Changes of resting-state neural activity and nerve fibers in ischemic stroke patients with hemiplegia

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Research Article

Keywords: ischemic stroke, hemiplegia, resting-state networks, diffusion tensor imaging, fiber tracking

Posted Date: May 3rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1582672/v1

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Additional Declarations: No competing interests reported.
Version of Record: A version of this preprint was published at Brain Topography on January 5th, 2023. See the published version at https://doi.org/10.1007/s10548-022-00937-6.
Abstract

Many neuroimaging studies have reported that stroke induces abnormal brain activities. Yet, little is known about resting-state networks (RSNs) and the corresponding white matter changes in stroke patients with hemiplegia. Here, we utilized functional magnetic resonance imaging (fMRI) to measure the neural activity and related fiber tracks in 14 ischemic stroke patients with hemiplegia and 12 healthy controls. The fractional amplitude of low-frequency fluctuations (fALFF) calculation and correlation analyses were used to assess the relationship between the regional neural activity and movement scores. Tractography was performed using the diffusion tensor imaging (DTI) data to analyze the fibers passing the regions of interest. Compared with controls, stroke patients showed abnormal functional connectivity (FC) in some brain regions of the RSNs. The fALFF was increased in the contralesional parietal lobe, with the regional fALFF being correlated to behavioral scores in stroke patients. And the tracked fibers across regions with reduced FC in the RSNs were increased in stroke patients. The study suggested that structural remodeling of functionally-relevant white matter tracts probably be an adaptive response that compensates for injury to the brain.

Introduction

Local lesions caused by stroke may result in extensive changes of connected functions in the brain. Resting-state functional magnetic resonance imaging (rs-fMRI) measures spontaneous brain activity in low-frequency fluctuations, which can be reflected by the blood oxygen level dependent (BOLD) signal. Many rs-fMRI studies on stroke focused on the functional connectivity (FC) within motor-related brain areas (Grefkes et al., 2014; Wu et al., 2015). Features of functional networks in stroke patients were also analyzed using cortical parcellation based on methods reported by Gordon et al. (Siegel et al., 2016; Gordon et al., 2016) and some studies explored the integrity of certain RSN in patients using an ICA approach (Jiang et al., 2018). Originally, the amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF) were used to measure the signal strength in low-frequency oscillations of spontaneous neural activity based on the rs-MRI (Yang et al., 2007; Zou et al., 2008). Studies using these imaging indicators on stroke patients could produce conflicting results. The discrepancies might be due to the difference in lesion locations, symptoms, or methods across the studied groups (Zhang et al., 2014; Liu et al., 2015).

Overall, researches indicated that stroke induces changes of FC within and between RSNs (Wang et al., 2014; Baldassarre et al., 2015). The single-modal MRI explains the limited characteristics of the brain. Furthermore, structure measures of cortex was added to explore the brain after stroke (Griffis et al., 2019; Dominguez et al., 2019). Many diffusion tensor imaging (DTI) studies assessed the white matter structural integrity of the lesioned regions and related fibers using diffusion tensor indicators, such as fractional anisotropy (FA). In addition of the crucial role of the corticospinal tract (CST) (Visser et al., 2019), recent studies suggested that cortico-cortical connections play a pivotal role in motor improvement after stroke (Riecker et al., 2010; Gerloff et al., 2006; Zarahn et al., 2011). However, a limited number of studies investigated RSNs and the underlying white matter structural changes in stroke
patients with motor impairment (Duering et al., 2015; Kalinosky et al., 2017). The correlation of the structural and functional remodeling was not clearly explored and illustrated in patients with hemiplegia.

Here, we combined the analysis on BOLD signals by rs-fMRI with the tractography of the DTI data to investigate the resting-state neural activity structural basis. Firstly, we compared the differences in RSNs and fALFF between stroke patients and closely matched healthy controls (HC). We identified RSNs in the stroke group and the control group using independent component analyses (ICA), a data-based approach (Calhoun et al., 2001). To capture possible abnormalities of brain networks corresponding to typical motor symptom domains, we focused on the following RSNs: the left and right fronto-parietal network (LFPN, RFPN), the default mode network (DMN), the dorsal attention network (DAN) and the sensory-motor network (SMN). Then DTI data were processed, and deterministic fiber tracking was performed for each subject. We defined the regions with significant differences of neural activities in RSNs between the groups as ROIs and reconstructed the track group passing the ROIs to investigate the fiber characteristics. This study used functional and structural information of the brain through multi-modal MRI analyses and may provide vital insights on mechanism of structural and functional remodeling after stroke.

**Materials And Methods**

**Participants**

Sixteen right-handed stroke patients were recruited in this study. The inclusion criteria were as follows: (1) first-onset stroke patients with motor deficits, stable conditions after treatment of acute stroke; (2) no history of neurological or psychiatric disorders; (3) age $\geq 18$ years; (4) conventional MRI did not find any abnormalities except for the infarct lesion. All the affected extremities were evaluated for motor functions. Motor outcomes of upper and lower extremities on the affected side were assessed by the Fugl-Meyer assessment (FMA) and the Brunnstrom stage (BRS) (Naghdi et al., 2010; Feng et al., 2015). Two of the patients were excluded due to image quality (excessive motion during fMRI). The clinical characteristics of the remaining 14 patients are summarized in Supplementary Information (SI) Table S1. Twelve age-matched healthy controls with no cerebral vascular or cognitive diseases were recruited (Table 1). All patients provided written, informed consent before the examination. The study protocol was approved by the Ethics Committee of Southeast University affiliated Zhongda Hospital.

**Magnetic resonance imaging**

All participants underwent T1-weighted, rs-fMRI and DTI scanning. The subjects were scanned using a 3.0 Tesla Philips (Ingenia) Medical Systems equipped with a Synergy-L Sensitivity Encoding (SENSE) head coil. Detailed image acquisition procedures are described in the Supplementary Information (SI).

**Lesion mapping**

Images acquired from patients with right hemisphere lesions were laterally flipped to unify the damaged side. Lesions were manually segmented on individual structural MRI images (T1-weighted images) using
MRIcron software (http://www.mricro.com) (Zhang et al., 2016). Then, all lesions (uniformly on the left side) were summed to display the number of patients with structural damage for each voxel (SI. Fig. S1).

**Imaging processing**

The rs-fMRI images were preprocessed using SPM12 and the rs-fMRI Data Analysis Toolkit RESTplus (http://www.restfmri.net) (Jia et al., 2016). The first steps involved slice-timing and bulk-head motion. Motion parameters were computed using estimations of translation and angular rotation in the x, y, and z axes. Datasets were excluded if motion was >3 mm (maximum displacement) in x, y, or z or if angular rotation was >3° within the 4-dimensional volume. Spatial normalization was performed using a standard echo-planar imaging template from the Montreal Neurological Institute (MNI). The normalized functional images were then spatially smoothed with a gaussian kernel (full width at half maximum, FWHM=6mm).

**Independent component analysis**

The spatial group ICA for participants in each group was done by the Group ICA fMRI Toolbox (GIFT software) (http://icatb.sourceforge.net/) (Calhoun et al. 2001) to identify temporally coherent RSNs, including the DMN, the DAN, the SMN, the LFPN and the RFPN. The details about ICA are described in the SI (Smith et al., 2009; Zuo et al., 2010). We further used two-sample t-tests with Gaussian random field (GRF) correction to compare the differences in RSNs between groups (Boehm et al., 2014; Bi et al., 2018).

**Calculation of fALFF**

The fALFF reflects the regional slow-wave brain activity strength. The smoothed functional images derived from the first preprocessing steps underwent linear detrending, and temporal filtering (0.01–0.08 Hz) to remove undesired components. The time series of each voxel was transformed into the frequency domain through Fourier transform. The sum of the magnitude of the spectrum between 0.01-0.08 Hz was divided by the sum of the entire acquired frequency band to get the fALFF (Zou et al., 2008).

**DTI data pre-processing and deterministic fiber tracking**

DTI data analysis was performed by a pipeline toolbox for analyzing brain diffusion images (PANDA, http://www.nitrc.org/projects/panda) (Cui et al., 2013). First, the diffusion-weighted images were corrected for head motion and eddy current distortion. Then, the diffusion tensor was reconstructed to calculate diffusion indices, including the FA for each voxel (Guo et al., 2019). Deterministic fiber tracking was applied using a fiber assignment through a continuous tracking algorithm (FACT) with an angle threshold of 45°. All voxels with FA ≥0.2 were used as seed points (Mori et al., 1999). The whole-brain tractography was performed for each subject in the native diffusion space, and then each tractography was normalized to MNI space.

**Tracks of ROI**
To analyze the tracks of interest, statistically significant clusters from the resting-state brain activities analysis (fALFF and RSNs) were used in tractography as regions of interest (ROIs) to reconstruct the track group and calculate the fibers through them. ROIs were placed at the levels of the precentral gyrus and the cerebral peduncle on the individual axial FA map (Fig. 2) as normal verification for the CST. Fibers that passed through the ROIs were considered as the CST (Lindenberg et al., 2010). The tractography and ROIs were normalized to MNI standard space using the Diffusion Toolkit (www.trackvis.org/dtk) and Trackvis (http://www.trackvis.org/). The numbers of tracks and mean length of fibers (mm) were recorded for each group and tracks of interest. The overall length was also calculated to find differences between the two groups.

### Statistical analysis

We compared the demographic, clinical, and imaging data between patients using SPSS20.0 and SPM12. Two-sample t-tests were used to determine the between-group differences in continuous variables and fALFF maps. GRF correction was applied for comparisons correction (voxel level \( P = 0.005 \), cluster level \( P = 0.05 \)). Finally, a Spearman rank correlation analysis was used to determine correlations between the regional mean fALFF and clinical scores in the stroke patients.

### Results

#### Subject characteristics and behavioral evaluation

In total, 14 stroke patients and 12 healthy controls were included in the final analysis. The subjects’ clinical and demographic data are listed in Table 1. Compared to the HC, the stroke group did not show any significant differences in age (\( P = 0.15 \)) and sex (\( P = 0.19 \)). All stroke patients had motor deficits, with the BRS ranging from 2 to 5 (SI. Table S1). Stroke lesions for each patient were overlaid onto a T1 template in MNI standard space (SI. Fig. S1).

#### Changes in fALFF after stroke

Compared to the control group, patients in the stroke group exhibited increased fALFF in the contralesional parietal lobe, and decreased fALFF in the ipsilesional sub-lobar areas and the contralesional frontal lobe (Fig. 1A and Table 2). Significant correlations between fALFF in the contralesional parietal regions (cluster1) and movement scores were detected in stroke subjects (BRS-total: \( r_s = 0.6696, p = 0.0088 \); FMA: \( r_s = 0.5501, p = 0.0416 \)), particularly the BRS of proximal portion of the upper limb movement (BRS-UL: \( r_s = 0.7746, p = 0.0011 \)) (Fig. 1B).

#### Tracks of ROI from fALFF analysis of the two groups

The tracked fibers of brain regions with increased fALFF from the stroke group did not show any significant difference when compared to the control group. However, the number of fibers was significantly increased (\( p < 0.001, p = 0.000 \)) across the contralesional frontal lobe (cluster 3) in brain
areas where fALFF was reduced in the stroke group, so was the total length ($p < 0.05$, $p = 0.037$). The mean fiber length was reduced ($p < 0.005$, $p = 0.016$) across cluster 2, an area overlapping the main lesions (basal ganglia regions) and the CST pathway. Additionally, the stroke group showed a significant decrease in the number and the total length of ipsilesional CST (left) compared to the control group (both: $p < 0.001$, $p = 0.000$). No difference in the average length of the CST was observed between the groups (Fig. 2).

**Changes in RSNs after stroke**

The RSNs in the two groups included similar brain regions but with different cluster sizes (SI Fig. S2). Compared to the HC, the stroke patients showed abnormal FC in several areas in the DAN, the SMN, the RFPN, the LFPN, and the DMN. Detailed results can be seen in Figure 3 and Table S2. The DAN showed increased connectivity to the occipital lobe, and reduced connectivity to the parietal lobe, as well as the cingulate gyrus in stroke subjects. The SMN displayed reduced FC in the bilateral medial parietal, where the connections between two hemispheres passing through. The stroke group showed increased FC in the right (contralesional) parietal lobe in the SMN and the RFPN. The patients showed decreased FC in the bilateral tempo-parietal (angular gyrus) and medial frontal lobes within the DMN.

**Tracks of ROI from RSNs with significant between-groups differences**

The stroke patients showed different FC in several areas of RSNs when compared with HC, together with the fiber tracks across these regions (Fig. 3F-H). The stroke group showed a shorter mean length of fibers ($p<0.05$, $p=0.027$) across the whole reduced FC regions in the DMN. They displayed an increased number of tracks ($p<0.001$, $p=0.000$) and the overall length of fibers ($p<0.005$, $p=0.003$) through declined FC regions in the SMN. In the DAN, the reduced FC areas were accompanied by ascending fiber number ($p<0.001$, $p=0.000$), as well as total fiber length ($p<0.001$, $p=0.000$). In the RFPN, the number of tracks elevated across both the decreased and increased FC areas ($p<0.05$, $p=0.017$; $p=0.022$). In the LFPN, the track number rose across the reduced FC regions ($p<0.05$, $p=0.023$).

Specifically, the SMN of the stroke group showed decreased FC strength in the bilateral medial parietal lobe, the ipsilesional white matter region connected to the temporal lobe and part of the cerebellum anterior lobe (SI. Table S2). This is not distinctly displayed in Figure 3, as the brain model in Figure 3 only shows the cerebral cortex projections of the clusters. Therefore, the SI Figure S3 separately displays the regions with reduced connectivity to the SMN in the stroke group, as well as examples of fiber tracks through the clusters.

In summary, except for the reduced FC areas in the DMN, the regions with lower FC in the other RSNs were accompanied by a rising number of tracks in the stroke patients. The most obvious increases in fiber numbers were seen across the reduced FC regions in SMN and the DAN.

We calculated the fiber tracks of the CST as normal evaluations. The decreased number and total length of the fibers confirmed the injuries to the CST in stroke patients. Therefore, the reduced FC regions in each
RSN were accompanied by the expansion of fiber tracks, which is a special phenomenon in stroke subjects.

**Discussion**

**Resting-state neural activity**

It has been reported that patients with subcortical infarct exhibit increased ALFF in the bilateral primary motor cortex (PMC) despite cortical thinning in the early stage of stroke (Liu et al., 2015). However, the findings were contradicted by a study that reported no significant increase in ALFF in the contralesional PMC in patients with chronic stroke, with only a few increases in brain activity in the ipsilesional PMC (Zhang et al., 2014). The fALFF reflects the regional slow-wave brain activity strength and gives an advantage over ALFF because it can reduce the contribution of irrelevant physiological noise to the signal of interest and provide improved sensitivity and specificity in detecting spontaneous brain activities (Song et al., 2019; Zou et al., 2008). In our study, the fALFF was increased in the contralesional parietal lobe, and significant correlations between fALFF in this area and movement scores were detected in stroke patients. Studies in healthy subjects have reported that several parietal regions were involved in motor learning (Ma et al., 2011) and the dorsolateral prefrontal cortex contributed to the formation of movement plans (Hartwigsen et al., 2012). We speculated that the planning of movements was impaired in the stroke patients due to reduced fALFF in the contralesional frontal lobe, and the process of motor learning was more frequent during rehabilitation after the acute stage of stroke.

Changes in FC were identified in multiple functional networks in well-recovered chronic stroke patients with a subcortical lesion in the motor pathway (Wang et al., 2014). The DMN is related to self-consciousness during the resting-state, estimation of acquired experience, and planning of future decisions (Buckner et al., 2008). Consistent with previous findings, our study showed that stroke patients displayed decreased FC within the DMN (Jiang et al., 2018; Zhang et al., 2017). The DAN is involved in the control of visuo-spatial attention and was associated with upper-arm and walking ability in stroke patients (Baldassarre et al., 2016; Carter et al., 2010). This highlights the DAN as a key network for targeting rehabilitation after stroke. Following motor impairment caused by brain lesions and the disuse of the affected limb, brain regions that were originally responsible for motor assistance undergo relative changes, such as attention and motor planning, reflected in the brain functional networks.

In the SMN, the stroke group exhibited increased FC in the contralesional parietal lobe and ipsilesional frontal lobe, coupled with decreased FC in several regions, including the medial parietal lobe. The parietal cortex is comprised of primary somatosensory areas and an associative cortical region. Different portions of the posterior parietal cortex engage in multiple movement-related processes, such as sensorimotor integration, spatial attention, working memory, and early motor planning (Fogassi and Luppino, 2005; Whitlock, 2017). Combined with the increase in nearby fALFF, we considered that the contralesional parietal lobe played an important role in the reuse of motor function after stroke with hemiplegia. Widespread lesions in the fronto-parietal network are associated with working memory...
deficits. Stroke patients show decrements of moderate magnitude in all subsystems of working memory (Lugtmeijer et al., 2020). The RFPN and the LFPN are largely left-right mirrors of each other. The connectivity changes within the RFPN and the LFPN are probably linked to limb pain and paradigms in motor-related cognition (Smith et al., 2009).

**Conjoint analysis of resting-state neural activity and tractography**

The fibers connecting the two hemispheres increased in the stroke group across the frontal lobe with reduced fALFF. The resting-state fMRI measures the temporal correlation of blood-oxygenated-level-dependent (BOLD) signals between different brain regions (Power et al., 2011). There are fewer neurons in the regions with higher fiber concentration, for fibers require less blood supply and lower oxygen levels than neurons (Gu et al., 2018). These regions with reduced activity probably result from the structural remodeling of white matter in the brain (Carmichael, 2003). Because of the structural changes in white matter or cortical thickness, the brain exhibits corresponding BOLD signal changes.

Most regions with reduced FC in the RSNs were accompanied by a growing number of fibers, especially the SMN and DAN in stroke subjects. The DAN showed reduced FC in the bilateral cingulate gyrus and the SMN showed reduced FC in the bilateral medial parietal lobe. Most of the fibers passing through these areas are interhemispheric connections. According to previous studies, white matter remodeling occurs in specific regions of the ipsilesional and contralesional hemispheres during the recovery period after stroke (Schaechter et al., 2009; Koch et al., 2016; Umarova et al., 2017). The interhemispheric connections between the motor regions have been reported to be significantly reduced after stroke (Duering et al., 2015), but recovery from motor deficits is typically associated with a steady increase of resting-state connectivity, particularly between the ipsilesional PMC and contralesional areas (Wang et al., 2010; Park et al., 2011). Then how the FC between the hemispheres was increased? It can potentially be answered by the growth of interhemispheric connections besides major motor regions (e.g. PMC). Our research did not calculate functional networks by parcellation of motor regions based on atlas. The increased inter-hemisphere fibers were not necessarily across the specified motor regions, but across the regions for motor assistance, or the changed parts of the motor areas after stroke. It was found due to the benefit of the multi-modal fMRI analyses.

There were no significant changes of fiber bundles passing through the regions with stronger FC in the studied RSNs, but fiber increment occurred in reduced FC regions in the stroke group. Each RSN map was defined by ICA, and a group comparison of the spatial maps reflected a group difference in the connectivity strength or signal synchronization of each voxel to the whole spatial component (Mueller et al., 2014). In other words, significantly reduced synchronization in the bilateral parietal lobe and the cingulate gyrus in the DAN, and increased fiber tracks across these regions were detected. Structure leaves an indelible mark on function, though the relationship between brain structure and function is complex (Suarez et al., 2020). In stroke patients, brain regions with significantly reduced synchronization in the RSNs, such as the parietal lobe in the SMN, were defined as ROIs to track the fibers across them. Brain regions with intensified fibers were decoupled to some extent with the overall functional network.
Combined with the increased fALFF in the contralesional parietal lobe, which correlated with motor scores in stroke patients, we speculate that it was the structural basis for the enhancement of the contralateral brain activity.

A finding suggest that the intact hemisphere contributes to the functional recovery early after stroke probably via the transcallosal rather than the corticospinal signals (Zaaimi et al., 2012). The variation theory suggested that recovery of function could be driven by intact areas. The important mechanisms supporting recovery contain the formation of new synapses and collateral sprouting of axons to rewire surviving tissues, especially in peri-infarct cortex (Wiesendanger et al., 2012; Finger et al., 2010). It could be concluded that the increased connections between the contralesional lobe and the ipsilesional regions through the corpus callosum were prepared to complement the functions of the lesioned side.

Motor attention and sensory-motor networks were originally associated and coordinated in the bilateral hemispheres. Loss of function in the lesioned hemisphere would stimulate the contralateral cortex to exert corresponding effects on the related regions, leading to the activation of a compensatory pathway and increase connections between hemispheres. The higher contralesional neural activity might not necessarily be adjacent to the increased fiber tracks, but the need for signal transmission could result in a proliferation of inferior nerve fibers.

Previous studies have shown that there is no unique reorganization scheme in certain brain areas after stroke (Koch et al., 2016). But it is difficult to accurately locate all the microstructural changes in the brain of every patient. Variations after stroke onset, individual differences, and the interaction between the two factors make it difficult to perform precise researches and generate effective personalized therapy. Overall, our results were similar to those of previous studies indicating elevated activity in the contralateral cortex after stroke and suggest a possible structural basis in the brain (Riecker et al., 2010; Gerloff et al., 2006). We made a relatively specific analysis at the group level and integrated it with previous reports to determine the possible mechanisms underlying reorganization after brain lesions.

The roles of the contralesional cortex and interhemispheric relationships in recovery are highly correlated to the efficiency of new treatment approaches, such as repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) (Grefkes and Fink, 2014). A well-balanced interhemispheric control of excitatory and inhibitory connections is required for sensorimotor function. So far, data about the treatment reactions of these approaches are inconsistent. Interindividual differences in treatment efficacy require precision medicine to seek the variable mechanisms in the reorganization patterns of the brain after stroke. Future longitudinal studies would help to investigate key neural alterations in well-recovered patients and provide insights for treatment implications.

Limitations And Expectations

The study sample was limited to a narrow range of subcortical ischemic stroke patients with motor deficit. The different infarct locations and intervals from disease onset among patients made the studied group less homogenous. Hemodynamic lags could affect measurements of FC from the lesions, for the
brains contain altered neurovascular coupling in stroke patients (Siegel et al., 2017), but our analysis did not calculate the lags. Another important limitation is that MRI studies do not record microstructural information at the level of axons and synapses. The FACT algorithm of tensor-guided deterministic tractography cannot resolve crossing-fiber geometries, so the results are inevitably influenced by the method used to perform the analyses and by the settings of the parameters. We could only sustain the same program and settings during the study process to minimize the variability. Future studies with larger samples are needed to validate our findings and perspectives.

**Conclusion**

The study analyzed resting-state brain activities and white matter structural characteristics in stroke patients with hemiplegia using fMRI methods. We found that the intrinsic brain activity is altered after stroke. The elevated fALFF in the contralesional parietal lobe correlated with the functions of the affected limb. The increased fiber tracks across regions with decreased FC in the RSNs, particularly those inter-hemisphere connections, were probably the structural basis for functional alterations in the lesioned brain (Fig. 4). It might provide an understanding of the structure-function relationships underlying compensatory changes after stroke.

**Declarations**

**Acknowledgments**

We thank all the patients and volunteers for participating in this study. X.J.C. and Y.J.G. conceived and designed the research. X.J.C., Z.W, X.H.C. and Y.L.L. performed the experiments and analyzed the data. S.H.J. and Y.C.W. reviewed and critiqued the results. S.Y.Z., and S.S.W. provided experimental assistance. X.J.C., I.A.A. and Y.J.G. wrote the manuscript.

**Funding**

This work was supported by the National Natural Science Foundation of China (grant number:6590000127, 81801680), Nanjing health science and technology development special fund project (grant number: YKK18218).

**Competing Interests**

The authors declare that they have no competing interests.

**Ethics approval**

The study was approved by the local Ethics Committee of the Southeast University affiliated Zhongda Hospital.

**Consent to participate**
Informed consent was obtained from all individual participants included in the study.

Consent to Publish

Not applicable.

Data and/or Code availability

The datasets generated and analyzed during the current study are not publicly available due the fact that they constitute an excerpt of research in progress but are available from the corresponding author on reasonable request.

References


**Tables**
Table 1
Demographic data of two groups

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Stroke group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>11/1</td>
<td>10/4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.6 ± 8.1</td>
<td>54.3 ± 12.5</td>
</tr>
<tr>
<td>range (years)</td>
<td>50–73</td>
<td>32–74</td>
</tr>
<tr>
<td>Lesion side (L/R)</td>
<td>-</td>
<td>4/10</td>
</tr>
<tr>
<td>Site of infarct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BG/PV</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>Pons</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>BRS (total)</td>
<td>-</td>
<td>9.0 ± 2.4</td>
</tr>
<tr>
<td>upper limb</td>
<td>-</td>
<td>3.1 ± 1.2</td>
</tr>
<tr>
<td>hand</td>
<td>-</td>
<td>1.9 ± 1.0</td>
</tr>
<tr>
<td>lower limb</td>
<td>-</td>
<td>4.0 ± 0.8</td>
</tr>
<tr>
<td>FMA</td>
<td>-</td>
<td>46 ± 23</td>
</tr>
<tr>
<td>Time since stroke (weeks)</td>
<td>-</td>
<td>6 ± 5</td>
</tr>
</tbody>
</table>

R = right; L = left; BG = basal ganglia; PV = periventricular; BRS: Brunnstrom stage. FMA: Fugl-Meyer assessment (full score = 100).

Table 2
Regions showing changes of fALFF in the stroke patients versus normal controls

<table>
<thead>
<tr>
<th>Color</th>
<th>Cluster</th>
<th>Brain regions</th>
<th>Cluster size (voxels)</th>
<th>Peak t values</th>
<th>Peak MNI coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red</td>
<td>1</td>
<td>Parietal Lobe.CL</td>
<td>227</td>
<td>4.58</td>
<td>30–63 57</td>
</tr>
<tr>
<td>Blue</td>
<td>2</td>
<td>Sub-lobar/Putamen/Extra nuclear.IL</td>
<td>224</td>
<td>-3.87</td>
<td>-27 -18 33</td>
</tr>
<tr>
<td>Blue</td>
<td>3</td>
<td>Frontal Lobe.CL</td>
<td>85</td>
<td>-4.09</td>
<td>18 30 33</td>
</tr>
</tbody>
</table>

IL = ipsilesional; CL = contralesional. Color: the color in Fig. 1; Red: the region with increased fALFF in the stroke patients; Blue: the region with decreased fALFF in the stroke patients.
Brain regions with significant intergroup differences in fALFF between the stroke group and HC group. (A) The fALFF was found increased in the contralesional parietal lobe (cluster 1), and decreased in the ipsilesional sub-lobar areas (cluster 2) and contralesional frontal lobe (cluster 3) among the stroke patients compared with the controls (GRF correction, cluster level $P < 0.05$). Locations of the three clusters were listed in Table 2. The color bar indicates the $T$ value. IL, ipsilesional; CL, contralesional. (B)
Significant correlations between fALFF in cluster1 and motor function in stroke patients. UL: the proximal portion of the upper limb; LL: the entire lower limb

Figure 2

(A) An example image showing the CST in a stroke patient. (C) An example image showing the tracks of ROI from the fALFF comparisons between the two groups. The orange clusters represent increased fALFF
and the blue clusters showed decreased fALFF in the stroke patients compared with the controls (GRF correction, cluster level P < 0.05). (B and D) Comparison results of the number of tracks, mean length and overall length of the CST and the tracks of ROI. +: areas with increased fALFF in stroke group. -: areas with decreased fALFF in stroke group. *p<0.05, **p<0.005, ***p<0.001

Figure 3
Brain regions with significant intergroup differences in RSNs between the two groups. (A-E) The FC were found increased in the red areas and decreased in the blue areas of the above RSNs compared with the controls (GRF correction, cluster level $P < 0.05$). L: left, also ipsilesional; R: right, also contralesional. The color bar indicates the T value. The transverse slices on the black background are example images exhibiting the tracks of ROI. The orange and blue clusters were the same areas to the brain models. (F-H) Comparison results of the number of tracks (F), mean length (G) and overall length (H) of the tracks across ROI from the comparison results of the RSNs between the two groups. +: areas with increased FC in stroke group; -: areas with decreased FC in stroke group. *$p < 0.05$, **$p < 0.005$, ***$p < 0.001$

Figure 4

Graphic Abstract. The elevated fALFF in the contralesional parietal lobe correlated with the functions of the affected limb. The increased fiber tracks across regions with decreased FC in the RSNs, particularly those inter-hemisphere connections, were probably the structural basis for functional alterations in the lesioned brain.
Supplementary Files

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- Supplementarymaterial.docx