The distinct disrupted plasticity in structural and functional network in mild stroke with basal ganglia region infarcts

Hua Zhu1 · Lijun Zuo2 · Wanlin Zhu2 · Jing Jing2 · Zhe Zhang2 · Lingling Ding2 · Fengjuan Wang3 · Jian Cheng4 · Zhenzhou Wu5 · Yongjun Wang2,6,7 · Tao Liu1 · Zixiao Li2,6,8,9

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Abstract
Stroke induced by basal ganglia infarction often impair cognitive function. The exploration of topological patterns in structural and functional networks associated cognitive impairment after stroke may contribute to understand the pathological mechanism of cognitive impairment caused by stroke. In this paper, graph theory analysis was applied to diffusion-weighted imaging (DWI) data and resting-state functional MRI (fMRI) data from 23 post-stroke patients with cognitive impairment (PSCI), 17 post-stroke patients without cognitive impairment (NPSCI), and 29 healthy controls (HC). Structural and functional connectivity between 90 cortical and subcortical brain regions was estimated and set threshold to construct a set of undirected graphs. Network-based statistics (NBS) was used to characterize altered connectivity patterns among the three groups. Compared to HC, the PSCI group demonstrated substantial reductions in all three types of connections—rich club, feeder, and local—in structural and functional networks. Specifically, in structural network analysis, reduced connections were observed within basal ganglia and basal ganglia-frontal networks, whereas in the functional network analysis, reduced connections were observed in fronto-parietal network (FPN) and cingulo-opercular networks (CON). Meanwhile, compared to HC, the NPSCI group demonstrated reductions in both feeder and local connections only within occipital area and occipital-temporal structural networks. The findings of reduced structural connectivity in regions stemming from a basal ganglia core and reduced functional connectivity in FPN and CON may indicate a bottom-up cognitive impairment induced by stroke. Graph analysis and connectomics may aid clinical diagnosis and serve as potential imaging biomarkers for post-stroke patients with cognitive impairment.

Keywords
Graph theory · DTI · Resting-state fMRI · Basal ganglia · Stroke · Cognitive impairment

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| AAL | Automated anatomical labeling template |
| CON | Cingulo-opercular network |
| FA | Fractional anisotropy |
| FLAIR | Fluid-attenuated inversion recovery |
| DTI | Diffusion tensor imaging |
| DWI | Diffusion-weighted imaging |
| CT | Computed tomography |

Hua Zhu and Lijun Zuo are Joint first authors.

1 Beijing Advanced Innovation Center for Biomedical Engineering, School of Biological Science and Medical Engineering, Behang University, Beijing, China
2 Department of Neurology, Beijing TianTan Hospital, Capital Medical University, Beijing, China
3 National Institute of Education, Nanyang Technological University, Singapore, Singapore
4 Beijing Advanced Innovation Center for Big Data-Based Precision Medicine, Beijing, China
5 BioMind Technology AI Center, China National Clinical Research Center for Neurological Disease, Beijing Tiantan Hospital, Beijing, China
6 China National Clinical Research Center for Neurological Diseases, Beijing, China
7 Center of Stroke, Beijing Institute for Brain Disorders, Beijing, China
8 Chinese Institute for Brain Research, Beijing, China
9 Research Unit of Artificial Intelligence in Cerebrovascular Disease, Chinese Academy of Medical Sciences, Beijing, China
FPN  Fronto-parietal network
HC  Healthy controls
MRI  Magnetic resonance imaging
NBS  Network-based statistics
NPSCI  Post-stroke patients without cognitive impairment
PSCI  Post-stroke patients with cognitive impairment
TIA  Transient ischemic attack

Introduction

Basal ganglia infarction is known to induce stroke, which may, in turn, impair cognitive function (Allan et al., 2011, Campbell et al., 2019). Through high spatial resolution imaging techniques (such as fMRI and DTI), it is possible to explore the neurophysiological plasticity characteristics of patients with cognitive impairment after stroke with basal ganglia infarction (Dacosta-Aguayo et al., 2015). This experimental pursuit is of great importance, and may contribute to the development of novel therapeutic approaches targeting restoration of normal brain function.

The human brain is a highly complex system where multiple brain areas work collaboratively (Bressler & Menon, 2010; Schedlbauer et al., 2014). The emergence of network science in the neuroscience field (Bassett & Sporns, 2017) provides a new perspective to model and topologically characterize structural and functional integrative bases supporting brain activity (Griffis et al., 2019). Previous studies have reported that post-stroke patients with basal ganglia infarcts may be resilient against cognitive impairment (Zuo et al., 2018). However, how brain structural and functional networks are impaired in patients with post-stroke cognitive impairment remains unclear.

The current research objective is to investigate changes in brain structural and functional networks associated with cognitive impairment in post-stroke patients with basal ganglia infarcts. Post-stroke patients with (PSCI) or without cognitive impairment (NPSCI) and healthy people were recruited. Neurobiological data was recorded with DWI and fMRI, and analyzed using graph theory to construct structural and functional networks. For structural networks, stroke with basal ganglia infarcts may damage cognitive function by impairing physical connections between regions (Stilley et al., 2004). Thus, we hypothesized that the PSCI group would exhibit impaired basal ganglia-related structural networks. Regarding functional networks, previous studies found that damage in the fronto-parietal network (FPN) and cingulo-opercular network (CON) contributes to cognitive impairment in disease states such as schizophrenia and psychotic disorder (Sheffield et al., 2015, 2019), not including stroke. For the current study, we hypothesized that FPN and CON aberrations would be present in stroke as well.

Methods

Participants

We recruited 23 first-time mild stroke patients with cognitive impairment (PSCI), 17 first-time stroke patients without cognitive impairment (NPSCI), and 29 healthy controls (HC) matched for age, sex, and education. All mild patients were recruited consecutively from one stroke ward in the Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, from December 1, 2014 to May 31, 2016.

The inclusion criteria for patients were being aged between 35 and 65 years, having experienced a mild stroke occurring in the basal ganglia, internal capsule, and/or thalamus, without other cortical or subcortical cerebrovascular abnormality, and having no previous history of stroke or transient ischemic attack (TIA). Acute ischemic stroke was diagnosed by neurologists using World Health Organization criteria and confirmed by brain computed tomography (CT) or MRI. Non-disabling cerebrovascular events, which include mild ischemic stroke (median NIHSS = 2, median mRS = 2) and transient ischemic attack (TIA), generally result in either short-lasting or mild neurological symptoms (Fischer et al., 2010). A separate MRI focusing on high quality DTI was carried out between the 10th to 14th days (mean = 12.23 days) after their admission when the patients’ conditions were relatively stable. The exclusion criteria were presence of stroke mimics (i.e., seizures, migraine), illiteracy, neurological (except stroke) or psychiatric diseases, acute stroke in cortex or other regions, or obvious demyelination on fluid-attenuated inversion recovery (FLAIR) image. An eligible patient required an informant who knew the patient’s medical history and cognitive status, and who had met with the patient on a weekly basis for at least 5 years prior to recruitment.

The inclusion of healthy control individuals was based on the absence of both a previous history of neurological or psychiatric diseases and obvious myelination and lacunar infarction.

All participants had given their informed written consent, and this study had been approved by the Beijing Tiantan Hospital Ethics Review Board. The number of approvals of the Beijing Tiantan Hospital Ethics Review Board is KY2015-001-01. The clinical and demographic characteristics of all participants are shown in Table 1.

Neuropsychological assessment

All participants underwent neuropsychological assessment within 10 days of the stroke. The MoCA-Beijing scale was used to screen the global cognitive status of participants.
A formal battery of neuropsychological tests including the following were employed: (1) Auditory Verbal Learning Test for immediate and delayed verbal memory; (2) Rey-Osterrieth Complex Figure Test – Delayed Recall (RCFT-DR) for delayed visual memory; (3) RCFT Copy for visuospatial ability; (4) Animal Fluency Test (AFT) and Boston Naming Test (BNT, 30-item) for language; (5) Symbol Digit Modality Test (SDMT) for visuomotor speed; (6) Chinese modified version of the Trail Making Test (TMT) – A, Trail Making Test (TMT) – B, Stroop Table 1  

Clinical and demographic characteristics of each diagnostic group

|                        | HC (n = 29) | NPSCI (n = 17) | PSCI (n = 23) | HC vs. NPSCI p | HC vs. PSCI p | NPSCI vs. PSCI p |
|------------------------|-------------|----------------|--------------|----------------|---------------|-----------------|
| Age (years)            | 51.07 (6.77)| 48.88 (10.12) | 55.35 (8.51) | 0.39           | 0.068         | 0.017           |
| Male (%)               | 18 (62%)    | 14 (82%)       | 19 (83%)     | 0.133          | 0.097         | 0.985           |
| Education (years)      | 11 (2.49)   | 11.19 (2.23)   | 9.55 (1.74)  | 0.786          | 0.023         | 0.027           |
| Left basal ganglia (%) | 0            | 58.9           | 52.1         | /              | /             | 0.157           |
| Diameter of lesion (mm) | 0         | 14.57 ± 4.95   | 19.02 ± 9.64 | /              | /             | 0.08            |
| HAMD                   | 1.58 (1.95) | 2.53 (2.42)    | 3.10 (2.77)  | 0.257          | 0.054         | 0.494           |
| BADL                   | 6 (0)       | 6.07 (0.26)    | 6.27 (0.94)  | 0.706          | 0.086         | 0.27            |
| IADL                   | 8 (0)       | 8.28 (0.73)    | 9.48 (1.60)  | 0.372          | < 0.001       | 0.001           |
| Current or ever smoking (%) | 10 (60%) | 60 (71%)        | 71            | < 0.001       | < 0.001       | 0.416           |
| Current or ever drinking (%) | 14 (80%) | 80 (62%)        | 62            | < 0.001       | < 0.001       | 0.204           |
| Family history of stroke (%) | 0 (0%)   | 13 (30%)       | 30            | 0.184          | 0.002         | 0.123           |
| Pathoglycemia (%)      | 0            | 13             | 29            | 0.183          | 0.002         | 0.153           |
| Diabetes (%)           | 0            | 20             | 43            | 0.076          | < 0.001       | 0.057           |
| Hypertension (%)       | 7            | 55             | 76            | < 0.001       | < 0.001       | 0.088           |
| Hyperlipidemia (%)     | 3            | 73             | 86            | < 0.001       | < 0.001       | 0.261           |
| Myocardial Infarction (%) | 0 (0%)   | 0              | 5             | ≈ 1            | 0.185         | 0.26            |
| Coronary Artery Disease (%) | 0 (0%) | 0              | 10            | ≈ 1            | 0.056         | 0.104           |
| Peripheral Artery Disease (%) | 0 (0%) | 20             | 10            | 0.019          | 0.207         | 0.239           |
| Intracranial Arterial Stenosis (%) | 0 (0%) | 0              | 19            | ≈ 1            | 0.005         | 0.016           |

Data are presented as mean and standard deviation (SD) or percentage number (%). Reported p-values were obtained from independent t tests for age, education, HAMD, BADL, and IADL, and chi-square test for independence for the other variants. All p values are corrected for multiple comparison using FDR correction.

HC healthy controls; NPSCI post-stroke patients without cognitive impairment; PSCI post-stroke patients with cognitive impairment. HAMD Hamilton depression rating scores; BADL basic activities of daily living; IADL instrumental activities of daily living scale.

Table 2  

The difference of cognitive function among three diagnostic groups

|                        | HC (n = 29) | NPSCI (n = 17) | PSCI (n = 23) | HC vs. NPSCI p | HC vs. PSCI p | NPSCI vs. PSCI p |
|------------------------|-------------|----------------|--------------|----------------|---------------|-----------------|
| MoCA                   | 26.21 (2.41)| 23.53 (3.80)   | 19.35 (5.35) | 0.029          | < 0.001       | 0.001           |
| Verbal delayed memory  | 2.83 (1.65) | 2.47 (1.50)    | 0.96 (1.26)  | 0.437          | < 0.001       | 0.002           |
| RCFT-DR                | 17.97 (5.62)| 16.06 (5.04)   | 5.13 (5.35)  | 0.259          | < 0.001       | < 0.001         |
| RCFT-C                 | 146 (38.65) | 174 (67.13)    | 174 (60.28)  | 0.179          | 0.121         | ≈ 1             |
| BNT                    | 27.21 (2.09)| 24.24 (5.63)   | 20.43 (6.44) | 0.048          | < 0.001       | 0.017           |
| Animal fluency test    | 19.76 (5.01)| 17.06 (3.72)   | 13.05 (5.09) | 0.068          | < 0.001       | 0.011           |
| SDMT                   | 49.24 (10.62)| 23.96 (14.72)  | 36.06 (8.23) | < 0.001       | < 0.001       | 0.002           |
| TMT-A                  | 50.55 (20.45)| 59.18 (23.94)  | 90.70 (35.21)| 0.3            | < 0.001       | 0.001           |
| TMT-B                  | 127.83 (42.50)| 166.24 (55.71)| 200.91 (52.78)| 0.013       | < 0.001       | 0.032           |
| CWT-A time             | 24.76 (4.44)| 32.44 (6.09)   | 40.43 (15.71)| 0.014          | < 0.001       | 0.017           |
| CWT time               | 38 (10.93)  | 47.53 (23.42)  | 51.57 (16.98)| 0.073          | 0.005         | 0.471           |

Data are presented as mean and standard deviation (SD). All p values are corrected for multiple comparison using FDR correction.

HC healthy controls; NPSCI post-stroke patients without cognitive impairment; PSCI post-stroke patients with cognitive impairment. MoCA Montreal Cognitive Assessment Test; BNT Boston Naming Test; RCFT-DR Rey-Osterrieth Complex Figure Test – Delayed Recall. RCFT-C Rey-Osterrieth Complex Figure Test – Copy. SDMT Symbol Digit Modality Test; TMT Trail Making Test; CWT Color Word Test
Color-Word Test-Chinese version (CWT) – Color time for attention/executive function.

**Image acquisition and preprocessing**

MR images were obtained using a Siemens Trio Tim 3 T MR scanner. Resting-state fMRI, DWI and 3D high resolution structural brain images were acquired using a 12-channel phased-array head coil with implementation of the parallel imaging scheme GRAPPA (GeneRalized Autocalibrating Partially Parallel Acquisitions).

DWI data were acquired using a single-shot twice-refocused spin-echo diffusion echo-planar imaging (EPI) sequence. The sequence parameters were repetition time (TR) = 8000 ms, echo time (TE) = 60 ms, 64 non-linear diffusion directions with $b = 1000$ s/mm$^2$ and an additional volume with $b = 0$ s/mm$^2$, data matrix = 128 x 128, field of view (FOV) = 256 mm x 256 mm, 2 mm slice thickness.

**Fig. 1** The correlation between functional connections and structural connections in healthy controls (HC), post-stroke patients without cognitive impairment (NPSCI), and post-stroke patients with cognitive impairment (PSCI). The results of correlation between functional connections (FC) and structural connections (SC) in all three groups. A showed the correlation between FC and SC in healthy controls (HC). B showed the correlation between FC and SC in post-stroke patients without cognitive impairment (NPSCI). C showed the correlation between FC and SC in post-stroke patients with cognitive impairment (PSCI). The value of fractional anisotropy (FA) was regarded as structural connections (SC) and the value of $r$ between time series of every pair of regions of interest (ROI) was regarded as functional connections (FC).

**Fig. 2** The results of global and small-world parameters in structural and functional network healthy controls (HC), post-stroke patients without cognitive impairment (NPSCI), and post-stroke patients with cognitive impairment (PSCI). The results of global and small-world parameters in structural and functional network in three groups. A showed the differences of global parameters in structural network among three groups. B showed the differences of global parameters in functional network among three groups. In each panel, (i) clustering coefficient; (ii) path length; (iii) global efficiency; (iv) small-worldness. Orange dot denoted healthy controls (HC). Green dot denoted post-stroke patients without cognitive impairment (NPSCI). Yellow dot denoted post-stroke patients with cognitive impairment (PSCI). Error bar were shown. ** denotes $p < 0.01$. *** denotes $p < 0.001$.
thickness, isotropic voxel size (2mm³), and 75 transverse slices with no gap, covering the whole brain. The acquisition time was approximately 12 min for each DWI scan.

We also acquired 3D high resolution brain structural images (voxel size = 1mm³, isotropic) using a T1-weighted MP-RAGE sequence for each participant. The sequence

Fig. 3 The distribution of rich club in functional and structural networks in healthy controls (HC), post-stroke patients without cognitive impairment (NPSCI), and post-stroke patients with cognitive impairment (PSCI). The distribution of rich club. A showed the rich club in structural network in all three groups. B showed the rich club in functional network in all three groups. The size of node denotes the nodal strength. The color of node denotes the module it belonged. The module in green comprises the regions in the parietal cortex; the module in cyan comprises the regions in the limbic system; the module in magenta comprises the regions of subcortical nuclei; the module in blue comprises the regions of occipital cortex. The color and size of line denotes the connection strength between each pair of nodes. A denotes rich club in structural network in HC group; B denotes rich club in functional network in HC group; C denotes rich club in structural network in NPSCI group; D denotes rich club in functional network in NPSCI group; E denotes rich club in structural network in PSCI; F denotes rich club in functional network in PSCI group; L = left; R = right; A = anterior; P = posterior. MFG, middle frontal gyrus; SFGdor, superior frontal gyrus, dorsolateral; IFGoperc, inferior frontal gyrus, opercular part; PreCG, precentral gyrus; ORBsup.L, superior frontal gyrus, orbital part; ORBmid = middle frontal gyrus, orbital part; IFGtriang = inferior frontal gyrus = triangular part; ORBinf, inferior frontal gyrus = orbital part; ROL = Rolandic operculum; SMA = supplementary motor area; OLF = olfactory cortex; SFGmed = superior frontal gyrus = medial; ORBsupmed = superior frontal gyrus = medial orbital; REC = gyrus rectus; INS = insula; ACG = anterior cingulate and paracingulate gyr; DC = median cingulate and paracingulate gyr; PC = posterior cingulate gyr; HIP = hippocampus; PHG = parahippocampal gyrus; AMYG = amygdala; CAL = calcarine; CUN = cuneus; LING = lingual gyrus; SOG = superior occipital gyrus; MOG = middle occipital gyrus; IOG = inferior occipital gyrus; FFG = fusiform gyrus; PoCG = postcentral gyrus; SPG = superior parietal gyrus; IPL = inferior parietal gyrus; SMG = supramarginal gyrus; ANG = angular gyrus; PCUN = precuneus; PCL = paracentral lobule; CAU = caudate nucleus; PUT = putamen; PAL = pallidum; THA = thalamus; HES = heschl gyrus; STG = superior temporal gyrus; TP = temporal pole; MTG = middle temporal gyrus; ITG = inferior temporal gyrus;
parameters were TR/TE = 2300 ms / 2.3 ms, inversion time (TI) = 900 ms, flip angle = 8°, FOV = 256 mm × 256 mm, slice thickness = 1 mm, and 176 sagittal slices covering the whole brain. All participants were scanned using the same MR scanner. For each participant, resting-state fMRI was acquired using an EPI sequence with TR = 2500 ms, TE = 30 ms, flip angle = 90°, voxel size = 2.86 × 2.86 × 3 mm³, image matrix = 70 × 70 × 43, 200 volumes.

For data preprocessing, both the DWI data and T1-weighted data were visually inspected for apparent artifacts arising from participant motion or instrument malfunction. Distortions in the diffusion tensor images caused by eddy currents and simple head motions were corrected by applying affine alignment. Particularly, EPI distortion induced by the presence of geometrical and intensity distortions along the phase-encode direction caused by field inhomogeneities and concomitant fields were corrected by registering the first B0 image in each DWI set to its corresponding undistorted T1-weighted image, with a cubic B-spline transformation of knot grid size 10 × 10 × 10 mm³, partitioning the image space into 2 × 2 × 1.65 cm³. After correction, 3D maps of the diffusion tensors and the FA were calculated (Irfanoglu et al., 2012). Correction and calculation were performed using FMRIB’s Diffusion Toolbox. Resting-state functional MRI data was slice-time corrected, re-aligned, co-registered to the corresponding structural images, normalized to atlas space and resampled to 3 mm cubic voxel resolution using a combination of linear transformations and non-linear warps. Confounds related to head motion, global signal fluctuations, and non-gray matter signal compartments were removed from the data by regression of the six head motion parameters obtained from rigid body correction, along with global signal, the cerebrospinal fluid (CSF) and white matter (WM) signal. The resting-state functional MRI data preprocessing was performed using the DPABI software (Yan et al., 2016).

### Table 3 Hub nodes in brain structural network in HC, NPSCI and PSCI groups

|   | H      | NPSCI | PSCI |
|---|--------|-------|------|
|   | Nodes  | K     | Module | Nodes  | K     | Module | Nodes  | K     | Module |
|   | PUT.R  | 33    | Subcortical | PCUN.R | 32    | Parietal | PUT.R  | 30    | Subcortical |
|   | PCUN.R | 32    | Parietal | PCUN.L  | 29    | Parietal | PCUN.L  | 29    | Parietal |
|   | PCUN.L | 32    | Parietal | PUT.L   | 27    | Subcortical | PUT.L   | 27    | Subcortical |
|   | PUT.L  | 28    | Subcortical | PUT.R   | 24    | Subcortical | PUT.L   | 27    | Subcortical |
|   | CAL.R  | 26    | Occipital | CAL.L   | 23    | Occipital | CAL.R   | 24    | Subcortical |
|   | CAL.L  | 26    | Occipital | CAL.L   | 22    | Occipital | CAL.R   | 23    | Occipital |
|   | LING.L | 23    | Occipital | LING.L  | 21    | Occipital | LING.L  | 22    | Occipital |
|   | TPOsup.R | 21   | Limbic | TPOsup.R | 20    | Limbic | ORBsup.L | 22    | Frontal |
|   | CAU.L  | 21    | Subcortical | ORBsup.L | 20    | Frontal | CAU.L  | 21    | Subcortical |
|   | SPG.R  | 21    | Parietal | TPOsup.R | 20    | Limbic | ORBsup.R | 20    | Frontal |
|   | CUN.R  | 21    | Occipital | ORBsup.R | 20    | Frontal | ORBsup.R | 20    | Frontal |
|   | HIP.R  | 21    | Limbic | ORBsup.R | 20    | Frontal | SFGmed.L | 20    | Frontal |
|   | LING.R | 20    | Occipital | SFGmed.L | 20    | Frontal | SFGmed.L | 20    | Frontal |
|   | ORBinf.R | 20  | Frontal | SFGmed.L | 20    | Frontal | SFGmed.L | 20    | Frontal |
|   | TPOsup.R | 20  | Frontal | SFGmed.L | 20    | Frontal | SFGmed.L | 20    | Frontal |

The cells of hubs in structural network in three groups.  
CAL calcarine; CAU caudate nucleus; CUN cuneus; HIP hippocampus; ITG inferior temporal gyrus; LING lingual gyrus; ORBinf Inferior frontal gyrus, orbital part; ORBsup superior frontal gyrus, orbital part; PCUN precuneus; PUT putamen; SFGmed superior frontal gyrus, medial; SPG superior parietal gyrus; TPOsup temporal pole, superior temporal gyrus.
Table 4  Hub nodes in brain functional network in HC, NPSCI and PSCI groups

| Nodes     | K | Module   | Nodes     | K | Module   | Nodes     | K | Module   |
|-----------|---|----------|-----------|---|----------|-----------|---|----------|
| ACG.L     | 61| Limbic   | MTG.L     | 59| Temporal | STG.R     | 61| Temporal |
| DCG.R     | 59| Limbic   | MTG.R     | 56| Temporal | ROL.R     | 56| Central  |
| DCG.L     | 58| Limbic   | PreCG.R   | 55| Central  | IFGoperc.R| 53| Frontal  |
| PreCG.L   | 57| Central  | STG.R     | 55| Temporal | IFGtriang.R| 53| Frontal  |
| ROL.L     | 57| Central  | IFGoperc.L| 54| Frontal  | ROL.L     | 52| Central  |
| INS.L     | 57| Insula   | IFGtriang.R| 53| Frontal  | DCG.L     | 52| Limbic   |
| ACG.R     | 57| Limbic   | ORBinf.R  | 53| Frontal  | STG.L     | 52| Temporal |
| PreCG.R   | 56| Central  | ORBsupmed.L.| 53| Frontal  | MTG.R     | 52| Temporal |
| ORBinf.R  | 56| Frontal  | INS.R     | 53| Insula   | IFGoperc.L.| 51| Frontal  |
| ORBmid.R  | 54| Frontal  | ORBinf.L  | 51| Frontal  | REC.L     | 51| Frontal  |
| IFGtriang.R| 54| Frontal  | IFGoperc.R| 50| Frontal  | ORBinf.L  | 50| Frontal  |
| INS.R     | 54| Insula   | IFGtriang.L.| 50| Frontal  | REC.R     | 50| Frontal  |
| MTG.R     | 54| Temporal | SFGmed.L  | 50| Frontal  | INS.R     | 50| Insula   |
| ORBsupmed.L.| 53| Frontal  | ORBsupmed.R| 50| Frontal  | DCG.R     | 50| Limbic   |
| ORBsupmed.R.| 52| Frontal  | REC.L     | 50| Frontal  | PUT.L     | 50| Subcortical |
| SFGdor.R  | 51| Frontal  | PoCG.L    | 50| Central  | IFGtriang.L.| 49| Frontal  |
| ORBsupmed.L.| 51| Frontal  | ROL.L     | 49| Central  | ORBsupmed.R| 49| Frontal  |
| HES.L     | 51| Temporal | INS.L     | 49| Insula   | MTG.L     | 49| Temporal |
| ORBmid.L  | 50| Frontal  | DCG.R     | 47| Limbic   | INS.L     | 48| Insula   |
| IFGoperc.R| 50| Frontal  | SOG.R     | 47| Occipital| PoCG.R    | 48| Central  |
| IFGtriang.L.| 50| Frontal  | SFG.med.L.| 47| Parietal | ORBinf.R  | 47| Frontal  |
| SFGmed.L  | 50| Frontal  | PUT.R     | 47| Subcortical| ACG.L       | 47| Limbic   |
| AMYG.R    | 50| Subcortical| STG.L     | 47| Temporal | ACG.R     | 47| Limbic   |
| PoCG.R    | 50| Central  | PoCG.R    | 46| Central  | PoCG.L    | 47| Central  |
| STG.R     | 50| Temporal | ANG.R     | 46| Parietal | THA.L     | 47| Subcortical |
| SFGdor.L  | 49| Frontal  | ORBmid.L  | 46| Frontal  |
| MFG.R     | 49| Frontal  | SMA L     | 46| Frontal  |
| SFGmed.R  | 49| Frontal  | ORBsupmed.L.| 46| Frontal  |
| FFG.L     | 49| Occipital| HES.R     | 46| Temporal |
| SPG.R     | 49| Parietal |
| CAU.L     | 49| Subcortical |
| MTG.L     | 49| Temporal |
| ROL.R     | 48| Central  |
| REC.L     | 47| Frontal  |
| PoCG.L    | 47| Central  |
| PCL.L     | 47| Frontal  |
| STG.L     | 47| Temporal |
| ITG.R     | 47| Temporal |
| IFGoperc.L.| 46| Frontal  |
| SMA.L     | 46| Frontal  |
| OLF.L     | 46| Frontal  |
| SMG.R     | 46| Parietal |
| PUT.R     | 46| Subcortical |

The cells of hubs in structural network in three groups

ACG anterior cingulate and paracingulate gyri; AMYG amygdala; ANG angular gyrus; CAU caudate nucleus; DCG median cingulate and paracingulate gyri; FFG fusiform gyrus; HES heschl gyrus; IFGoperc inferior frontal gyrus, opercular part; IFGtriang inferior frontal gyrus, triangular part; INS insula; ITG inferior temporal gyrus; MTG middle temporal gyrus; OLF olfactory cortex; ORBinf Inferior frontal gyrus, orbital part; ORBmid middle frontal gyrus, orbital part; ORBsupmed superior frontal gyrus, medial orbital; PCL paracentral lobule; PreCG precentral gyrus; PoCG postcentral gyrus; PUT putamen; REC gyrus rectus; ROL Rolandic operculum; SFGdor superior frontal gyrus, dorsolateral; SMA supplementary motor area; SMG supramarginal gyrus; SOG superior occipital gyrus; SPG superior parietal gyrus; STG superior temporal gyrus; THA thalamic
for each subject in the native diffusion space using a deterministic streamline fiber tractography algorithm (the Fiber Assignment by Continuous Tracking Algorithm, FACT) implemented in the PANDA. All voxels with fractional anisotropy (FA) ≥ 0.2 were used as seed points. Fiber tracking stopped when either consecutive voxels in tracking showed FA less than 0.1 or the angle between the eigenvectors of two consecutive voxels was larger than 35°. The total number of fiber streamlines for whole-brain tractography was 84,591.23 ± 99,054.76 in the HC, 9721.81 in PSCI. To determine the edge of the brain network, the value obtained by the mean fractional anisotropy (FA) along the fiber bundles connecting a pair of regions was used to weight the edge and reveal the white matter. FA described the degree of directional preference (anisotropy) of water diffusion values along the midpoint of the tracked fiber and was calculated from the eigenvalues of the diffusion tensor in three dimensions. Large FA values represent confined diffusion in one direction. Therefore, we obtained the matrix of an anatomically connected network formed by weighted connections for threshold values FA ≥ 0.1 in each participant. Data preprocessing and network construction were performed using the Pipeline for Analyzing Brain Diffusion Images (PANDA) toolbox (Cui et al., 2013).

For functional network construction, we also used the automated anatomical labeling (AAL) template to define network nodes. For each participant, the time series of all voxels in each ROI were extracted and averaged to obtain a mean time series. The spurious sources of variance, six head motion parameters, were removed from the meantime series using a multiple regression model. The time series were also band-pass filtered (0.01–0.08 Hz) to reduce low-frequency drift and high-frequency respiratory and cardiac noise. Pearson’s correlation analysis was performed between the processed time series of every pair of ROIs to produce a 90 × 90 temporal symmetric correlation matrix for each participant. Then we computed networks for threshold values r = 0. The negative connections were excluded because the negative connections may decrease the reliability of results in network analysis (Shehzad et al., 2009; Wang et al., 2011). Functional networks were constructed using the MATLAB-based Graph Theoretical Network Analysis (GRETNA) toolbox (Wang et al., 2015).

A correlation analysis was used to test the coupling between structural and functional connections among the three experimental groups.

### Global network parameters

We selected some global parameters to analysis the overall organization characteristics in structural and functional networks. Global parameters included (1) weighted clustering coefficient ($C_p$), computed as the average likelihood that the neighbors of a node are interconnected; (2) average path length ($L_p$), computed as the average of the shortest path length for all possible connections among the nodes in the network (Latora & Marchiori, 2001); (3) global efficiency ($E_{global}$), computed as the average inverse shortest path

### Table 5: Global graph analysis properties of brain structural network among healthy controls (HC), post-stroke patients without cognitive impairment (NPSCI), and post-stroke patients with cognitive impairment (PSCI)

|       | HC          | NPSCI       | PSCI       | F  | p-value | NPSCI vs HC | P: PSCI vs HC | P: NPSCI vs PSCI |
|-------|-------------|-------------|------------|----|---------|-------------|---------------|-----------------|
| $C_p$ | 0.2451 ± 0.0148 | 0.2419 ± 0.0192 | 0.2302 ± 0.0168 | 5.418 | 0.0066 | $P > 0.05$   | $P < 0.01^{**}$ | $P > 0.05$      |
| $L_p$ | 5.196 ± 0.2268 | 5.377 ± 0.4169 | 5.593 ± 0.4319 | 8.033 | 0.0008 | $P > 0.05$   | $P < 0.001^{***}$ | $P > 0.05$      |
| $E_{global}$ | 0.1922 ± 0.0084 | 0.1869 ± 0.0136 | 0.1782 ± 0.0143 | 9.864 | 0.0002 | $P > 0.05$   | $P < 0.001^{***}$ | $P > 0.05$      |
| $\sigma$ | 2.768 ± 0.1949 | 2.746 ± 0.3864 | 2.822 ± 0.3565 | 0.3343 | 0.717 | $P > 0.05$   | $P > 0.05$     | $P > 0.05$      |

Values are number or mean ± SD. F and P Values refer to one-way ANOVA, followed by post hoc pairwise comparisons (Bonferroni-corrected for multiple comparisons). $C_p$ means clustering coefficient; $L_p$ denotes path length; $E_{global}$ denotes global efficiency; $\sigma$ denotes small-worldness.

### Table 6: Global graph analysis properties of brain functional network among healthy controls (HC), post-stroke patients without cognitive impairment (NPSCI), and post-stroke patients with cognitive impairment (PSCI)

|       | HC          | NPSCI       | PSCI       | F  | p-value | NPSCI vs HC | P: PSCI vs HC | P: NPSCI vs PSCI |
|-------|-------------|-------------|------------|----|---------|-------------|---------------|-----------------|
| $C_p$ | 0.3727 ± 0.0183 | 0.3324 ± 0.0167 | 0.3588 ± 0.0191 | 1.927 | 0.1537 | $P > 0.05$   | $P > 0.05$     | $P > 0.05$      |
| $L_p$ | 4.87 ± 0.1647 | 4.83 ± 0.1286 | 4.626 ± 0.1473 | 1.942 | 0.1515 | $P > 0.05$   | $P > 0.05$     | $P > 0.05$      |
| $E_{global}$ | 0.2071 ± 0.0064 | 0.2092 ± 0.0058 | 0.218 ± 0.0067 | 1.835 | 0.1677 | $P > 0.05$   | $P > 0.05$     | $P > 0.05$      |
| $\sigma$ | 2.945 ± 0.1282 | 2.865 ± 0.1171 | 2.838 ± 0.1342 | 0.4529 | 0.6378 | $P > 0.05$   | $P > 0.05$     | $P > 0.05$      |

Values are number or mean ± SD. F and P Values refer to one-way ANOVA, followed by post hoc pairwise comparisons (Bonferroni-corrected for multiple comparisons). $C_p$ means clustering coefficient; $L_p$ denotes path length; $E_{global}$ denotes global efficiency; $\sigma$ denotes small-worldness.
### Table 7 Result of NBS-analysis in structural network between PSCI and HC

| Rich club NodeA | Feeder NodeB | t | Local NodeA (hub) | NodeB (nonhub) | t |
|-----------------|--------------|---|------------------|----------------|---|
| CAL.L           | CUN.R        | 2.73 | ACG.L           | 2.99 | AMYG.L | 2.18 |
| PCUN.L          | PCUN.R       | 2.6  | PUT.R           | 2.16 | AMYG.R | 2.07 |
| CAL.R           | PUT.R        | 2.13 | CAL.L           | 2.78 | ANG.R | 2.66 |
|                 |              |      | STG.R           | 2.19 | ANG.R | 2.03 |
|                 |              |      | SOG.L           | 2.1  | CUN.L | 2.04 |
|                 |              |      | DCG.R           | 2.52 | PCUN.L | 2.65 |
|                 |              |      | FFG.R           | 3.46 | PCUN.L | 3.21 |
|                 |              |      | HIP.R           | 2.47 | CAL.L | 2.29 |
|                 |              |      | IFGoper.L       | 2.93 | PUT.R | 2.95 |
|                 |              |      | IFGtriang.R     | 2.33 | PUT.R | 2.92 |
|                 |              |      | IOG.R           | 2.15 | PUT.R | 2.36 |
|                 |              |      | LING.R          | 3.06 | PUT.R | 3.21 |
|                 |              |      | MOG.R           | 2.17 | ITG.R | 2.39 |
|                 |              |      | MTG.R           | 2.71 | ITG.R | 2.76 |
|                 |              |      | OLB.F           | 2.39 | ORBf.L | 2.64 |
|                 |              |      | ORBmid.L        | 2.71 | ORBf.L | 2.4 |
|                 |              |      | ORBmid.L        | 2.47 | ORBf.L | 2.38 |
|                 |              |      | INS.L           | 3.4  | ORBf.L | 2.14 |
|                 |              |      | SPG.L           | 2.14 | ORBf.L | 2.15 |
|                 |              |      | ORBsupmed.L     | 2.94 | CAU.L | 3.38 |
|                 |              |      | ORBsupmed.L     | 2.96 | CAU.L | 2.11 |
|                 |              |      | MFG.R           | 3.1  | CAU.L | 2.15 |
|                 |              |      | MOG.R           | 2.34 | CAL.L | 2.16 |
|                 |              |      | MOG.R           | 2.62 | CAL.L | 2.73 |
|                 |              |      | PCUN.L          | 2.9  | PCUN.L | 2.08 |
|                 |              |      | PHG.L           | 2.72 | PCUN.L | 2.09 |
|                 |              |      | REC.L           | 2.06 | CAU.L | 2.95 |
|                 |              |      | REC.L           | 2.8  | CAU.L | 2.35 |
|                 |              |      | REC.L           | 2.55 | CAU.L | 2.57 |
|                 |              |      | REC.L           | 2.78 | CAU.L | 2.3 |
|                 |              |      | SFGdor.R        | 2.4  | ORBf.L | 2.9 |
|                 |              |      | SPG.L           | 2.12 | SPG.R | 3.23 |
|                 |              |      | ANG.R           | 4.35 | SPG.R | 2.45 |
|                 |              |      | TPOmid.R        | 2.07 | ITG.R | 2.1 |

The cells of results in NBS in structural network between PSCI and HC

ACG anterior cingulate and paracingulate gyri; AMYG amygdala; ANG angular gyrus; CAL calcarine; CAU caudate nucleus; CUN cuneus; DCG median cingulate and paracingulate gyri; FFG fusiform gyrus; HES heschl gyrus; HIP hippocampus; IFGoperc inferior frontal gyrus, opercular part; IFGtriang inferior frontal gyrus = triangular part; INS insula; IOG inferior occipital gyrus; IPL inferior parietal gyrus; ITG inferior
energy (Watts & Strogatz, 1998); and (4) small-worldliness ($\sigma$), computed as the ratio of $C_p$ to $L_p$ with normalization to a null random network. All global parameters were computed using the GRETNA toolbox.

**Statistical analysis**

The differences in global parameters ($C_p$, $L_p$, $E_{glob}$, $\sigma$) of networks were tested by one-way ANOVA and corrected by permutation test (Zhang et al., 2011). A null distribution of differences for global parameters was generated after 5000 permutations repeat. Finally, we assigned a $p$-value to the differences after computing the proportion of the differences that exceeded the null distribution values. The $p < 0.05$ was used as a significant threshold to correct for multiple comparisons when testing for statistically significant differences among all global parameters.

Similarly, between-group differences in the results of clinical and demographic information, and neuropsychological assessment. In demographic information, the independent sample t-test was used to test the age, education, HAMD, clinical and demographic information, and neuropsychological assessment. In demographic information, the independent sample t-test was used to test the neuropsychological assessment. A cutoff of $p < 0.05$ was used as the significance threshold.

**Rich club determination and network segmentation**

A rich-club analysis was performed for determining the hubs and nonhubs in constructed group-level brain network. The rich-club coefficient ($\Phi^w(k)$) was used to determine the degree ($k$) threshold for a hub in the network. Nodes with degree larger than $k$ belong to a hub. Therefore, nodes with degree larger than $k$ belong to a rich club. $\Phi^w(k)$ measures the extent to which well-connected nodes in a network also connect to each other (Opsahl et al., 2008). Firstly, to obtain the group-level matrix, all linking matrices of subjects in each group were averaged and the elements of the averaged matrices with values less than the threshold (structural network: $FA = 0.1$; functional network: $r = 0$-) were removed. For the rich club analysis, all connections in the network were first ranked by weighted values, resulting in a vector $W_{ranked}$. The procedure of determination of $k$ started with presetting $k = 1$. A subset of nodes was selected with this preset $k$ value. $E_{>k}$ was defined as the total number of connections between the nodes in this subset with nodal degree larger than $k$. From this subset, consisting of $n$ nodes and connection of $E_{>k}$ connections, their total sum of weights $W_{>k}$ was determined. The weighted rich-club (subset) parameter $\Phi^w(k)$ was then computed as the ratio between $W_{>K}$ and the sum of all possible weighted connections among the nodes in the subset with respect to the ranking vector ($W_{ranked}$) (van den Heuvel & Sporns, 2011). Mathematically, $\Phi^w(k)$ is computed with the formula (Opsahl et al., 2008):

$$\Phi^w(k) = \frac{W_{>k}}{\sum_{l=1}^{E_{>k}} W_{ranked}}$$

Random distribution of nodes in a network potentially reduces $\Phi(k)$. We normalized $\Phi(k)$ with a random network ($\Phi_{norm}$, ratio of $\Phi(k)$ to that of random network) to minimize this effect (Colizza et al., 2006; McAuley et al., 2007). A random network was constructed with the same size as the brain network being tested. Therefore, $\Phi_{norm}$ values greater than one reflect the existence of rich-club organization in the underlying network. We repeated the procedure by increasing the value of $k$ gradually to generate the $\Phi_{norm}$ with an expected value of more than one. The corresponding $k$ indicating the existence of a rich club was recorded. Accordingly, the nodes were classified into hub nodes (with nodal degree greater than $k$) and non-hub nodes. Similarly, connections in the network were classified as rich club connections (linking hubs), feeder (linking hubs and nonhubs), and local (linking nonhubs) (van den Heuvel et al., 2012).

**Network-based statistics analysis**

A network-based statistic (NBS) analysis was used to explore the differences in network components (rich club, feeder or local) in brain network among the three groups. We used the correction for family-wise error rate to control the power of the analysis (Zalesky et al., 2010). A nonparametric two-tail sign test was performed to compare structural and functional network connections between groups. Connections with a test-statistic $t > 2.66$ (corresponding to
**Table 8** Result of NBS-analysis in functional network between PSCI and HC

| Rich club   | Feeder          | Local          |
|-------------|-----------------|----------------|
| NodeA       | NodeB  | t  | NodeA       | NodeB   | t  | NodeA       | NodeB   | t  |
| IFGoperc.L  | ORBinf.R | 2.86 | ORBmid.L    | MFG.L   | 2.94 | SFGdor.R    | ORBmid.R | 2.03 |
| ROL.L       | SMA.R    | 3.23 | ORBmid.L    | MFG.L   | 2.39 | ORBsup.L    | SFGmed.L | 2.02 |
| SMA.R       | INS.L    | 2.16 | ROL.L       | PreCG.R | 2.84 | SFGdor.L    | PCG.L    | 2.12 |
| SMA.R       | INS.R    | 2.45 | ROL.R       | PreCG.R | 2.53 | SFGdor.L    | PCG.L    | 2.12 |
| ROL.L       | ACG.R    | 3.44 | ORBinf.L    | SFGmed.L | 3.55 | SFGmed.L    | PCG.L    | 2.62 |
| INS.R       | DCG.L    | 2.6  | ORBinf.R    | SFGmed.L | 2.11 | SFGmed.L    | PCG.L    | 2.92 |
| ACG.L       | DCG.L    | 2.47 | ORBinf.L    | SFGmed.L | 4.37 | SFGmed.L    | PCG.R    | 2.31 |
| ROL.L       | DCG.L    | 2.42 | ORBinf.R    | SFGmed.L | 3.4  | SFGmed.L    | PCG.R    | 2.05 |
| INS.R       | DCG.R    | 2.86 | ORBsupmed.L | SFGdor.L | 2.03 | MOG.L       | SPG.L    | 2.66 |
| INS.R       | DCG.R    | 2.35 | ORBsupmed.L | SFGmed.L | 2.76 | MOG.R       | SPG.L    | 3.2  |
| ACG.L       | DCG.R    | 2.04 | ORBsupmed.L | SFGmed.L | 2.31 | SOG.R       | SPG.R    | 2.17 |
| ROL.L       | PaCG.L   | 3.54 | ORBsupmed.R | SFGdor.L | 3.11 | MOG.R       | SPG.R    | 2.12 |
| ROL.L       | PaCG.L   | 2.3  | ORBsupmed.R | SFGdor.L | 2.57 | MOG.L       | IPL.L    | 2.4  |
| ROL.L       | PaCG.R   | 2.89 | ORBsupmed.R | SFGdor.L | 2.09 | MFG.R       | SMG.R    | 2.11 |
| ROL.R       | PaCG.R   | 2.62 | REC.L       | SFGmed.L | 2.59 | SFG.L       | SMG.R    | 3.29 |
| PaCG.L      | PaCG.L   | 2.3  | REC.L       | SFGmed.L | 2.3  | SFGdor.L    | PCUN.L   | 2.1  |
| IFGtriang.L | ANG.L    | 2.82 | ORBsupmed.R | PCG.L    | 2.82 | MOG.R       | PUT.R    | 2.6  |
| PaCG.R      | HES.R    | 2.84 | ACG.L       | PCG.L    | 3.06 | SMG.R       | PUT.R    | 2.59 |
| ROL.L       | STG.L    | 2.7  | ACG.R       | PCG.L    | 2.14 | SMG.R       | TPOsup.R | 2.36 |
| DCG.L       | STG.L    | 2.87 | ORBinf.L    | HIPR     | 2.35 | SFGmed.R    | TPOmid.R | 2.36 |
| PaCG.L      | STG.L    | 2.85 | REC.R       | HIPR     | 4.24 | MFG.L       | ITG.L    | 3.62 |
| PaCG.R      | STG.L    | 2.28 | REC.L       | PHG.R    | 2.84 | ITG.L       |         |     |
| PaCG.L      | STG.R    | 2.02 | REC.R       | PHG.R    | 2.49 | ITG.L       |         |     |
| PaCG.R      | STG.R    | 3.25 | PaCG.L      | FFG.R    | 2.11 | ITG.L       |         |     |
| ORBsupmed.L | MTG.L    | 3.19 | PaCG.R      | CAL.R    | 2.55 | ITG.L       |         |     |
| PaCG.R      | LING.L   | 2.44 | IFGoperc.R  | IPL.L    | 3.21 | ITG.L       |         |     |
| PaCG.R      | LING.L   | 2.58 | IFGoperc.R  | IPL.R    | 2.65 | ITG.L       |         |     |
| PaCG.R      | LING.L   | 2.38 | IFGtriang.R | SFGdor.L | 2.56 | ITG.L       |         |     |
| PaCG.R      | LING.L   | 2.49 | ANG.L       | MFG.L    | 3.11 | ITG.L       |         |     |
| ROL.L       | PCL.L    | 2.3  | ROL.R       | PCL.L    | 2.31 | ITG.L       |         |     |
| ROL.R       | PCL.L    | 2.31 | SMA.R       | PCL.L    | 2.13 | ITG.L       |         |     |
| SMA.R       | PCL.L    | 2.95 | STG.R       | PCL.L    | 2.95 | ITG.L       |         |     |
| SMA.R       | PCL.L    | 2.95 | STG.R       | PCL.L    | 2.95 | ITG.L       |         |     |
| INS.L       | TPOsup.R | 2.34 | IFGoperc.R  | ITG.L    | 2.12 | ITG.L       |         |     |
| INS.L       | TPOsup.R | 2.34 | IFGoperc.R  | ITG.L    | 2.12 | ITG.L       |         |     |

The cells of results in NBS in functional network between PSCI and HC

*ACG* anterior cingulate and paracingulate gyri; *AMYG* amygdala; *ANG* angular gyrus; *CAL* calcarine; *CAU* caudate nucleus; *CUN* cuneus; *DCG* median cingulate and paracingulate gyri; *FFG* fusiform gyrus; *HIP* hippocampus; *HES* heschl gyrus; *IFGoperc* inferior frontal gyrus, opercular part; *IFGtriang* inferior frontal gyrus, triangular part; *INS* insula; *ITG* inferior temporal gyrus; *LING* lingual gyrus; *MFG* middle frontal gyrus; *MOG* middle occipital gyrus; *MTG* middle temporal gyrus; *OLF* olfactory cortex; *ORBinf* inferior frontal gyrus, orbital part; *ORBmid* middle frontal gyrus, orbital part; *ORBsup.L* superior frontal gyrus, orbital part; *ORBsupmed* superior frontal gyrus, medial orbital; *PCL* pallidum; *PCG* posterior cingulate gyrus; *PCL* paracentral lobule; *PCUN* precuneus; *PHG* parahippocampal gyrus; *PoCG* postcentral gyrus; *PreCG* precentral gyrus; *PUT* putamen; *REC* gyrus rectus; *ROL* Rolandic operculum; *SFGdor* superior frontal gyrus, dorsolateral; *SFGmed* superior frontal gyrus, medial; *SMA* supplementary motor area; *SMG* supramarginal gyrus; *SOG* superior occipital gyrus; *SPG* superior parietal gyrus; *STG* superior temporal gyrus; *THA* thalamus; *TPOmid* temporal pole: middle temporal gyrus; *TPOsup* temporal pole: superior temporal gyrus
were marked 1, and 0 otherwise. A binary matrix could be generated to represent the changed connections of network between groups. The largest matrix with all possibly connected brain areas was identified from the network and the size of the matrix was stored. Random assignment with 5,000 permutations of corresponding voxels between two groups was performed to investigate the effect of different components. A t-test was used to examine whether the initial matrix was different from the new matrix generated by the permutation. P < 0.05 indicated altered connectivity between groups. Then the altered connections from NBS analysis were divided into three different components (rich club, feeder and local).

**Inter- and intra-module alterations determination**

We have tried to analyze and located the connections to find out which components had the greatest influence on the global efficiency of network after NBS-analysis. We divided the whole brain network into eight modules: central, frontal, insula, limbic, occipital, parietal, subcortical and temporal modules (Cheng et al., 2016, Rolls et al., 2015). We subsequently classified the all altered connections according to the modules they connected. Finally, we quantified the proportion of intra- and inter-modal connections using the sum of connections located inter- and intra-modules divided by all altered connections.

**Correlation analysis**

The correlation analysis was performed to test the relationship between global efficiency and MOCA scores among three groups. Also we performed the correlation analysis to test the relationship between the changes of inter- or intra-module structural and functional connections and MOCA scores in PSCI group. We regarded the sum of the weighted values of all changed edges connected the eight modules of each subject's brain network as the connection strength. Then we calculated the correlation between the connection strength of NBS in post-stroke patient with cognitive impairment and their own MOCA scores.

**Results**

**Clinical and demographic characteristics**

Clinical and demographic characteristics of each diagnostic group are summarized in Table 1. Briefly, the PSCI group was significantly greater than NPSCI group and HC group in education, IADL, and intracranial arterial stenosis. The PSCI had significantly greater metrics than HC in smoking or drinking history, hypertension and hyperlipidemia. There were no significant differences in age, sex, site and diameter of lesions, HAMD, BADL, myocardial infarction, and coronary artery disease among three diagnostic groups.

All patients had acute infarcts in the basal ganglia regions, which included the left caudate nucleus (n = 4), left corona radiate (n = 13); left putamen (n = 1); left internal capsule (n = 12); left thalamus (n = 3); right centrum semiovale (n = 4); right internal capsule (n = 7); right thalamus (n = 4) and right caudate nucleus (n = 5). A total of 40 patients had lesions in the basal ganglia (24 in the left basal ganglia, 15 in the right basal ganglia, 1 bilateral lesions). There were no significant differences in number of patients with multiple or multi-site infarcts between the PSCI group and the NPSCI group.

**Neuropsychological test**

The differences in cognitive function between diagnostic groups are summarized in Table 2. We found that PSCI had significantly worse cognitive scores than NPSCI and HC in the verbal delayed memory, visual delayed memory, language, visuomotor speed, and attention/executive function. NPSCI had significantly worse cognitive performance than the HC in the language, visuomotor speed, and attention/executive function. However, there were no significant differences in visuospatial ability among the three diagnostic groups.

**Correlation analysis between structural and functional metric**

We constructed brain networks for the three participant groups based on the weighted FA values obtained from DTI and correlation values obtained from resting-state fMRI. Correlation analysis between structural and functional networks revealed that connectivity strength in the structural brain network was strongly positively correlated with connectivity strength in the functional brain network within the three groups (in HC, r = 0.4422, p < 0.0001; in NPSCI, r = 0.4822, p < 0.0001; in PSCI, r = 0.4295, p < 0.0001) (Fig. 1). Correlation analysis between structural and functional connectivity strength indicated that stronger connectivity in the structural network was closely related to stronger connectivity in the functional network (Fig. 2).

**Rich club organization**

For the structural network, the three groups had the same k = 20 threshold for determination of hub nodes. We found
14 hub nodes in HC, 10 hub nodes in NPSCI, and 16 hub nodes in PSCI (Fig. 3A, Table 3). Most hubs in the HC structural network were in basal ganglia (PUT, CAU), occipital cortex (CAL, CUN, LING), and parietal cortex (SPG, PCUN). Most hubs in the NPSCI structural network were in parietal cortex (PCUN), basal ganglia (PUT, CAU), and occipital cortex (CAL, LING). Most hubs in the PSCI structural network were in basal ganglia (PUT, CAU), parietal cortex (PCUN, SPG), and frontal cortex (ORBsup, ORBinf, SFGmed). For the functional network, the three groups had the same k = 46 threshold for determination of hub nodes (Fig. 3B, Table 4). Most hubs in the HC functional network were in frontal cortex (IFG, SFG, MFG, REC, SMA, OLF), central cortex (PoCG, ROL, PreCG), and temporal cortex (MTG, HES, STG, ITG). Most hubs in the NPSCI functional network were in frontal cortex (IFG, SFG, REC), temporal cortex (MTG, STG), and central cortex (ROL, PoCG, PreCG). Most hubs in the PSCI functional network were in frontal cortex (IFG, REC, SMA), temporal cortex (STG, MTG, HES), limbic system (DCG, ACG), and central gyrus (ROL, PoCG).

NPSCI relative to HC

NPSCI showed no global network abnormalities relative to HC in structural and functional network (Fig. 2, Table 5, and Table 6). At the regional connectivity level, in the structural network, relative to HC, NPSCI were characterized by 26 reduced connections composed of 10 feeder and 16 local connections (Fig. 4C, Table 9) while there were no altered connections in the functional network. After qualifying the proportion of intra- and inter-modal connectivity, the disrupted connections of the structural subnetwork were mainly located in intra-occipital (26.9%) and occipital-temporal (19.2%) networks (Fig. 5C).

Correlation analysis between brain network characteristics and MOCA scores

Correlation analysis between global efficiency and MOCA scores revealed that he values of MOCA was significantly negative correlated to the global efficiency of brain network in HC group while both PSCI and NPSCI showed no significant correlation between global efficiency and MOCA (Figure S1A). For functional connectivity, there were no significant correlation between global efficiency and MOCA among three groups (Figure S1B). Furthermore, we didn’t find significant correlation between the changes of inter- or intra-module SC and MOCA scores in PSCI group. Neither nor FC and MOCA scores (Figure S2).

Discussion

Using graph analysis in comparison with HC, PSCI patients exhibited structural connectivity breakdown in basal-frontal and intra-frontal pathways, and functional connectivity breakdown in both FPN and CON, which may indicate a bottom-up pathological mechanism of stroke with cognitive impairment. However, NPSCI showed reduced connectivity in intra-occipital and occipital-temporal networks. In addition, the global topologic organization of the PSCI structural network was significantly disrupted, whilst that of NPSCI was relatively preserved. In terms of connection components, PSCI showed a large number of reduced connections in all three types of connections while NPSCI
As part of the cortical-striatal-thalamic-cortical loops, the basal ganglia in the cognitive processing network. Concentrated in basal ganglia-frontal, as well as in intra-parietal gyri and paracentral lobule, the basal ganglia-frontal and paracentral lobule show more flexible characteristics, whereas the structural connectivity topology is relatively stable (Bullmore & Sporns, 2009). Global properties of functional connectivity network in PSCI might get back to normal levels in a relatively short time period through compensatory connections in intact regions. Thus, structural connectivity may be more sensitive to stroke-induced cerebral lesions than functional connectivity network across the brain network. Our findings expand the understanding of network reorganization in patients with brain injury after stroke at the system level.

Interestingly, we found that the PSCI group had the most structural network hubs and the second most functional network hubs across the three groups. Specifically, the new hubs in the PSCI structural network were the superior orbital frontal gyrus and superior medial frontal gyrus. Generally, abnormal hub reduction was found in brain networks across acute brain injury. Nevertheless, the observation of more new hubs in the PSCI structural network may indicate that the increased importance of normal nonhubs could balance the decreased hubs. Such hub alternation have been found previously in Alzheimer’s disease (Supelak et al., 2008; Yao et al., 2010), stroke (Desmurs et al., 2007) and schizophrenia (Lynall et al., 2010). As we show here, the reorganized location of network hubs radically in PSCI, implying that a specific topological-spatial pattern is critical for network topology underlying cognitive processing.

In the NBS results, brain structural and functional networks in the PSCI group showed significantly reduced connection strength compared to HC networks. In the structural network, the connection strength of nearly 90 connections was significantly reduced in PSCI. These connections included all three types of connections (rich club, feeder and local). However, reduced connections in NPSCI structural networks were feeder and local connections. Due to the importance of rich clubs in the network (Van Den Heuvel & Sporns, 2011), alterations of rich club parameters will cause massive network paralysis (van den Collin et al., 2017; Heuvel et al., 2013). Meanwhile, feeder connections maintain the balance between efficiency and cost of brain network information transmission (van den Heuvel & Sporns, 2019; Zhu et al., 2019). Combined with current results, it is possible that rich club and feeder damage may be the basis of structural network breakdown involved in cognitive impairment following stroke.

Notably, structural connectivity breakdown in PSCI is concentrated in basal ganglia-frontal, as well as in intra-parietal pathways. This may explain the core position of the basal ganglia in the cognitive processing network. As part of the cortical-striatal-thalamic-cortical loops,
cognitive functions such as working memory (Schroll et al., 2012), rule-guided behavior (Badre & Frank, 2012), cognitive skill learning (Hélie et al., 2010) are mediated by frontal-basal ganglia network. However, functional network disruptions are mainly distributed in the FPN and CON. FPN and CON are extremely important in the support of cognitive control (Marek & Dosenbach, 2018) and execution function (Engelhardt et al., 2019). Studies have found that FPN and CON damage not only causes dyskinesia, but also cognitive dysfunction in domains including decision-making, executive control (Bhandari & Badre, 2020), and verbal processing in disorders such as stroke (Siegel et al., 2018), major depressive disorder (Wu et al., 2016), Alzheimer’s disease (Tumati et al., 2020), and ADHD (Cai et al., 2019). Our results are consistent with the point of view that a major role of the basal ganglia is to train cortico-cortical connection (Hélie et al., 2015). In this study, we speculate that low structural connectivity in the basal ganglia-frontal circuit may be associated with the low cortical functional connectivity and cognitive impairment in stroke patients. The different changes in structural and functional networks may just reflect this bottom-up mechanism of cognitive impairment in the brain networks.

As compared with HC, NPSCI showed reduced structural connectivity in intra-occipital and occipital-temporal networks. Especially, the areas in intra-occipital included the calcarine area, cuneus, and lingual gyrus. Collectively, the peripheral striatum are made up with

| Table 9 | Result of NBS-analysis in structural network between NPSCI and HC |
|---------|---------------------------------------------------------------|
| Feeder  | Local                                                        |
| NodeA (hub) | NodeB (nonhub) | t | NodeA | NodeB | t |
| ORBInf.R | OLF.R | 2.1 | OLF.R | DCG.R | 2.25 |
| CAL.L | INS.L | 2.7 | DCG.L | DCG.R | 2.34 |
| CAL.R | INS.R | 2.15 | INS.L | PHG.L | 2.03 |
| CAL.R | CUN.L | 2.18 | OLF.R | PHG.R | 2.17 |
| HIP.R | LING.R | 2.99 | DCG.L | CUN.L | 2.27 |
| CAL.R | LING.R | 2.1 | HIP.L | CUN.L | 3.13 |
| CAL.L | FFG.L | 2.08 | INS.L | LING.L | 2.06 |
| ORBInf.R | FFG.R | 2.49 | CUN.L | LING.L | 2.76 |
| CAL.R | STG.R | 2.11 | CUN.L | SOG.L | 2.25 |
| ITG.R | FFG.R | 2.06 | IOG.L | FFG.L | 2.17 |
|         |         |   | IOG.R | FFG.R | 2.25 |
|         |         |   | FFG.R | THA.R | 2.38 |
|         |         |   | CUN.L | TPOsup.L | 2.27 |
|         |         |   | MOG.L | ITG.L | 2.99 |
|         |         |   | IOG.L | ITG.L | 2.62 |
|         |         |   | FFG.L | ITG.L | 3.06 |

The cells of results in NBS in structural network between NPSCI and HC

CAL calcarine; CUN cuneus; DCG median cingulate and paracingulate gyri; FFG fusiform gyrus; HIP hippocampus; INS insula; IOG inferior occipital gyrus; ITG inferior temporal gyrus; LING lingual gyrus; MOG middle occipital gyrus; OLF olfactory cortex; ORBInf inferior frontal gyrus, orbital part; TPOsup temporal pole: superior temporal gyrus

Fig. 5 Determination of inter- and intra-module differences in brain structural and functional networks in three groups. Color-coded connectivity matrix showed differences in intra- and inter-module connectivity in structural and functional network in three groups. Connectivity differences were qualified as the proportion of decreased connections. (A) showed weaker connections in structural network in post-stroke patients with cognitive impairment (PSCI) vs healthy controls (HC). (B) showed weaker connections in functional network in post-stroke patients with cognitive impairment (PSCI) vs healthy controls (HC). The color bar denotes the proportion of intra- and inter-module connections which was qualified using the sum of connections located inter- and intra-modules divided by all altered connections.
these areas which are critical for visual information process and multiple visual scene representations (Saint-Cyr et al., 1990). Moreover, the occipital-temporal pathway is in charge of identifying and recognizing objects (Milner & Goodale, 2008). The findings align with previous statements that visual field loss after stroke has largely been attributed to damaged visual pathway in cortical stroke (François & Neetens, 1954), and occipital and temporal infarct especially is responsible for visual field loss related stroke (Pambakian & Kennard, 1997). A previous study reported that post-stroke patients with visual field loss had blurred vision, perceptual difficulties, eye movement deficits and visual perceptual difficulties (Rowe et al., 2013). Taken together, the findings highlight the potential risk of visual field loss to NPSCI. Furthermore, the relationship between visual field loss and cognitive impairment needs to be investigated in future studies.

Functional networks have been inferred from the strength of temporal correlations of blood oxygenation level-dependent fluctuations, and structural networks have been extracted from tractography using information about water diffusion along myelinated nerve fiber tracts (Catani et al., 2002; Johansen-Berg & Rushworth, 2009). Structurally connected cortical regions exhibit stronger resting-state functional connections than structurally unconnected regions, showing that the structural connection between two brain areas predicts the functional connection between those areas (Hagmann et al., 2008, Skudlarski et al., 2008, Honey et al., 2009). In addition, the functional network is constantly reconfigured around the underlying anatomical framework through a plasticity mechanism (Hermundstad et al., 2014). The coupling of structural–functional connectivity is destroyed in pathological states such as epilepsy (Chiang et al., 2015; Zhang et al., 2011). Moreover, the coupling strength is related to the epilepsy duration, indicating that structural–functional connectivity coupling may serve as a more sensitive biomarker of disease burden in patients with epilepsy than biomarkers based on single imaging modalities. In the present study, we combined DTI and rs-fMRI techniques to investigate the structural–functional relationships in large-scale brain networks in three groups. At the global-level, the network coupling between structural and functional connectivity was retained in all three groups. However, the structural–functional decoupling occurred in the network area where the connection is damaged such as basal ganglia-frontal network, frontoparietal network, and cingulo-opercular network (Figure S3), providing evidence for the decoupling of structural and functional connectivity following stroke. This decoupling might be produced by different degrees of alteration in structural and functional connectivity networks or by different patterns of altered networks in stroke. Hence, we conclude that structural–functional connectivity decoupling may serve as a novel biomarker of changes in brain integration and cognitive impairment in patients with stroke. Finally, we tried to correlate the graph theory and NBS findings with clinical test (e.g. MOCA) (see supplementary materials). However we didn’t find any significant relationship between global efficiency and MOCA in both PSCI and NPSCI. Neither to connectivity strength of inter- or intra-module and MOCA. We guessed that it may be caused by the small number of patients. Furthermore, data collection for clinical test, especial for the MOCA, was prone to inaccuracy because it was dependent on the subjects’ attitudes when filling out the question in MOCA, and educational level of patients.

Our study was not without limitations. First, the participant sample size was relatively small. Further studies with larger sample size are required to replicate our current findings. Second, the AAL90 atlas were used to parcellate the brain regions for node definition. However, the choice of atlas is somewhat arbitrary across studies, either based on anatomic or functional parcellations (Wig et al., 2011). It is likely that more refined brain atlases (e.g., power264) would have produced different network parameter estimates. Third, we only used FA values to construct the structural weighted network. Alternative weighted networks, including measures such as fiber number and distance between ROIs, and unweighted networks are needed to further verify current findings.

Our study showed that the approach of characterizing the brain as a network using multimodal MRI and graph theoretical analysis can provide new insights into how cognitive impairment affects brain structural and functional topological organization in first-time mild stroke patients with or without cognitive impairment. Future studies that integrate different clinical symptoms and brain network models will be helpful to clarify the mechanisms underlying cognitive impairment in stroke patients at the network level.
## Appendix 1—Authors

| Name             | Location                                                                 | Role                                      | Contribution                                                                 |
|------------------|--------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------------------------------|
| Hua Zhu, MA      | Beijing Advanced Innovation Center for Biomedical Engineering, School of Biological Science and Medical Engineering, Beihang University, Beijing, China | Author                                    | Drafting and revision of the manuscript for content, analysis and interpretation of data |
| Lijun Zuo, MD    | Department of Neurology, Beijing TianTan Hospital, Capital Medical University, Beijing, China | Author                                    | Revision of the manuscript for content, study concept and design, interpretation of data |
| Wanlin Zhu, MD   | Department of Neurology, Beijing TianTan Hospital, Capital Medical University, Beijing, China | Author                                    | Discussion of study, revision of manuscript for intellectual content          |
| Jing Jing, MD    | Department of Neurology, Beijing TianTan Hospital, Capital Medical University, Beijing, China | Author                                    | Analysis of data, discussion of study                                        |
| Zhe Zhang, MD    | Department of Neurology, Beijing TianTan Hospital, Capital Medical University, Beijing, China | Author                                    | Analysis of data, discussion of study                                        |
| Lingling Ding, MD| Department of Neurology, Beijing TianTan Hospital, Capital Medical University, Beijing, China | Author                                    | Revision of manuscript for intellectual content                             |
| Fengjuan Wang, MA| National Institute of Education, Nanyang Technological University, Singapore | Author                                    | Revision of manuscript for intellectual content                             |
| Jian Cheng, PhD  | Beijing Advanced Innovation Center for Big Data-Based Precision Medicine, Beijing, China | Author                                    | Acquisition and interpretation of data, revision of manuscript for intellectual content |
| Zhenzhou Wu, PhD | BioMind Technology AI Center, China National Clinical Research Center for Neurological Disease, Beijing Tiantan Hospital, Beijing, China | Author                                    | Acquisition and interpretation of data, revision of manuscript for intellectual content |
| Yongjun Wang, MD | Department of Neurology, Beijing TianTan Hospital, Capital Medical University, Beijing, China; China National Clinical Research Center for Neurological Diseases, Beijing, China; Center of Stroke, Beijing Institute for Brain Disorders, Beijing, China | Author                                    | Acquisition and interpretation of data, revision of manuscript for intellectual content |
| Tao Liu, PhD     | Beijing Advanced Innovation Center for Biomedical Engineering, School of Biological Science and Medical Engineering, Beihang University, Beijing, China; Beijing Tiantan Hospital, Capital Medical University, Beijing, China; China National Clinical Research Center for Neurological Diseases, Beijing, China; Center of Stroke, Beijing Institute for Brain Disorders, Beijing, China | Author                                    | Study concept and design, interpretation of data, critical revision of manuscript for intellectual content |
| Zixiao Li, MD    | Department of Neurology, Beijing TianTan Hospital, Capital Medical University, Beijing, China; China National Clinical Research Center for Neurological Diseases, Beijing, China; Chinese Institute for Brain Research, Beijing, China; Research Unit of Artificial Intelligence in Cerebrovascular Disease, Chinese Academy of Medical Sciences, Beijing, China | Author                                    | Interpretation of data, critical revision of manuscript for intellectual content |
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Authors’ contributions Hua Zhu, MA, Drafting and revision of the manuscript for content, analysis and interpretation of data.

Lijun Zuo, MD, Revision of the manuscript for content, study concept and design, interpretation of data.

Wanlin Zhu, MD, Discussion of study, revision of manuscript for intellectual content.

Jing Jing, MD, Analysis of data, discussion of study.

Zhe Zhang, MD, Analysis of data, discussion of study.

Lingling Ding, MD, Revision of manuscript for intellectual content.

Fengjuan Wang, MA, Revision of manuscript for intellectual content.

Jian Cheng, PhD, Acquisition and interpretation of data, revision of manuscript for intellectual content.

Zhenzhou Wu, PhD, Acquistion and interpretation of data, revision of manuscript for intellectual content.

Yongjun Wang, MD, Acquisition and interpretation of data, revision of manuscript for intellectual content.

Tao Liu, PhD, Study concept and design, Interpretation of data, critical revision of manuscript for intellectual content.

Zixiao Li, MD, Interpretation of data, critical revision of manuscript for intellectual content.

Jing Jing, MD, Acquisition and interpretation of data, revision of manuscript for intellectual content.

Fengjuan Wang, MA, Revision of manuscript for intellectual content.

Data availability The dataset used and analyzed are available to other researchers subject to review of the request by the Scientific Committee of the study and ethical approval.

Code availability Applicable.

Declarations

Ethics approval This study had been approved by the Beijing Tiantan Hospital Ethics Review Board. This study met the guidelines of Capital Medical University, which abides by the Helsinki Declaration on ethical principles for medical research involving human participants.

Consent to participate All participants had given their informed written consent.

Consent to publication Not applicable.

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