Analysis of correlation between white matter changes and functional responses in post-stroke depression

CURRENT STATUS: UNDER REVIEW

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DOI:
10.21203/rs.2.21660/v1

SUBJECT AREAS
Neurology

KEYWORDS
Post-stroke depression, functional connectome, structural connectome, structural-functional coupling, resting-state fMRI, diffusion tensor imaging (DTI)
Abstract

Objective

PSD is one of the most common neuropsychiatric symptoms with high prevalence, however, the mechanism of brain network in PSD and the relationship between the structural network and functional network remain unclear. This study incorporated multiple structural and functional connectivity metrics into a graph analysis framework in patients with PSD and PSND.

Method

Forty-five patients with acute ischemic stroke were divided into PSD group and non-PSD group respectively and underwent the magnetic resonance imaging scans. For the structural network, we compared commonly used connectivity metrics, including FA and MD. Moreover, we investigated the relationship between functional and structural connectivity networks. The whole brain network was characterized with graph theoretical metrics and decomposed into modules. Subsequently, the graph metrics and the connectivity within modules were related to depression.

Results

Structural network disturbances in PSD were related to decreased clustering and increased path length compared to PSND, while being less modular.

Conclusion

SC-FC coupling may serve as a biomarker for post-stroke depression. Some regional characteristics were altered in structural connectivity network, involving attention, sensorimotor, subcortical and default-mode networks. These regions with altered nodal characteristics likely reflect the pathophysiology of PSD. The similarity of structural-functional are associated with cognitive dysfunction, retardation and desperation. Our findings highlighted the distinction in brain structural-functional networks in PSD.
Introduction

Post-stroke depression (PSD) is one of the most common mood disorders in stroke patients. A meta-analysis showed that the prevalence of major depression is about 18% (range 8%-46%)(1). The main symptoms of PSD include negative emotions, cognitive deficits and physical symptoms. The default mode network, dorsal attention network, and the salience network have been shown to be the “hub” of different depression subtypes (2–4). Neuroimaging evidence from our studies and others have identified the structural and functional network disruption in post-stroke depression and other neurological diseases (2, 5, 6). A graph-based approach provides insight into the structural and functional connectivity of these diseases, and the Graph-based network analyses allowed us to quantitatively characterize the topological characteristics of the structural and functional networks in the human brain, such as SW, modularity, and hub regions (7–9).

Although connectivity-based analysis incorporating graph theory is potentially useful for investigating disease-related changes in network topology, the interpretation of the findings strongly depends on the connectivity indices used for network construction. For brain network analysis of DTI data, FA commonly used as SC metrics. Most functional network studies applied Pearson correlation as the measure for FC.

Graph theory was used in previous studies to study the white matter connectivity between brain regions of PSD (10, 11). Compared with the control group, increased path lengths and decreased local and global efficiency were observed in Alzheimer's disease (12–14). Similarly, our previous have been found functional connectivity interruptions in PSD (15, 16). However, the topological attributes of the whole white matter structure and the relation between the structural and the functional brain networks in patients with PSD are still largely unknown.

Recent studies have found that using SC-FC coupling values to quantify the consistency
between structural connectivity and functional connectivity in combination with rs-fMRI and DTI data (17). It has been used for many other neurological diseases including idiopathic generalized epilepsy (18) and schizophrenia (19).

The structural-functional relationship of large-scale brain networks may be disrupted in diseases (20, 21). Both human and animal studies have shown that the FC in health is more similar to SC (22). Compared with healthy people, the SC-FC coupling values were decreased in depressed patients and the capacity to process negative emotion might be more directly related to the SC abnormally (23).

Here, we aimed to investigate: (i) How SC-FC coupling changed in PSD compared with PSND; (ii) Whether SC-FC coupling is related to the course of PSD; (iii) how the topological organization of the brain networks changes at different levels (including connectional, global and nodal properties);

Materials And Methods

Participants

In total, 45 subjects divided into two groups (23 PSD, 22 PSND) participated in this study. This study was approved by the Ethics Committee of the Zhujiang Hospital of Southern Medical University, China. The subjects were all patients admitted to the Department of Rehabilitation Medicine of the Zhujiang Hospital of Southern Medical University from August 2017 to February 2019. The inclusion criteria included: All subjects met the criteria of the World Health Organization diagnosis of cerebral infarction; single infarction (3–5 cm). The exclusion criteria included: 1) patients with history of neurological disease (e.g. epilepsy); 2) patients with malingering, or any psychiatric disorders (e.g. mood and anxiety disorders, schizophrenia and psychosis). 3) antidepressant use at stroke onset or a family history of mental disorders; The following information was collected from each subject: demographics (i.e., age, sex, level of education, and living alone) and stroke
severity as measured by NIHSS, MMSE, BI, and HAMD. Each subject received a detailed description and full instructions of the experimental procedure and signed an informed consent form. Clinical interviews were conducted by experienced neuropsychologists according to the DSM-V criteria. In the PSD group, participants had to meet DSM-V criteria for depressive disorder, with HAMD score of 17 or higher. Other participants were assigned to the PSND group. HAMD-24 was used to assess the severity of depression.

**Brain Imaging**

Experimental data were obtained with a Philips 3.0 Tesla magnetic resonance scanner (Royal Philips Electronics, Eindhoven, the Netherlands). During data acquisition, subjects were instructed to relax with their eyes closed, and to keep their heads still. Foam padding and earplugs were used to reduce head motion and scanner noise. The helmet of the magnetic resonance apparatus was used to limit movement of the patient's head. All subjects underwent T1-weighted magnetic resonance imaging and rs-fMRI scanning. High-resolution T1-weighted anatomical images were also acquired using a magnetization-prepared rapid gradient-echo sequence. TR/TE = 8.1/3.8 ms; flip angle = 90; field of view = 256×256 mm2; in-plane matrix = 256×256; voxel size = 1×1×1 mm3, no slice gap, 176 sagittal slices) for each subject. The structural sequence took 6 mins. The DTI scan uses a single-shot spin echo-plane echo sequence (DW-EPI). (TR/TE = 12500/112 ms; flip angle = 90°; field of view = 230×230 mm2; in-plane matrix = 128×128; voxel size = 1.88×1.88×2 mm3, slice thickness 3.0 mm). Blood oxygenation level-dependent functional imaging was acquired using a gradient echo-planar imaging sequence as follows: (TR/TE = 2000/35 ms; flip angle = 90; field of view = 230×230 mm2; in-plane matrix = 64×64; no slice gap; 33 axial slices, slice thickness = 2 mm). The fMRI sequence took 8 mins.

**Data analysis**

We studied the network topological changes in PSD and PSND. Subject-level structural
connectome was derived from diffusion MRI data using probabilistic fiber tracking based on 90 regions of interests (see Methods for details). Subject-level functional connectome was derived from task-free fMRI data based on pairwise Pearson's correlations between the 90 regions of interests (24). Graph theoretical global-wise and nodal-wise metrics were computed for both connectomes. Furthermore, SC-FC coupling was evaluated as the Pearson's correlation between the structural matrices and functional matrices both at the individual and group levels. Alterations in structural and functional network topology metrics as well as SC-FC coupling measures were compared across groups and subsequently associated with HAMD factor score. (Fig.1)

**TBSS Image processing**

Diffusion-weighted images were preprocessed with functional MR imaging of the brain (FMRIB) Software Library (FSL) (http://www.fmrib.ox.ac.uk/fsl). Following the TBSS guideline, we normalized individual FA volumes of the two groups to the MNI space via affine registration. A mean FA image was created by averaging all the registered FA images, and from the mean FA image, the FA skeleton which represents the center of all WM tracts was created. Then, the FA threshold (>0.2) was set on the skeleton to exclude the peripheral brain areas, including WM voxels only. All the registered FA images were further projected onto the skeleton, resulting in a 4D file of all skeletonized images from the individual subject. Then, we generated the mean diffusivity (MD) data by applying the FA nonlinear registration to the individual parametric maps and projecting them onto the skeleton.

**Construction of the structural network**

To construct the structural network, diffusion tensors were reconstructed based on DTI theory (25). Following DTI reconstruction, a streamline-based fiber tracking algorithm (26) was applied on voxel-wise diffusion tensors with the following tracking parameters:
random whole-brain seeding, 200,000 reconstructed streamlines, anisotropy threshold of 0.15, angular threshold of 45°, and streamline length between 30 and 300 mm. All DTI reconstructions and streamline-based fiber tracking procedures were performed in PANDA (https://www.nitrc.org/projects/panda/). To construct the structural brain network, the 90 cerebral regions from the AAL template were used as nodes of a network (24). We quantified the network edge between two distinct AAL regions by calculating multiple DTI metrics along the interconnected streamlines. Because not all DTI metrics are positively associated with the strength or integrity of WM connections, to distinguish between natures of network edges, we referred to DTI metrics as SC metrics only if they are designed to reflect the strengths of WM connections.

**Construction of the functional network**

To construct the functional network, rs-fMRI data of individual patients were preprocessed using the DPARSF toolbox (27). Preprocessing comprised the removal of the first 10 volumes, slice timing correction, coregistration to 3D T1WI, nuisance signal regression (head motion, WM signals and cerebrospinal fluid signals), nonlinear spatial normalization using T1WI, and band-pass filtering (0.01–0.1 Hz). Images with head motion exceeding half of the voxel width (1.5 mm) were excluded from the study. On completing preprocessing, the mean time series of each AAL region was obtained by averaging the voxel-wise BOLD signals within the selected cerebral region (24).

**Multiparametric graph theoretical analysis**

Following the construction of each individual network, graph theoretical analysis was employed to characterize its structural and functional network topologies. A threshold connectivity metric is usually applied to filter out unwanted spurious edges of a network prior to graph theoretical analysis. We employed a multiple-sparsity thresholding method, rather than a single threshold, to reduce variations caused by different thresholding
values (28). Different ranges of thresholding values were used for constructing the structural and functional networks.

For each individual sparsity threshold, the sparsity thresholding process was applied to the streamline count matrix such that connections with few streamlines were removed from the graph to match the designated graph sparsity. This process was applied for every sparsity threshold value, yielding a set of thresholded SC matrices corresponding to each sparsity value. These thresholded SC matrices were then used as masks to filter out the unwanted entries in other structural network matrices. Finally, structural network metrics were calculated from each thresholded matrix, and averaged metric values across all sparsity thresholds were used for subsequent analyses. Similarly, this method was used for functional network analysis;

**Small-world properties**

Small-world properties were measured by the Cp and the Lp, which computed the respective extent of interconnectivity of a network at local and global levels (29). The small-worldness was used to measure the balance between integration and segregation of network (30). Besides, efficiency metrics were also used to measure the small-world properties. The Eglob quantifies the extent of information transmission at the global networks, and the Eloc quantifies the extent at individual node levels (31).

We investigated the topological properties of brain networks at both global and nodal levels using the GRETNA toolbox (32). The degree for each of the nodes was quantified and used here as a reliable index of regional connectivity. The small-world coefficient $\sigma$ was used to evaluate small-world behavior. For the whole brain network, we also calculated local and global efficiency.

Individual correlation matrices were transformed to the binary format at a wide range of network sparsity levels for extensive evaluation. Network sparsity measures the
percentage of the number of existing edges in all possible connections and is used as threshold. Small-world properties were compared between groups at each sparsity level.

**Network modularity**

A module in the complex network is defined as a subset of nodes tightly connected within the modules but sparsely connected between the modules. The modularity of a network was computed using a modified greedy optimization algorithm (33, 34), details of which are provided in Supplementary materials. The modules are non-overlapping, with each node assigned to only one module. The process of modularity optimization does not need to specify either the number or the size of the modules.

To measure the potential regional role played by each brain region, the DC for each region (node) were defined as the indices of their inter-module connection density (35). For example, for a node in modules, the DC will be close to 0 if all weights are largely intramodular (36).

**Statistical Analysis**

We first computed global topological properties (SW, γ, λ, σ) of weighted functional and structural connectivity networks for each subject. We also calculated the AUC for global topological properties, which provides a summarized scalar for brain topological properties independent of single threshold selection. Then, a nonparametric permutation test method was performed to detect the significant group differences in global topological properties. A significance threshold of p<0.05 (FDR-corrected) was used for testing global topological properties, except AUC of each global topological property for which an uncorrected threshold of p<0.01 was used since no multiple comparisons were performed. before the permutation tests, age and gender for each network properties were regressed out as covariates by multiple linear regression analyses. Furthermore, the coupling of functional-structural connectivity was compared by using permutation tests.
Result

1.1 Demographic characteristics and clinical symptoms.
There were no significant differences in the basic data (i.e., age, sex, education, duration) and functional assessment scores (i.e., MMSE, MOCA and NIHSS scores) between the PSD and non-PSD groups (p > 0.05). Detailed demographics are listed in Tab.1. (see Table 1)

1.2 Tract based spatial statistics TBSS
Compared with controls, FA values in PSD group were significantly decreased in the white matter of the left precentral gyrus, the left cingulate gyrus, the left parahippocampal gyrus, the left putamen, the right calcarine (P < 0.05, TFCE Correction). MD value of PSD group was increased with statistically significant differences in the left cingulate gyrus, the left hippocampal, parahippocampal gyrus, and the left fusiform gyms between two groups (P < 0.05, TFCE Correction) (Fig.2).

A total of 90 interregional pairs were compared, and multiple-comparison statistical correction was performed. Based on FA differences between two groups, we set the left precentral gyrus, the left cingulate gyrus, the left parahippocampal gyrus, the left putamen, the right calcarine as ROI, to obtain the FA value between the two ROI, respectively. Similarly, based on the MD differences between two groups of, we set the left cingulate gyrus, left hippocampal and parahippocampal gyrus, left fusiform as ROI, to obtain the MD value between the two ROI, respectively (see Table 2).

There is a significantly reduced FA values in brain regions in PSD patients compared with non-PSD; for the FA metric, significant difference was found in the preCG.L-to-PUT.L→ACG.L-PHG.L that PSD group showed significantly decreased FA when compared with the non-PSD group (Fig. 3). A significantly increased MD values were obtained in brain regions in PSD patients compared with non-PSD; for the MD metric, significant difference was found in the PHG.L-to-ACG.L→PHG.L-to-FFG.L, in which PSD group showed significant
increase of MD when compared with the non-PSD group (Fig.3).

**1.3 Small world attributes and network topology**

PSD group and non-PSD group had small world attributes whereas, the small-world attribute of PSD group was smaller than non-PSD group (P<0.05). The brain network DC, Cp, Lp, γ, λ, σ, Eglob, Eloc of the two groups were compared (P<0.05, S2). We observed that the SW of PSD group was smaller than non-PSD group (P<0.05) and the Cp (P<0.05).

In addition, the γ of the PSD group, the λ and the Lp of PSD group were lower than those of the Non-PSD group (P<0.05).

Compared with controls, degree centrality was reduced in the brain area including superior parietal lobule, anterior cingulated gyrus, putamen, pallidum (P<0.05). The nodal global efficiencies of the orbit frontal cortex, superior parietal lobule, cuneus, precentral gyrus, olfactory cortex, pallidum, calcarine and anterior cingulate gyrus in the PSD group were lower than the non-PSD group (P<0.05, Fig.4). (The color bar represents the module and the size represents the weight of node).

**Modular organizations**

Module I (red) responsible for cognition control and DMN functions. Module II (yellow) are related to executive and strategic functions during cognition processing. Module III (green) corresponding to sensory-motor, auditory and verbal functions. Module IV (blue) are known to be involved in both visual and verbal functions. Finally, module V (Navy blue) are related to affective processing (37). (Fig.5)

The brains of patients in the two groups were divided into 90 nodes (based on the AAL brain map), and the node aggregation coefficient of each patient was analyzed. There was a significant difference in whole brain modularity between PSD patients and non-PSD patients (p = 0.039, t = 0.35). The two regions showed significant inter-module changes comparing to PSND. The region with decreased DC was located in the left superior orbital
frontal gyrus and the right amygdala. In PSD patients, the right bar chart shows two brain regions with significantly reduced degree coefficient (DC), with the left superior orbital frontal gyrus (p = 0.0286, t = 2.343); the right amygdala (p = 0.0029, t = 3.353) (Fig.5); A significant difference in module I between the two groups of patients (p = 0.029, t = 1.456). There is a significant difference in module V (p = 0.038, t = 2.126) (Fig.6).

Associations Between Global-wise Metrics and depression Performance

HAMD can be divided into 7 factors: (1) anxiety/somatization; (2) weight loss; (3) cognitive dysfunction; (4) atypical circadian rhythm; (5) sleep disorder; (6) retardation; (7) desperation. The sum of the scores of each factor is the factor score. Factor analysis found significant differences in cognitive dysfunction, retardation and desperation (P<0.05). There was a significant correlation between the nodal global efficiency and the cognitive dysfunction score (r=-0.5586, p=0.0472). In Module I, there was a significant correlation between the nodal global efficiency and the retardation score (r = -0.8204, p < 0.001). The nodal global efficiency in modules v showed a significant correlation with the desperation score (r = -0.7488, p < 0.0032) (Fig.7).

Correlation between SC -FC coupling of post-stroke depression

The mean structural connectivity of the whole brain in patients with post-stroke depression was lower than that in non-depressed patients after stroke (P=0.0238), the mean functional connectivity of the whole brain in PSD was decreased significantly (P<0.0001). The correlation coefficient between structural and functional connectivity in patients with post-stroke depression was r=0.03926 (p=0.7133). The correlation coefficient between structural and functional connectivity in non-PSD group was r=0.2178 (p=0.0180). PSD had a lower SC-FC coupling than non-PSD (Fig. 8c, Fig. 8d).

Discussion

In this study we used graphical theoretical analysis to investigate the network topology
and the coupling between functional and structural connectivity networks in post-stroke depression patients. This is the first study about the brain module and its relationship with depressive symptoms. The abnormal nodes are important causes of cognitive control and emotional processing. The decrease in node efficiency (the superior orbital frontal gyrus, anterior cingulated gyrus and amygdala) leads to the patient's core symptoms such as dullness and despair. In addition, many regions are altered in the structural connection network, involving attention, sensory motion, subcortical and default mode networks. Most importantly, we found that module-level anomalies and SC-FC coupling was significantly reduced in PSD group, which may be helpful to diagnose depression in stroke patients. It is worthwhile to further explore the link between the module and its core symptoms in PSD. The potential use of multimodal neuroimaging biomarkers for post-stroke depression is highlighted.

**Modular organization**

Module I responsible for cognition control and DMN functions. Due to the decreased aggregation coefficient of Module I, PSD patients may not be able to effectively adjust their thoughts and behaviors. The results of this study showed that the mean value of the nodal efficiency of Module I was negatively correlated with the retardation score of HAMD. This correlation means that the higher efficiency in the module I, the less retardation in PSD. Cognition impairment may also be related to the network of Module I in PSD patients. In assessing the relationship between the module and the core symptoms of MDD, it is important to note that the composition of module in PSD was significantly different from that found among the PSND. Among PSD patients, module I appeared to be responsible for DMN, while cognition control and strategic/executive function was divided into modules I and II (Fig. 9). This difference implies that PSD patients may not efficiently adjust thoughts and actions due to the separation of module I. PSD patients have previously been
characterized by helpless cognition, viewing themselves as personal helplessness and then acting with a passive mood. By extension, the cognition of helplessness may then be related to the structural network of module I among PSD patients.

**Altered Regional Topology of Functional and Structural Connectivity Networks**

Both the nodal efficiency and DC may contribute to the alteration of module organization (Fig. 9). Our study found that decreased DC in PSD was mainly located in the left superior orbital frontal cortex and the right amygdala. Emotional processing receives inputs from the amygdala that encodes emotional valence, and motivation-related inputs from the orbitofrontal cortex that is involved in binding stimulus to response (38). In our study, the decreased DC was found in the DMN region of the PSD patient, and we further confirmed the separation of the DMN in Module I. Similarly, previous studies reported that decreased FC between the amygdala and prefrontal cortex is the basis for fear, anxiety and depression (39). Changes mainly found in module I and module V, which may be the cause of abnormal cognitive processing (function of module I) and emotion processing (function of module V), which is associated with the appearance of clinical symptoms, such as dullness and helpless.

Compared with post-stroke non-depression group, patients in post-stroke depression group showed altered topological patterns: reduced clustering coefficients and increased path lengths. Since the small-worldness reflects the balance between the local and integration, our results suggest that the balance in the functional and structural connectivity networks of post-stroke depression patients is disrupted. At present, the rate of misdiagnosis of post-stroke depression is very high, delaying treatment has serious consequences for patients, and it is important to distinguish whether depression is caused after stroke. Previous studies have shown that the brain network in PSD patients tend to be more randomized than non-depressed after stroke. In this study, we found a decrease in degree
centrality and node efficiency in PSD patients, and this finding may provide new neuroimaging markers to help diagnose post-stroke depression.

The orbital frontal cortex is related to working memory and mood (40). Therefore, reduced node efficiency in the area may support the hypothesis that depression is associated with orbitofrontal lesion altering brain dynamics of emotion-attention and emotion-cognitive control interaction in humans (41).

The reduction of node efficiency has also been found in some areas (ROL) belonging to the sensory motor network. Sensory motor networks involve self-starting movements as well as unconscious movement inhibition.

In addition, some brain regions (PHG, SFG), part of the default mode network, also exhibit reduced node efficiency. Previous studies have found that DMN damage is associated with depression (42). Our findings also support the damage to the default network of PSD patients.

The increased path length region is primarily related to the subcortical regions (AMYG, CAU, PUT, and HIP). The subcortical region plays an important role in the overall regulation and regulation of mood and cognition (38). Impairment in the subcortical region will result in behaviors such as executive dysfunction, memory recovery deficits, and uncontrolled emotional, which is consistent with clinical manifestations in patients with PSD.

In this study, we found that connectivity changes in functional networks vary more than structural network, which is not surprising, since there are studies reporting that network nodes are more susceptible to functional connection disorders due to changes in neurotransmitter levels (17).

**Decoupling between Functional and Structural Connectivity Networks**

This study investigated the functional-structural coupling in large-scale brain networks
between PSD patients and post-stroke non-depressive groups. The functional network represents the temporal coherence of the brain region, and the structural network measures the anatomical integrity of the white matter region and is the material backbone of communication between the brain regions (43). Structural connections are highly predictive and restrictive for functional connections. In contrast, functional connections exert an effect on structural connectivity through plasticity mechanisms (20), which indicates a complex relationship between functional and structural connections. Whereas, in this study, we only studied the functional-structural relationship of structural connections.

As we predicted, the coupling of functional-structural connectivity in PSD patients was reduced, which reflecting the abnormal mechanism of the brain network of PSD patients. Specifically, via using coupling intensity as an indicator, we can distinguish PSD patients from non-PSD, which is potentially useful for improving the diagnosis and evaluation of PSD. However, it is difficult to explain the causal relationship between the disrupted function and structural connection network, and further studies are needed in future work. Our study showed some regional characteristics were altered in structural connectivity network, involving attention, sensorimotor, subcortical and default-mode networks.

Strengths and Limitations

First, the patient sample size is relatively small. However, even in this small group, statistically significant changes in connectivity were found. Secondly, a functional and structural connectivity network was established at the network level, including 90 brain regions from the AAL brain map. There are also different spatial scales those may show different network topology organizations. Secondly, it is difficult to explain the causal relationship between the function and structural connection network, which needs to be further studied in combination with dynamic connection analysis.
Conclusions

For the first time, we have combined functional and structural connectivity networks to study the topological organization of large-scale brain networks in patients with PSD, which can serve as potential imaging biomarkers for patients with PSD. In addition, we also found that the decreased SC-FC coupling value in post-stroke depression is associated with increasing disease duration within half a year of depression. The structural connectivity network exhibits reduced node efficiency in some areas related with attention, sensory motion, subcortical and default systems in the PSD. More importantly, we can distinguish between PSD patients and post-stroke non-depressed patients by the coupling strength of functional-structural connections in PSD, which suggests that the coupling intensity of functional-structural connectivity may be an important feature involved in the PSD mechanism. Our study provides a new way to understand the pathophysiological mechanisms of PSD.

Abbreviations

PSD, Post-stroke depression; PSND, Post-stroke without depression; FA, fractional anisotropy; MD, mean diffusivity; SC, structural connectivity; FC, functional connectivity; DTI, diffusion tensor imaging; rs-fMRI, resting-state functional magnetic resonance imaging; TBSS, tract-based spatial statistics; SW, small-worldness; NIHSS, National Institutes of Health Stroke Score; MMSE, Mini-Mental State Examination; BI, Barthel Index; HAMD, Hamilton Depression Scale; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; TR, repetition time; TE, echo time; MNI, Montreal Neurological Institute; FWHM, full width at half maximum; WM, white matter; DPARSF, Data Processing Assistant for Resting-State fMRI; BOLD, blood oxygen level-dependent; FDR, false discovery rate; TFCE, Threshold-Free Cluster Enhancement; AAL, automated anatomical
labeling; GLM, general linear modeling; DC, degree coefficient; Cp, clustering coefficient; Lp, feature path length; γ, normalized clustering coefficient; λ, standard feature path length, σ, small world attribute value; Eglob, global efficiency; Eloc, local efficiency; AUC, the area under the curve; ROI, region of interest; DMN, Default Mode Network; PreCG, Precentral gyrus; HP, hippocampus gyrus; PHP, parahippocampal gyrus; ACG, anterior cingulate cortex; PUT, putamen; CAL, calcarine; FFG, fusiform gyrus; ROL, Rolandic_Oper_L; SFG, superior frontal gyrus; AMYG, amygdala.

Declarations

Ethics approval and consent to participate

This study was conducted according to the Declaration of Helsinki. The experimental procedures were approved by the Ethics Committee of Zhujiang Hospital affiliated to Southern Medical University. Written informed consent was obtained from all participants prior to the experiments.

Consent for publication

We obtained written consent to publish the data from all participants prior to the experiments.

Availability of data and material

The datasets acquired and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by 1) National Natural Science Foundation of China (NNSFC), China; Contract grant number: 81772430; and 2) Clinical Research Foundation of Southern Medical University, China; Contract grant number: LC2016PY037.
Authors' contributions

Study concept and design: XF.Z and W.W. Acquisition, analysis, interpretation of data: XF.Z., SM.H., and T.F. Drafting of the manuscript: XF.Z. and W.W. Critical revision of the manuscript: KL.W. and W.W. Statistical analysis: XF.Z., SM.H. MRI technical support: J.Y.

Study supervision: W.W.

Acknowledgements

We thank Yang JM from the Department of Neurology, Zhujiang Hospital, Southern Medical University in China for assistance. We thank all subjects for the assistance in the scanning.

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Tables

Table 1. Demographic details of the recruit participants in this study.
| Subject group              | PSD         | PSND        | P-value |
|---------------------------|-------------|-------------|---------|
| Number of subjects        | 23 (11/12)  | 22 (10/12)  | 0.6547  |
| Education (years)         | 7.5 ± 4.4   | 6.8 ± 4.3   | 0.063   |
| BMI (years)               | 75.6 ± 13.8 | 73.1 ± 21.0 | 0.29    |
| MMSE                      | 27.6 ± 2.2  | 24.7 ± 3.8  | 0.074   |
| MoCA                      | 26.9 ± 2.9  | 27.6 ± 5.1  | 0.054   |
| Age (years)               | 73.1 ± 5.7  | 71.2 ± 8.3  | 0.324   |
| Duration (months)         | 2.8 ± 2.5   | 3.2 ± 2.8   | 0.61    |
| NIHSS score               | 1.2 ± 1.4   | 2.1 ± 2.2   | 0.06    |
| HAMD score                | 26.2 ± 3.8  | 13.3 ± 5.1  | < 0.001 |
| MoCA                      | 27.5 ± 1.5  | 19.7 ± 5.1  | <0.01   |
| Anxiety/Somatization      | 4 ± 3.2     | 3 ± 2.6     | 0.053   |
| Weight loss               | 1 ± 0.4     | 1 ± 0.4     | 0.276   |
| Cognitive dysfunction     | 8 ± 3.2     | 1 ± 2.6     | < 0.001 |
| Atypical circadian rhythm | 1 ± 3.2     | 1 ± 2.6     | 0.68    |
| Sleep Disorder            | 2 ± 2.2     | 2 ± 2.6     | 0.56    |
| Retardation               | 6 ± 3.2     | 1 ± 2.1     | < 0.001 |
| Desperation               | 3 ± 2.7     | 2 ± 3.4     | 0.019   |

BI = Barthel Index; MMSE = Mini Mental State Examination; NIHSS = National Institutes of Health Stroke Score; std. dev = standard deviation.

a: The p values are obtained by using χ² test.

b: The p values are obtained by using a two-sample t-test.

P < 0.05 is considered significant.

Table 2. A total of 90 interregional pairs were compared, and multiple-comparison statistical correction was performed. For the FA metric and the MD metric.
**indicates p<0.01. PreCG: Precental gyrus, HP: hippocampus gyrus, PHP: parahippocampal gyrus, ACG: anterior cingulate cortex, PUT: putamen, CAL: calcarine, FFG: fusiform gyrus, L: left, R: RIGHT. (*: Bonferroni correction p < .05; Bonferroni correction **: p < .01; Bonferroni correction ***: p < .001).**

Figures
Study design schematic. We constructed SC and FC based on a predefined set of 90 regions of interest (ROIs). Furthermore, SC-FC coupling was evaluated as the Pearson's correlation between the structural matrices and functional matrices both at the individual and group levels.
Figure 2

The post-stroke depression (PSD) group had a reduced FA value (red) compared to the non-PSD group. (A) the green was the average FA fiber bundle skeleton; (B) the PSD group had an increased MD value (red) relative to the non-PSD group, the green is the average MD fiber bundle skeleton.

Figure 3

(A) Connections showing significant between-group differences in FA. (B) Connections showing significant between-group differences in MD.
The results of the nodal global efficiency and degree centrality. Compared with controls, the result of the nodal global efficiency (A) and degree centrality(B) in PSD group. SPG: superior parietal lobule, ACG: anterior cingulated gyrus, ORB supmed: Superior frontal gyrus, medial orbital, CAL: calcarine, CUN: cuneus, OLF: olfactory cortex, ROL: Rolandic operculum, PAL: pallidum.
The region with decreased DC in PSD group than non-PSD group was located in the left superior orbital frontal gyrus and the right amygdala. (* p < 0.05 [** p < 0.01, FDR correction]). In PSD patients, the right bar chart shows two brain regions with significantly reduced degree coefficient (DC). ORBsup: superior orbital frontal gyrus; AMY: amygdala; L: left; R: right.
A significant difference in module I between the two groups of patients ($p = 0.029, t = 1.456$). There is a significant difference in module V ($p = 0.038, t = 2.126$).
Correlation analysis between clinical variables and global efficiency in the PSD group.  
(a) There was a significant correlation between the nodal global efficiency and the cognitive dysfunction score; (b) In Module I, there was a significant correlation between the nodal global efficiency and the retardation score; (c) The nodal global efficiency in modules v showed a significant correlation with the desperation score.
Figure 8

(a) mean SC in both groups, (b) mean FC in both groups, (c) SC-FC coupling in PSD group, (d) SC-FC coupling in non-PSD group, (e) correlation between changes in mean SC and FC and duration of post-stroke depression. SC, structural connectivity; FC, functional connectivity, W-SC: weighted SC.
Between group comparisons of global network measures. DC (degree coefficient), clustering coefficient (Cp), feature path length (Lp), normalized clustering coefficient (γ), standard feature path length (λ), Small-worldness (σ), global efficiency (Eglob) and local efficiency (Eloc) (P<0.05). (The difference was statistically significant (P<0.05). * indicates p<0.05, ** indicates p<0.01; The color bar represents the module and the size represents the weight of node).
