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MAGNETIC RESONANCE

Brain connectivity markers in advanced Parkinson's disease for predicting mild cognitive impairment

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Abstract

Objectives Mild cognitive impairment (MCI) is a well-defined non-motor manifestation and a harbinger of dementia in Parkinson's disease. This study is to investigate brain connectivity markers of MCI using diffusion tensor imaging and resting-state functional MRI, and help MCI diagnosis in PD patients.

Methods We evaluated 131 advanced PD patients (disease duration > 5 years; 59 patients with MCI) and 48 healthy control subjects who underwent a diffusion-weighted and resting-state functional MRI scanning. The patients were randomly assigned to training (n = 100) and testing (n = 31) groups. According to the Brainnetome Atlas, ROI-based structural and functional connectivity analysis was employed to extract connectivity features. To identify features with significant discriminative power for patient classification, all features were put into an all-relevant feature selection procedure within cross-validation loops.

Results Nine features were identified to be significantly relevant to patient classification. They showed significant differences between PD patients with and without MCI and positively correlated with the MoCA score. Five of them did not differ between general MCI subjects and healthy controls from the ADNI database, which suggested that they could uniquely play a part in the MCI diagnosis of PD. On basis of these relevant features, the random forest model constructed from the training group achieved an accuracy of 83.9% in the testing group, to discriminate patients with and without MCI.

Conclusions The results of our study provide preliminary evidence that structural and functional connectivity abnormalities may contribute to cognitive impairment and allow to predict the outcome of MCI diagnosis in PD.

Key Points

- *Nine MCI markers were identified using an all-relevant feature selection procedure.*
- *Five of nine markers differed between MCI and NC in PD, but not in general persons.*
- *A random forest model achieved an accuracy of 83.9% for MCI diagnosis in PD.*

Keywords Parkinson disease · Cognition disorders · Diffusion tensor imaging · Magnetic resonance imaging

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Abbreviations

AAL	Automated Anatomical Labeling
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
BDI	Beck Depression Inventory
DAN	Dorsal attention network
DMN	Default-mode network
FA	Fractional anisotropy
FDR	False discovery rate
FPN	Frontoparietal network
HAMA	Hamilton Anxiety Scale
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobule
LEDD	Levodopa equivalent daily dose
MCI	Mild cognitive impairment
MoCA	Montreal Cognitive Assessment Scale
NC	Normal cognition
PCC	Posterior cingulate cortex
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire
PhG	Parahippocampal gyrus
PoG	Postcentral gyrus
PPMI	Parkinson Progression Markers Initiative
PrG	Precentral gyrus
PSQI	Pittsburgh Sleep Quality Index
rs-fMRI	Resting-state functional MRI
SD	Standard deviation
SFG	Superior frontal gyrus
STG	Superior temporal gyrus
STN	Subthalamic nucleus
UPDRS-III	Unified Parkinson's Disease Rating Scale part III

Introduction

Mild cognitive impairment (MCI), a common non-motor manifestation of Parkinson's disease (PD), is defined as a cognitive decline that is not normal for the age and educational level of the patient but where normal functional activities can be maintained [1, 2]. MCI patients in PD have a high risk of developing dementia, which can occur in more than 80% of PD patients over the long term [3]. MCI is regarded as a potential early stage of dementia. Early MCI diagnosis in PD may help prevent dementia in advance, based on the identification of brain abnormalities underlying cognitive impairment.

Over the past decade, modern neuroimaging techniques, including PET and MRI, have provided useful tools to investigate brain abnormalities in PD-MCI patients [4–8]. In a PET study, PD-MCI patients showed hypometabolism in the angular gyrus, occipital, orbital, and anterior frontal lobes [6]. Wu et al found that all the cognitive domain scores with the exception of language in PD patients correlated with ^{18}F-FDG metabolisms primarily in posterior temporo-parieto-occipital association cortical areas [7]. Structural abnormalities in gray and white matter associated with cognitive impairment in PD are measured using structural MRI images and diffusion tensor imaging (DTI), respectively. Previous structural MRI studies in PD-MCI patients have demonstrated a pattern of cortical volume loss in posterior, parietal and frontal cortices, and atrophy in the hippocampus [9–11]. Conversely, Wang et al showed that the volume of the hippocampal fissure was enlarged in PD-MCI patients compared with healthy controls [12]. Moreover, white matter abnormalities of the corpus callosum might contribute to cognitive impairment in PD by disrupting information transfer across interhemispheric and callosal-cortical projections [13, 14].

In addition to intra-regional abnormalities, cognitive impairment in PD was also related to inter-regional connectivity, defined by two MRI-based measures [15–20], diffusion tractography [21] and resting-state functional MRI (rs-fMRI) [22]. In a DTI study analyzing global and local network metrics in the whole-brain, PD-MCI patients showed lower global efficiency and larger shortest path length than healthy controls [20]. And the nodal efficiency of the orbitofrontal part was closely associated with the overall cognitive ability and multiple cognitive sub-domains [20]. Baggio et al found reduced within-network connectivity in the dorsal attention network (DAN) and default-mode network (DMN), and functional connectivity between DAN and frontoparietal network (FPN), as well as loss of normal DAN-DMN anticorrelation in PD-MCI patients [17]. However, whether and how these intra- and inter-regional abnormalities contribute to clinical MCI diagnosis in PD are currently not well known. Building machine learning-based classifiers to discriminate patients with and without cognitive impairment can allow screening potential imaging markers of MCI in a data-driven manner. Their clinical value can be evaluated by the accuracy of the classifiers. Moreover, this evaluation has the potential to lead to a deeper understanding of neural substrates of cognitive impairment in PD.

In our study, DTI and rs-fMRI data were acquired from advanced PD patients and healthy control subjects in our cohort. Secondly, structural and functional connectivity features were extracted on basis of the Brainnetome Atlas [23] and put into an all-relevant feature selection procedure within cross-validation loops to identify all the features with significant discriminative power for patient classification. On basis of these relevant features, the performance of the model constructed from the training group was assessed in the testing group, to discriminate patients with and without MCI.

Materials and methods

Participants and clinical assessment

The present study was approved by the local ethics committee of the hospital for human research. Written informed consent was obtained from all participants after full explanation of the procedure involved. We evaluated 165 consecutive advanced PD patients (disease duration > 5 years) recruited from the Department of Functional Neurosurgery, Shenzhen Second People's Hospital, between July 2017 and March 2020, and 48 healthy control subjects. PD was diagnosed according to the UK Parkinson's Disease Brain Bank criteria [24]. Participants were excluded if they were (a) meeting the diagnostic criteria for dementia in PD; (b) presence of other significant psychiatric, neurological, or systemic comorbidity; (c) having obvious abnormal findings on brain imaging; and (d) having MRI artefacts. After screening, 131 PD patients were included in our study (Supplementary Figure S1). Forty-eight healthy controls without MCI were matched to PD patients in terms of age, gender, and education.

The motor and non-motor symptoms of patients when medication off were assessed by two experienced clinical neurologists (L.J.L. and Z.D.D.) using multiple rating scales. The Montreal Cognitive Assessment Scale (MoCA), comprising tests of verbal, visuospatial, visual memory, and attention, is suitable to evaluate overall cognitive ability in PD. Besides, a comprehensive neuropsychological assessment was employed in each patient for the five cognitive domains of attention and working memory, executive, language, memory, and visuospatial, according to the Movement Disorder Society Task Force Level II criteria [1].

The diagnosis of PD-MCI was made according to the Movement Disorder Society Task Force Level II criteria [1]. PD-MCI was diagnosed when (1) impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains, and (2) with scores 1.5 standard deviations (SDs) below the average. Patients who did not meet the criteria for PD-MCI were classified as PD patients with normal cognition (PD-NC). After clinical assessment, 59 PD patients fulfilled the criteria for MCI and the rest 72 patients were PD-NC.

Image acquisition and preprocessing

Scanning was performed on a 3 Tesla MR system (Prisma, Siemens Healthcare) equipped with a 64-channel head coil. Patients underwent a scan more than 12 h after the withdrawal of their dopaminergic medications in a clinically defined "off-state." The protocol included high-resolution T1-weighted MR images (magnetization-prepared rapid acquisition gradient echo sequence, resolution $0.9 \times 0.9 \times 0.9$ mm^3, TE/TR = 4 ms/2300 ms), diffusion-weighted images (echo-planar imaging, 60 weighted directions and 2 b0 images, b = 1000 s/mm^2, resolution $2 \times 2 \times 2$ mm^3, TE/TR = 80 ms/8300 ms), and rs-fMRI images (echo-planar imaging, resolution $3 \times 3 \times 3.5$ mm^3, TE/TR = 28 ms/2000 ms, 240 volumes in 8 min, eyes closed).

The preprocessing of DTI data was performed using the toolbox of PANDA [25] in MATLAB (MathWorks). It consisted of skull removal and cropping the gap, correcting motion and eddy current distortions, calculating diffusion tensors. The rs-fMRI data was preprocessed in FSL [26]. The main steps included brain extraction, slice timing correction, rigid-body motion correction, spatial smoothing using a Gaussian kernel of FWHM of 6 mm, and high-pass temporal filtering of 150 s. To remove the effects of motion, non-neural physiology, scanner artifacts, and other confounds, we used the tool of FIX [27–29] for noise cleaning as described previously [30]. Despite noise cleaning, the mean absolute displacement still showed a significant difference between PD patients and healthy controls ($p = 0.004$), but not between PD-MCI and PD-NC patients ($p = 0.16$).

The extraction of connectivity features

The Brainnetome Atlas [23] provides a more elaborate framework for whole-brain connectome analysis in human brain research than the traditional Automated Anatomical Labeling (AAL) atlas. The atlas parcellates the brain into 210 cortical and 36 subcortical sub-regions. In addition, four specific sub-nuclei including the red nucleus, substantia nigra, subthalamic nucleus (STN), and hypothalamus were added into the segmented brain, which resulted in a total of 254 network nodes. The network edges (connectivity features) are defined by structural and functional connectivity strength evaluated from DTI and rs-fMRI data, respectively. The structural connectivity strength between two nodes was computed to be the average FA value of all the tracts through the corresponding two nodes after tractography as described previously [31]. For the preprocessed rs-fMRI data, the mean time series were extracted from each sub-region. Pairwise functional connectivity strength was then estimated by calculating Pearson's correlation coefficients on the time series and transforming the correlation coefficients into z-scores with Fisher's r-to-z transformation. After the processing, we extracted 64262 connectivity features in total.

Feature selection

bWe randomly split all the patients into 2 groups, and then we used the one group including 100 patients as the training group and the other one including 31 patients as the testing group. In each group, the percentage of PD-MCI and PD-NC patients was nearly the same. All steps

Table 1 The demographic and clinical outcome of all participants

	PD-MCI (n = 59)	PD-NC (n = 72)	HC (n = 48)	p value[a]	PD-MCI versus PD-NC p value[b]	PD-MCI versus HC p value[b]	PD-NC versus HC p value[b]
Age (years)	62.8 ± 8.8 (51–76)	59.3 ± 10.8 (48–78)	60.4 ± 10.2 (45–75)	0.14	0.12	0.44	0.83
Sex (M/F)	27/32	42/30	25/23	0.36[c]	0.15[c]	0.52[c]	0.50[c]
Education (years)	7.8 ± 4.3 (2–16)	8.9 ± 4.5 (3–16)	9.3 ± 4.1 (5–16)	0.15	0.29	0.16	0.86
Disease duration (years)	9.1 ± 3.3 (5–16)	8.5 ± 3.5 (5–15)	NA	NA	0.32	NA	NA
LEDD (mg)	810.6 ± 288.5 (425–1750)	744.1 ± 259.3 (250–1488.5)	NA	NA	0.17	NA	NA
UPDRS-III	53.9 ± 11.9 (33–83)	49.7 ± 15.1 (15–82)	NA	NA	0.084	NA	NA
MoCA	21.8 ± 4.5 (11–28)	26.8 ± 2.6 (23–30)	27.1 ± 2.2 (24–30)	< 0.001	< 0.001	< 0.001	0.88
PDQ-39	61.5 ± 26.0 (13–130)	52.9 ± 28.3 (5–148)	NA	NA	0.075	NA	NA
BDI	11.9 ± 9.1 (3–42)	9.3 ± 8.5 (0–39)	8.4 ± 7.2 (0–32)	0.075	0.18	0.083	0.83
HAMA	17.1 ± 8.0 (3–38)	14.0 ± 8.1 (0–33)	12.9 ± 7.4 (0–30)	0.016	0.068	0.019	0.73
Apathy scale	12.9 ± 5.8 (3–29)	13.3 ± 6.2 (3–31)	9.6 ± 5.1 (2–20)	0.002	0.92	0.011	0.002
PSQI	15.2 ± 8.9 (0–21)	13.1 ± 8.2 (3–20)	11.6 ± 7.5 (0–18)	0.078	0.32	0.067	0.59

BDI, Beck Depression Inventory; *F*, female; *HAMA*, Hamilton Anxiety Scale; *HC*, healthy controls; *LEDD*, levodopa equivalent daily dose; *M*, male; *MoCA*, Montreal Cognitive Assessment Scale; *NA*, not applicable; *PD-MCI*, PD patients with mild cognitive impairment; *PD-NC*, PD patients with normal cognition; *PSQI*, Pittsburgh Sleep Quality Index; *UPDRS-III*, Unified Parkinson's Disease Rating Scale part III; *PDQ-39*, Parkinson's Disease Questionnaire

Values are represented as the mean ± standard deviation with the range in parentheses, except for the gender distribution

[a] Unless otherwise indicated, p values were calculated with one-way ANOVA tests among three groups

[b] Unless otherwise indicated, p values were calculated with two-tailed t-tests

[c] p value was obtained using chi-squared tests

of feature selection and model training were just performed in the training group.

To select features with significant discriminative power for MCI diagnosis, all connectivity features were put into an all-relevant feature selection procedure within cross-validation loops using the random forest algorithm (Supplementary Figure S2), which was detailed in our previous study [30]. Features with significantly higher selection frequency than random values defined by permutation test (permuted 1000 times) were regarded as MCI-related selections, with p value < 0.05 after false discovery rate (FDR) correction for multiple comparisons [32].

MCI subjects and matched healthy controls from the ADNI database

After feature selection, connectivity markers were identified to be relevant to MCI diagnosis in PD. Next, we wanted to know whether these markers also acted for the discrimination between general MCI patients and healthy controls. Fifty MCI subjects and 50 healthy, age-, gender-, and education-matched controls were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. T1-weighted MRI, DTI, and rs-fMRI images were all available for these 100 participants. After the same data processing flow mentioned above, connectivity features in MCI subjects and healthy controls were extracted for further group comparisons.

External validation using the PPMI database

To evaluate the generalizability of our random forest model, we used an external validation sample including 50 PD-MCI patients and 50 age-, gender-, and education-matched PD-NC controls from the Parkinson Progression Markers Initiative (PPMI) database. Using the same data processing flow mentioned above, connectivity markers were extracted and put into the model being constructed on our database, to predict the outcome of MCI diagnosis in the external validation sample.

Results

Demographic characteristics and clinical outcome

The demographic characteristics and clinical outcome of all participants are listed in Table 1. Fifty-nine PD patients (45.0%) fulfilled the criteria for MCI and the rest (55.0%) were cognitively normal. No significant differences were found in age, gender, or education among PD-MCI patients, PD-NC patients, and healthy controls (one-way ANOVA and chi-squared tests, p values > 0.05). In the post hoc comparisons, PD-MCI and PD-NC patients showed significant differences only in the MoCA score (two-tailed t-tests, p values < 0.001 after Tukey's correction for multiple comparisons).

The performance of random forest classifiers

We performed 100 runs of 10-fold cross-validation during the all-relevant feature selection procedure in the training group, which resulted in a total of 1000 training-validation cycles and the corresponding random forest classifiers to discriminate PD-MCI patients from PD-NC ones. The accuracy and Cohen's kappa coefficient of the classifiers were 85.2 ± 7.4% and 0.63 ± 0.18, respectively. The corresponding sensitivity and specificity were 88.1 ± 7.9% and 82.6 ± 7.0%, respectively.

Significantly relevant connectivity features

During the all-relevant feature selection procedure, a total of 1000 feature subsets were created and the corresponding classifiers were built. The mean number of features in the subsets was 15.4 (range from 8 to 20, 0.012–0.031% of all features). Using the permutation test, nine features (Fig. 1) were identified to be significantly relevant to patient classification (Table 2). These nine features were listed as follows: the structural connectivity between superior frontal gyrus (SFG) and STN; between superior temporal gyrus (STG) and inferior parietal lobule (IPL); between hippocampus and thalamus, and the functional connectivity between SFG and insula; between inferior frontal gyrus (IFG) and precentral gyrus (PrG); between PrG and insula; between STG and precuneus; between parahippocampal gyrus (PhG) and postcentral gyrus (PoG); and between PoG and insula. Moreover, there were significant differences in these relevant features between PD-MCI and PD-NC patients (all p values < 0.01, after FDR correction; Fig. 1 and Table 2). These features also significantly correlated with MoCA score in all patients (all p values < 0.005, after FDR correction; Fig. 2).

Group comparisons of identified markers were performed in PD-MCI and PD-NC patients, and also between general MCI subjects and healthy controls from the ADNI database, using the Mann-Whitney tests with FDR correction for multiple comparisons. Compared to the healthy controls, these nine features were significantly different in PD-MCI patients and six of them (SFG-STN and hippocampus-thalamus structural connectivity, and IFG-PrG, PrG-insula, PhG-PoG, and PoG-insula functional connectivity) were significantly different in PD-NC patients (ANCOVA tests and post hoc comparisons, p values < 0.01; Fig. 1), after regarding

Table 2 Significantly relevant connectivity features to discriminate PD-MCI and PD-NC patients

Selection frequency (%)*	Feature description	PD-MCI	PD-NC	HC
92.3	SFG-insula FC	0.28 ± 0.23	0.50 ± 0.17	0.48 ± 0.10
90.6	SFG-STN SC	0.31 ± 0.03	0.34 ± 0.03	0.37 ± 0.04
89.1	STG-precuneus FC	0.17 ± 0.18	0.38 ± 0.21	0.45 ± 0.15
86.5	IFG-PrG FC	0.15 ± 0.20	0.33 ± 0.19	0.43 ± 0.11
85.8	PrG-insula FC	0.15 ± 0.23	0.32 ± 0.16	0.46 ± 0.12
84.3	STG-IPL SC	0.32 ± 0.06	0.36 ± 0.07	0.37 ± 0.04
82.1	Hippocampus-thalamus SC	0.35 ± 0.05	0.38 ± 0.04	0.41 ± 0.04
78.5	PhG-PoG FC	0.12 ± 0.17	0.28 ± 0.19	0.41 ± 0.14
76.9	PoG-insula FC	0.17 ± 0.23	0.35 ± 0.20	0.49 ± 0.10

FC, functional connectivity; *HC*, healthy controls; *IFG*, inferior frontal gyrus; *IPL*, inferior parietal lobule; *PD-MCI*, PD patients with mild cognitive impairment; *PD-NC*, PD patients with normal cognition; *PhG*, parahippocampal gyrus; *PoG*, postcentral gyrus; *PrG*, precentral gyrus; *SC*, structural connectivity; *SFG*, superior frontal gyrus; *STG*, superior temporal gyrus; *STN*, subthalamic nucleus

Values are represented as the mean ± standard deviation, except for the selection frequency

*Defined as the number of iterations in which the feature was selected divided by the total number of iterations performed

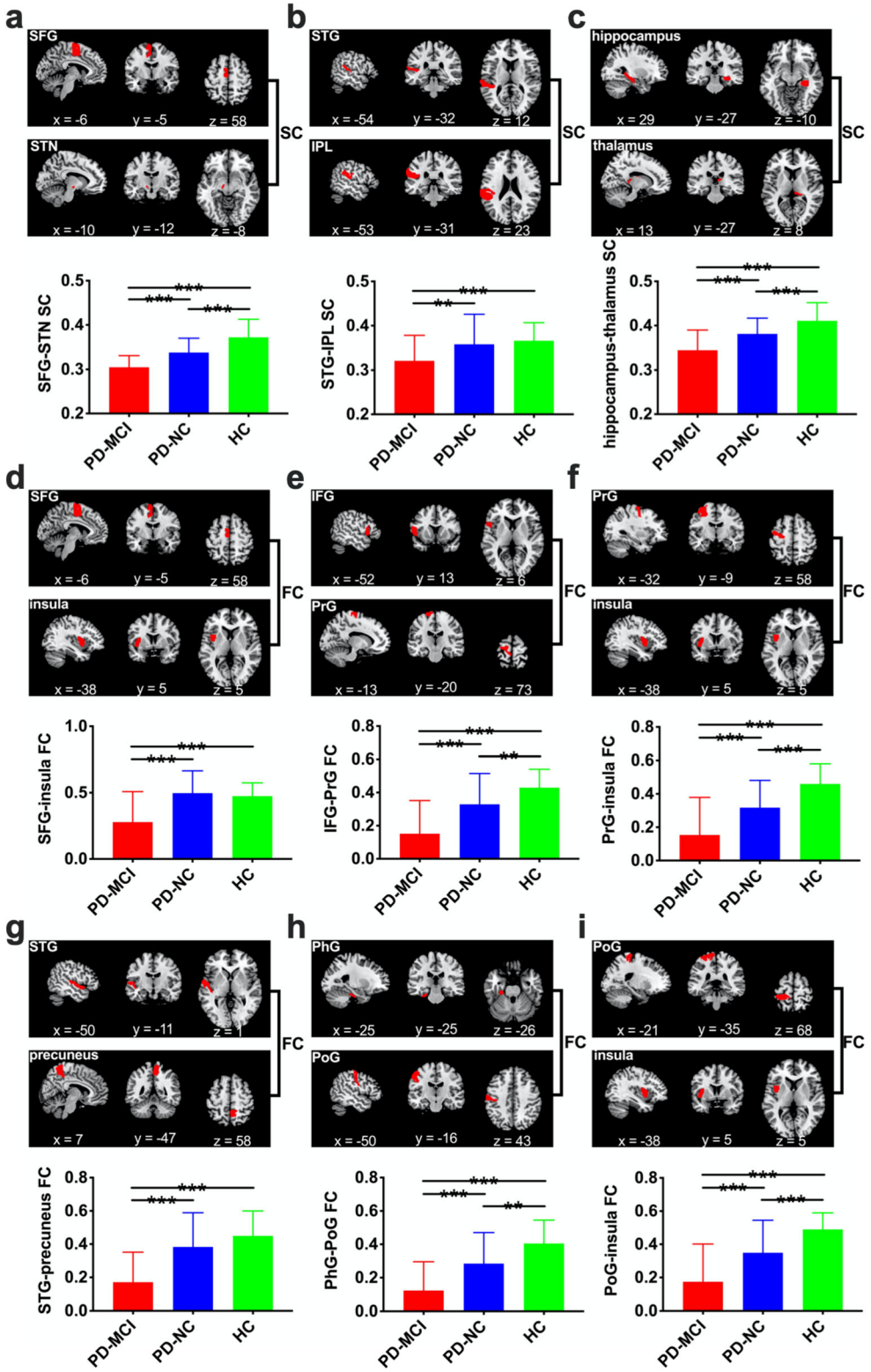

Fig. 1 Nine identified connectivity features using the all-relevant feature selection algorithm. These features were listed as follows: SFG-STN SC (**a**), STG-IPL SC (**b**), hippocampus-thalamus SC (**c**), SFG-insula FC (**d**), IFG-PrG FC (**e**), PrG-insula FC (**f**), STG-precuneus FC (**g**), PhG-PoG FC (**h**), PoG-insula FC (**i**). They all showed significant differences between PD-MCI and PD-NC patients. Compared to the healthy controls, these nine features were significantly different in PD-MCI patients and six of them (SFG-STN SC, hippocampus-thalamus SC, IFG-PrG FC, PrG-insula FC, PhG-PoG FC and PoG-insula FC) were significantly different in PD-NC patients, after regarding the mean absolute displacement as a covariate (ANCOVA tests and post hoc comparisons). Statistical significance is indicated by asterisks (***, $p < 0.001$; **, $p < 0.01$). FC, functional connectivity; HC, healthy controls; PD-MCI, PD patients with mild cognitive impairment; PD-NC, PD patients with normal cognition; SC, structural connectivity

the mean absolute displacement as a covariate to consider the difference in the level of head motion during MRI scanning. For the comparisons between general MCI subjects and healthy controls, five relevant features (SFG-STN and hippocampus-thalamus structural connectivity, and PrG-insula, PhG-PoG, and PoG-insula functional connectivity) showed no significant differences (p values > 0.05, after FDR correction; Fig. 3).

Connectivity-based prediction for the outcome of MCI diagnosis

Nine connectivity markers of MCI were screened during the feature selection procedure in the training group (100 patients). On basis of them, the random forest model constructed from the training group achieved an accuracy of 83.9% in the testing group (31 patients), to discriminate patients with and without MCI. For the external validation sample from the PPMI database, it performed unsatisfactorily in patient classification, with an accuracy of 67%. However, all these nine connectivity markers of MCI showed significant differences between PD-MCI and PD-NC patients from the PPMI database (all p values < 0.01, after FDR correction; Supplementary Figure S3).

Discussion

In brief, our study revealed that structural and functional connectivity could independently characterize cognitive ability and help MCI diagnosis in advanced PD patients. Using the all-relevant feature selection procedure, we identified nine connectivity markers of MCI. On basis of these markers, the random forest model achieved an accuracy of 83.9% to discriminate between PD-MCI and PD-NC patients.

In this study, we focused on MCI and excluded dementia in advanced PD patients. MCI is considered to be a potential transitional state between normal cognition and dementia in PD and also an independent risk factor for dementia [33]. It is important to investigate the neural mechanism of MCI in PD and identify objective biomarkers that allow clinical diagnosis. More and more studies have concentrated on PD-MCI and made substantial progress [34, 35], since the Movement Disorder Society Task Force established criteria for PD-MCI [1]. In our study, we extracted features of whole-brain structural and functional connectivity from a considerable number of PD patients. Connectivity features were put into an all-relevant feature selection procedure. Compared with the commonly used methods such as t-test and Pearson's correlation analysis to select related features and primary component analysis to reduce the dimensionality of feature space, the

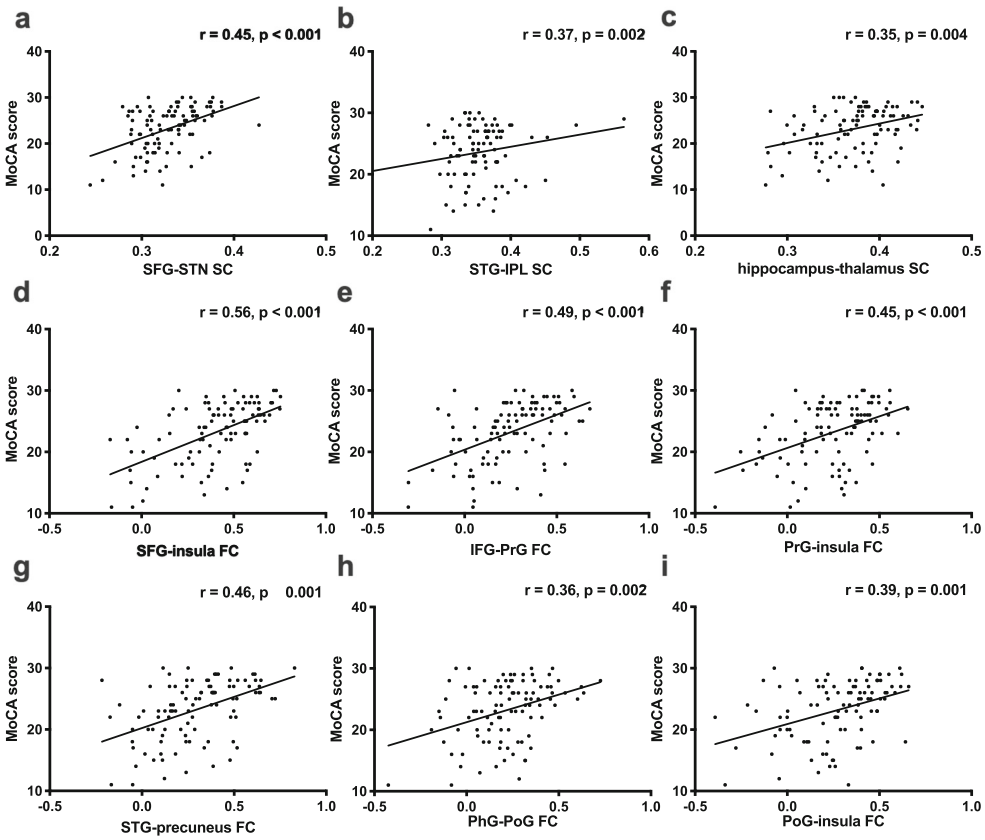

Fig. 2 Relationship between the MCI-related features and MoCA score. Significant correlations were revealed between the nine identified connectivity features and MoCA score in all patients (**a-i**, all p values < 0.005, after FDR correction). FC, functional connectivity; MoCA, Montreal Cognitive Assessment Scale; SC, structural connectivity

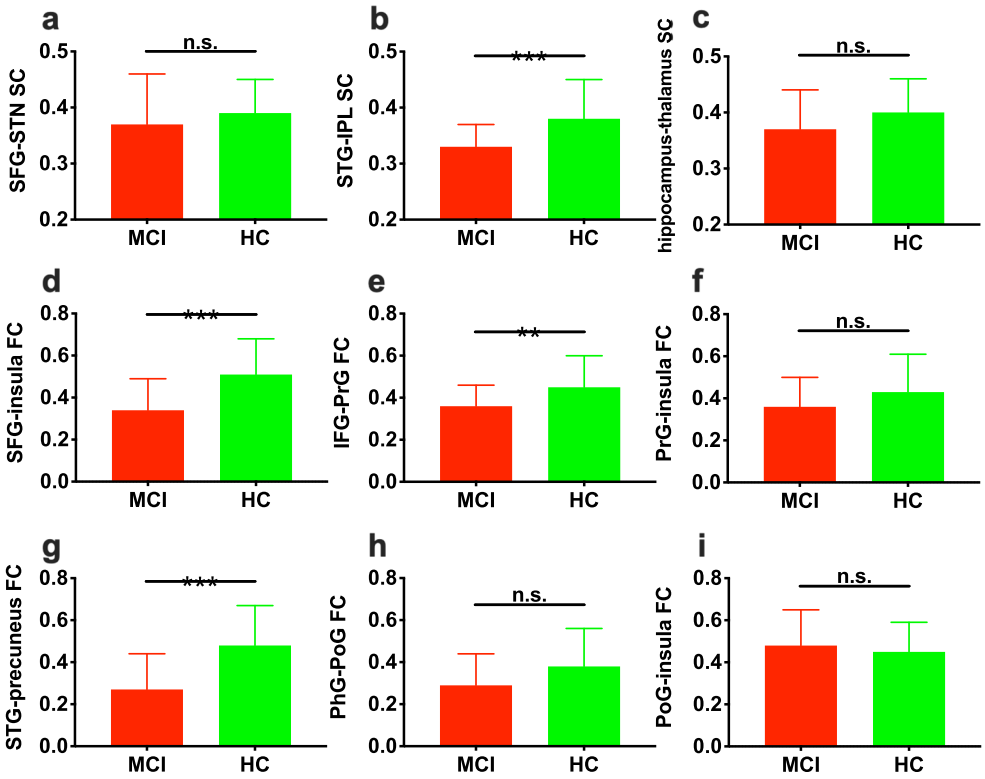

Fig. 3 The comparisons of MCI-related features between general MCI subjects and healthy controls from the ADNI database (**a**-**i**). Five relevant features (SFG-STN and hippocampus-thalamus structural connectivity, and PrG-insula, PhG-PoG, and PoG-insula functional connectivity) showed no significant differences (Mann-Whitney tests, p values > 0.05, after FDR correction). Statistical significance is indicated by asterisks and n.s. (***, $p < 0.001$; **, $p < 0.01$; n.s., not significant). FC, functional connectivity; HC, healthy controls; MCI, mild cognitive impairment; SC, structural connectivity

all-relevant feature selection algorithm can identify all features that significantly contribute to classification in a data-driven manner.

Among all the involved sub-regions of connectivity, the IPL and precuneus are both the key nodes of the DMN, which is the most studied network related to cognitive impairment in PD due to its implication in Alzheimer's disease (AD). Hypometabolism in the IPL and precuneus is a predictor of cognitive decline from MCI to dementia [36]. In PD, a tau PET study has shown increased signal in the precuneus, which was associated with heightened cognitive impairment [37]. Early task-fMRI studies revealed that PD had a close relation with altered patterns of deactivation in the precuneus, which had been previously observed in AD [38, 39]. Tessitore et al first found that cognitively unimpaired patients with PD compared with healthy controls showed a decreased functional connectivity in bilateral IPL, which significantly correlated with cognitive parameters [40]. In a more recent study comparing early-stage drug-naïve PD-MCI patients and healthy controls, a significant reduction was found in functional connectivity between the posterior IPL and posterior cingulate cortex (PCC), between the left precuneus and left SFG/PCC [41]. In our case, structural and functional connectivity was decreased in the comparison of PD-MCI and PD-NC patients between the IPL/precuneus and STG, which was a part of cognitive control network. These findings provide evidence supporting the hypothesis that these IPL/precuneus-related connectivity alterations underlie cognitive impairment in PD and may be considered to be neuroimaging biomarkers for clinical diagnosis.

The insula, a cortical region beneath the frontal, temporal, and parietal lobes, is one of the core brain regions that anchor the salience network [42, 43]. The connectivity of insula and its relationship with cognitive impairment in PD were assessed in previous studies [18, 44, 45]. Aracil-Bolaños et al found that functional and graph theoretical changes appeared in anterior insula and its node degree positively correlated with global cognition in PD-MCI patients [18]. In a rs-fMRI study segmenting the insula into ventral and dorsal subregions, the functional connectivity between the dorsal anterior insula and DMN highly correlated with the scores from a battery of cognitive tests in PD [45]. These observations were in line with the insular cortex atrophy and dopaminergic deficits in early-stage PD with MCI [46, 47]. In this study, we used the Brainnetome Atlas in which the unilateral insular cortex was parcellated into six sub-regions [23]. The connectivity abnormalities of the dorsal dysgranular insula with the primary somatosensory and motor cortex (the somatomotor network) positively correlated with global cognition. The dysgranular insula is involved in olfactory function and olfactory dysfunction is a cardinal premotor symptom of PD, which might explain our finding that these insula-related connectivity abnormalities occurred in PD-MCI patients but not in general MCI subjects, compared to healthy controls.

Based on relevant connectivity features, our random forest model achieved an accuracy of 83.9% to distinguish between PD patients with and without MCI. In a previous rs-fMRI study, a mean accuracy of 80.0% was obtained in separating PD patients with MCI from those without it in the validation sample [44]. PD-MCI is a heterogeneous entity in phenotype, timing, and progression, affecting a range of cognitive domains including attention and working memory, executive, language, memory, and visuospatial [48]. According to the Movement Disorder Society Task Force criteria [1], MCI diagnosis in PD is based on the assessment result of an insidious decline in cognitive abilities reported by the patient or observed by the clinician, not caused by other comorbidities. A range of standard neuropsychological tests were recommended for this assessment [1]. However, the assessment need be performed by experienced clinicians and the involved neuropsychological tests may be difficult for some PD patients such as patients with speech disorder, dementia, or a low degree of compliance. In this situation, the machine learning model in our study was constructed on the basis of patients' DTI and rs-fMRI data without performing any specific task, which revealed its potential clinical applicability for MCI diagnosis in PD. In addition, the role of these objective connectivity markers can be further explored in the diagnosis criteria for PD-MCI.

We recruited 165 PD patients in a single cohort and used an all-relevant feature selection procedure within cross-validation loops to increase the generalizability of random forest classifiers. The machine learning model performed moderately effectively to predict the outcome of MCI diagnosis in the internal split sample, but not in the external validation sample from the PPMI database. There were some possible explanations for the unsatisfactory generalization ability of the model, such as the different race, MRI scanner, and sequences. More importantly, the patients from the PPMI database were in the early stage of PD and unmedicated, while we included advanced PD patients (disease duration > 5 years) with an average levodopa equivalent daily dose (LEDD) of 774.1 mg from our cohort. These variables might contribute to the poor performance. Now we proceed to a longitudinal study to test the accuracy of our findings and evaluate the predictive value of identified connectivity markers for cognitive decline in early-stage PD patients of our cohort. Despite the unsatisfactory performance of the model in the external sample, the main objective of this study was to identify connectivity features significantly contributing to MCI diagnosis in PD. The group differences of these nine connectivity features existed both in our database and the external sample, which suggested that they could become potential MCI markers in PD.

Conclusions

Compared to PD patients with normal cognition and healthy controls, we found an abnormal pattern of structural and functional connectivity in advanced PD patients with MCI, which independently contributed to patient classification. Under the combination of the connectivity markers for MCI, moderately successful discrimination was achieved for MCI diagnosis in advanced PD patients.

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Declarations

Guarantor The scientific guarantor of this publication is Mr. Cai.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry Not applicable.

Informed consent Written informed consent was obtained from all participants after full explanation of the procedure involved.

Ethical approval The present study was approved by the local ethics committee of the hospital for human research.

Methodology
- retrospective
- observational
- performed at one institution

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