# Functional connectivity markers of depression in advanced Parkinson's disease

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## ABSTRACT

*Background:* Depression is a common comorbid condition in Parkinson's disease and a major contributor to poor quality of life. Despite this, depression in PD is under-diagnosed due to overlapping symptoms and difficulties in the assessment of depression in cognitively impaired old patients.
*Objectives:* This study is to explore functional connectivity markers of depression in PD patients using resting-state fMRI and help diagnose whether patients have depression or not.
*Methods:* We reviewed 156 advanced PD patients (duration > 5 years; 59 depressed ones) and 45 healthy control subjects who underwent a resting-state fMRI scanning. Functional connectivity analysis was employed to characterize intrinsic connectivity networks using group independent component analysis and extract connectivity features. Features were put into an all-relevant feature selection procedure within cross-validation loops, to identify features with significant discriminative power for classification. Random forest classifiers were built for depression diagnosis, on the basis of identified features.
*Results:* 42 intrinsic connectivity networks were identified and arranged into subcortical, auditory, somato-motor, visual, cognitive control, default-mode and cerebellar networks. Six features were significantly relevant to classification. They were connectivity within posterior cingulate cortex, within insula, between posterior cingulate cortex and insula/hippocampus + amygdala, between insula and precuneus, and between superior parietal lobule and medial prefrontal cortex. The mean accuracy achieved with classifiers to discriminate depressed patients from the non-depressed was 82.4%.
*Conclusions:* Our findings provide preliminary evidence that resting-state functional connectivity can characterize depressed PD patients and help distinguish them from non-depressed ones.

## 1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder characterized by the clinical tetrad of motor dysfunction, including resting tremor, rigidity, akinesia (bradykinesia) and postural instability (Jankovic, 2008). Besides predominant motor symptoms, a wide range of non-motor symptoms (NMS) is highly prevalent in PD patients. Depression is one of the most common NMS, occurring in around 35% of patients (Reijnders et al., 2008). Although depression is also a common symptom of other illnesses and often occurs in elderly population without PD, it's suggested by some evidence that depression is more frequent in PD patients than in general persons with the same age or patients with other chronic and disabling diseases, such as diabetes (Nilsson et al., 2002). Along with the progression of PD, depression has been associated with reduced functioning, cognitive impairment and increased stress, which greatly contribute to the poor quality of life for PD patients (Wang et al., 2013). Despite of its great impact, the neural basis of depression in PD is still not well understood and research is underway to investigate brain abnormalities underlying depressive symptoms as well as to assist clinical diagnosis on the basis of identified markers.

Modern imaging methods, including PET and MRI, have provided useful tools to explore brain differences between PD patients with and without depression. Within the last few years, neuroimaging reports

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**Table 1**
The demographic and clinical information of all participants.

| | D-PD ($n = 59$) | ND-PD ($n = 97$) | HC ($n = 45$) | P value |
|---|---|---|---|---|
| Age (years) | 57.6 ± 10.7 (41 - 75) | 61.2 ± 9.5 (44 - 79) | 59.4 ± 10.0 (45 - 75) | 0.092[*,a] |
| Sex (M/FM) | 28/31 | 51/46 | 24/21 | 0.77[†] |
| PD duration (years) | 9.5 ± 2.9 (5 - 14) | 7.8 ± 2.4 (5 - 12) | NA | 0.001[‡] |
| LEDD | 1056.4 ± 483.6 (250 - 1750) | 1004.8 ± 452.9 (250 - 1750) | NA | 0.43[‡] |
| UPDRS III | 46.4 ± 15.2 (30 - 81) | 44.6 ± 13.5 (23.5 - 76) | NA | 0.48[‡] |
| HDRS | 24.1 ± 10.5 (12 - 54) | 13.9 ± 6.7 (2 - 24) | 6.7 ± 4.6 (0 - 15) | < 0.001[*,b] |
| BDI | 21.5 ± 11.1 (9 - 48) | 8.1 ± 6.2 (2 - 20) | 4.9 ± 3.5 (0 - 12) | < 0.001[*,b] |
| PSQI | 15.7 ± 8.4 (4 - 34) | 14.2 ± 7.6 (2 - 32) | 12.7 ± 6.7 (1 - 26) | 0.14[*,a] |
| MoCA | 23.1 ± 5.4 (14 - 30) | 24.2 ± 4.6 (15 - 30) | 26.9 ± 2.4 (26 - 30) | < 0.001[*,c] |
| MMSE | 26.9 ± 3.1 (20 - 30) | 27.6 ± 2.8 (22 - 30) | 28.2 ± 2.1 (26 - 30) | 0.065[*,a] |

BDI = Beck Depression Inventory, D-PD = depressed PD, FM = female, HC = healthy controls, HDRS = Hamilton Depression Rating Scale, LEDD = levodopa equivalent daily dose, $M$ = male, MMSE = Mini-Mental State Examination, MoCA = Montreal Cognitive Assessment Scale, NA = not applicable, ND-PD = non-depressed PD, PSQI = Pittsburgh Sleep Quality Index, UPDRS III = Unified Parkinson's Disease Rating Scale part III.
Values are represented as the mean ± standard deviation with the range in parentheses, except for the gender distribution. For comparisons of demographic and clinical characteristics:.

[*] P values were calculated with One-way ANOVA tests.
[†] P value was obtained using a chi-squared test.
[‡] P values were calculated with two-tailed t tests.
[a] Post-hoc paired comparisons showed no significant differences between each two of the three groups.
[b] Post-hoc paired comparisons showed significant differences between each two of the three groups.
[c] Post-hoc paired comparisons showed significant differences between D-PD and HC, and between ND-PD and HC. $P < 0.05$ was considered significant.

have provided evidence that depression was the result of regional abnormalities in the prefrontal cortex, the basal ganglia and the limbic system (including the thalamus, ventral striatum, amygdala, insula and cingulate cortex), which were modulated by the neurotransmitter systems of dopaminergic, serotoninergic, cholinergic and noradrenergic (Remy et al., 2005; Etkin et al., 2011; Ballanger et al., 2012). Specifically in a PET study investigating depression in PD, the decrease of serotonin 1A receptor availability was exhibited in the right insula, left hippocampus, left superior temporal cortex and orbitofrontal cortex of patients with depression, compared to those without depression (Ballanger et al., 2012). Moreover, increased gray matter volume in bilateral mediodorsal thalamic nuclei was found in depressed PD patients by voxel-based morphometry (Cardoso et al., 2009).

In addition to the regional abnormalities, depression in PD was also related to network differences (Sheng et al., 2014; Luo et al., 2014; Lou et al., 2015; Hu et al., 2015). Resting-state functional MRI (rs-fMRI) can characterize spontaneous brain activity and identify brain networks with co-varied patterns, which make it a powerful technique to examine network abnormalities associated with depression in PD patients without performing any specific task. In a rs-fMRI study analyzing the amplitude of low-frequency fluctuations and functional connectivity (FC) in the whole brain, depressed PD patients were characterized by increased regional spontaneous neural activity in the orbitofrontal area and decreased functional integration within the prefrontal-limbic network, compared to non-depressed patients and healthy controls (Luo et al., 2014). Lou et al. (2015) showed that depressed PD patients had decreased FC in the left dorsolateral prefrontal cortex and right superior temporal gyrus, and increased FC in the right posterior cingulate cortex (PCC), in comparison to non-depressed patients. In addition, the FC in the PCC was negatively correlated with depression scores. However, these regional and network abnormalities were found in PD patients from a small cohort. With sufficient number of patients, classifiers can be constructed to distinguish between depressed and non-depressed patients, which potentially help depression diagnosis in PD patients.

In this study, we collected rs-fMRI data from advanced PD patients (PD duration > 5 years) and healthy control subjects in our cohort. To investigate the relationship between the whole-brain functional connectivity and depression, we extracted FC features based on the patient-specific intrinsic connectivity networks, and identified all the features with significant discriminative power for depression diagnosis under the combination of random forest model and cross validation, which

might advance our understanding for the neural substrates of depression in PD.

## 2. Materials and methods

### 2.1. Participants and clinical assessment

According to the UK Parkinson's Disease Brain Bank criteria (Hughes et al., 1992), advanced idiopathic PD patients (PD duration > 5 years) were consecutively recruited from the Department of Functional Neurosurgery, Shenzhen Second People's Hospital between March 2014 and October 2018. Participants were excluded if they were: (a) having cerebrovascular disorders, including a history of head injury, a previous stroke, a history of seizure, intracranial mass, hydrocephalus, previous neurological surgery and other neurological diseases; (b) having psychiatric diseases other than depression; (c) treated with antidepressants or other psychiatric therapy; (d) having excessive head movement (mean absolute displacement > 3.5 mm) during MRI scanning. After screening, a total of 156 PD patients were enrolled into the study. 59 of them were diagnosed to have depression according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria (Starkstein et al., 2011) by an experienced psychiatrist. 45 healthy, age- and sex-matched participants who did not have any neurological or psychiatric disorders were included as healthy controls. This study was approved by the local ethics committee of our hospital for human research. All participants were fully informed about the purpose and procedures of the study, and provided written informed consent before enrollment.

The motor and non-motor symptoms of patients were assessed by an experienced clinical neurologist using multiple rating scales when medication off, including the Unified Parkinson's Disease Rating Scale part III (UPDRS-III), the 24-item Hamilton Depression Rating Scale (HDRS), the Beck Depression Inventory (BDI), the Montreal Cognitive Assessment Scale (MoCA), the Mini-Mental State Examination (MMSE) and the Pittsburgh Sleep Quality Index (PSQI).

### 2.2. MRI dataset acquisition and preprocessing

Scanning was performed on a 3T MRI system (Prisma, Siemens, Erlangen, Germany) using a 32-channel head coil. Patients were scanned more than 12 h after the withdrawal of their dopaminergic medications in a clinically defined "off-state". The protocol included
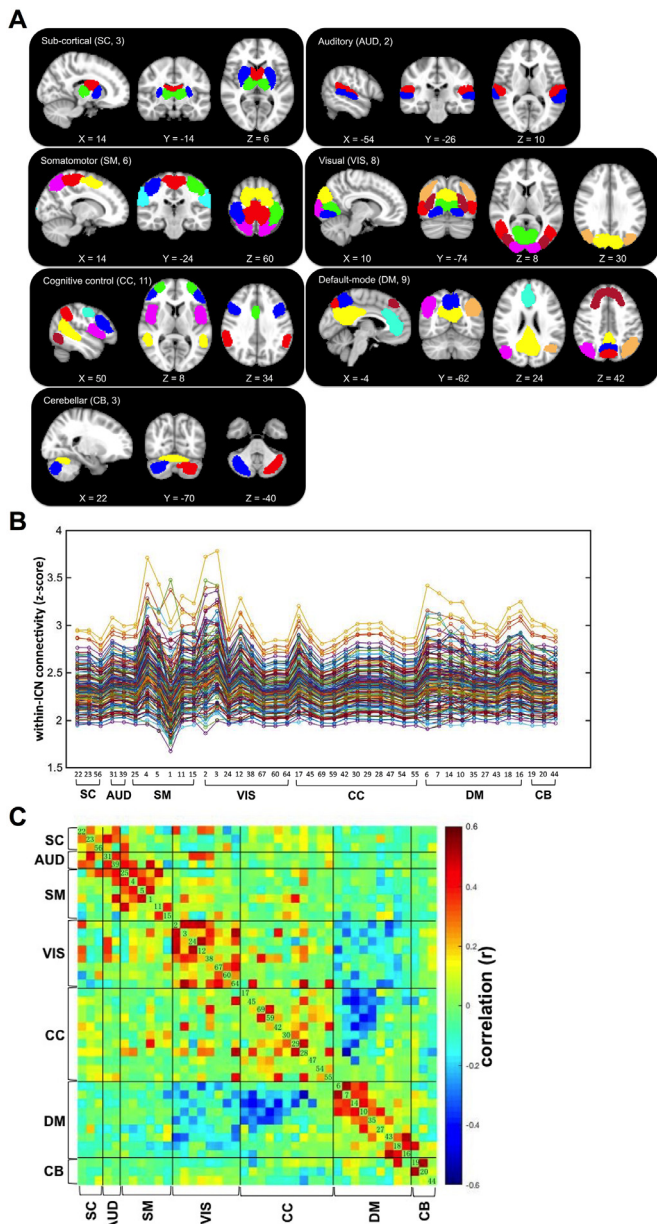
**Fig. 1.** Spatial maps of the 42 ICNs in the patient-specific template and FC features including within-ICN and between-ICN connectivity strength. (A) 42 ICNs being arranged into subcortical (SC), auditory (AUD), somatomotor (SM), visual (VIS), cognitive control (CC), default-mode (DM) and cerebellar (CB) networks. Each color in a sub-network represents a different ICN. (B) The distribution of within-ICN connectivity strength (z-score) among patients. Each colored line corresponds to a different patient. (C) The FC strength between each two ICNs, averaged over patients and inverse Fisher transformed for display.

high-resolution T1-weighted MR images and rs-fMRI images (EPI, resolution $3 \times 3 \times 3.5$ mm$^3$, TE/TR = 28 ms/2000 ms, 240 vol in 8 min, eyes closed).

The preprocessing of rs-fMRI data as performed in FSL (Jenkinson et al., 2012), 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. 24 motion parameters of each participant, derived from the six rigid-body parameter time series, were extracted for subsequent motion artifact removal. They consisted of the six rigid-body parameter time series, the backward-looking temporal derivatives, and the squares of

the twelve resulting regressors. Using the MELODIC tool in FSL, Single-subject probabilistic independent component analysis (ICA) was performed with automated dimensionality estimation for ICA-based artifact removal (Beckmann and Smith, 2004).

To remove the effects of motion, non-neural physiology, scanner artifacts and other confounds, we used the tool of FMRIB's ICA-based Xnoiserfier – FIX (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014) for noise cleaning. The FIX employed machine learning approaches to classify the single-subject ICA results of rs-fMRI data into 'good' and 'bad' components, respectively. First, the FIX was trained on the randomly chosen sample of 50 participants in our cohort by an experienced imaging expert, which obtained an accuracy of 95.6% true-positive ratio and 88.1% true-negative ratio at a leave-one-out test. After training, FIX automatically classified the ICA output of all the participants into 'good' and 'bad' components. $53.2 \pm 14.9\%$ of components were classified as 'bad' components and removed for all participants ($49.5 \pm 11.8\%$ of the total variance). And then, the bad components and motion confounds with 24 motion parameters were regressed out from the preprocessed rs-fMRI data. After noise cleaning, the level of motion-related noise in term of the mean absolute displacement was significantly reduced in rs-fMRI data ($p$ values < 0.001 for both PD patients and healthy controls). However, the mean absolute displacement of PD patients still significantly differed from that of healthy controls ($p < 0.01$). No difference was revealed between depressed and non-depressed patients ($p > 0.1$).

### 2.3. The creation of patient-specific ICN template

A patient-specific template of intrinsic connectivity network (ICN) was created by group-ICA from temporally concatenating data of all the patients. The group-ICA was performed using the MELODIC tool, with the number of components set to 100. By visual inspection, an independent component was categorized as an artifact when it had the following characteristics: 1) low spatial overlap with gray matter or high spatial overlap with the sagittal sinus, white matter, cerebrospinal fluid or brain's boundary in structural templates, 2) a large number of small clusters, 3) large high-frequency (> 0.1 Hz) power in the time-course spectrum, and 4) the time series was bimodal or had sharp peaks or large jumps (Smith et al., 2013; Salimi-Khorshidi et al., 2014). Moreover, the component was not categorized as signal if it was driven by a single outlier subject (Pyka et al., 2009). With the template, the approach of dual regression (Filippini et al., 2009) was used to identify individual time courses and the associated spatial maps of all the ICNs for all participants.

### 2.4. The extraction of depression-related FC features

After dual regression, FC features including within-ICN and between-ICN connectivity strength were extracted for each participant. The within-ICN connectivity strength was computed to be the average value of the spatial map with z-score for each ICN. The between-ICN connectivity strength was estimated from the covariance matrix with the individual time courses of all the ICNs. The covariance was calculated from the regularized precision matrix using the graphical LASSO method (Friedman et al., 2008), placing a penalty on the L1 norm of the precision matrix to promote sparsity with the regularization parameter $\lambda$ set to 0.1. After Fisher transformation, a between-network connectivity matrix was obtained for each participant.

To identify features with significant discriminative power for depression diagnosis, FC features were put into an all-relevant feature selection procedure within cross-validation loops using the random forest algorithm (Supplementary Fig. 1), as described in a previous study (Sun et al., 2017). All PD patients were divided into two groups: patients with and without depression. The selection procedure was embedded in a repeated 10-fold cross-validation framework (repeated 100 times) to obtain unbiased estimates of classification error. For each
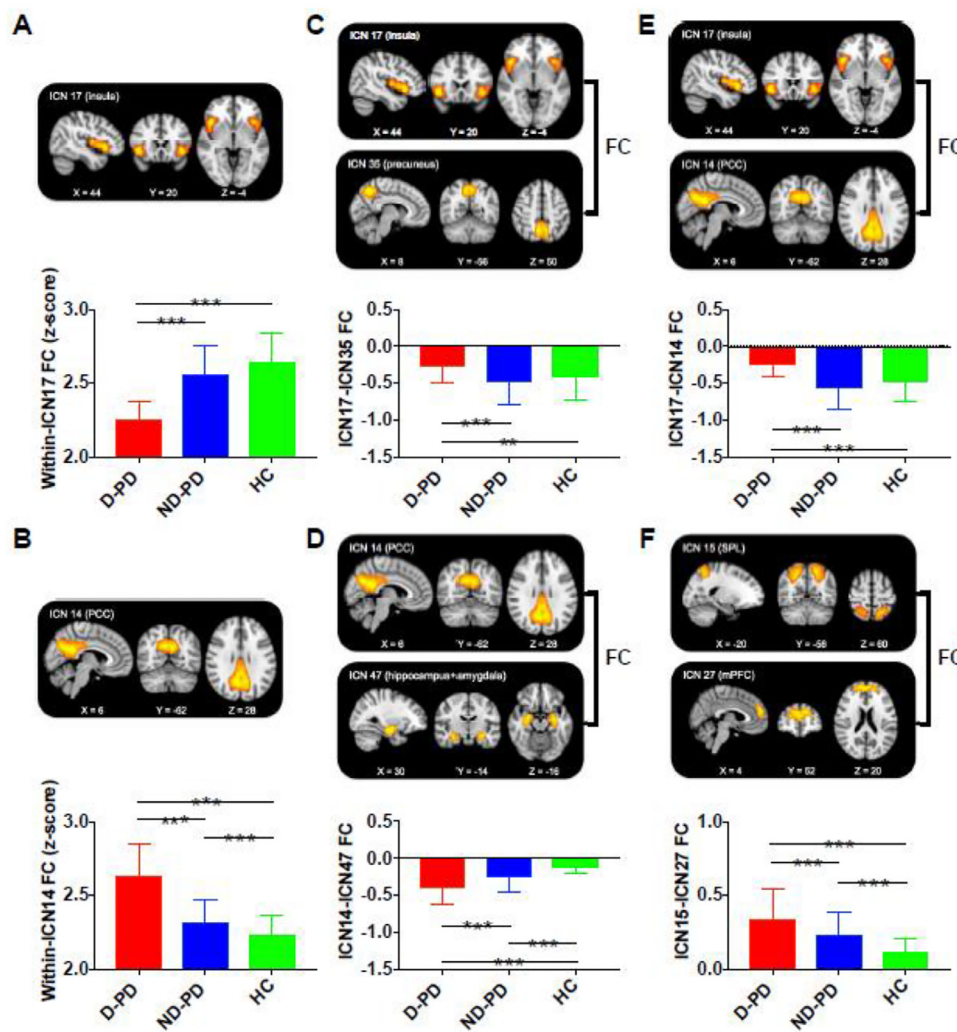
**Fig. 2.** Six identified FC features using the all-relevant feature selection algorithm. These features were FC within insula (A), within PCC (B), between insula and precuneus (C), between PCC and hippocampus + amygdala (D), between insula and PCC (E), and between SPL and mPFC (F). They showed significant differences between depressed and non-depressed patients. Compared to the healthy controls, these six features were significantly different in depressed patients and three of them (FC within PCC, between PCC and hippocampus + amygdala, and between SPL and mPFC) were significantly different in non-depressed patients, after regarding the mean absolute displacement and MoCA score as covariates. Statistical significance is indicated by asterisks (***, $p < 0.001$; **, $p < 0.01$). D-PD: depressed PD, HC: healthy controls, ND-PD: non-depressed PD.

**Table 2**

Significantly relevant FC features to discriminate depressed and non-depressed PD patients.

| Selection Frequency (%)* | Feature Description | D-PD | ND-PD | HC |
|---|---|---|---|---|
| 91.1 | FC within PCC (ICN14) | $2.63 \pm 0.03$ | $2.31 \pm 0.02$ | $2.22 \pm 0.02$ |
| 90.3 | FC between insula (ICN17) and PCC (ICN14) | $-0.25 \pm 0.16$ | $-0.56 \pm 0.31$ | $-0.46 \pm 0.28$ |
| 88.4 | FC between insula (ICN17) and precuneus (ICN35) | $-0.27 \pm 0.23$ | $-0.47 \pm 0.33$ | $-0.42 \pm 0.31$ |
| 86.1 | FC within insula (ICN17) | $2.25 \pm 0.02$ | $2.56 \pm 0.02$ | $2.64 \pm 0.03$ |
| 82.1 | FC between PCC (ICN14) and hippocampus + amygdala (ICN47) | $-0.39 \pm 0.23$ | $-0.24 \pm 0.22$ | $-0.11 \pm 0.10$ |
| 80.7 | FC between SPL (ICN15) and mPFC (ICN27) | $0.34 \pm 0.21$ | $0.22 \pm 0.16$ | $0.11 \pm 0.09$ |

D-PD = depressed PD, FC = functional connectivity, HC = healthy controls, mPFC = medial prefrontal cortex, ND-PD = non-depressed PD, PCC = posterior cingulate cortex, SPL = superior parietal lobule.

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.

iteration, a random forest classifier was constructed on the training set using the randomForest package (Svetnik et al., 2003) in Matlab (MathWorks, Natick, Massachusetts, USA). The performance of the classifier was evaluated on the validation set. Among all iterations, different subsets of features were selected on the basis of different folds. The selection frequency of each feature was defined as the number of iterations in which the feature was selected divided by the total number of iterations. Features with significantly higher selection frequency than random values defined by permutation test (permuted 1000 times; Sun et al., 2017) were identified as depression-related selections, with p value < 0.05 after false discovery rate (FDR) correction for multiple comparisons (Benjamini and Hochberg, 1995).

## 3. Results

### 3.1. Demographic characteristics and clinical assessment

The demographic characteristics and clinical assessment of all participants were listed in Table 1. There were no significant differences in age, sex, PDQI or MMSE among depressed patients, non-depressed patients and healthy controls (one-way ANOVA tests, p values > 0.05). Depressed and non-depressed patients showed significant differences only in PD duration, HDRS and BDI scores (two-tailed t tests, p values < 0.05), which implied that we could identify functional connectivity markers for depression and ignore some other factors including motor symptoms (UPDRS-III), sleep disorders (PSQI) and cognition
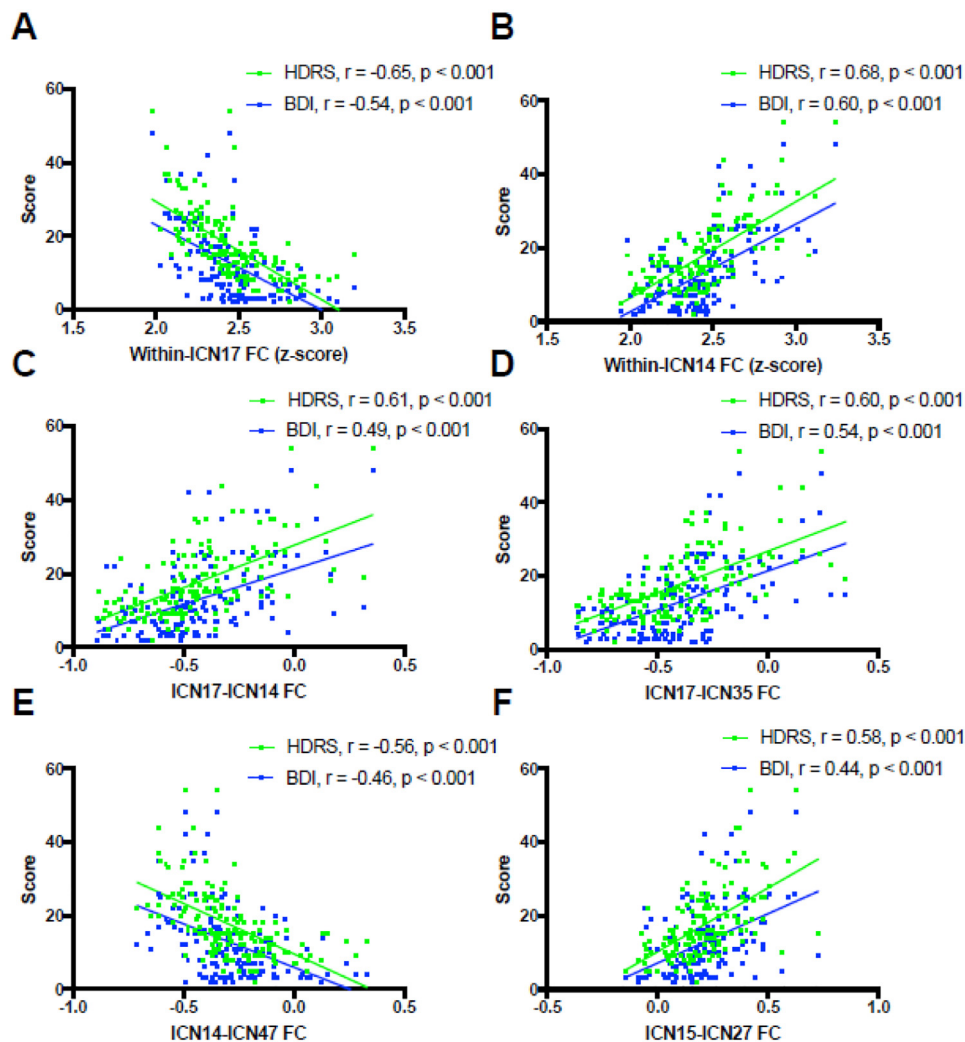
**Fig. 3.** Correlations between depression-related features and depression scores in all patients. Significant correlations were revealed between six identified FC features and depression scores (HDRS, in green, and BDI, in blue; all *p* values < 0.001, after FDR correction). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

impairment (MoCA and MMSE).

### 3.2. Patient-specific ICN template and FC features

42 ICNs in the patient-specific template were identified and arranged into subcortical (SC; 3 ICNs), auditory (AUD; 2 ICNs), somato-motor (SM; 6 ICNs), visual (VIS; 8 ICNs), cognitive control (CC; 11 ICNs), default-mode (DM; 9 ICNs) and cerebellar (CB; 3 ICNs) networks, on the basis of their anatomical and presumed functional properties (Fig. 1A). FC features consisted of within-ICN and between-ICN connectivity strength. Fig. 1B displays the distribution of within-ICN connectivity strength among patients and Fig. 1C shows the FC strength between each two ICNs, averaged over patients and inverse Fisher transformed. The arrangement of ICNs was manually reordered based on network categories to optimize modularity and diagonal structure in Fig. 1C, using the Brain Connectivity Toolbox (http://www.brain-connectivity-toolbox.net/).

### 3.3. The performance of random forest classifiers

In constructing and evaluating the classifiers to discriminate depressed patients from the non-depressed, we repeated 100 times of 10-fold cross validation, which resulted in a total of 1000 training-testing cycles. The accuracy and Cohen's kappa coefficient of the random forest

classifiers were 82.4 ± 5.1% and 0.61 ± 0.17, with features from the all-relevant feature selection procedure. The corresponding sensitivity and specificity were 78.5 ± 6.3% and 86.1 ± 7.2%, respectively.

### 3.4. Significantly relevant FC features

After the feature selection was embedded into the 10-fold cross-validation procedure, a total of 1000 feature subsets were created for each random forest classifier. In the construction of the classifier discriminating between PD patients with and without depression, the mean number of features in each subset was 9.8 (range from 5 to 14; 0.55%−1.55% of all features). Six features (Fig. 2) were identified to be significantly relevant to classification by the permutation test (Table 2). These six features were FC within PCC, within insula, between insula and PCC, between insula and precuneus, between PCC and hippocampus + amygdala, and between superior parietal lobule (SPL) and medial prefrontal cortex (mPFC). Moreover, They showed significant differences between depressed and non-depressed patients (all p values < 0.01, after FDR correction; Fig. 2 and Table 2). And significant correlations were revealed between these features and depression scores (HDRS and BDI) in all patients (all p values < 0.001, after FDR correction; Fig. 3).

Compared to the healthy controls, these six features were significantly different in depressed patients and three of them (FC within

PCC, between PCC and hippocampus + amygdala, and between SPL and mPFC) were significantly different in non-depressed patients (ANCOVA tests, p values < 0.05; Fig. 2), after regarding the mean absolute displacement and MoCA score as covariates to consider the difference in the level of head motion during MRI scanning.

## 4. Discussion

In brief, our study indicated that resting-state functional connectivity, based on the patient-specific template, could characterize depression in PD and help diagnose whether advanced PD patients had depression or not. Six functional connectivity markers of depression were identified and listed as follows: FC within PCC, within insula, between insula and PCC, between insula and precuneus, between PCC and hippocampus + amygdala, and between SPL and mPFC. The mean accuracy of random forest classifiers to discriminate depressed patients from the non-depressed was 82.4%.

In this study, we focused on depression in advanced PD patients (duration > 5 years). Previous studies showed that the duration of PD was a risk factor for incident depression in PD patients (Ravina et al., 2009; Becker et al., 2011). In our cohort, the PD duration of depressed patients was significantly longer than that of non-depressed ones. And the incidence of depression in a total of 156 patients was 37.8%, relatively higher than that in early PD patients reported in some studies (Ravina et al., 2009; Aarsland et al., 2011), which was helpful to the direct comparison of functional connectivity patterns between depressed and non-depressed patients. On account of the high incidence of depression in advanced PD and its great effect on patients' quality of life, the neural basis of depression in PD had been investigated through resting-state functional connectivity analysis in some fMRI studies (Sheng et al., 2014; Luo et al., 2014; Lou et al., 2015; Hu et al., 2015). In our study, we extracted FC features including the whole-brain within-ICN and between-ICN connectivity strength on the basis of the patient-specific ICN template from a large number of PD patients. The specific template created by group-ICA and the direct comparison between depressed and non-depressed patients were to identity FC markers only for depression rather than PD. Next, FC features were put into an all-relevant feature selection procedure. In comparison with the commonly used feature selection methods such as t-test or Pearson's correlation analysis, the all-relevant feature selection algorithm could identify all features that significantly contributed to group discrimination. Moreover, there were no significant differences in patients' age, sex, dopaminergic medications (levodopa equivalent daily dose, LEDD), motor symptoms (UPDRS III), cognitive level (MoCA and MMSE) or sleep situation (PSQI) between depressed and non-depressed groups. Thus, it was valid to identify functional connectivity markers of depression in advanced PD patients through the mentioned analyses.

On the basis of identified features, our random forest classifiers achieved the mean accuracy of 82.4% to discriminate between patients with and without depression. Depression is a major factor in health-related quality of life in PD patients (Wang et al., 2013). Menon et al. (2015) even revealed that the most important predictor for poor quality of life is not the severity of the motor symptoms or the duration of the illness but the presence of depression. However, depression in PD is under-diagnosed and under-treated due to overlapping symptoms and difficulties in the assessment of depression in old patients (Shulman et al., 2002; Jacob et al., 2010). Depression diagnosis in PD is not straightforward when several clinical presentations of depression and PD overlap (McDonald et al., 2006). Physicians tend to concentrate on physical complaints and thus ignore emotional states in old PD patients, and many old patients are unwilling to share their feelings or deny being depressed (Murray et al., 2006). Moreover, many of depression-related symptoms, such as feelings of worthlessness, social withdrawal and isolation, may be dismissed by the clinicians as the natural consequence of physical mobility reduction and speech impairment in PD (Menon et al., 2015). In this situation, the classifier in

our study was derived from patients' rs-fMRI data without performing any specific task, which revealed its potential clinical value for depression diagnosis in PD patients.

In our study, six FC features were identified to be relevant to group classification. All of these features not only showed group differences between depressed and non-depressed patients, but also significantly correlated with depression scores. Among all the involved ICNs, the PCC, mPFC and precuneus are the key nodes of the DMN, which has been proved to be associated with depression in previous studies (Zhu et al., 2012; Belzung et al., 2014). The DMN is activated during the resting state while deactivated during certain goal-oriented tasks in normal persons (Smith et al., 2009), whereas it failed to deactivate in depressed patients (Belzung et al., 2014). Specifically, the PCC was involved in internally directed cognition including self-referential processing and rumination. Depressed patients tend to process negative information with regard to the self (self-referential processing) and fall into a persistent, repetitive and self-critical state (rumination), which can explain our findings about the increased FC within the PCC. Furthermore, we found that depressed patients had abnormal FC between the PCC and insula/hippocampus + amygdala, compared to non-depressed patients. And Bluhm et al. (2009) showed reduced FC between the PCC and bilateral caudate for the comparison between depressed patients and healthy controls. These findings suggested that the FC within the PCC should be a contributing factor for depression, which was in accord with its important role in the group classification.

The insula, a cortical region beneath the frontal, temporal and parietal lobes, is an important part of the limbic system and has a well-established role in processing affect and emotion. Sprengelmeyer et al. (2011) found that the gray matter volume in the insula was correlated with the severity of depression measured by the scores of clinical scales in patients with depression. In a rs-fMRI study, decreased regional homogeneity was revealed in the right insula in participants with depression (Liu et al., 2010), which was consistent with our results about the decreased FC within the insula and the neural correlate of depression in PD. Moreover, we found that depressed patients had abnormal FC between insula and PCC/precuneus, and between hippocampus + amygdala and PCC. These results indicated that the interaction between the limbic system and DMN was closely associated with depression in PD patients.

We acknowledge a few limitations to our study. First, we did not recruit patients only with depression in this study. We identified six FC markers relevant to depression diagnosis in PD, but we did not know whether these markers also acted for the discrimination between general depressed patients and healthy controls. Second, the mean HDRS and BDI scores of non-depressed patients were 13.9 and 8.1 respectively, which meant some of them might have mild depression. All patients were diagnosed to have depression or not according to the DSM-IV criteria by an experienced psychiatrist. HDRS and BDI could be less accurate than DSM as the diagnostic criteria for depression in PD, due to overlapping mental symptoms such as apathy and anxiety. If we excluded non-depressed patients with a BDI score > 14 or HDRS score > 20 (18 patients in total) and performed the feature selection procedure again, the subset of depression-related features did not change while the mean accuracy of the classifiers was 86.7%, a bit higher than the original one. However, one of our aims in the study was to help clinical diagnosis of depression in PD and we tried to make the classifiers target as general PD patients as possible. Thus we preferred to include these non-depressed patients.

In conclusion, compared to advanced PD patients without depression and healthy control subjects, we found abnormal functional connectivity within and between the limbic system and default mode network in patients with depression, which significantly contributed to group classification. On the basis of identified FC markers of depression, moderately successful discrimination was achieved for clinical diagnosis of depression in advanced PD patients.

## 5. Disclosures

The authors report no biomedical financial interests or potential conflicts of interest. The data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at NeuroImage: Clinical. All authors have reviewed the contents of the manuscript being submitted, approve of its contents and validate the accuracy of the data.

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## CRediT authorship contribution statement

**Hai Lin:** Methodology, Software, Formal analysis, Writing - original draft. **Xiaodong Cai:** Conceptualization, Data curation, Funding acquisition. **Doudou Zhang:** Visualization, Investigation. **Jiali Liu:** Visualization, Investigation. **Peng Na:** Formal analysis, Validation. **Weiping Li:** Conceptualization, Supervision, Writing - review & editing.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2019.102130.

## References

Aarsland, D., Påhlhagen, S., Ballard, C.G., et al., 2011. Depression in Parkinson disease—epidemiology, mechanisms and management. Nat. Rev. Neurol. 8, 35–47.

Ballanger, B., Klinger, H., Eche, J., et al., 2012. Role of serotonergic 1A receptor dysfunction in depression associated with Parkinson's disease. Mov. Disord. 27, 84–89.

Becker, C., Brobert, G.P., Johansson, S., et al., 2011. Risk of incident depression in patients with Parkinson disease in the UK. Eur. J. Neurol. 18, 448–453.

Beckmann, C.F., Smith, S.M., 2004. Probabilistic independent component analysis for functional magnetic resonance imaging. IEEE Trans. Med. Imaging 23, 137–152.

Belzung, C., Willner, P., Philippot, P, 2014. Depression: from psychopathology to pathophysiology. Curr. Opin. Neurobiol. 30C, 24–30.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soci. Ser. B (Methodol.) 57, 289–300.

Bluhm, R., Williamson, P., Lanius, R., et al., 2009. Resting state default-mode network connectivity in early depression using a seed region-of-interest analysis: decreased connectivity with caudate nucleus. Psychiatry Clin. Neurosci. 63, 754–761.

Cardoso, E.F., Maia, F.M., Fregni, F., et al., 2009. Depression in Parkinson's disease: convergence from voxel-based morphometry and functional magnetic resonance imaging in the limbic thalamus. Neuroimage 47, 467–472.

Etkin, A., Egner, T., Kalisch, R, 2011. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn. Sci. 15, 85–93.

Filippini, N., Rao, A., Wetten, S., et al., 2009. Anatomically-distinct genetic associations of Apoe epsilon4 allele load with regional cortical atrophy in Alzheimer's disease. Neuroimage 44, 724–728.

Friedman, J., Hastie, T., Tibshirani, R, 2008. Sparse inverse covariance estimation with the graphical lasso. Biostatistics 9, 432–441.

Griffanti, L., Salimi-Khorshidi, G., Beckmann, C.F., et al., 2014. ICA-based artefact removal and accelerated fMRI acquisition for improved resting state network imaging. Neuroimage 95, 232–247.

Hu, X., Song, X., Yuan, Y., et al., 2015. Abnormal functional connectivity of the amygdala is associated with depression in Parkinson's disease. Mov. Disord. 30, 238–244.

Hughes, A.J., Daniel, S.E., Kilford, L., Lees, A.J, 1992. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J. Neurol. Neurosurg.Psychiatr. 55, 181–184.

Jacob, E.L., Gatto, N.M., Thompson, A., et al., 2010. Occurrence of depression and anxiety prior to Parkinson's disease. Parkinsonism Relat. Disord. 16, 576–581.

Jankovic, J., 2008. Parkinson's disease: clinical features and diagnosis. J. Neurol. Neurosurg. Psychiatry 79, 368–376.

Jenkinson, M., Beckmann, C.F., Behrens, T.E., et al., 2012. FSL. Neuroimage 62, 782–790.

Liu, Z., Xu, C., Xu, Y., et al., 2010. Decreased regional homogeneity in insula and cerebellum: a resting-state fMRI study in patients with major depression and subjects at high risk for major depression. Psychiatry Res. 30, 211–215.

Lou, Y., Huang, P., Li, D., et al., 2015. Altered brain network centrality in depressed Parkinson's disease patients. Mov. Disord. 30, 1777–1784.

Luo, C., Chen, Q., Song, W., et al., 2014. Resting-state fMRI study on drug-naive patients with Parkinson's disease and with depression. J. Neurol. Neurosurg. Psychiatry 85, 675–683.

McDonald, W.M., Holtzheimer, P.E., Byrd, E.H, 2006. The diagnosis and treatment of depression in Parkinson's disease. Curr. Treat. Option Neurol. 8, 245–255.

Menon, B., Nayar, R., Kumar, S., et al., 2015. Parkinson's disease, depression, and quality-of-life. Indian J. Psychol. Med. 37, 144–148.

Murray, J., Banerjee, S., Byng, R., et al., 2006. Primary care professionals' perceptions of depression in older people: a qualitative study. Soc. Sci. Med. 63, 1363–1373.

Nilsson, F.M., Kessing, L.V., Sorensen, T.M., et al., 2002. Major depressive disorder in Parkinson's disease: a register-based study. Acta Psychiatr. Scand. 106, 202–211.

Pyka, M., Beckmann, C.F., Schoning, S., et al., 2009. Impact of working memory load on FMRI resting state pattern in subsequent resting phases. PLoS ONE 4, e7198.

Ravina, B., Elm, J., Camicioli, R., et al., 2009. The course of depressive symptoms in early Parkinson's disease. Mov. Disord. 24, 1306–1311.

Reijnders, J.S., Ehrt, U., Weber, W.E., et al., 2008. A systematic review of prevalence studies of depression in Parkinson's disease. Mov. Disord. 23, 183–189.

Remy, P., Doder, M., Lees, A., et al., 2005. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain 128, 1314–1322.

Salimi-Khorshidi, G., Douaud, G., Beckmann, C.F., et al., 2014. Automatic denoising of functional MRI data: combining independent component analysis and hierarchical fusion of classifiers. Neuroimage 90, 449–468.

Sheng, K., Fang, W., Su, M., et al., 2014. Altered spontaneous brain activity in patients with Parkinson's disease accompanied by depressive symptoms, as revealed by regional homogeneity and functional connectivity in the prefrontal-limbic system. PLoS ONE 9, e84705.

Shulman, L.M., Taback, R.L., Rabinstein, A.A., Weiner, W.J, 2002. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat. Disord. 8, 193–197.

Smith, S.M., Fox, P.T., Miller, K.L., et al., 2009. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. USA 106, 13040–13045.

Smith, S.M., Beckmann, C.F., Andersson, J., et al., 2013. Resting-state fMRI in the human connectome project. Neuroimage 80, 144–168.

Sprengelmeyer, R., Steele, J.D., Mwangi, B., et al., 2011. The insular cortex and the neuroanatomy of major depression. J. Affect. Disord. 133, 120–127.

Starkstein, S., Dragovic, M., Jorge, R., et al., 2011. Diagnostic criteria for depression in Parkinson's disease: a study of symptom patterns using latent class analysis. Mov. Disord. 26, 2239–2245.

Sun, H., Chen, Y., Huang, Q., et al., 2017. Psychoradiologic utility of mr imaging for diagnosis of attention, deficit hyperactivity disorder: a radiomics analysis. Radiology, 170226.

Svetnik, V., Liaw, A., Tong, C., et al., 2003. Random forest: a classification and regression tool for compound classification and QSAR modeling. J. Chem. Inf. Comp. Sci. 43, 1947–1958.

Wang, B., Luo, W., Zhang, W.Y., et al., 2013. The effect on health-related quality of life in depressed Parkinson's disease. Chin. J. Neurol. 46, 252–253.

Zhu, X., Wang, X., Xiao, J., et al., 2012. Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naive major depression patients. Biol. Psychiatry 71, 611–617.