-NC. PD-MCI, Parkinson's disease with mild cognitive impairment; HC, healthy control; GRF, Gaussian random field; PD-NC, Parkinson's disease with normal cognition; FC, functional connectivity.

α-synuclein-immunopositive Lewy neurites and Lewy bodies deposition in Ch4 in patients with PDD (7). Some positron emission tomography (PET) studies identified that acetylcholinesterase activity was significantly decreased in the cerebral cortex in patients with PDD and cortical hypometabolism in patients with PD with Ch4 atrophy (35,36). Interestingly, cortical cholinergic deficit was more severe in patients with PDD than patients with Alzheimer's disease (AD) (7). Furthermore, atrophy of Ch4 observed in patients with PD without cognitive impairment precedes and predicts future dementia, and increased microstructural deficit of NBM in patients with PD predicts cognitive impairment (9,37). Consistent with these changes, reduced FC between Ch4 and anatomical cortical areas was detected in patients with PD-MCI in this study. The volume of NBM was not significantly different between PD-MCI and PD-NC, and, thus, the possibility that reduced FC in Ch4-corticocal network caused by NBM atrophy was not considered in this study. Similar results have not yet been

reported in patients with PD-MCI. Therefore, the potential for neuromodulatory treatments targeting the Ch4, such as repetitive transcranial magnetic stimulation (rTMS) and deep brain stimulation (DBS), is under active investigation. Previous studies have shown impairment of structural and FC in different cholinergic BF nuclei in patients with PD (10). In contrast, we hardly found any significant regions in left Ch1-3 seed-based FC except for reduced FC in the right middle cingulate and paracingulate gyri in patients with PD-MCI compared to PD-NC. A postmortem study found cholinergic septal neurons were largely spared, but a nearly 50% cholinergic neurons loss in Ch4 was observed in patients with PD (7). Similarly, lower volume of Ch4 is followed by changes in Ch1/Ch2, reflecting a posterior-anterior pattern of BF atrophy in a longitudinal structural MRI study (37). All of these results may indicate that MCI in the participants with PD appeared firstly as abnormal FC between Ch4 and cortex, but abnormal FC in Ch1-3 may have arisen when cognitive impairment was aggravated.
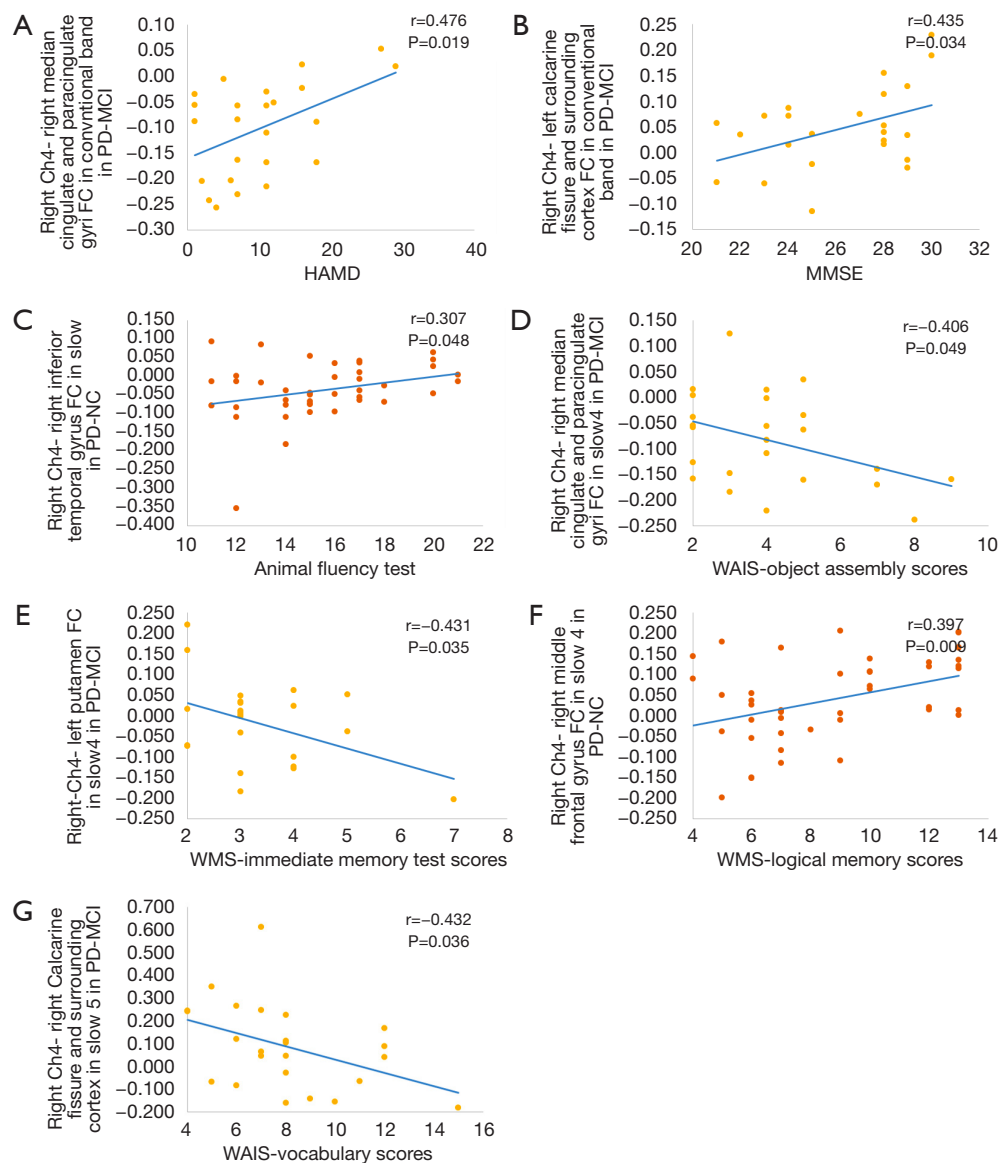
Figure 5 Correlation analyses of patients with PD-MCI and patients with PD-NC between cognitive test scores and functional connectivity values in significantly abnormal regions detected in the right Ch4 seed-based analyses. (A) HAMD scores were positively correlated with FC values in the right middle cingulate and paracingulate gyri detected in the right Ch4 seed-based analysis in the conventional frequency band in PD-MCI. (B) MMSE scores were positively correlated with FC values in the left calcarine fissure and surrounding cortex detected in the right Ch4 seed-based analysis in the conventional frequency band in PD-MCI. (C) Animal fluency scores were negatively correlated with FC values in the right inferior temporal gyrus detected in the right Ch4 seed-based analysis in slow4 in PD-NC. (D) WAIS-object assembly scores were negatively correlated with FC values in the right middle cingulate and paracingulate gyri detected in the right Ch4 seed-based analysis in slow4 in PD-MCI. (E) WMS-Immediate memory test scores were negatively correlated with FC values in the left putamen detected in the right Ch4 seed-based analysis in slow4 in PD-MCI. (F) WMS-Logical memory test scores were positively correlated with FC values in the right middle frontal gyrus detected in the right Ch4 seed-based analysis in slow4 in PD-NC. (G) WMS-Vocabulary test scores were negatively correlated with FC values in the right calcarine fissure and surrounding cortex detected in the right Ch4 seed-based analysis in slow5 in PD-MCI. FC, functional connectivity; PD-MCI, Parkinson's disease with mild cognitive impairment; PD-NC, Parkinson's disease with normal cognition; WMS, Wechsler Memory Scale; HAMD, Hamilton Depression Scale; MMSE, Mini-Mental State Examination; WAIS, Wechsler Adult Intelligence Scale.

In addition, no significant FC was observed between Ch1-3 and the other regions of cortex except for the right middle cingulate and paracingulate gyri adjacent to the hippocampus, which may be explained by indirect FC.

Consistent with previous results, FC values were decreased in the occipital, parietal, and temporal areas and the limbic system, and possibly correlated with global cognition (MMSE), and executive and memory function based on right Ch4-seed analysis. In *de novo* patients with PD, degeneration of BF and concomitant cholinergic cortical denervation are associated with impaired memory, attention, and executive dysfunction (8,38,39). Executive tasks require planning and working memory, which requires a frontoparietal network that includes the prefrontal associative cortex (DLPFC) and posterior parietal cortex (40,41). These regions receive afferents from Ch4, possibly reflecting functional deficits of BF cholinergic circuits in patients with PD-MCI. The cognitive deficits that related closely with functional alterations of the BF cholinergic system were consistent with those brought out by acetylcholinesterase inhibitors medication (42). However, in this study, patients with PD taking anticholinergic medication were excluded, suggesting our findings were due to the degeneration of NBM. However, as the correlations did not persist following Bonferroni correction, the finding should be interpreted with caution. One explanation for this could be the small sample size, and longitudinal studies with larger sample sizes are needed to verify these results.

Unexpected results in this study were that the right cingulate areas were positively correlated with HAMD scores in patients with PD-MCI in the right Ch4 seed-based analysis. Previous structural and functional studies confirmed that patients with damaged cingulate cortex and reduced cortical cholinergic activity are susceptible to depression with PD and primary depression (43-45). Given these findings, there may be an analogous pathophysiological mechanism between depression with PD and primary depression, as the cingulate cortex is largely involved in the pathophysiology of primary depression as well as depression with PD. In addition, there were possibly negative associations between the middle cingulate cortex and visuospatial function, the left putamen and memory function, as well as the occipital cortex and language function, which is inconsistent with previous studies (10,38). Although the interpretation of negative correlations in fMRI in these regions is challenging, a possible interpretation of negative correlations is a loss of inhibition. Taylor *et al.* (46) suggested a loss of inhibition in

the visual system in dementia with Lewy bodies, indicating possibly a negative association between cortical excitability in the visual system and cognitive function. Moreover, opposite findings were reported between the left and right calcarine fissure and the surrounding cortex in patients with PD-MCI. Increased FC in the right calcarine fissure and surrounding cortex were possibly correlated with reduced cognitive performance in patients with PD-MCI in slow 5, but reduced FC in the left calcarine fissure and surrounding cortex was possibly correlated with reduced cognitive performance in conventional band. An explanation for these discrepant findings may be that the frequency is specific with slow 5 being more sensitive for detecting abnormality in the dorsolateral prefrontal cortex, and also a stronger connectivity in the fronto-occipital pathways has been found in neurodegenerative disease (47), and thus increased FC in the occipital cortex could be observed in patients with PD-MCI in slow 5.

Consistent with our finding of reduced FC between the right Ch4, rather than the left, and the cortex in patients with PD-MCI, Teipel *et al.* (48) also found right NBM dominance both in the extent of atrophy and in the effects on fiber tracts in patients with MCI and AD, which may indicate different stages of NBM degeneration in both hemispheres. The prealpha neurons in entorhinal regions receive cholinergic projection from the BF (49). Numbers of prealpha neurons were significantly lower in the right entorhinal region compared with the left entorhinal region in postmortem brains from individuals ranging from 18 to 86 years of age (50), which may suggest that cholinergic neurons in the right rather than the left entorhinal region were more prone to degenerate (48). However, data on both hemispheres of neuron numbers in BF cholinergic nuclei in patients with PD-MCI are still lacking. More studies are needed to address this question in the future.

We explored FC values associated with BF in the different frequency bands, mainly in conventional, slow 4, and slow 5. This is an effective method to seek out abnormal functional changes in patients with PD-MCI. We found that right Ch4 presented reduced FC values with associative frontal, occipital, and parietal cortex in patients with PD-MCI in the conventional band, which is consistent with those in slow 4 to some extent, but different from those in slow 5. We also found reduced abnormal FC in the left putamen in slow 4 but not in the conventional band nor in slow 5. Previous studies have highlighted that neural activity in the brain is found in various frequency bands (51,52). Thus, merely discovering neural activity in

the conventional band possibly omits significant findings from spontaneous blood-oxygen-level-dependent (BOLD) fluctuations at specific frequencies.

Previous studies suggested slow 4 exhibited less power and was more likely to be localized within the subcortical structure (including basal ganglia) (52,53). Our results indicated that slow 4 might be sensitive to abnormal putamen activity, which is consistent with related findings in patients with depressed PD (54). The FC in patients with PD-MCI was significantly decreased in the frontal and parietal cortex in slow 4, which was almost consistent with those found in the conventional band. These analogous patterns might indicate slow 4 was more sensitive for detecting abnormal FC changes in patients with PD-MCI. Moreover, slow 5 might be more sensitive for detecting abnormality in the dorsolateral prefrontal cortex and limbic system (12,55). Similarly, patients with PD-MCI in our study mainly exhibited FC changes in the calcarine fissure and surrounding cortex.

There were several limitations to the current study, which should be considered. First, this is a cross-sectional study with a relatively small sample size. To overcome this issue, the patients with PD enrolled in this study were clinically confirmed and matched with HC for age, sex, and education. In addition, the voxel threshold was set as P<0.005. In the future, more multicenter prospective and multimodal studies with stricter statistical thresholds are needed to verify these results. Second, there were some patients enrolled in our study who had been treated by medications but their MRI scans were performed without antiparkinsonian drugs. To overcome this issue, we matched the levodopa equivalent daily dose of each PD group. Furthermore, rs-fMRI were used to detect changes of FC, but the histological changes of the cholinergic system are poorly understood, and we cannot determine these changes due to the degeneration of cholinergic neurons in the BF.

Conclusions

Our study showed that connectivity changes in the cholinergic BF nuclei were possibly associated with the cognitive impairments in nondemented PD from the perspective of resting-state FC in different frequency bands, and the study identified an imbalanced association between different cholinergic BF nuclei and cortical regions, which may provide new insights into functional changes within cholinergic BF nuclei in cognitive impairment associated with PD.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-582/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-582/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All participants in this study signed informed consent prior to the study, which was in accordance with the ethical standards of the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2018338H [R1]).

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