Aberrant Intra- and Internetwork Functional Connectivity in Depressed Parkinson’s Disease

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Much is known concerning the underlying mechanisms of Parkinson’s disease (PD) with depression, but our understanding of this disease at the neural-system level remains incomplete. This study used resting-state functional MRI (rs-fMRI) and independent component analysis (ICA) to investigate intrinsic functional connectivity (FC) within and between large-scale neural networks in 20 depressed PD (dPD) patients, 35 non-depressed PD (ndPD) patients, and 34 healthy controls (HC). To alleviate the influence caused by ICA model order selection, this work reported results from analyses at 2 levels (low and high model order). Within these two analyses, similar results were obtained: 1) dPD and ndPD patients relative to HC had reduced FC in basal ganglia network (BGN); 2) dPD compared with ndPD patients exhibited increased FC in left frontoparietal network (LFPN) and salience network (SN), and decreased FC in default-mode network (DMN); 3) dPD patients compared to HC showed increased FC between DMN and LFPN. Additionally, connectivity anomalies in the DMN, LFPN and SN correlated with the depression severity in patients with PD. Our findings confirm the involvement of BGN, DMN, LFPN and SN in depression in PD, facilitating the development of more detailed and integrative neural models of PD with depression.

Depression is one of the most common non-motor symptoms of Parkinson disease (PD), with a prevalence of around 35% and an increasing incidence with progression of the disease. Converging evidence indicates that depression in PD may be a consequence of the neurodegenerative process of the disease rather than a reactive process to the chronic, disabling symptoms. Depression associated with reduced functioning and cognitive impairment is a key determinant of poor health-related quality of life in patients with PD. Understanding depression in patients with PD is, therefore, crucial to achieve the optimal diagnosis and treatment that is needed for patients with this disease.

Functional neuroimaging investigations of depression in PD can advance both the diagnosis biomarkers and treatment evaluation of this debilitating illness. With positron emission tomography (PET), single-photon emission computed tomography (SPECT), and task-based functional magnetic resonance imaging (fMRI), functional anomalies in several brain regions are related to depressed PD patients (dPD), including the dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), insula, thalamus, amygdala, ventral striatum, and caudate. Those findings lend support to the viewpoint that prefrontal cortex, basal ganglia (BG), and limbic system are involved in dPD. More recently, resting-state fMRI (rs-fMRI), as a novel non-invasive approach to measuring baseline brain activity and connectivity, has been increasingly utilized to uncover the neural underpinnings of dPD. Those rs-fMRI studies using the amplitude of low-frequency fluctuation (ALFF) and regional homogeneity (ReHo) methods highlighted that dPD patients had abnormal resting brain activity in the prefrontal and limbic regions, such as amygdala, OFC, DLPFC, MPFC, ACC, compared with non-depressed PD (ndPD) patients. Also reported were aberrant resting brain connectivity between regions of OFC-insula, OFC-amygdala, middle temporal gyrus (MTG)-putamen, amygdala-putamen, median cingulate cortex (MCC)-MPFC, and MCC-PCC/precuneus (PCC/PCu), suggesting disrupted functional integrity in prefrontal, cingulated, BG, and limbic areas in dPD patients. Overall, the above neuroimaging findings allow us to propose that depression in PD could depend on the damage to specific brain regions.

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neural networks rather than on the dysfunction of single, discrete brain region. Attempting to understand dPD from a network-level perspective, hence, may yield an incremental advancement to existing neural models of dPD. Although former researchers using region-of-interest (ROI) approach have noted the potential benefits of exploring dPD at the neural-system level, 10-15, neural network disruption in dPD remains largely obscure.

Independent component analysis (ICA), as a powerful data-driven approach with no a priori definition of seed regions, offers an effective means for identification of functional systems within the brain during rest, typically referred to as “resting state networks” (RSNs) or “intrinsic connectivity networks” (ICNs) 15, 16. The study of RSNs or ICNs has already been shown to be of great potential clinical value, providing rich and sensitive markers of Parkinson's disease; HDRS, Hamilton Depression Rating Scale; MMSE, Mini-Mental State Exam; UPDRS, Unified Parkinson’s Disease Rating Scale; H&Y, Hoehn&Yahr staging; LED, L-dopa equivalent daily dose.

### Results

#### Demographic and clinical characteristics.  
Demographic and clinical features of the sample were listed in Table 1. Age, gender, education level, and MMSE score were not significantly different among the three groups. No significant difference in disease duration, Hoehn and Yahr (H&Y) stage, the motor component of the Unified Parkinson's Disease Rating Scale (UPDRS-III) score, and levodopa equivalent dose (LED) were found between dPD and ndPD patients. By definition, the Hamilton Depression Rating Scale (HDRS) scores of dPD patients were significantly higher than that of ndPD patients (p < 0.001).

#### Intranetwork connectivity analysis.  
At the 28-component level, the spatial maps of the 5 selected ICNs for each group are shown in Fig. 1 (one-sample t-test, p < 0.001, FDR corrected). Our procedure for independent component classification produced consistent ICNs 17, 22, 28.

| Groups          | HC(N=34)         | ndPD(N=35)       | dPD(N=20)        | P Value |
|-----------------|-----------------|-----------------|-----------------|--------|
| Age (years)     | 57.26 ± 5.95    | 57.80 ± 7.11    | 58.30 ± 7.66    | 0.86*  |
| Education (years)| 11.62 ± 4.91    | 10.69 ± 3.29    | 11.15 ± 3.12    | 0.62*  |
| Gender (male/female) | 16/18          | 19/16           | 8/12            | 0.58***|
| HDRS            | 1.91 ± 2.48     | 7.06 ± 3.11     | 19.80 ± 4.37    | < 0.001*|
| MMSE            | 29.12 ± 1.77    | 28.66 ± 1.66    | 28.60 ± 1.10    | 0.39*  |
| UPDRS-III       | —               | 27.24 ± 13.39   | 28.95 ± 13.14   | 0.65** |
| H&Y             | —               | 1.77 ± 0.68     | 1.45 ± 0.58     | 0.07***|
| Disease duration| —               | 6.06 ± 3.53     | 5.45 ± 2.84     | 0.51** |
| LED (day/mg)    | —               | 474.0 ± 375.67  | 512.8 ± 361.07  | 0.71** |

Table 1. Demographic and clinical characteristics of the total sample. *Comparisons of Age, Education, HDRS and MMSE among three groups used one-way ANOVA; **Differences of HARS, UPDRS-III, Disease duration and LED between ndPD and dPD calculated using two-sample t test; ***Gender distribution in three groups assessed by chi-squared test; ****Comparison of H&Y between ndPD and dPD utilized Wilcoxon rank sum test. Abbreviations: HC, healthy control; ndPD, non-depressed Parkinson’s disease; dPD, depressed Parkinson’s disease; HDRS, Hamilton Depression Rating Scale; MMSE, Mini-Mental State Exam; UPDRS, Unified Parkinson’s Disease Rating Scale; H&Y, Hoehn&Yahr staging; LED, L-dopa equivalent daily dose.
subgroups, dPD patients had increased connectivity in the LFPN (e.g. DLPFC) and SN (e.g. ACC), and decreased connectivity in the DMN (e.g. LPC).

At the 70-component level, 7 components were identified as the most representative ICNs for BGN, DMN, LFPN, RFPN, and SN. The DMN was represented in 3 components, including anterior DMN (aDMN; MPFC), inferior-posterior (ipDMN; PCC), and superior-posterior DMN (spDMN; bilateral precuneus and angular gyrus). The BGN, SN, LFPN, and RFPN were represented in one component, respectively. The selected ICNs were shown as Supplementary Fig. S1. With respect to 28-component level, the similar changes were discovered within these networks among dPD, ndPD, and HC groups for 70-component level (p < 0.05, uncorrected, see Supplementary Table S1, Fig. S2). Nonetheless, these results did not survive after cluster-level FDR (topoFDR) correction. This may attribute to the fact that component’s spatial features, volume, and mean z-score will change significantly as a function of model order. The different spatial features and z-score distribution for the chosen components can affect the subsequent cluster-level FDR correction.

Internetwork connectivity analysis. At the 28-component level, connectivity between BGN and DMN, and between bilateral FPN and DMN were altered among the three groups (Fig. 3, Table 4). The post-hoc analysis showed that (1) dPD patients compared to HC had increased connectivity between DMN and LFPN; (2) ndPD patients in contrast to HC had increased connectivity between DMN and bilateral FPN, and between BGN and DMN; (3) no significant differences were found among dPD and ndPD patients (Table 4). At the 70-component level, we found that (1) dPD patients compared with HC exhibited increased connectivity between aDMN and LFPN, as well as decreased connectivity between ipDMN and RFPN; (2) ndPD patients relative to HC exhibited increased connectivity between aDMN and bilateral FPN, and between BGN and aDMN; (3) dPD and ndPD patients did not show any significant differences. The similar results were obtained using the two ICA decomposition methods. More details about the results of ICA dimensionality = 70 were presented in Supplementary Table S2 (see Supplementary Fig. S3).

At the 70-component level, we also used the identified 26 components (see Supplementary Fig. S4) to further verify the internetwork connectivity. The results were acquired by using the network-based statistic (NBS) method and post-hoc analysis. No significant differences were found between dPD and ndPD patients, and dPD patients relative to healthy subjects had altered connectivity between DMN and LFPN, in line with the above
Figure 2. Inranetwork connectivity changes in dPD, ndPD and HC. (A) The ANOVA results for abnormal inranetwork connectivity among dPD, ndPD and HC groups (one-way ANOVA, p < 0.05, topoFDR corrected). (B), (C), (D) and (E) were the results for post-hoc comparison of inranetwork connectivity in dPD, ndPD and HC. (B) BGN showed decreased connectivity in dPD and ndPD by comparing with HC. (C) DMN displayed decreased connectivity in dPD compared with ndPD. (D) LFPN exhibited increased connectivity in dPD relative to ndPD. (E) SN showed increased connectivity in dPD compared to ndPD. Brian regions with cool (warm) color indicated significant decreased (increased) connectivity (two-sample post hoc t-tests, p < 0.05, topoFDR corrected).

Table 2. Comparisons of intranetwork connectivity among dPD, ndPD and HC groups (one-way ANOVA, p < 0.05, topoFDR corrected). L, left; R, right; BA, Brodman area; MNI, Montreal Neuroscience Institute template; BGN, basal ganglia network; DMN, default-mode network; FPN, frontoparietal network; SN, salience network; LPC, Lateral parietal cortex; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex.
mentioned results obtained using the interested 5 or 7 components. Besides, compared to healthy controls, both dPD and ndPD patients had abnormal connectivity between BGN, sensorimotor, auditory, visual, and frontal networks. These results may explain the motor, visual, and auditory disturbance exhibited by all PD patients. More details were presented in Supplementary Table S3 (see Supplementary Figs S5 and S6).

**Correlation analysis.** Significant intranetwork connectivity differences among three groups were detected on the 28-component level (survived after topoFDR correction), and then these results were applied to correlated with clinical severity in patients with PD. Connectivity in the detected regions of BGN, DMN, LFPN, and SN were used for correlation analysis with the UPDRS-III and HDRS scores in all PD patients. The results showed that (1) connectivity in the BGN was uncorrelated with the UPDRS-III and HDRS scores; (2) connectivity in the DMN was correlated negatively with the HDRS scores, and connectivity in the LFPN and SN was correlated positively with the HDRS scores; (3) connectivity in the DMN, LFPN and SN was uncorrelated with the UPDRS-III scores (Fig. 4). For patients with dPD, connectivity in the confirmed significant regions did not show any correlation with the UPDRS-III and HDRS scores. This may be owing to the small sample size in dPD group, and further studies would be needed to test the relationship between connectivity anomalies and the severity of depression in dPD.

Since dPD and ndPD patients did not show any significant differences in internetwork connectivity, the correlation analysis between internetwork connectivity and the UPDRS-III and HDRS scores were not performed on the whole PD group. Besides, we exam the correlation between DMN and LFPN connectivity, and between ipDMN and RFPN, obtained using high model order ICA, were uncorrelated with the UPDRS-III (p = 0.73, r = −0.08; p = 0.98, r = 0.005) in dPD.

**Discussion**

In the current study, we applied rs-fMRI combined with two ICA decomposition methods to explore intrinsic connectivity changes within and between large-scale neural networks in PD with depression. Similar results can be obtained using these two decomposition algorithms: 1) dPD and ndPD patients relative to healthy subjects had decreased BGN connectivity; 2) dPD patients compared with ndPD patients exhibited increased LFPN and SN connectivity, and decreased DMN connectivity; 3) dPD patients in contrast to healthy controls showed hyperconnectivity between DMN and LFPN. Furthermore, connectivity abnormalities in the DMN, LFPN and SN correlated

| Anatomic region | Side | BA | Cluster Size | MNI coordinates | T value |
|-----------------|------|----|-------------|-----------------|--------|
| dPD vs HC       |      |    |             |                 |        |
| **BGN**         |      |    |             |                 |        |
| Thalamus        | R    | —  | 13          | 12, −6, 12      | −3.28  |
| Thalamus        | L    | —  | 31          | −12, −6, 12     | −3.54  |
| Caudate         | R    | —  | 9           | 9, 3            | −2.03  |
| Caudate         | L    | —  | 7           | −12, 0          | −2.89  |
| Putamen         | R    | —  | 21          | 21, 3           | −3.24  |
| Putamen         | L    | —  | 13          | −12, 9, −3      | −2.73  |
| ndPD vs HC      |      |    |             |                 |        |
| **BGN**         |      |    |             |                 |        |
| Thalamus        | R    | —  | 45          | 18, −15, 15     | −2.92  |
| Thalamus        | L    | —  | 27          | −6, 15, 9       | −3.13  |
| Caudate         | R    | —  | 9           | 9, 3            | −2.28  |
| Putamen         | R    | —  | 19          | 21, 6           | −2.66  |
| Putamen         | L    | —  | 17          | −24, 9, 3       | −3.11  |
| dPD vs ndPD     |      |    |             |                 |        |
| **FPN**         |      |    |             |                 |        |
| DLPEF           | L    | 9  | 139         | −12, 42, 39     | 4.36   |
| **DMN**         |      |    |             |                 |        |
| LPC             | L    | 40 | 48          | −51, 51         | −3.38  |
| **SN**          |      |    |             |                 |        |
| ACC             | R    | 24 | 108         | 3, 15, 27       | 3.00   |

Table 3. Post-hoc comparison of intranetwork connectivity between dPD, ndPD and HC groups (two-sample post hoc t-tests, p < 0.05, topoFDR corrected). L, left; R, right; BA, Brodman area; MNI, Montreal Neuroscience Institute template; BGN, basal ganglia network; DMN, default-mode network; FPN, frontoparietal network; SN, salience network; LPC, lateral parietal cortex; DLPEF, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex.
with the severity of depression in PD. Our results confirmed the BGN, LFPN, DMN, and SN dysfunction associated with depression in PD.

The BG subserves a wide range of functions, including motor, cognitive, motivational, and emotional processes, and disruption of this circuit has been implicated in numerous neurological and psychiatric disorders. In patients with PD, the degeneration of dopaminergic neurons in the substantia nigra pars compacta triggers a cascade of functional changes affecting the whole BG network. Dopaminergic changes in BG network are responsible for the development of the cardinal motor features in PD, such as tremor, rigidity, and akinesia. However, the dopaminergic degeneration in BG circuit was not thought to be associated purely with motor control in PD. Previous studies with PET or SPECT have found that depressed PD patients are related to dopamine loss in the striatum, indicating the role of BG dopaminergic circuit in the occurrence of depression in PD. Indeed, the BG is intimately connected with the cortex through several segregated but parallel loops, which have been subdivided into motor, associative (cognitive), and limbic (emotional) domains. They deal with the control of movement, behavior and cognition, and reward and emotions, respectively. Dysfunction of nonmotor BG circuit has been proposed to explain the mood disturbances exhibited by PD patients. In the present study, we found dPD and ndPD patients had reduced BGN connectivity, demonstrating that functional disruption in BGN was a common pathological change in depressed and non-depressed PD patients, and reinforcing the view that the BG dopaminergic circuit plays an essential part in the pathogenesis of depression in PD.

The DMN is a constellation of brain regions characterized by functions of self-referential processes, and impairment in this network contributes to the characteristic symptom of self-focused rumination in primary depression. Although the involvement of DMN in primary depression is well documented, its role in PD with depression remains uncertain. To our knowledge, only three rs-fMRI studies have delineated the role of DMN in depression in PD...
depression in PD. Two rs-fMRI studies reported that dPD exhibited abnormalities in the nodes of DMN, such as decreased ALFF value in the ventral MPFC \textsuperscript{14}, and increased eigenvector centrality (EC) value in the PCC \textsuperscript{40}, supporting the DMN impairment related to depression in PD. While another rs-fMRI study found that both dPD and ndPD patients had connectivity alterations in the DMN (e.g. PCu) \textsuperscript{12}, demonstrating the DMN dysfunction is a common pathological condition in PD. A former literature provided further evidence for the above viewpoint by showing that there was an early functional disruption of the DMN in cognitively unimpaired PD patients \textsuperscript{19}. Taken together, previous findings on the DMN dysfunction in depression in PD are contradictory. Here we found dPD patients had reduced DMN connectivity (e.g. LPC) relative to ndPD patients, in accordance with previous two rs-fMRI studies \textsuperscript{14, 40}, lending support to the DMN dysfunction relevant to depression in PD. The current result may indicate that depressed PD patients, like patients with primary depression, had a failure to normally regulate self-referential activity due to the DMN's impairment \textsuperscript{41}. As mentioned above, conflict findings are reported with respect to the role of DMN in PD with depression, and thus the present result of abnormal DMN connectivity involved in depressed PD should be further validated.

The FPN consisting of DLPFC and PPC takes the charge of top-down regulation of attention and emotion \textsuperscript{42}. Abnormal communication within the FPN may underlie deficits in cognitive control and emotional regulation in primary depression \textsuperscript{42}. The DLPFC including portions of the middle and superior frontal gyrus on the lateral surface of the frontal lobes is a key component in FPN, and dysfunction of this area has been recognized as a hallmark for the pathophysiology of depression in PD \textsuperscript{8, 14, 43–46}. SPECT and PET studies found that dPD patients exhibited increased blood flow \textsuperscript{45} and serotonin transporter density \textsuperscript{44} in the DLPFC. Two rs-fMRI studies reported that dPD patients had reduced ALFF \textsuperscript{14} and EC \textsuperscript{40} value in the DLPFC. Moreover, the DLPFC was identified as a potential therapeutic target for dPD patients \textsuperscript{43}. Those findings demonstrate the association of DLPFC dysfunction with depression in PD. This study found dPD patients exhibited increased connectivity in the DLPFC, adding to the growing evidence for the DLPFC disruption devoted to the presence of depression in PD. According to former literature, dysfunction of the DLPFC involved in dPD patients may be secondary to pathology in the dopaminergic projections from the ventral tegmental area (VTA) to the prefrontal cortex \textsuperscript{16, 47}. Consequently, dopamine depletion in the mesocortical pathway could be used to explain the altered DLPFC connectivity with dPD in our study. Since the DLPFC anomalies are secondary to prefrontal dopaminergic deficiency, patient's dopaminergic state (“ON” or “OFF”) would influence connectivity patterns in this region. Two fMRI studies have demonstrated administration of levodopa relatively normalized the DLPFC connectivity in PD \textsuperscript{48, 49}. This is one possible cause for the DLPFC changes in opposite direction in our study (“ON” state) compared with previous two rs-fMRI

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{The correlations between intranetwork connectivity abnormalities and the severity of depression and motor symptoms in PD. (A) DMN connectivity correlated negatively with HDRS scores ($p < 0.001$, $r = -0.48$), and uncorrelated with UPDRS-III ($p = 0.98$, $r = -0.004$) scores in PD. (B) LFPN connectivity correlated positively with HDRS scores ($p < 0.001$, $r = 0.58$), and uncorrelated with UPDRS-III ($p = 0.96$, $r = 0.008$) scores in PD. (C) SN connectivity correlated positively with HDRS scores ($p = 0.004$, $r = 0.38$), and uncorrelated with UPDRS-III ($p = 0.89$, $r = -0.02$) scores in PD.}
\end{figure}
dPD patients may attribute to dysfunction of BG dopaminergic circuits and mesocorticolimbic dopamine systems, as well as hyperconnectivity between DMN and LFPN. These neuroimaging deficits exhibited by dPD patients include reduced connectivity in the BGN and DMN, increased connectivity in the LFPN and SN, as well as hyperconnectivity between DMN and LFPN. These neuroimaging deficits exhibited by dPD patients include reduced connectivity in the BGN and DMN, increased connectivity in the LFPN and SN, as well as hyperconnectivity between DMN and LFPN. These neuroimaging deficits exhibited by dPD patients include reduced connectivity in the BGN and DMN, increased connectivity in the LFPN and SN, as well as hyperconnectivity between DMN and LFPN.
Methods
Participants. 70 right-handed PD patients (21 dPD and 49 ndPD) were recruited from the movement disorder outpatient clinic of Nanjing Brain Hospital (Nanjing, China). All had a diagnosis of idiopathic PD by an experienced neurologist according to the UK Parkinson Disease Society Brain Bank Criteria. To minimize the impact of head motion, PD patients were studied while taking their usual medications ("ON" state). Exclusion criteria were: (1) moderate to severe head tremor; (2) cerebrovascular disorders, including previous stroke, history of head injury, history of seizure, hydrocephalus, intracranial mass, previous neurological surgery and other neurologic diseases; (3) antiparkinsonian treatment with dopamine agonists, (4) antidepressant treatment or other psychiatric therapy; (5) Mini Mental State Examination (MMSE) score < 24; and (6) incomplete clinical information. 4 ndPD patients were excluded from the present analyses due to the stringent exclusion criteria. The remaining 66 PD patients were on stable dopaminergic treatment for at least 4 weeks prior to study entry. In addition, 50 right-handed healthy controls (HC) were recruited from local individuals who volunteered to participate in scientific studies. 1 HC with MMSE < 24 was discarded. The remaining 49 control subjects had a normal neurological status with no history of either neurological or psychiatric diseases. Table 1 contains additional demographic details. The study was carried out in accordance with the Declaration of Helsinki. Experimental protocols were approved by the medical research ethical committee of Nanjing Brain Hospital. Written informed consent was obtained from all participants.

Neuropsychological Evaluation. Psychometric and neurologic assessments with all PD patients were done in the "ON" state, i.e. with their usual antiparkinsonian medication. Each patient's disease severity was measured by H&Y stage and UPDRS-III. Only mild to moderate stage patients were enrolled in the study in order to complete a long scan. Non-depressed patients were matched with depressed patients on the basis of disease severity. Diagnosis of depression was using the Diagnostic and Statistical manual of Mental Disorders, Fifth Edition (DSM-V) criteria by an experienced, board-certified psychiatrist trained for Structured Clinical Interview. The severity of depression was evaluated using the 17-item Hamilton Depression Rating Scale (HDRS-17). All depressed PD patients had a HDRS-17 score higher than 14 points. All the subjects were administered the MMSE, and individuals with MMSE score < 24 were not included. Data pertaining to age, gender, handedness, education level, disease duration, and clinical symptom ratings were collected by a movement disorder specialist prior to MRI examination.

Image data acquisition. All the patients were in the "ON" state before and during scanning. Image data were acquired using a Siemens 3.0-Tesla signal scanner (Siemens, Verio, Germany). Subjects were instructed to stay awake and close their eyes, and to try not to think of anything. Functional imaging data were collected transversely by using a gradient-recalled echo-planar imaging (GRE-EPI) pulse sequence with the following settings: TR/TE = 200 ms/30 ms, flip angle = 90°, matrix = 64 × 64, FOV = 220 mm × 220 mm, thickness/gap = 3.5 mm/0.6 mm, in-plane resolution = 3.4 mm × 3.4 mm, slices = 31. For each subject, a total of 140 volumes were obtained, resulting in a total scan time of 280 s. High resolution anatomical images were acquired using a T1 fluid attenuated inversion recovery (FLAIR) sequence (TR/TE = 2530 ms/3.34 ms, flip angle = 7°, matrix = 256 × 192, FOV = 256 mm × 256 mm, slice thickness/gap = 1.33 mm/0.5 mm, 128 slices covered the whole brain).

Data preprocessing. Structural images were reoriented to the anterior commissure and segmented into grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), skull, and soft tissue outside the brain, using the standard segmentation option in SPM 12 (http://www.fil.ion.ucl.ac.uk/spm/). Then the segmented tissue class images (e.g., GM, WM) were employed to generate a group-specific template (across all subjects) using DARTEL toolbox in SPM12. The subject-specific flow fields yielded from the DARTEL procedure can be applied to corresponding functional data in the next stage. Resting-state functional images preprocessing was carried out using both SPM12 and AFNI (http://afni.nimh.nih.gov/afni) packages. In the steps including slice acquisition correction, head motion correction, spatial normalization, and smoothing were performed with SPM 12, and the despiking procedure was achieved in AFNI software. Briefly, the first 5 volumes were discarded to allow for magnetization stabilization. The remaining 135 consecutive images were then corrected for the acquisition delay between slices using the middle slice as the reference frame and further realigned to the first volume to correct for head movement with SPM12. 6 subjects (3 HC and 3 dPD) with head motion exceeding ± 2.5 mm of translation or ± 2.5 degrees of rotation were excluded from the dataset. To minimize the impact of motion artifact on functional connectivity analysis, 20 subjects (1 dPD, 7 ndPD, and 12 HC) with excessive instantaneous head motion (mean framewise displacement (FD) exceeding 0.3) were discarded, resulting 20 dPD, 35 ndPD, and 34 HC for the following analyses. The instantaneous head motion was calculated using the six head realignment parameters, as described in (33). The motion-corrected volumes were then despiked using AFNI's 3dDespike algorithm to mitigate the impact of outliers. The mean functional image across all realigned volumes was coregistered with the structural image, and the resulting warps applied to all the despiked functional volumes by utilizing SPM12. Finally, all the coregistered functional images were non-linearly normalized, subject by subject, to the sample-specific group template (using subject-specific flow fields), affine-aligned into stereotactic space of the Montreal Neurological Institute (3 mm isotropic voxel size), and smoothed using a 6 mm full-width at half maximum Gaussian filter (33). In addition, six head motion parameters obtained in the realigning step, WM signal, CSF signal, and Legendre polynomials orders up to 2nd were included in a linear regression to remove possible spurious variances from the data. CSF and WM mean signals were determined by averaging the native-space functional time series of all voxels contained inside the corresponding masks obtained from the segmentation of the structural images using DARTEL.
Intranetwork connectivity analysis. Preprocessed images were analyzed with the Group ICA of fMRI Toolbox (GIFT) software, and following three main steps: (1) data reduction, (2) group ICA, and (3) back reconstruction. First, principal components analysis (PCA) was applied to reduce the data dimensionality for each subject. The reduced data from all subjects were then concatenated and entered into a second data reduction step using PCA. Second, the reduced, group concatenated data were entered into the ICA algorithm (Infomax) to calculate spatially independent group components. The number of independent group components was set at 28 and 70 respectively, based on the minimum description length criterion described in and high model order ICA used in. The reliability of the independent components decomposition was tested by running Infomax 20 times in the ICASSO toolbox. Third, individual subject components were back reconstructed from the group components using GICA approach, during which the aggregate components and the results from data reduction step were used to compute the individual subject components. Each back-reconstructed component consists of a spatial z-maps reflecting component's functional connectivity pattern across space and an associated time course reflecting component's activity across time. The group-level components corresponding to BGN, DMN, SN, and bilateral FPN, were selected by visual inspection and confirmed using the template-matching procedure. The template for BGN, DMN, SN, and FPN was provided in GIFT software (the RSN template), and the map of each component was spatially correlated with specific network template. The component with the largest spatial correlation coefficients with each of these templates was chosen and reconfirmed by visual inspection. To further confirm our selected ICNs, we also generated the network templates using the WFU Pickatlas on the basis of the Brodmann areas and cluster peaks reported in the literature (DMN; SN; FPN; BGN). Spatial correlation was performed between the components and the generated templates. For high model order ICA, the RSN template, the generated network template, and the template came from online T-maps of 28 components (http://mialab.mrn.org/data/hcp/RSN_HC_unthresholded_tmaps.nii) was employed to match with our 70 independent components' spatial maps. The subsystems of BGN, DMN, FPN, and SN were chosen based on the largest spatial correlation with these templates. Functional connectivity within each selected ICN was calculated using the reconstructed component's spatial z-maps.

Internetwork connectivity analysis. To evaluate functional connectivity between the selected ICNs, subject specific ICN's time courses were detrended, desped, filtered using a fifth-order Butterworth low-pass filter with a high frequency cutoff of 0.15 Hz, and pairwise correlated by Pearson's correlation, following the approach of Jafri and colleagues. Correlation coefficients were then transformed to z-scores using Fisher's z-transformation. At the 28-component level, the number of pair-wise combinations is 10 for each subject as 5 components were identified. At 70-component level, 7 components were identified as the most representative ICNs for BGN, DMN, LFPN, RFPN, and SN, and the number of pair-wise combinations is 21 for each subject.

To further verify the internetwork connectivity, we also used the identified 26 components derived from 70 components to conduct the internetwork connectivity analysis. The identified 26 components reflected the BGN, DMN, auditory, visual, sensorimotor, attention, and frontal networks, respectively. The NBS method and post-hoc analysis was applied to determine connectivity changes between three groups.

Statistical analysis. Differences between groups in terms of demographic and clinical variables were conducted by Pearson chi-square test, One-way analysis of variance (ANOVA), Wilcoxon rank sum test, and Student t test in SPSS software package (SPSS Inc, Chicago, Illinois, USA), as appropriate. The level of statistical significance was set at P < 0.05.

To statistically evaluate functional connectivity within each selected ICN, we calculated voxel-wise one-sample t-tests on participants' reconstructed spatial maps for each group using SPM12 (p < 0.001, false discovery rate (FDR) corrected). Comparisons of connectivity within each ICN among dPD, ndPD, and HC groups were performed by using a design model of one-way ANOVA in SPM12, followed by post-hoc two-sample t tests. The significance threshold was set at p < 0.05, corrected for multiple comparisons using topoFDR in SPM12. Between-group differences of connectivity among selected ICNs were assessed using an ANOVA model in SPSS, and post-hoc two-sample t tests were carried out to determine connectivity changes between each pair of the three groups (p < 0.05, Bonferroni corrected).

The correlations between the detected connectivity abnormalities and the HDRS, UPDRS-III scores were assessed for overall PD and dPD patients respectively, by using Spearman correlation coefficient. The statistical level with P < 0.05 was considered as significant.

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Author Contributions
W.L. and H.C. designed the study. X.H., Y.Z. and Y.Y. collected the data. L.W. analyzed the data and wrote the manuscript. L.W. and H.C. revised the manuscript. All authors reviewed the manuscript.

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