Effective Connectivity of Default Mode Network Subsystems in Parkinson’s Disease with Mild Cognitive Impairment Based on Spectral Dynamic Causal Modeling

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Abstract

Objective: The objective of this study is to compare the differences in effective connectivity within the default mode network (DMN) subsystems between patients with Parkinson’s disease with mild cognitive impairment (PD-MCI) and patients with Parkinson’s disease with normal cognition (PD-CN). The mechanisms underlying DMN dysfunction in PD-MCI patients and its association with clinical cognitive function in PD-MCI are aimed to be investigated. Methods: The spectral dynamic causal model (spDCM) was employed to analyze the effective connectivity of functional magnetic resonance imaging (fMRI) data in the resting state for the DMN subsystems, which include the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), left and right angular gyrus (LAG, RAG) in 23 PD-MCI and 22 PD-CN patients, respectively. The effective connectivity values of DMN subsystems in the two groups were statistically analyzed using a two-sample t-test. The Spearman correlation analysis was used to test the correlation between the effective connectivity values of the subsystems with significant differences between the two groups and the clinical cognitive function (as measured by Montreal Cognitive Assessment Scale (MoCA) score). Results: Statistical analysis revealed significant differences in the effective connections of MPFC-LAG and LAG-PCC between the two patient groups (MPFC-LAG: t = –2.993, p < 0.05; LAG-PCC: t = 2.174, p < 0.05). Conclusions: The study findings suggest that abnormal strength and direction of effective connections between DMN subsystems are found in PD-MCI patients.

Keywords: Parkinson’s disease; mild cognitive impairment; spectral dynamic causal model; default mode network; effective connection

1. Introduction

Parkinson’s disease (PD) is a neurodegenerative disorder frequently observed in middle-aged and older adults [1]. Cognitive dysfunction represents one of the most prevalent non-motor symptoms of PD [2], encompassing two stages: Parkinson’s disease with mild cognitive impairment (PD-MCI) and Parkinson’s disease dementia (PDD). Multiple studies consistently report a significantly elevated risk of dementia development in individuals diagnosed with PD, ranging from four to six times higher than the general population [3]. Moreover, PD-MCI is established as an independent risk factor for subsequent PDD development [4]. In the middle stages of the disease, PD-MCI prevalence reached up to 40% [5]. The transition from PD-MCI to PDD substantially compromises the quality of life for both patients and caregivers. Consequently, early diagnosis and intervention for PD-MCI are of great clinical significance [6]. Currently, the diagnosis of PD-MCI is mainly based on the criteria developed by the International Movement Disorder Society [7]. To better solve clinical problems, finding novel ways to apply neuroimaging techniques to achieve non-invasive and objective visual assessment of PD-MCI has become an important direction of current research.

The default mode network (DMN) has been extensively linked to a wide range of complex human cognitive activities, making it a pivotal focus in the field of cognitive research [8]. The DMN has different subsystems, each with specific cognitive functions, primarily achieved through task allocation and collaborative efforts to fulfill the DMN’s functional objectives [9]. Modern imaging techniques, particularly functional magnetic resonance imaging (fMRI), offer great potential for early screening and diagnosis of PD-MCI [10]. However, the use of imaging technology to investigate the DMN in PD-MCI has been limited, with only a few studies available. Previous research has indicated functional or metabolic abnormalities in the DMN of individuals with PD-MCI. For instance, Ruppert et al. [11] observed reduced glucose metabolism in the DMN nodes of PD-MCI compared to healthy individuals, along with increased metabolic and functional connectivity in the frontal-parietal junction. Hou et al. [12] found a disruption in the dorsomedial prefrontal cortex subsystem of the DMN in PD-MCI. Additionally, another study reported a significant decrease in functional connectivity within the DMN in PD-MCI compared to healthy controls [13]. Relevant studies have explored the functional connectivity between the DMN and other brain regions using fMRI, re-
vealing abnormal connectivity patterns between the DMN and other brain regions in PD-MCI [14–16]. Previous studies on the DMN in PD-MCI have typically examined the DMN as a whole or specific subsystems within the DMN, without investigating the impact of abnormal connectivity between DMN subsystems on PD-MCI. Moreover, most of these studies have primarily focused on exploring brain functional connectivity, describing temporal signal correlation strength among different brain regions without capturing causal relationships. In contrast, effective connections provide a means to identify cause-and-effect relationships among various brain regions. “Causal relationships” refer to situations where the activation or inhibition of one neural region induces changes in the activation or inhibition of other neural regions through interregional connections and modifies its own activation or inhibition through self-connections. Currently, various methods can be used to calculate effective connections, such as Granger causality analysis [17] and dynamic causality models [18]. Among these, Dynamic Causal Modeling (DCM) is considered the most accurate and mature. One specific DCM method suitable for analyzing resting-state fMRI data is spectral dynamic causal modeling (spDCM), based on the frequency domain. The spDCM method is known for its superior computational efficiency, accuracy, and heightened sensitivity in detecting inter-group differences [18].

In this study, we hypothesized that alterations in the strength of effective connectivity of certain subsystems of the DMN or abnormalities in the pattern of regulation between these subsystems may be a contributing factor to DMN dysfunction in patients with PD-MCI. This study utilizes fMRI technology to analyze effective connectivity using spDCM [19,20]. The objective is to reveal the direction of information flow within DMN subsystems (i.e., the causal relationships among DMN subsystems) and gain further insights into the underlying mechanisms of DMN dysfunction in PD-MCI during resting states.

2. Materials and Methods

2.1 Participants

In this study, 45 patients with PD were included. They were admitted to the Affiliated Hospital of Yangzhou University from January to June 2023. The Hoehn & Yahr staging scale (H&Y) and the Unified PD Rating Scale (UPDRS) were used to assess the severity of PD. Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS) were used to quantify depression and anxiety, respectively. Two expert doctors assessed the cognitive function of all PD patients using the Montreal Cognitive Assessment Scale (MoCA) [21]. This assessment led to the categorization of PD patients into two groups: PD-MCI group and Parkinson’s disease with normal cognition (PD-CN) group. The diagnosis of PD-MCI followed the criteria established by the International Society for Movement Disorders [7], with adherence to their recommended Movement Disorder Society (MDS) Task Force Level 1 standard. This diagnosis is confirmed when (1) objective cognitive deficits are observed in at least two cognitive domains based on MoCA scores from a limited set of neuropsychological tests, and (2) there is evidence of subjective cognitive decline reported by clinicians or family members, along with a MoCA score below twenty-six points. Prior to clinical evaluation, all patients refrained from using anti-Parkinson’s disease medications for a minimum of 12 hours, and their previous medication use was documented and converted into a daily levodopa dosage equivalent.

Before participating in the experiment, informed consent was obtained from all subjects or their legal guardians. The Ethics Committee of the Affiliated Hospital of Yangzhou University granted approval for this study (approval number: 2017-YKL12-15).

The inclusion criteria were as follows. (1) Patients with PD who meet the clinical diagnostic criteria established by the UK Brain Bank [22]. (2) H&Y classification ≤3 [23]. (3) Subjects aged between 45 and 80 years. (4) All participants in the study were of Han ethnicity. (5) All participants in the study were right-handed. (6) At the time of the experiment, all participants were stable, conscious, and able to communicate effectively.

The Exclusion criteria were as follows. (1) Participants with a clinical dementia rating (CDR) ≥1 [24]. (2) Participants with intracranial tumors, trauma, or other confirmed organic lesions from prior examinations. (3) Participants with a mental or neurological disorder that is distinct from PD. (4) Participants with congenital brain abnormalities. (5) Individuals with substance addiction, including drug dependency and alcohol misuse. (6) Individuals who have contraindications for undergoing magnetic resonance imaging (MRI) (Patients and their legal guardians must thoroughly review the MRI safety review form prior to scanning). (7) Individuals who lost consciousness during the scan.

2.2 Methods

2.2.1 Data Acquisition

All patients were stable and were scanned in an “on” state on Parkinson’s medication. The image acquisition was carried out using a 3.0T MRI scanner (GE Discovery MR750W, manufactured by GE Healthcare, Waukesha, WI, USA) equipped with a 16-channel head and neck coil. Patient’s head motion was minimized by securing it with a soft cushion. To reduce potential interference from light and sound, patients were provided with an eye mask and earplugs. Routine structural imaging scans were conducted to confirm the absence of structural brain abnormalities and other brain diseases.

Routine structural imaging scans were conducted on each subject to confirm the absence of structural brain abnormalities and other brain diseases. The scanning parameters for the T1 structural image were as follows: Repeat
Time (TR) = 7.2 ms, Echo Time (TE) = 3.1 ms, Matrix Size = 256 × 256, Field of View (FOV) = 256 mm × 256 mm, Flip Angle (FA) = 12°, and a continuous acquisition of 188 image slices with a thickness and spacing of 1 mm covering the entire brain.

For the Blood Oxygenation Level Dependent (BOLD) functional image, echo planar imaging (EPI) was used for cross-sectional scanning. Patients were instructed to keep their eyes closed and remain mentally composed during the imaging procedure. The scanning parameters were as follows: TR = 2000 ms, TE = 30 ms, Matrix Size = 64 × 64, FOV = 224 mm × 224 mm, FA = 90°. Each layer had a thickness of 4 mm with a spacing of 1 mm. A total of 28 continuous layers covering the entire brain were obtained during an approximately 8-minute scan.

2.2.2 Preprocessing of fMRI Data

Data preprocessing was performed using the DPABI v6.1 software package (http://rfmri.org/dpabi), which is based on MATLAB 2013b version, developed by the DPARSF Group at the Institute of Psychology, Chinese Academy of Sciences, Beijing, China. The following specific steps were taken: (1) Conversion of images from the original Dicom format to the Nifti format. (2) Exclusion of the initial 5 images of each subject’s fMRI data to eliminate the effects of uneven magnetic fields. (3) Slice timing: Time correction based on the intermediate time point. (4) Head motion correction: Subjects with head motion correction parameters exceeding 1.5 mm or 1.5° in absolute value were excluded, and the head motion correction parameters and the average functional images of each subject were obtained. (5) Spatial standardization: The T1 structural image and fMRI functional image of each subject were spatially registered. Subsequently, the registered T1 image underwent segmentation to obtain gray matter, white matter, and cerebrospinal fluid. The resulting segmented tissue probability map was then aligned with the Montreal Neurological Institute template for standard spatial transformation. Finally, the obtained transformation parameters were applied to perform spatial standardization on the fMRI functional image. (6) Spatial smoothing: Spatial smoothing was carried out using a Gaussian kernel with a half-height and width of 8 mm to mitigate the impact of affine transformation and enhance statistical efficiency. Before data preprocessing, we corrected the susceptibility distortion due to magnetic field inhomogeneity in fMRI images using the TOPUP tool (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/topup) in FSL (FMRIB Software Library).

2.2.3 ROI Definition

In this study, the DMN, which is closely associated with cognitive function, was chosen as the network of interest for spDCM analysis based on prior literature [25–27]. We used preprocessed data and employed the data-driven analysis model of independent component analysis (ICA) integration software GIFT (Group ICA of fMRI Toolbox) version 4.0 software (https://trendscenter.org/software/gift/) for independent component analysis. In selecting the model order parameters, we performed a series of evaluations and comparisons, including using independent component analysis by stability approach with a self-organizing algorithm (ICASSO) to compare with 20 iterative estimates, assessing the reliability of the information-maximizing ICA algorithm estimates, and selecting independent components with an average intra-cluster similarity greater than 0.8 for the analysis. Ultimately, we identified 34 components as components of the resting state network. In identifying the DMN, we referred to the standard template (https://www.neurosynth.org/analyses/terms/dmn/) and utilized the spatial correlation values between the independent components and the template to identify the DMN from the selected 34 independent components. This process involved combining the template information with the spatial correlation values of the independent components and identifying them based on their anatomical characteristics.

By applying independent component analysis, four different regions in the DMN: medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), left angular gyrus (LAG), and right angular gyrus (RAG) were successfully identified as the specific brain regions-regions of interest (ROI) for our study, and their peak point coordinates were obtained. The Montreal Institute of Neurology (MNI) coordinates for the peak points of these four regions in the brain are detailed in Table 1 (The peak point coordinates of the region of interest are the coordinate locations of the areas of the brain that have the most active or peak ICA weights in the resting state). The spatial coordinates of four different regions in the DMN on the standard MNI template are depicted in Fig. 1.

<table>
<thead>
<tr>
<th>ROI</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPFC</td>
<td>6</td>
<td>58</td>
<td>–2</td>
</tr>
<tr>
<td>PCC</td>
<td>0</td>
<td>–50</td>
<td>24</td>
</tr>
<tr>
<td>LAG</td>
<td>50</td>
<td>–60</td>
<td>32</td>
</tr>
<tr>
<td>RAG</td>
<td>–46</td>
<td>–66</td>
<td>32</td>
</tr>
</tbody>
</table>

ROI, regions of interest; MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; LAG, left angular gyrus; RAG, right angular gyrus.
The second step is to extract the time series of MPFC, PCC, LAG, and RAG. After we applied ICA in conjunction with the resting-state fMRI template provided by FIND to obtain the coordinates of the brain regions of interest MPFC, PCC, LAG, and RAG, we used the Statistical Parametric Mapping (SPM) toolkit to further extract the time series of the regions of interest. Select the Volume of Interest (VOI) tool in the SPM toolbox (https://www.fil.ion.ucl.ac.uk/spm/). When setting the VOI, all were centered on the MNI coordinates of the peak point of the brain region of interest at the group level, and a ball was drawn with a radius of 8 mm as a mask at the group level for each VOI. Then, individual-specific peak points were searched for within each mask, and then the MNI coordinates of the peak point were used as the center of the circle, and a ball was drawn with a radius of 8 mm, and the drawn balls were confined to the mask at the level of each VOI group, which was used as the final VOI. The purpose of this process is to ensure that all regions of the brain area of interest are covered and that the brain area of interest can be more accurately defined for each subject in the study so that subsequent analyses can more accurately examine the activity characteristics of the brain area. Then, in the VOI tool, the time series data are extracted: the VOI tool will extract the average time series signal of the region of interest from the fMRI data of each voxel according to the defined spatial coordinates. Save extracted time series data: the extracted time series data can be saved as a mat file or other formats. Finally, the time series extracted in each VOI for each subject was entered into the subsequent spDCM analysis.

2.2.5 Spectral DCM Analysis

spDCM analysis was conducted using Statistical Parametric Mapping (SPM 12, https://www.fil.ion.ucl.ac.uk/spm/) software package. In the first step, models were constructed for each subject in both the PD-MCI group and the PD-CN group. Our main idea for constructing the DCM model is to first construct a complete connectivity model loop to ensure that each brain region is interconnected and consider all brain regions of interest as signal inputs and outputs (to obtain 16 connectivity parameters, including 4 intrinsic self-connectivity parameters). Then, based on a priori knowledge [29–32], the connections between two of the brain regions were eliminated (elimination of the connection between MPFC and each brain region or elimination of the connection between PCC and each brain region); and finally, the connections between one brain region and the other two brain regions were eliminated (elimination of the connection between MPFC and the other two brain regions or the connection between PCC and the other two brain regions). A total of 17 models were constructed in this study (see Supplementary Fig. 1a–q). The resting state functional magnetic resonance imaging (rs-fMRI) spDCM focused exclusively on endogenous connectivity, quantified by the A matrix parameter [18], which represents the strength of the connection between two regions, referred to as intrinsic connectivity. Effective connectivity describes the instantaneous speed of response of one neuron or brain region to another, usually measured in hertz (change per second) [33]. The second step involved optimizing the model evidence by iteratively tuning the model parameters and balancing model fit and complexity. In the third step, Bayesian Model Selection (BMS) [34] was employed alongside a fixed-effects analysis approach to select the best model from a set of specified models based on model evidence. The best model was the one that provided the best fit to the data and balanced simulation complexity among all alternative models, as described by the posterior probability (Pp) in the BMS method. Finally, after determining the optimal spDCM model using Bayesian model evidence, the connection coefficient A matrix of the optimal model for each subject in both the PD-MCI and PD-CN
Fig. 2. Results of two sets of Bayesian model selection. Note: (a,b) presents the outcome of Bayesian model selection in the PD-MCI group, with Model 12 identified as the optimal choice and a posterior probability (Pp) of 1. (c,d) displays the results of Bayesian model selection in the PD-CN group, where Model 14 is considered optimal with a Pp value of 0.8. Posterior probabilities indicate the degree of model fit. FFX stands for Fixed Effect analysis. PD-MCI, Parkinson’s disease with mild cognitive impairment; PD-CN, Parkinson’s disease with normal cognition.

groups was extracted. A single-sample t-test was applied to obtain the average group parameters for the optimal models of both the PD-MCI and PD-CN groups, respectively.

2.2.6 Statistical Analysis

Demographic and clinical differences were compared using SPSS 26.0 software (SPSS Inc., Chicago, IL, USA). For continuous variables, the normality of data was assessed with the Shapiro-Wilk test. Data conforming to a normal distribution were expressed as mean ($\bar{x}$) ± standard deviation (s), while non-conforming data were expressed as median and upper/lower quartiles. Group comparisons were conducted using two independent samples t-tests for normally distributed data and nonparametric tests for data that did not meet normality criteria. Categorical variables were presented as frequencies, and inter-group comparisons were performed using the Pearson $\chi^2$ test. After obtaining the optimal models for both the PD-MCI group and the PD-CN group, t-tests were carried out on the effective connection values from the optimal models for the two groups. Within-group analysis used the one-sample t-test, while between-group analysis employed the two-sample t-test. The purpose of the two-sample t-test was to test whether the difference in the means of the effective connection values of the DMN subsystems between the two groups was significant; the purpose of the one-sample t-test was to test whether the means of the effective connection values of the DMN subsystems within the groups were significantly different from zero. The threshold for statistical significance was set at $p < 0.05$. Because the two sets of continuous variables, effective connection parameters of the subsystems with statistically significant differences between the two
Table 2. Demographic data of subjects in the two groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PD-MCI group (n = 23)</th>
<th>PD-CN group (n = 22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender [male/female]</td>
<td>6/17</td>
<td>12/10</td>
<td>0.071*</td>
</tr>
<tr>
<td>Age [years, M (Q_R)]</td>
<td>71 (10)</td>
<td>63.5 (16)</td>
<td>0.059*</td>
</tr>
<tr>
<td>Duration of disease [years, ( \bar{x} \pm s )]</td>
<td>5.37 ± 2.96</td>
<td>4.45 ± 3.01</td>
<td>0.309</td>
</tr>
<tr>
<td>Years of education [years, M (Q_R)]</td>
<td>9 (3)</td>
<td>9 (3)</td>
<td>0.053</td>
</tr>
<tr>
<td>Handedness (L:R)</td>
<td>0/23</td>
<td>0/22</td>
<td>/</td>
</tr>
<tr>
<td>H&amp;Y [M (Q_R)]</td>
<td>2 (1)</td>
<td>2 (1.13)</td>
<td>0.466</td>
</tr>
<tr>
<td>UPDRS-III [( \bar{x} \pm s )]</td>
<td>27.39 ± 2.56</td>
<td>23.27 ± 1.72</td>
<td>0.193</td>
</tr>
<tr>
<td>LEDD [mg]</td>
<td>300 (200)</td>
<td>300 (262.5)</td>
<td>0.461</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or median (interquartile range). \( \bar{x} \pm s \), mean ± standard deviation; M (Q_R), median (interquartile range); a, Chi-square test; b, Two-sample nonparametric test; c, Two-sample t-test; PD-MCI, Parkinson’s disease with mild cognitive impairment; PD-CN, cognitively normal Parkinson’s disease; H&Y, Hoehn & Yahr scale; UPDRS-III, Unified Parkinson’s Disease Rating Scale, Part III; LEDD, the equivalent daily dose of levodopa.

Table 3. Average effective connection parameters of DMN subsystems for each group and their comparison.

<table>
<thead>
<tr>
<th>Connection</th>
<th>PD-MCI group</th>
<th>PD-CN group</th>
<th>T</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPFC-MPFC</td>
<td>-0.1770 ± 0.1000</td>
<td>-0.0373 ± 0.0720</td>
<td>-1.12</td>
<td>0.27</td>
</tr>
<tr>
<td>PCC-PCC</td>
<td>0.1791 ± 0.0740*</td>
<td>0.1086 ± 0.0793</td>
<td>0.65</td>
<td>0.52</td>
</tr>
<tr>
<td>LAG-LAG</td>
<td>-0.1196 ± 0.1156</td>
<td>-0.0041 ± 0.0728</td>
<td>-0.84</td>
<td>0.41</td>
</tr>
<tr>
<td>RAG-RAG</td>
<td>0.0287 ± 0.0951</td>
<td>0.2050 ± 0.0757*</td>
<td>-1.44</td>
<td>0.16</td>
</tr>
<tr>
<td>MPFC-LAG</td>
<td>-0.3283 ± 0.0990*</td>
<td>0.0695 ± 0.0878</td>
<td>-2.99</td>
<td>0.01*</td>
</tr>
<tr>
<td>PCC-MPFC</td>
<td>0.0796 ± 0.0949</td>
<td>-0.0336 ± 0.0928</td>
<td>0.85</td>
<td>0.40</td>
</tr>
<tr>
<td>LAG-MPFC</td>
<td>0.0165 ± 0.0770</td>
<td>-0.1159 ± 0.1011</td>
<td>1.05</td>
<td>0.30</td>
</tr>
<tr>
<td>LAG-PCC</td>
<td>0.1187 ± 0.0750</td>
<td>-0.1445 ± 0.0959</td>
<td>2.17</td>
<td>0.03*</td>
</tr>
<tr>
<td>LAG-RAG</td>
<td>0.2861 ± 0.0748*</td>
<td>0.0800 ± 0.1073</td>
<td>1.59</td>
<td>0.12</td>
</tr>
<tr>
<td>RAG-MPFC</td>
<td>-0.0757 ± 0.0688</td>
<td>-0.1786 ± 0.0547*</td>
<td>1.17</td>
<td>0.25</td>
</tr>
<tr>
<td>RAG-PCC</td>
<td>0.2239 ± 0.0646*</td>
<td>0.2923 ± 0.0680*</td>
<td>-0.73</td>
<td>0.47</td>
</tr>
<tr>
<td>RAG-LAG</td>
<td>0.0730 ± 0.0941</td>
<td>0.1386 ± 0.0659*</td>
<td>-0.57</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Note: DMN, default mode network. The T value and p values were obtained by a two-tailed two-sample t-test. *Indicates statistically significant differences.

3. Results

3.1 Demographic and Clinical Characteristics

The study included a total of 23 patients with PD-MCI and 22 patients with PD-CN. There were no statistically significant differences in terms of age and gender between the two groups. Detailed information is presented in Table 2.

3.2 Bayesian Model Selection

BMS was applied to the 17 constructed models to compare the modeling evidence of each model using a fixed-effects analysis. In the PD-MCI group, Model 12 (p = 1) was identified as the optimal model, as shown in Fig. 2a,b; Similarly, in the PD-CN group, Model 14 was selected as the optimal model (p = 0.8), as depicted in Fig. 2c,d.

3.3 Group-Averaged Model with Two Optimal Models

Following the BMS results for both groups, we applied a single-sample t-test to derive the average group parameters for the optimal models in the PD-MCI and PD-CN groups, respectively (connection strength is measured in Hz). As a result, we obtained the average effective connection model for both groups—PD-MCI and PD-CN (see Fig. 3a–c).

After performing a one-sample t-test for within-group statistical analysis, we found that there was a statistical difference in effective connectivity within the PD-MCI group for MPFC-LAG (p = 0.003), MPFC-RAG (p = 0.026), PCC-PCC (p = 0.024), LAG-RAG (p = 0.001), RAG-PCC (p = 0.002).

In the PD-CN group, statistically different effective connections were RAG-MPFC (p = 0.004), RAG-PCC (p = 0.000), RAG-LAG (p = 0.048) and RAG-RAG (p = 0.013).

Unlike in the PD-CN group: the inhibitory connections of MPFC-LAG were significant in the PD-MCI group (p = 0.003); the excitatory connections of PCC-PCC were significant (p = 0.024); and the excitatory connections of LAG-RAG were significant (p = 0.001).

3.4 Differences in Effective Connection between the Two Groups

Inter-group analysis also revealed statistically significant effective connections between MPFC-LAG and LAG-

...
PCC in both groups (MPFC-LAG: t = -2.993, p < 0.05; LAG-PCC: t = 2.174, p < 0.05). The analysis findings are presented in Table 3.

3.5 Correlation Analysis

Spearman correlation was used to assess the correlation between the effective connections of the subsystems with significant differences between the two groups and MoCA scores. Scatter plots revealed a monotonic relationship between MoCA scores and the MPFC-LAG effective connection. The results of Spearman’s correlation analysis demonstrated a significant positive correlation between MoCA scores and the MPFC-LAG effective connection (rho = 0.461, p = 0.001. See Fig. 4). The results of Spearman’s correlation analysis demonstrated no correlation between MoCA scores and LAG-PCC effective connection (rho = -0.241, p = 0.111). Detailed data are provided in Supplementary Tables 1,2.
4. Discussions

In this study, we employed the spDCM-based analysis method in conjunction with fMRI data to explore the effective connectivity among DMN subsystems during rest in PD-MCI patients and investigate the underlying mechanism of DMN dysfunction in this population. Our study findings revealed that, when compared to the PD-CN group, the effective connection strength and connection direction within and between DMN subsystems in PD-MCI patients were abnormal. Statistical analysis of a two-sample t-test showed that there was a significant difference in the effective connectivity between MPFC-LAG and LAG-PCC in the PD-MCI group and the PD-CN group. Statistical analysis of one-sample t-test showed that unlike in the PD-CN group: the inhibitory connections of MPFC-LAG in the PD-MCI group were significant; the excitatory connections of PCC-PCC and LAG-RAG were significant.

Our current research identified DMN abnormalities in PD-MCI patients, manifested as abnormalities in the direction of effective connectivity between internal subsystems. Notably, our study found a significant MPFC-LAG inhibitory connection in the PD-MCI group compared to the PD-CN group. Previous studies have identified the MPFC as a brain region involved in numerous neurological and psychiatric disorders [35]. It plays a crucial role in high-level executive functions, including cognition, learning, working memory, and emotional processing and control [36]. The MPFC is known for its diverse cell types and projections [37] and acts as a control center, integrating information from various input structures and transmitting updated information to output structures through connections with other cortical and subcortical regions [38]. The abnormal inhibition observed in PD-MCI patients may disrupt the normal flow of information between the two subsystems, preventing the effective transmission of integrated information from the MPFC to the LAG. This disruption in the circuitry could result in an inability to coordinate between the two subsystems for task execution.

Furthermore, we observed significant excitatory connections of PCC-PCC and LAG-RAG in the PD-MCI group. Existing evidence strongly suggests that individuals with PD-MCI exhibit deficits in one or multiple cognitive domains, including language and visual-spatial abilities. Several studies have highlighted the crucial role of angular gyrus (AG) in integrating spatial information, language, and concepts [39], while PCC is implicated in various cognitive domains such as memory, learning, decision-making, and executive control [40]. The abnormal activation observed in PD-MCI may represent a pathological compensatory response or an excessive utilization of cognitive reserve, implying an underlying neuropathological condition or an overloaded state that could potentially indicate impending cognitive decline in patients.

Compared to the PD-CN group, DMN abnormalities in PD-MCI patients were also characterized by changes in the strength of effective connections between its internal subsystems. A two-sample t-test revealed that the differences in MPFC-LAG and LAG-PCC effective connectivity between patients in the PD-MCI group and patients in the PD-CN group were statistically significant. These abnormal alterations in the strength of interregional connections within the DMN in PD-MCI patients, aberrant alterations in the strength of interregional connections within the DMN among PD-MCI patients disrupt the synchronization of normal brain circuit oscillations, which play a pivotal role in facilitating accurate information flow between regions [35]. These abnormal alterations impede regular information transmission within DMN subsystems and thus may affect the normal functioning of the DMN.

In addition, based on the results showing a positive correlation between the effective connection (MPFC-LAG) with significant differences between the two groups and MoCA scores, it can be inferred that the less inhibitory modulation of MPFC-LAG is associated with better cognitive function in PD patients. This finding suggests that targeting this specific region could potentially serve as an intervention strategy for cognitive impairment. Moreover, reduced inhibition of MPFC-LAG may serve as a predictive marker for improvements in cognitive abilities.

5. Limitation

This study has several limitations. Firstly, the sample size is relatively small, and a larger sample size is necessary in future research to enhance the persuasiveness of results. Secondly, all PD patients were assessed during medication intake, which may have influenced the findings. Thirdly, due to the limited sample size and patient education level, only the MoCA scale was used to evaluate overall cognitive function in PD patients without a detailed assessment of cognitive sub-functions. Future studies should expand the sample size and assess each sub-item of cognitive function for more precise conclusions.

6. Conclusions

Our study utilized spDCM analysis to identify abnormal alterations in the effective connectivity of DMN internal subsystems in PD-MCI patients. These aberrant changes not only impair the distinctive functions of DMN subsystems but also disrupt the collaboration among these subsystems, leading to a disruption in the effective connectivity network loop between these regions. Consequently, this results in a deceleration of information processing speed, dysfunction in integration, and other functional abnormalities within the DMN. These aberrant alterations observed in PD patients may contribute to cognitive decline. Our findings contribute to enhancing the understanding of the underlying neuropathological mechanisms of MCI in PD. Meanwhile, our study can serve as an exploratory finding to provide initial clues and a theoretical basis for subsequent studies.
Availability of Data and Materials
The article already contains all relevant data. If necessary, the corresponding author can be contacted for further information.

Author Contributions
TTP: Data curation, Investigation, Methodology, Formal analysis, Writing—original draft. HQ: Data curation, Methodology. YP: Data curation. WW: Conceptualization, Funding acquisition. YZ: Conceptualization, Investigation, Formal analysis, Writing—review & editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate
This study was approved by the Ethics Committee of the Affiliated Hospital of Yangzhou University (approval number: 2017-YKLI2-15), and all patients signed the informed consent form.

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Conflict of Interest
The authors declare no conflict of interest.

Supplementary Material
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