

Differential functional connectivity of insular subdivisions in de novo Parkinson's Disease with mild cognitive impairment

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Abstract

The insula, consisting of functionally diverse subdivisions, plays a significant role in Parkinson's disease (PD)-related cognitive disorders. However, the functional connectivity (FC) patterns of insular subdivisions in PD remain unclear. Our aim is to investigate the changes in FC patterns of insular subdivisions and their relationships with cognitive domains. Three groups of participants were recruited in this study, including PD patients with mild cognitive impairment (PD-MCI, $n = 25$), PD patients with normal cognition (PD-NC, $n = 13$), and healthy controls (HCs, $n = 17$). Resting-state functional magnetic resonance imaging (rs-fMRI) was used to investigate the FC in insular subdivisions of the three groups. Moreover, all participants underwent a neuropsychological battery to assess cognition so that the relationship between altered FC and cognitive performance could be elucidated. Compared with the PD-NC group, the PD-MCI group exhibited increased FC between the left dorsal anterior insular (dAI) and the right superior parietal gyrus (SPG), and altered FC was negatively correlated with memory and executive function. Compared with the HC group, the PD-MCI group showed significantly increased FC between the right dAI and the right median cingulate and paracingulate gyri (DCG), and altered FC was positively related to attention/working memory, visuospatial function, and language. Our findings highlighted the different abnormal FC patterns of insular subdivisions in PD patients with different cognitive abilities. Furthermore, dysfunction of the dAI may partly contribute to the decline in executive function and memory in early drug-naïve PD patients.

Introduction

Parkinson's disease (PD) has been defined on the basis of specific motor features (Postuma et al., 2015). However, nonmotor symptoms, such as cognitive dysfunction, autonomic dysfunction, and sleep disorders, contribute to the entire course of PD and even appear to precede motor symptoms (Schapira, Chaudhuri, & Jenner, 2017). With the progression of PD, nonmotor symptoms, such as cognitive impairment, are the main determinants of quality of life (Schapira et al., 2017; Svenningsson, Westman, Ballard, & Aarsland, 2012). Up to 42.5% of newly diagnosed PD patients were diagnosed with mild cognitive impairment (MCI) (Yarnall, Breen, & Duncan, 2013) and 39.1% of PD with mild cognitive impairment (PD-MCI) progressed to dementia after five years (Pedersen, Larsen, Tysnes, & Alves, 2017). PD-MCI is a stage of clinical cognitive impairment between PD with normal cognition (PD-NC) and PD dementia (PDD) (Caviness et al., 2007). PDD has a substantial impact with major consequences of impaired functioning (Szeto et al., 2016), increased costs (Postuma et al., 2011), psychiatric morbidity (Aarsland et al., 2007), caregiver burden (Szeto et al., 2016), and mortality. Therefore, early diagnosis and progression tracking of PD-MCI and its biological markers would be crucial for clinicians identify the patient's status and make corresponding decisions.

Recently, noninvasive neuroimaging techniques have become the main means to study the neural bases of cognitive deficits in PD (Baggio & Junque, 2019). A growing number of neuroimaging studies have highlighted the role of the insula in PD-related cognitive disorders. Christopher et al found that insular D2 receptor loss was unique to PD-MCI patients, suggesting that the insula plays a crucial role in facilitating PD cognitive function (Christopher, Marras, et al., 2014). Mak et al. considered insular atrophy to be associated with cognitive impairment in PD-MCI (Mak et al., 2014). Li et al determined that the abnormal functional connectivity (FC) between the insular and limbic regions was associated with cognitive test results in PD-MCI patients (M. G. Li et al., 2019). Therefore, the insular should be considered a region of interest when we study cognitive changes in PD patients.

Simultaneously, a variety of functional magnetic resonance imaging (fMRI) studies have focused on the functional activity of diverse parts in the insula. There are abnormal connectivity patterns of insular subdivision in schizophrenia (Duan et al., 2020). In task-based fMRI studies, cognitive tasks (attention, language, memory, working memory, and speech) led to activation in the anterior-dorsal region of the insula (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010). In healthy adults, intrinsic connectivity within the right dorsal anterior insula (dAI) network was associated with attention and processing speed (Touroutoglou, Hollenbeck, Dickerson, & Feldman Barrett, 2012). A review suggested that the insula, particularly the anterior division, played a critical role in high-level cognitive control and attentional processes (Menon & Uddin, 2010). With the development of research, the insula has recently been considered a central hub for interacting with multiple brain networks (e.g., default mode networks and central executive networks) (Christopher, Marras, et al., 2014). In Alzheimer's disease (AD), different insular subdivisions presented different connectivity patterns belonging to distinct intrinsic connectivity networks, such as default mode networks (DMNs), the executive control network (ECN), and the salience network (SN) (Liu et al., 2018). Therefore, insular subdivision has a hand in different brain networks and exhibits diverse functions. However, very little is known about whether there is abnormal FC of insular subdivisions in PD patients with different cognitive abilities and whether there is corresponding cognitive domain impairment.

Thus, this study attempted to investigate the changes in FC patterns of the insular subdivisions in PD patients with or without MCI. We hypothesized that (1) altered FC patterns exist in the insular subdivisions of diverse cognitive state PD patients and (2) FC alterations are correlated with cognitive function in PD patients.

Materials And Methods

2.1 Subjects

Forty drug-naïve PD patients and 19 healthy controls (HCs) were recruited from the Affiliated Brain Hospital of Nanjing Medical University. However, 2 PD patients were excluded due to significant brain atrophy ($n=2$), and 2 HCs were excluded due to significant brain atrophy ($n=1$) and excessive head motion (cumulative translation or rotation >3.0 mm or 3.0° , $n=1$). Finally, 38 PD and 17 HCs were available for analysis. The diagnosis of PD was made by an experienced neurologist according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Gibb & Lees, 1988), and clinical follow-up continued at least 1 year to confirm the diagnosis. According to the MCI criteria recommended by the International Parkinson and Movement Disorder Society (MDS) Task Force, PD-MCI met Level II diagnostic criteria (Litvan et al., 2012): impaired performance, i.e., 1.5 standard deviations (SDs) below appropriate norms, on at least two tests in a comprehensive neuropsychological battery. No PD patients took any anti-Parkinson's drugs. All PD patients completed the magnetic resonance imaging (MRI) scan and comprehensive assessments. We utilized Part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III) and Hoehn and Yahr (H-Y) stage to assess motor function, the Non-Motor Symptoms Scale (NMSQ) to assess the severity of nonmotor symptoms, and the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Scale (HAM-A) to examine the symptoms of depression and anxiety, respectively. The inclusion criteria for HCs were as follows: (1) normal cognitive performance of age- and education-matched volunteers and (2) at least a primary school education. Other inclusion criteria for all participants were as follows: (1) 40-80 years old, (2) right-handed, and (3) Chinese native speakers. The exclusion criteria were as follows: (1) history of serious diseases or circumstances that could influence cerebral function, such as brain damage, cerebrovascular disease, white matter disease, and brain operation; (2) the presence of PD with dementia; (3) failure to complete the MRI scan; (4) history of serious diseases, such as cancer, diabetes, hyperthyroidism, severe psychiatric and systemic illnesses; (5) illiteracy or did not complete the assessment; and (6) medication, such as anticholinergic drugs or antidepressants (Huang et al., 2017).

This study was approved by the Medical Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University. All subjects understood the study and provided written informed consent.

2.2 Cognitive Assessment

All participants were administered a formal, comprehensive neuropsychological battery that included the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MOCA), and five cognitive domains. As recommended by the MDS Task Force (Litvan et al., 2012), cognitive domains were assessed by the following tests: 1) attention and working memory was measured with the Digit Span Backward Test (DST), Trail Making Test A (TMT-A) and Stroop Color-Word Test (SCWT); 2) executive function was evaluated with Trail Making Test B (TMT-B) and the Clock Drawing Test (CDT); 3) memory was assessed with the Auditory Verbal Learning Test (AVLT) and Logical Memory Test (LMT); 4) visuospatial function was measured with the Benton's Judgment of Line Orientation Test (JLOT), and Hooper Visual Organization Test (HVOT); 5) language was evaluated with the Boston Naming Test (BNT) and Wechsler Adult Intelligence Scale III (WAIS-III) Similarities Test.

2.3 MRI Data Acquisition

All participants underwent brain structural and resting-state functional magnetic resonance imaging (rs-fMRI) with a 3T Verio Siemens scanner. The details are provided in the Supplementary Materials (materials and methods).

2.4 Image Preprocessing

All fMRI data were preprocessed by Data Processing and Analysis for (Resting-State) Brain Imaging, version 4.3 (DPABI 4.3, <http://rfmri.org/dpabi>), which is based on Statistical Parametric Mapping (SPM) program, version 8 (SPM8, <http://www.fifil.ion.ucl.ac.uk/spm>) implemented in MATLAB 2014b platform (<http://www.mathworks.com/products/matlab>). Data preprocessing referred to previous studies of our research group (Shen et al., 2020; Xue et al., 2019), including removal first image volumes, slice timing, realignment, nuisance covariate regression, spatial standardization, spatial smoothing, and filtering. Herein, we provide details in the Supplementary Materials (materials and methods).

2.5 Functional Connectivity Analysis

To explore the FC of insula subregions implicated in different cognitive states in PD patients, three bilateral insular subdivisions were defined from a previous study (Deen, Pitskel, & Pelphrey, 2011), including the left ventral anterior insula (vAI_L), right ventral anterior insula (vAI_R), left dorsal anterior insula (dAI_L), right dorsal anterior insula (dAI_R), left posterior insula (PI_L), and right posterior insula (PI_R). We defined regions of interest (ROIs) as six spherical 6 mm radius seeds centered on the coordinates in Montreal Neurological Institute (MNI 152) space, which are shown in Supplementary Materials (Table S1) (Peng et al., 2018). The average time courses of all voxels were separately extracted for each ROI, and then voxel-wise cross-correlation analysis was carried out between the ROIs and the whole brain within the group mean

gray matter (GM) mask. Finally, to improve normality, the correlation coefficient map was converted to Z scores by Fisher's r-to-z transform, thereby generating a Z score map for the entire brain.

2.6 Statistical Analysis

All statistical analyses of demographic and clinical data were performed using the Statistical Package for the Social Sciences (SPSS) statistical software package (version 25). Demographic and clinical data were expressed as the mean \pm standard deviation (SD) and were analyzed using Student's t test, the Mann-Whitney U test, one-way analysis of variance (ANOVA), and the Kruskal-Wallis test. Categorical variables were analyzed by the chi-squared test. $P < 0.05$ was considered significant.

Statistical analyses of fMRI data were performed using statistical module of DPABI. Covariance of analysis (ANCOVA) was applied to compare the differences in FC among the PD-MCI, PD-NC and HC groups for each ROI, controlling the effect of GM volume, which was derived from image preprocessing. We used a permutation test with threshold-free cluster enhancement (TFCE) as a strict multiple comparison correction (Chen, Lu, & Yan, 2018). Significant clusters were detected when $p < 0.05$ with family-wise error (TFCE-FWE) correction and a cluster size > 50 voxels. After that, a two-sample T test was used with the mask resulting from ANCOVA, controlling for the effects of age, sex, education, and GM volume. Significant clusters were detected when $p < 0.05$ with TFCE-FWE correction and a cluster size > 10 voxels. The FC values of significantly altered regions were extracted by DPABI, then correlation analyses between the FC values and cognitive domains were performed in SPSS, with sex, age, education, UPDRS-III and HAMD as covariates ($p < 0.05$).

Notably, the scores of some cognitive tests were reversed so that higher scores indicate better performance. For analysis purposes, we transformed the scores of eleven cognitive tests into z scores using the mean and SD values of the HC group, and then individual neuropsychological test z scores were averaged to calculate a domain z score (Chahine et al., 2016) (Table 1 shows the different domains and the corresponding neuropsychological tests).

Results

3.1 Demographic and Neurocognitive Characteristics

The subjects were classified into 3 groups: PD-MCI ($n = 25$), PD-NC ($n = 13$), and HC ($n = 17$), of which demographics and clinical characteristics are presented in Table 1. There were no significant differences in sex, years of education, disease duration, H-Y stage, UPDRS-III, NMSQ, HAMA, HAMD, and MMSE score between the PD-MCI and PD-NC groups. Compared with the HC group and PD-NC group, the PD-MCI group had poorer MOCA and domain cognition test scores, except for the DST, SCWT, and JLOT (see Table 1).

3.2 Functional Connectivity Differences

Regarding the left dAI as the ROI, ANCOVA results showed two significantly altered clusters among the HC group and PD groups, including the bilateral precentral gyrus (PreCG), bilateral postcentral gyrus (PoCG), bilateral paracentral lobule (PCL), bilateral superior parietal gyrus (SPG), left precuneus (PCUN), left inferior parietal gyrus (IPG), right median cingulate and paracingulate gyri (DCG) (TFCE-FWE corrected, cluster size > 50 , $p < 0.05$, see Table 2 and Figure 1). Compared with the PD-NC group, the PD-MCI group showed significantly increased FC between the left dAI and right SPG (TFCE-FWE corrected, cluster size > 10 , $p < 0.05$).

Regarding the right dAI as the ROI, ANCOVA results were consistent with those of the left dAI. Compared with the PD-NC group, the PD-MCI group exhibited increased FC between the right dAI and left IPG, between the right dAI and the left PreCG, and between the right dAI and the right SPG. Compared with the HC group, the PD-MCI group showed significantly increased FC between the right dAI and right DCG, between the right dAI and the bilateral PoCG, between the right dAI and the left PreCG, and between the right dAI and the left PCL (TFCE-FWE corrected, cluster size > 10 , $p < 0.05$). All results controlled for the effects of age, sex, years of education, and GM volume (see Table 2 and Figure 1).

3.3 Correlation Analysis

In the PD-MCI and PD-NC groups, altered FC between the left dAI and right SPG was negatively correlated with memory ($r = -0.366$, $p = 0.024$) and executive function ($r = -0.323$, $p = 0.048$). In the PD-MCI and HC groups, the difference in FC between the right dAI and right DCG was positively correlated with attention/working memory ($r = 0.420$, $p = 0.036$), visuospatial function ($r = 0.493$, $p = 0.012$), and language ($r = 0.443$, $p = 0.027$). All results controlled the effects of age, sex, years of education, UPDRS-III score, and HAMD score ($p < 0.05$). (see Figure 2).

Discussion

The objective of the present work was to explore the changes in FC patterns of different insular subregions between different groups (HC, PD-NC, PD-MCI). Corresponding with our hypothesis, we found that FC of the bilateral dAI of drug-naïve PD-MCI patients was significantly higher than that of control subjects. Then, correlation analysis indicated that altered FC has different effects on cognitive function. Thus, our study further confirms that the bilateral dAI is functionally independent and suggests that bilateral dAI might contribute to cognitive impairment in PD patients.

Previous studies have indicated that the insula is mainly affected by alpha-synuclein deposition in PD, showing altered FC and abnormalities in dopaminergic and serotonergic function related to cognition (Christopher, Koshimori, Lang, Criaud, & Strafella, 2014; Christopher, Marras, et al., 2014). Now, we found that abnormal FC of bilateral dAI was related to cognition, proving the dorsal anterior insula is more involved in human cognition than the ventral anterior and posterior networks (Chang, Yarkoni, Khaw, & Sanfey, 2013; Kurth et al., 2010; Touroutoglou et al., 2012). Compared with the PD-NC group, the PD-MCI group showed increased FC between the left dAI and right SPG, which were positively correlated with executive and memory domain z scores. In past studies, the SPG, a hub of the central executive network (CEN) (Wang et al., 2020), was considered a key region affected by different kinds of deficits in MCI. Meta-analysis revealed, both in rs-fMRI and task-related MRI studies, hyperactivation in the SPG was present in MCI patients (Gu & Zhang, 2019). In subcortical vascular mild cognitive impairment (svMCI) patients, increased intermodule connectivity was also observed in the SPG and was associated with worse memory performance (Yi et al., 2015). Besides fMRI results, the FDG-PET study showed that significant hypometabolism was observed in the SPG in newly diagnosed PD-MCI patients (Pappata et al., 2011); structural MRI also demonstrated that SPG atrophy in PD-MCI patients was related to memory and executive function (Pereira et al., 2014; Uribe et al., 2016; Zhang et al., 2015). In sum, SPG dysfunction was related to executive function and memory impairment in PD-MCI. In addition, in newly diagnosed PD cases, impairment was the most frequent in executive function and memory (Muslimovic, Post, Speelman, & Schmand, 2005). Abnormal FC between the left dAI and right SPG was not shown in PD-NC and HC groups. Therefore, our study indicates that the abnormal FC between the left dAI and right SPG contributes to executive function and memory impairment in PD-MCI patients.

Interestingly, compared with the HC group, the current study found increased FC between the right dAI and right DCG in PD-MCI patients but not in PD-NC patients, which might represent a characteristic change in PD-MCI patients. The anterior insula (AI) is one of the core brain regions anchoring the SN (Chong, Ng, Lee, & Zhou, 2017), and the DCG is part of the DMN. In healthy adults, interactions between the SN and the DMN were thought to be important for cognitive control (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). To our knowledge, changes were detected in the DMN subnetworks in three preclinical stages of AD (Xue et al., 2019), and DMN hubs could be the first to show disruptions in early, cognitively unimpaired PD patients (Disbrow et al., 2014; Hou et al., 2018). Nevertheless, Jones et al proposed that the DMN in AD seems to follow the model of cascaded network failure (Jones et al., 2016), and the successive failure of intrinsic connectivity networks in each stage of PD (DMN dysfunction in PD-NC patients, SN dysfunction in PD-MCI patients) seems to follow such a model as well (Aracil-Bolanos et al., 2019). Therefore, as the disease progresses, disruption in SN hubs, such as the dAI, appears to signal the onset of PD-MCI (Aracil-Bolanos et al., 2019). On the other hand, a previous study indicated increased FC between the SN and DMN, a relative decrease in the DMN and an increase in the SN; these changes were viewed as a rapid allocation of resources toward potential external risks (Jilka et al., 2014). Thus, increased FC values between the right dAI and the right DCG were positively correlated with attention/working memory, visuospatial function, and language, which was considered as compensatory mechanisms in PD-MCI.

In sum, the increased FC between the left dAI and the right SPG and the increased FC between the right dAI and the right DCG were a feature in PD-MCI patients. In terms of networks, the SN, the dAI in particular, plays the critical role in switching between activating the DMN and the CEN in the triple model of cognition (Aracil-Bolanos et al., 2019; Menon & Uddin, 2010), and dAI dysfunction may lead to abnormalities in the DMN and CEN.

We acknowledge some limitations of our study. First, in our research, 65% of PD patients were diagnosed with PD-MCI, which is higher than the percentage in previous reports (Y. Li et al., 2019). There are several reasons for this discrepancy: a small sample size and the use of level 2 criteria for PD-MCI. However, we've been recruiting volunteers to participate in this study and will perform regular follow-up in the future. In addition, we used MDS PD-MCI Task Force Level 2 diagnostic criteria to obtain a reliable diagnosis of PD-MCI and facilitate subsequent analysis of cognitive domains. Second, compared with the PD-NC patients, the PD-MCI patients are older, have less education and higher UPDRS-III scores in numerical value. Indeed, meta-analysis revealed that PD-MCI patients were characterized by older age, more severe motor symptoms, and less education compared with PD-NC patients (Baiano, Barone, Trojano, & Santangelo, 2020). Moreover, to exclude the influence of the above factors, we used age, years of education, and UPDRS-III score as covariates in analysis. Third, the MCI group was missing in our research, so we may ignore alter FC in individual with MCI. We will recruit MCI group in the future to avoid all possibilities of potential bias in our data. Last, it was a pilot exploratory study, we performed the correlation analyses between the altered FC in insular subregion and cognitive function. Future studies, with more patients recruited, will help to confirm the current results.

Conclusion

To our knowledge, the present study is the first to demonstrate the abnormal FC patterns of insular subdivisions in PD-MCI patients and suggests that dAI dysfunction may contribute to the decline in executive function and memory in drug-naïve PD patients. This study may provide clues for the future study of neuropathology in PD cognitive impairment. In terms of networks, our findings contribute to a better understanding of different parts of SN (i.e., different insular subdivisions) play distinct roles in the triple model of cognition.

Declarations

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Declarations

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Conflicts of interest The author declares that there is no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to Publish Not applicable

Availability of data and materials The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability Not applicable

Author Contribution Conception and study design, J.C., C.P., and W.L., data collection or acquisition, C.P., J.R., Y.L., L.L., and J.X., statistical analysis, J.C., C.P., Y.C., W.Z., L.Z., C.X., G.H., M.Y., X.H. and S.Y., writing – original draft, C.P.; writing – review & editing, validation, J.C., W.L., W.L. and J.C. approved the final version of the manuscript to be published. All authors contributed to the article and approved the submitted version.

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Tables

TABLE 1. Clinical and demographic characteristics of PD patients and control subjects.

	PD-MCI _{n=25}	PD-NC _{n=13}	HC _{n=17}	P
Age(y)	60.72±6.97	54.85±7.01	63.29±5.82	0.004 ^{a,d*,f**}
Gender(M/F)	8/17	8/5	8/9	ns ^b
Disease duration(m)	17.56±11.76	19.38±11.79	-	ns ^c
H-Y stage	1.56±0.49	1.35±0.32	-	ns ^c
Education(y)	8.68±2.94	10.08±3.07	11.21±2.62	0.033 ^{c,e*}
UPDRS- \square score	24.20±9.94	21.15±9.05	0.53±1.46	0.000 ^{c,e***,f***}
NMSQ	8.04±5.94	9.15±4.63	1.88±2.03	0.000 ^{c,e***,f***}
HAMA	6.24±4.15	6.46±7.81	0.59±1.33	0.000 ^{c,e***,f***}
HAMD	10.48±6.42	10.85±11.30	1.29±2.52	0.000 ^{c,e***,f***}
MMSE	27.48±2.22	28.00±2.04	28.59±1.28	0.236 ^c
MOCA	20.76±3.44	24.54±3.60	26.82±2.56	0.000 ^{a,d**,e***}
Attention/Working memory				
DST	11.08±2.53	11.77±1.92	12.18±2.74	ns ^a
TMT-A(s)	132.92±58.70	79.69±17.73	84.00±24.48	0.000 ^{c,d**,e**}
SCWT-C-right	48.08±2.38 [#]	48.50±4.58	48.24±2.14	ns ^c
SCWT-C-time(s)	85.79±35.76 [#]	78.67±26.05	62.41±13.01	0.033 ^{c,e*}
Executive				
TMT-B(s)	268.50±133.68 [#]	160.38±26.68	158.35±33.27	0.001 ^{c,d*,e**}
CDT	7.68±2.43	9.85±0.56	9.88±0.49	0.000 ^{c,d**,e***}
Memory				
AVLT-delayed recall	4.48±2.31	6.54±1.85	6.76±2.82	0.006 ^{a,d*,e*}
LMT-delayed recall	4.46±2.64	7.08±1.61	6.29±2.54	0.005 ^{a,d**}
Visuospatial function				
JLOT	22.88±3.57	24.62±1.79	24.94±2.52	ns ^a
HVOT	11.32±4.43	16.77±3.73	16.82±4.00	0.000 ^{a,d**,e***}
Language				
similarities	12.32±4.56	16.54±5.49	16.59±3.76	0.005 ^{c,d*,e*}
BNT	21.24±4.67	25.46±2.93	24.94±3.11	0.004 ^{c,d*,e*}

[#]only 24 participants complete this test.

Data are presented as mean \pm SD.

^a parametric test (Student t test or one-way ANOVA, as appropriate).

^b chi-square test.

^c nonparametric test (Mann-Whitney U test or Kruskal-Wallis, as appropriate).

The results of post hoc multiple comparisons (Bonferroni or Games-Howell for one-way ANOVA, Bonferroni for Kruskal-Wallis test) were indicated as:

^d MCI-NC.

^e MCI-HC.

^f NC-HC.

* P<0.05.

** P<0.01.

*** P<0.001.

Abbreviations: s second; m month; y year.

TABLE 2. The differences in functional connectivity in different insular subdivisions.

Seed ROI	Brain region (aal)	Peak MNI coordinates			Cluster number	F/t
		x	y	z		
dAI_L						
ANOVO						
	Postcentral_B/Paracentral_Lobule_B/Precentral_B/Parietal_Inf_L/Parietal_Sup_B/Cingulum_Mid_R/Precuneus_L	33	-36	66	1002	19.0155
	Precentral_R	45	-6	48	68	9.5048
	MCI>NC					
	Parietal_Sup_R	36	-57	63	19	4.729
dAI_R						
ANOVO						
	Postcentral_B/Paracentral_Lobule_B/Precentral_B/Parietal_Inf_L/Parietal_Sup_B/Cingulum_Mid_R/Precuneus_L	33	-36	66	1002	19.0155
	Precentral_R	45	-6	48	68	9.5048
	MCI>HC					
	Postcentral_B/Precentral_L/Paracentral_Lobule_B	33	-36	69	725	5.6248
	Cingulum_Mid_R	0	-3	48	107	4.1498
	MCI>NC					
	Parietal_Inf_L	-39	-33	48	54	3.8145
	Precentral_L	-42	-15	66	29	4.2857
	Parietal_Sup_R	36	-51	63	47	4.8834

The x, y, z coordinates are the primary peak locations in the MNI space.

Cluster size >50 voxels in ANOVA analysis, p<0.05, TFCE-FWE corrected;

Cluster size>10 voxels in two-sample T-test, p < 0.05, TFCE-FWE corrected.

Abbreviations: L, left, R, right, B, bilateral.

Figures

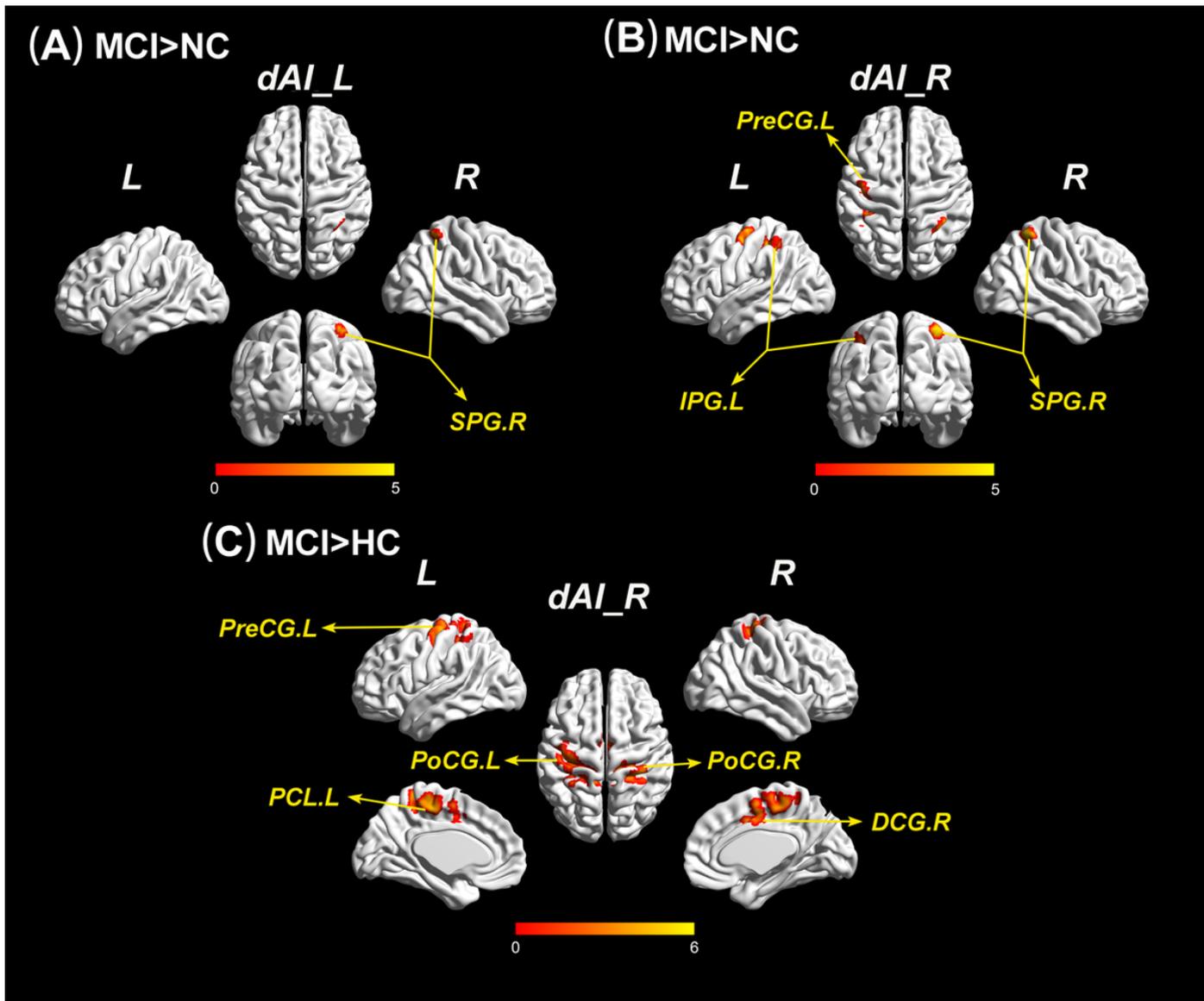


Figure 1

Brain regions that have significant differences between two groups. (A) A brain region (SPG.R) showed a significant FC difference in the left dAI between the PD-MCI and PD-NC groups. (B) Brain regions exhibited significant FC differences in the right dAI between the PD-MCI and PD-NC groups. (C) Brain regions exhibited significant FC differences in the right dAI between the PD-MCI and HC groups. All results based on analysis of two-sample T-tests, and age, gender, years of education were used as covariates (TFCE-FWE corrected, cluster size ≥ 10 , $p < 0.05$). Abbreviations: MCI, mild cognitive impairment; NC, normal cognition; FC, functional connectivity; dAI, dorsal anterior insula; SPG, superior parietal gyrus; IPG, inferior parietal gyrus; PreCG, precentral gyrus; PoCG, postcentral gyrus; PCL, paracentral lobule; PCUN, precuneus; DCG, paracingulate gyri; L, left; R, right.

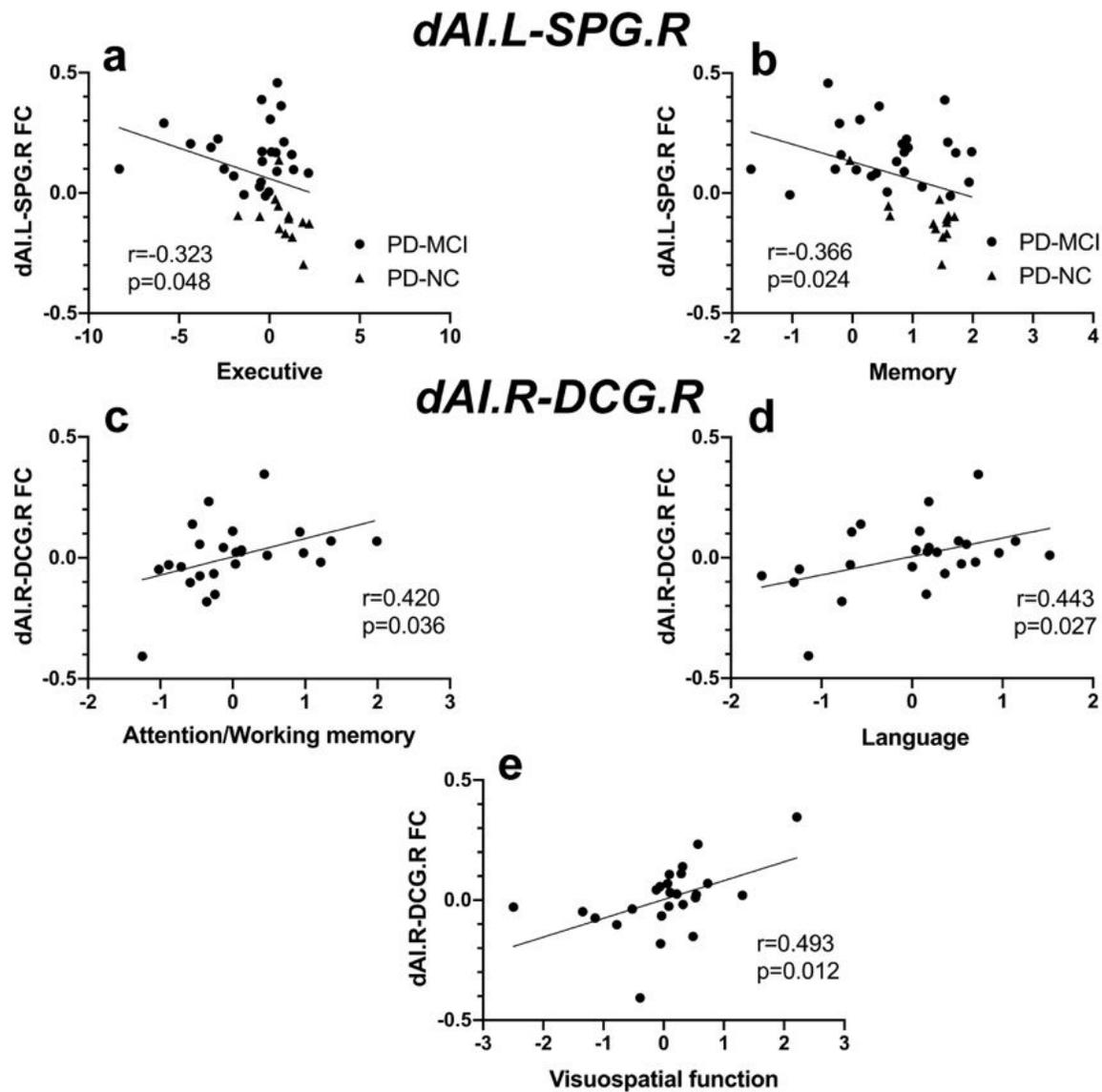


Figure 2

Correlation analysis between altered FC values and cognitive domains. (a-b) Significantly negative correlation between altered FC values and cognitive domains in PD patients ($p < 0.05$). (c-e) Significantly positive correlation analysis between altered FC values and cognitive domains in PD-MCI ($p < 0.05$). Age, sex, years of education, UPDRS-III score, and HAMD score were used as covariates for all these results but were uncorrected. Abbreviations: dAI.R, right dorsal anterior insula; dAI.L, left dorsal anterior insula; SPG.R, right superior parietal gyrus; DCG.R, right median cingulate and paracingulate gyri; FC, functional connectivity.

Supplementary Files

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