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

Xuejin Cao

Southeast University Zhongda Hospital

Zan Wang

Southeast University Zhongda Hospital

Xiaohui Chen

Southeast University Zhongda Hospital

Yanli Liu

Southeast University Zhongda Hospital

Idriss Ali Abdoulaye

Southeast University

Shenghong Ju

Southeast University Zhongda Hospital

Yuancheng Wang

Southeast University Zhongda Hospital

Yi Jing Guo (✉ guoyijingseu@126.com)

Southeast University Zhongda Hospital <https://orcid.org/0000-0002-6638-8963>

Research Article

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

Posted Date: January 31st, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1274925/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Cardiology and Cardiovascular Medicine on January 1st, 2022. See the published version at <https://doi.org/10.26502/fccm.92920244>.

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). 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).

Overall, researches indicated that stroke induces changes of FC within and between RSNs (Wang et al., 2014; Baldassarre et al., 2015). Furthermore, structure measures were added to explore the brain after stroke. Many diffusion tensor imaging (DTI) studies assessed fractional anisotropy (FA) of the lesioned regions and related fibers using diffusion tensor indicators (Griffis et al., 2019; Dominguez et al., 2019). In addition 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, few 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 the patients.

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 the healthy controls (HC). We identified RSNs in the two groups 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 deterministic fiber tracking was performed based on the DTI data. We defined the regions with different FC in RSNs between the groups as ROIs, and reconstructed the fiber tracking 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 ≥ 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 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. 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. 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 deriving from the first preprocessing steps underwent linear detrending, and temporal filtering to remove undesired components. 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 $FA \geq 0.2$ 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

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

Compared to the HC, the stroke patients showed different FC in several areas in the RSNs (SI Fig. S2). 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 displayed 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.

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 (Fig. 2A-B).

Discussion

Resting-state neural activity

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). 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 (Fig. 1), 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 (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). 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 functional networks.

The stroke group exhibited increased fALFF and increased FC in the contralesional parietal lobe of the SMN (Fig. 1A and Fig. 3). 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). We considered that the contralesional parietal lobe played a key 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 rs-fMRI measures the temporal correlation of 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). The stroke group displayed increased fibers connecting the two hemispheres across the frontal lobe with reduced fALFF. 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.

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 hemisphere.

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. 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). It is difficult to accurately locate all the microstructural changes in the brain of every patient. Our results were similar to those 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 infer the possible reorganization mechanisms after brain lesions.

The study sample was limited to a narrow range of subcortical ischemic stroke patients with motor deficit. An 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. 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. 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.

Authors Contributions

XJ.C. and YJ.G. conceived and designed the research. XJ.C., Z.W, XH.C. and YL.L. performed the experiments and analyzed the data. SH.J. and YC.W. reviewed and critiqued the results. SY.Z., and SS.W. provided experimental assistance. XJ.C., IA.A. and YJ.G. wrote the manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (grant number:6590000127, 81801680).

Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

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

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

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.

Code availability

Not applicable.

References

1. Baldassarre, A., Ramsey, L., Rengachary, J., Zinn, K., Siegel, J. S., Metcalf, N. V., . . . Shulman, G. L. (2016). Dissociated functional connectivity profiles for motor and attention deficits in acute right-hemisphere stroke. *Brain*, *139*, 2024-2038. [https:// doi. org/10.1093/brain/aww107](https://doi.org/10.1093/brain/aww107)
2. Baldassarre, A., Ramsey, L. E., Siegel, J. S., Shulman, G. L., & Corbetta, M. (2016). Brain connectivity and neurological disorders after stroke. *Curr Opin Neurol*, *29*(6), 706-713. [https:// doi. org/10.1097/WCO.0000000000000396](https://doi.org/10.1097/WCO.0000000000000396)
3. Bi, X. A., Sun, Q., Zhao, J. X., Xu, Q., & Wang, L. Q. (2018). Non-linear ICA Analysis of Resting-State fMRI in Mild Cognitive Impairment. *Frontiers in Neuroscience*, *12*. [https:// doi. org/10.3389/fnins.2018.00413](https://doi.org/10.3389/fnins.2018.00413)
4. Boehm, I., Geisler, D., King, J. A., Ritschel, F., Seidel, M., Araujo, Y. D., . . . Ehrlich, S. (2014). Increased resting state functional connectivity in the fronto-parietal and default mode network in anorexia nervosa. *Frontiers in Behavioral Neuroscience*, *8*. [https:// doi. org/10.3389/fnbeh.2014.00346](https://doi.org/10.3389/fnbeh.2014.00346)
5. Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci*, *1124*, 1-38. [https:// doi. org/10.1196/annals.1440.011](https://doi.org/10.1196/annals.1440.011)
6. Calhoun, V. D., Adali, T., Pearlson, G. D., & Pekar, J. J. (2001). A method for making group inferences from functional MRI data using independent component analysis. *Human Brain Mapping*, *14*(3), 140-151. [https:// doi. org/10.1002/hbm.1048](https://doi.org/10.1002/hbm.1048)

7. Carmichael, S. T. (2003). Plasticity of cortical projections after stroke. *Neuroscientist*, 9(1), 64-75. [https:// doi. org/10.1177/1073858402239592](https://doi.org/10.1177/1073858402239592)
8. Carter, A. R., Astafiev, S. V., Lang, C. E., Connor, L. T., Rengachary, J., Strube, M. J., . . . Corbetta, M. (2010). Resting Interhemispheric Functional Magnetic Resonance Imaging Connectivity Predicts Performance after Stroke. *Annals of Neurology*, 67(3), 365-375. [https:// doi. org/10.1002/ana.21905](https://doi.org/10.1002/ana.21905)
9. Cui, Z. X., Zhong, S. Y., Xu, P. F., He, Y., & Gong, G. L. (2013). PANDA: a pipeline toolbox for analyzing brain diffusion images. *Frontiers in Human Neuroscience*, 7. [https:// doi. org/10.3389/fnhum.2013.00042](https://doi.org/10.3389/fnhum.2013.00042)
10. Dominguez, D. J. F., Nott, Z., Horne, K., Prangley, T., Adams, A. G., Henry, J. D., & Molenberghs, P. (2019). Structural and functional brain correlates of theory of mind impairment post-stroke. *Cortex*, 121, 427-442. [https:// doi. org/10.1016/j.cortex.2019.09.017](https://doi.org/10.1016/j.cortex.2019.09.017)
11. Duering, M., Righart, R., Wollenweber, F. A., Zietemann, V., Gesierich, B., & Dichgans, M. (2015). Acute infarcts cause focal thinning in remote cortex via degeneration of connecting fiber tracts. *Neurology*, 84(16), 1685-1692. [https:// doi. org/10.1212/WNL.0000000000001502](https://doi.org/10.1212/WNL.0000000000001502)
12. Feng, W., Wang, J., Chhatbar, P. Y., Doughty, C., Landsittel, D., Lioutas, V. A., . . . Schlaug, G. (2015). Corticospinal tract lesion load: An imaging biomarker for stroke motor outcomes. *Annals of Neurology*, 78(6), 860-870. [https:// doi. org/10.1002/ana.24510](https://doi.org/10.1002/ana.24510)
13. Finger, S. (2010). Chapter 51: recovery of function: redundancy and vicariation theories. *Handb Clin Neurol*, 95, 833-841. [https:// doi. org/10.1016/S0072-9752\(08\)02151-9](https://doi.org/10.1016/S0072-9752(08)02151-9)
14. Fogassi, L., & Luppino, G. (2005). Motor functions of the parietal lobe. *Curr Opin Neurobiol*, 15(6), 626-631. [https:// doi. org/10.1016/j.conb.2005.10.015](https://doi.org/10.1016/j.conb.2005.10.015)
15. Gerloff, C., Bushara, K., Sailer, A., Wassermann, E. M., Chen, R., Matsuoka, T., . . . Hallett, M. (2006). Multimodal imaging of brain reorganization in motor areas of the contralesional hemisphere of well recovered patients after capsular stroke. *Brain*, 129(Pt 3), 791-808. [https:// doi. org/10.1093/brain/awh713](https://doi.org/10.1093/brain/awh713)
16. Gordon, E. M., Laumann, T. O., Adeyemo, B., Huckins, J. F., Kelley, W. M., & Petersen, S. E. (2016). Generation and Evaluation of a Cortical Area Parcellation from Resting-State Correlations. *Cerebral Cortex*, 26(1), 288-303. [https:// doi. org/10.1093/cercor/bhu239](https://doi.org/10.1093/cercor/bhu239)
17. Grefkes, C., & Fink, G. R. (2014). Connectivity-based approaches in stroke and recovery of function. *Lancet Neurol*, 13(2), 206-216. [https:// doi. org/10.1016/S1474-4422\(13\)70264-3](https://doi.org/10.1016/S1474-4422(13)70264-3)
18. Griffis, J. C., Metcalf, N. V., Corbetta, M., & Shulman, G. L. (2019). Structural Disconnections Explain Brain Network Dysfunction after Stroke. *Cell Reports*, 28(10), 2527-+. [https:// doi. org/10.1016/j.celrep.2019.07.100](https://doi.org/10.1016/j.celrep.2019.07.100)
19. Gu, X., Chen, W., Volkow, N. D., Koretsky, A. P., Du, C., & Pan, Y. (2018). Synchronized Astrocytic Ca(2+) Responses in Neurovascular Coupling during Somatosensory Stimulation and for the Resting State. *Cell Rep*, 23(13), 3878-3890. [https:// doi. org/10.1016/j.celrep.2018.05.091](https://doi.org/10.1016/j.celrep.2018.05.091)
20. Guo, X. L., Liu, R. H., Lu, J. C., Wu, C. W., Lyu, Y. Y., Wang, Z., . . . Tong, S. B. (2019). Alterations in Brain Structural Connectivity After Unilateral Upper-Limb Amputation. *Ieee Transactions on Neural Systems*

- and Rehabilitation Engineering*, 27(10), 2196-2204. [https:// doi. org/10.1109/Tnsre.2019.2936615](https://doi.org/10.1109/Tnsre.2019.2936615)
21. Hartwigsen, G., Bestmann, S., Ward, N. S., Woerbel, S., Mastroeni, C., Granert, O., & Siebner, H. R. (2012). Left dorsal premotor cortex and supramarginal gyrus complement each other during rapid action reprogramming. *J Neurosci*, 32(46), 16162-16171a. [https:// doi. org/10.1523/JNEUROSCI.1010-12.2012](https://doi.org/10.1523/JNEUROSCI.1010-12.2012)
 22. Jia, X. Z., Wang, J., Sun, H. Y., Zhang, H., Liao, W., Wang, Z., . . . Zang, Y. F. (2019). RESTplus: an improved toolkit for resting-state functional magnetic resonance imaging data processing. *Science Bulletin*, 64(14), 953-954. [https:// doi. org/10.1016/j.scib.2019.05.008](https://doi.org/10.1016/j.scib.2019.05.008)
 23. Jiang, L., Geng, W., Chen, H., Zhang, H., Bo, F., Mao, C. N., . . . Yin, X. (2018). Decreased functional connectivity within the default-mode network in acute brainstem ischemic stroke. *Eur J Radiol*, 105, 221-226. [https:// doi. org/10.1016/j.ejrad.2018.06.018](https://doi.org/10.1016/j.ejrad.2018.06.018)
 24. Kalinosky, B. T., Berrios Barillas, R., & Schmit, B. D. (2017). Structurofunctional resting-state networks correlate with motor function in chronic stroke. *Neuroimage Clin*, 16, 610-623. [https:// doi. org/10.1016/j.nicl.2017.07.002](https://doi.org/10.1016/j.nicl.2017.07.002)
 25. Koch, P., Schulz, R., & Hummel, F. C. (2016). Structural connectivity analyses in motor recovery research after stroke. *Ann Clin Transl Neurol*, 3(3), 233-244. [https:// doi. org/10.1002/acn3.278](https://doi.org/10.1002/acn3.278)
 26. Lindenberg, R., Renga, V., Zhu, L. L., Betzler, F., Alsop, D., & Schlaug, G. (2010). Structural integrity of corticospinal motor fibers predicts motor impairment in chronic stroke. *Neurology*, 74(4), 280-287. [https:// doi. org/10.1212/WNL.0b013e3181ccc6d9](https://doi.org/10.1212/WNL.0b013e3181ccc6d9)
 27. Lugtmeijer, S., Lammers, N. A., de Haan, E. H. F., de Leeuw, F. E., & Kessels, R. P. C. (2020). Post-Stroke Working Memory Dysfunction: A Meta-Analysis and Systematic Review. *Neuropsychol Rev*. [https:// doi. org/10.1007/s11065-020-09462-4](https://doi.org/10.1007/s11065-020-09462-4)
 28. Ma, L., Narayana, S., Robin, D. A., Fox, P. T., & Xiong, J. (2011). Changes occur in resting state network of motor system during 4 weeks of motor skill learning. *Neuroimage*, 58(1), 226-233. [https:// doi. org/10.1016/j.neuroimage.2011.06.014](https://doi.org/10.1016/j.neuroimage.2011.06.014)
 29. Mori, S., Crain, B. J., Chacko, V. P., & van Zijl, P. C. M. (1999). Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Annals of Neurology*, 45(2), 265-269. [https:// doi. org/10.1002/1531-8249\(199902\)45:2<265::Aid-Ana21>3.0.Co;2-3](https://doi.org/10.1002/1531-8249(199902)45:2<265::Aid-Ana21>3.0.Co;2-3)
 30. Mueller, S., Costa, A., Keeser, D., Pogarell, O., Berman, A., Coates, U., . . . Meindl, T. (2014). The Effects of Methylphenidate on Whole Brain Intrinsic Functional Connectivity. *Human Brain Mapping*, 35(11), 5379-5388. [https:// doi. org/10.1002/hbm.22557](https://doi.org/10.1002/hbm.22557)
 31. Naghdi, S., Ansari, N. N., Mansouri, K., & Hasson, S. (2010). A neurophysiological and clinical study of Brunnstrom recovery stages in the upper limb following stroke. *Brain Inj*, 24(11), 1372-1378. [https:// doi. org/10.3109/02699052.2010.506860](https://doi.org/10.3109/02699052.2010.506860)
 32. Park, C. H., Chang, W. H., Ohn, S. H., Kim, S. T., Bang, O. Y., Pascual-Leone, A., & Kim, Y. H. (2011). Longitudinal changes of resting-state functional connectivity during motor recovery after stroke. *Stroke*, 42(5), 1357-1362. [https:// doi. org/10.1161/STROKEAHA.110.596155](https://doi.org/10.1161/STROKEAHA.110.596155)

33. Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., . . . Petersen, S. E. (2011). Functional network organization of the human brain. *Neuron*, 72(4), 665-678. [https:// doi. org/10.1016/j.neuron.2011.09.006](https://doi.org/10.1016/j.neuron.2011.09.006)
34. Riecker, A., Groschel, K., Ackermann, H., Schnaudigel, S., Kassubek, J., & Kastrup, A. (2010). The role of the unaffected hemisphere in motor recovery after stroke. *Human Brain Mapping*, 31(7), 1017-1029. [https:// doi. org/10.1002/hbm.20914](https://doi.org/10.1002/hbm.20914)
35. Schaechter, J. D., Fricker, Z. P., Perdue, K. L., Helmer, K. G., Vangel, M. G., Greve, D. N., & Makris, N. (2009). Microstructural status of ipsilesional and contralesional corticospinal tract correlates with motor skill in chronic stroke patients. *Human Brain Mapping*, 30(11), 3461-3474. [https:// doi. org/10.1002/hbm.20770](https://doi.org/10.1002/hbm.20770)
36. Siegel, J. S., Ramsey, L. E., Snyder, A. Z., Metcalfe, N. V., Chacko, R. V., Weinberger, K., . . . Corbetta, M. (2016). Disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. *Proc Natl Acad Sci U S A*, 113(30), E4367-4376. [https:// doi. org/10.1073/pnas.1521083113](https://doi.org/10.1073/pnas.1521083113)
37. Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., . . . Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*, 106(31), 13040-13045. [https:// doi. org/10.1073/pnas.0905267106](https://doi.org/10.1073/pnas.0905267106)
38. Song, D., Chang, D., Zhang, J., Ge, Q., Zang, Y. F., & Wang, Z. (2019). Associations of brain entropy (BEN) to cerebral blood flow and fractional amplitude of low-frequency fluctuations in the resting brain. *Brain Imaging Behav*, 13(5), 1486-1495. [https:// doi. org/10.1007/s11682-018-9963-4](https://doi.org/10.1007/s11682-018-9963-4)
39. Suarez, L. E., Markello, R. D., Betzel, R. F., & Misic, B. (2020). Linking Structure and Function in Macroscale Brain Networks. *Trends Cogn Sci*, 24(4), 302-315. [https:// doi. org/10.1016/j.tics.2020.01.008](https://doi.org/10.1016/j.tics.2020.01.008)
40. Umarova, R. M., Beume, L., Reiser, M., Kaller, C. P., Kloppel, S., Mader, I., . . . Weiller, C. (2017). Distinct white matter alterations following severe stroke: Longitudinal DTI study in neglect. *Neurology*, 88(16), 1546-1555. [https:// doi. org/10.1212/WNL.0000000000003843](https://doi.org/10.1212/WNL.0000000000003843)
41. Visser, M. M., Yassi, N., Campbell, B. C. V., Desmond, P. M., Davis, S. M., Spratt, N., . . . Bivard, A. (2019). White Matter Degeneration after Ischemic Stroke: A Longitudinal Diffusion Tensor Imaging Study. *J Neuroimaging*, 29(1), 111-118. [https:// doi. org/10.1111/jon.12556](https://doi.org/10.1111/jon.12556)
42. Wang, C. H., Qin, W., Zhang, J., Tian, T., Li, Y., Meng, L. L., . . . Yu, C. S. (2014). Altered functional organization within and between resting-state networks in chronic subcortical infarction. *Journal of Cerebral Blood Flow and Metabolism*, 34(4), 597-605. [https:// doi. org/10.1038/jcbfm.2013.238](https://doi.org/10.1038/jcbfm.2013.238)
43. Wang, L., Yu, C., Chen, H., Qin, W., He, Y., Fan, F., . . . Zhu, C. (2010). Dynamic functional reorganization of the motor execution network after stroke. *Brain*, 133(Pt 4), 1224-1238. [https:// doi. org/10.1093/brain/awq043](https://doi.org/10.1093/brain/awq043)
44. Whitlock, J. R. (2017). Posterior parietal cortex. *Curr Biol*, 27(14), R691-R695. [https:// doi. org/10.1016/j.cub.2017.06.007](https://doi.org/10.1016/j.cub.2017.06.007)

45. Wiesendanger, M. (2006). Constantin von Monakow (1853-1930): A pioneer in interdisciplinary brain research and a humanist. *Comptes Rendus Biologies*, 329(5-6), 406-418. [https:// doi. org/10.1016/j.crv.2006.03.011](https://doi.org/10.1016/j.crv.2006.03.011)
46. Wu, J., Quinlan, E. B., Dodakian, L., McKenzie, A., Kathuria, N., Zhou, R. J., . . . Cramer, S. C. (2015). Connectivity measures are robust biomarkers of cortical function and plasticity after stroke. *Brain*, 138(Pt 8), 2359-2369. [https:// doi. org/10.1093/brain/awv156](https://doi.org/10.1093/brain/awv156)
47. Yang, H., Long, X. Y., Yang, Y. H., Yan, H., Zhu, C. Z., Zhou, X. P., . . . Gong, Q. Y. (2007). Amplitude of low frequency fluctuation within visual areas revealed by resting-state functional MRI. *Neuroimage*, 36(1), 144-152. [https:// doi. org/10.1016/j.neuroimage.2007.01.054](https://doi.org/10.1016/j.neuroimage.2007.01.054)
48. Zaaime, B., Edgley, S. A., Soteropoulos, D. S., & Baker, S. N. (2012). Changes in descending motor pathway connectivity after corticospinal tract lesion in macaque monkey. *Brain*, 135(Pt 7), 2277-2289. [https:// doi. org/10.1093/brain/aws115](https://doi.org/10.1093/brain/aws115)
49. Zarahn, E., Alon, L., Ryan, S. L., Lazar, R. M., Vry, M. S., Weiller, C., . . . Krakauer, J. W. (2011). Prediction of Motor Recovery Using Initial Impairment and fMRI 48 h Poststroke. *Cerebral Cortex*, 21(12), 2712-2721. [https:// doi. org/10.1093/cercor/bhr047](https://doi.org/10.1093/cercor/bhr047)
50. Zhang, Y., Liu, H., Wang, L., Yang, J., Yan, R., Zhang, J., . . . Qiu, M. (2016). Relationship between functional connectivity and motor function assessment in stroke patients with hemiplegia: a resting-state functional MRI study. *Neuroradiology*, 58(5), 503-511. [https:// doi. org/10.1007/s00234-016-1646-5](https://doi.org/10.1007/s00234-016-1646-5)
51. Zhang, Y., Wang, L., Yang, J., Yan, R., Zhang, J., Sang, L., . . . Qiu, M. (2017). Abnormal functional networks in resting-state of the sub-cortical chronic stroke patients with hemiplegia. *Brain Res*, 1663, 51-58. [https:// doi. org/10.1016/j.brainres.2017.02.012](https://doi.org/10.1016/j.brainres.2017.02.012)
52. Zou, Q. H., Zhu, C. Z., Yang, Y. H., Zuo, X. N., Long, X. Y., Cao, Q. J., . . . Zang, Y. F. (2008). An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: Fractional ALFF. *Journal of Neuroscience Methods*, 172(1), 137-141. [https:// doi. org/10.1016/j.jneumeth.2008.04.012](https://doi.org/10.1016/j.jneumeth.2008.04.012)
53. Zuo, X. N., Kelly, C., Adelstein, J. S., Klein, D. F., Castellanos, F. X., & Milham, M. P. (2010). Reliable intrinsic connectivity networks: Test-retest evaluation using ICA and dual regression approach. *Neuroimage*, 49(3), 2163-2177. [https:// doi. org/10.1016/j.neuroimage.2009.10.080](https://doi.org/10.1016/j.neuroimage.2009.10.080)

Tables

Table 1 Demographic data of two groups

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

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

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

IL = ipsilesional; CL = contralesional. Color: the color in Figure 1; Red: the region with increased fALFF in the stroke patients; Blue: the region with decreased fALFF in the stroke patients.

Figures

Figure 1

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. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [AuthorChecklist.pdf](#)
- [SupplementaryInformation.docx](#)