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Changes in brain functional network connectivity after stroke

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Abstract

Studies have shown that functional network connection models can be used to study brain network changes in patients with schizophrenia. In this study, we inferred that these models could also be used to explore functional network connectivity changes in stroke patients. We used independent component analysis to find the motor areas of stroke patients, which is a novel way to determine these areas. In this study, we collected functional magnetic resonance imaging datasets from healthy controls and right-handed stroke patients following their first ever stroke. Using independent component analysis, six spatially independent components highly correlated to the experimental paradigm were extracted. Then, the functional network connectivity of both patients and controls was established to observe the differences between them. The results showed that there were 11 connections in the model in the stroke patients, while there were only four connections in the healthy controls. Further analysis found that some damaged connections may be compensated for by new indirect connections or circuits produced after stroke. These connections may have a direct correlation with the degree of stroke rehabilitation. Our findings suggest that functional network connectivity in stroke patients is more complex than that in healthy controls, and that there is a compensation loop in the functional network following stroke. This implies that functional network reorganization plays a very important role in the process of rehabilitation after stroke.

Key Words: nerve regeneration; brain injury; stroke; motor areas; functional magnetic resonance imaging; brain network; independent component analysis; functional network connectivity; neural plasticity; NSFC grant; neural regeneration

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Introduction

Many stroke patients still have long-term functional deficits, especially in motor function[1-4]. There are many investigators who have attempted to explore the mechanism of functional recovery after stroke[5-7], yet until now there have been no breakthroughs in this area[8]. In this study, we ask the question: are there changes in the connectivity of motor areas following stroke, and what kinds of changes happen?

In the past two decades, functional magnetic resonance imaging (fMRI), as one of the most recently developed forms of neuroimaging, has been used as a reliable method of clinical diagnosis and assessment for stroke[9-11]. Owing to the relatively low invasiveness and high spatial resolution of fMRI, scientists have started to use this method of neuroimaging to focus on cerebral connectivity[12-14].

A growing number of studies have tried to use connectivity analysis to understand the changes in brain networks between stroke patients and healthy controls as well as the mechanism of neural plasticity after stroke[15-17]. Using dynamic causal models, Mintzopoulos et al.[18] illustrated that stroke patients showed increased coupling from the SMA to M1 and the SMA to the cerebellum. The intrinsic neural coupling between M1 and the cerebellum has also been found to decrease. The results suggest that alterations in brain connectivity between motor areas could compensate for the abnormal function of M1 in chronic stroke patients[18].

With graph-theoretical approaches to the fMRI data of stroke patients, Wang et al.[19] explored functional changes in and the reorganization of the brain network after stroke. The study illustrated that the brain network may evolve to a random mode during the process of rehabilitation after stroke[19]. Grefkes and Gereon[20] pointed out that connectivity analysis could be a useful way to develop new hypothesis-driven treatment methods to promote motor function recovery for stroke patients[20]. Westlake and Nagarajan[21] also found that cerebral network modeling is a powerful tool to explore cerebral reorganization and to predict the prog-

nosis of stroke.

Previous studies on brain connectivity for stroke focused on functional connectivity and effective connectivity among motor areas[15, 18]. Functional connectivity is defined as the correlation between spatially remote neurophysiological events, and can be used to study the relationship among individual voxels or regions with fMRI activation images[22].

Effective connectivity can be defined as the influence that one neural system exerts over another. The various approaches of effective connectivity, such as dynamic causal modeling, accommodate the nonlinear and dynamic performance of the interactions of neural units[23], and can describe the task-dependent influence that the activation of one area exerts over another to infer the connectivity between selected areas within a brain network[23-24]. However, these methods always require a priori knowledge about neurophysiology and the experimental paradigm, or given assumptions about the specific processing of fMRI data.

Can we use a data-driven approach to study the connectivity between brain areas? Independent component analysis is a useful method of studying functional connectivity with little reliance on previous knowledge[25-27]. It can decompose fMRI data into time courses of spatially independent components to distinguish task-related or non-task-related signal components[28-31]. A significant advantage of independent component analysis is that it is a model-free and data-driven approach. Thus, independent component analysis is a good selection for the study of brain network connectivity when we lack a priori knowledge to use other techniques.

McKeown et al.[25] showed that independent component analysis is an useful way to decompose fMRI datasets into mutually independent components of the space, from both the experimental fMRI (artificially constructed fMRI datasets) datasets and the real datasets (actually collected fMRI datasets)[25]. Many studies have used independent component analysis to decompose such datasets and produce meaningful results. For example, Demirci et al.[12] used independent component analysis to pretreat the fMRI datasets, after which a Granger causality model was established among the independent component analysis components. Their results suggested that there was a significant difference in the models of healthy controls and patients with schizophrenia. These results have important theoretical and clinical significance for the diagnosis and treatment of schizophrenia[12]. Other studies have also used independent component analysis to investigate fMRI datasets, and have achieved good results[31].

Functional network connectivity, into which independent component analysis is integrated, has been regarded as a strong tool to study the functional interactions among selected independent components that represent different activated regions without an a priori model. It can also describe the constrained maximal time-lagged correlation for every pair of component combinations. Therefore, functional network connectivity approaches have been applied in both the study of brain network changes in schizophrenia[26] and the temporal sequence of the activated hemispheric network during semantic processing[32]. Using this method, Jafri et al.[26] reported that there was more functional connectivity and a longer lag time between the independent component analysis components in patients with schizophrenia than in healthy controls.

Assaf et al.[32] used a similar method to study functional network connectivity among brain areas in the left and right hemispheres during the processing of semantic memory. The results indicated an early activation in the right hemisphere that was closely followed by an area of activation in the left hemisphere. However, there is as yet no research that uses functional network connectivity to investigate possible alterations in the brain network after stroke. A major question is whether a new theory of neurological rehabilitation can be discovered by exploring the brains of stroke patients using functional network connectivity.

In this study, acute stroke patients and healthy controls were recruited to take part in blood oxygenation level dependent (BOLD) fMRI experiments while performing alternating unilateral finger-to-thumb opposition movements. Group independent component analysis was used to obtain spatially independent components of brain activation with the time courses of decomposed components[25, 27]. Then, to study brain connectivity changes after stroke, functional network connectivity was constructed from the selected components.

Based on the previous study in stroke patients versus healthy controls, it has been hypothesized that the functional network connectivity of stroke patients is more complex than that of healthy controls; moreover, we assumed that functional compensation could be achieved through the other neural circuits in the stroke patients. The purpose of this study was to explore the changes in brain network connectivity after stroke.

Results

Quantitative analysis of participants

The fMRI datasets of eight right-handed patients with acute stroke and eight healthy controls were collected in this study. The independent component analysis method was used to decompose the datasets to independent components after preprocessing each dataset.

In the preprocessing of fMRI datasets, two patients and two healthy controls were excluded for exceeding the head movement parameters. Therefore, in the final analysis, six stroke patients and six healthy controls were used.

Baseline data analysis of subjects

There were six stroke patients, five males and one female, with a mean age of 41.5 (range 17–65) years. Detailed clinical and demographic data for all patients are shown in Table 1. There were six healthy controls, four males and two females, with a mean age of 53 (range 40–58) years.

There were no significant differences in age, gender, and years of education between stroke patients and healthy controls (Table 2).

Selection of independent components

To obtain the connectivity differences between stroke pa-

Table 1 Clinical and demographic data of stroke patients

Patient number	Age (year)	Gender	Year of education	Affected hand	Myodynamia (grade)	Localization of infarct
1	35	Male	12	Right	4	Left basal ganglia
2	17	Male	9	Right	4	Left basal ganglia
3	65	Male	9	Right	2	Left thalamus
4	60	Female	9	Right	3	Left paraventricular corona radiata
5	31	Male	12	Right	4	Left thalamus and left corpus callosum
6	41	Male	9	Right	3	Left basal ganglia

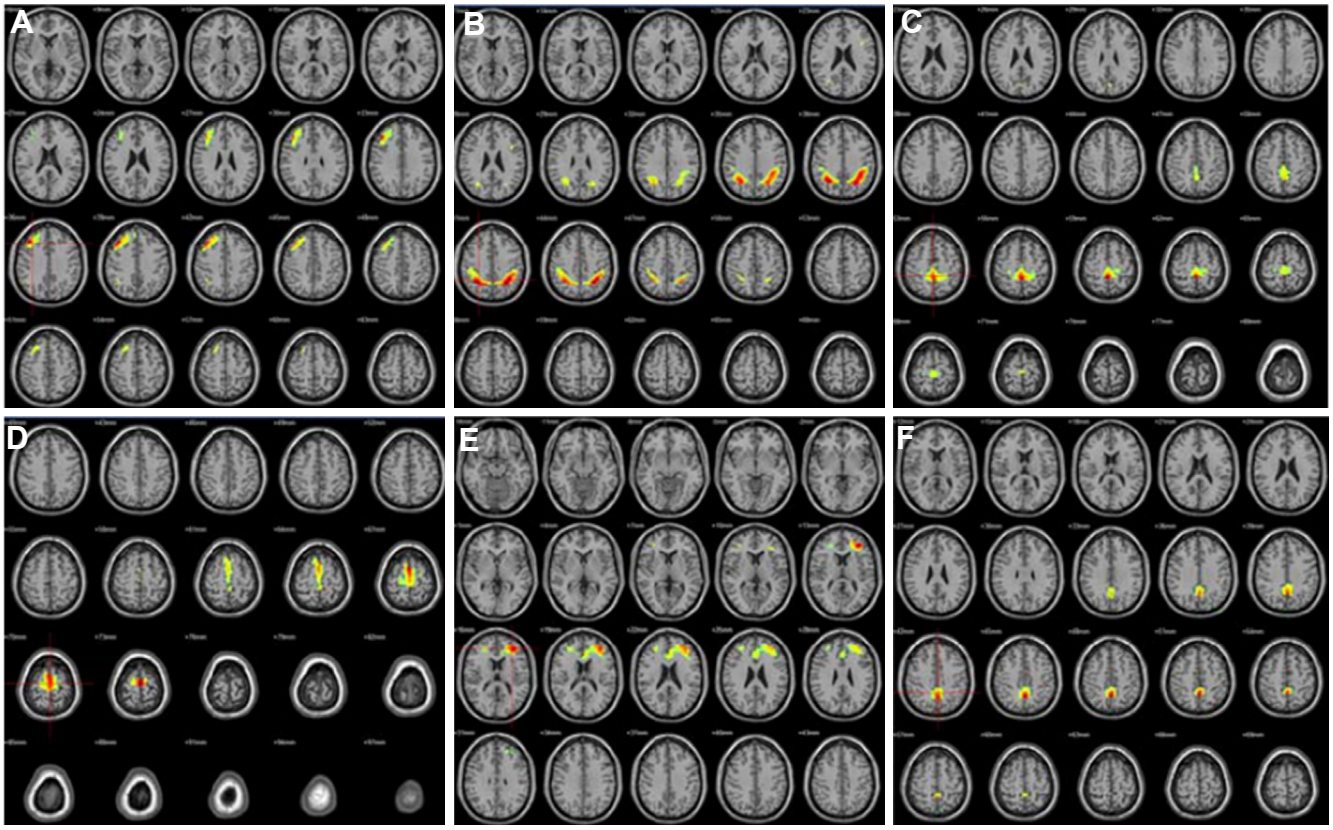

Figure 1 Six independent components highly correlated to the experimental paradigm were chosen.
A–F represent the selection components obtained by the group independent component analysis, and the regions comprising each component are shown in Table 3. Component A mainly includes frontal lobe, medial frontal gyrus, and superior frontal gyrus. Component B includes frontal lobe and temporal lobe. Component C includes paracentral lobule, culmen, and cerebellum anterior lobe. Component D includes superior frontal gyrus, occipital lobe and inferior frontal gyrus. Component E includes the covarying regions in limbic lobe and anterior cingulate cortex. Component F includes parietal lobe and precuneus. The color illustrated the activation level. In this study, the components, which were highly correlated to the paradigm of experiments, took priority over other components. Because the purpose of this study was related to motor function, components that had no apparent relationship to motor execution were excluded.

tients and healthy controls, six independent components highly correlated to the experimental paradigm were chosen. The components chosen (A–F) are shown in Figure 1. The Brodmann areas (BA)[33] and MNI coordinates corresponding to the activated regions are also shown in Table 3. The temporal multiple regression correlation between each selected component and the experimental paradigm was computed by temporal sorting analysis as follows. Component A: R = 0.22; component B: R = 0.22; component C: R = 0.215; component D: R = 0.200; component E: R = 0.186; component F: R = 0.185.

Establishment of the functional network connectivity model

Functional network connectivity for healthy controls and stroke patients is shown in Figure 2 and Figure 3. The links indicate that there was a significant correlation between two different components ($P < 0.05$). From the figures, there were four links in healthy controls, and 11 links in stroke patients. The arrow direction describes the relationship of the lag between the two linked components. For example, A ~~B~~ means that component A preceded component B according to the group lag average. Through graphical analysis, we found

Table 2 Baseline data of stroke patients and healthy controls

Item	Stroke patients	Healthy controls
Age (year)	41.5 (17–65)	53(40–58)
Sex (male/female)	5/1	4/2
Year of education	10.0 (9–12)	11.2 (27–30)

There were no significant differences in age, gender and years of education between stroke patients and healthy controls (all $P > 0.05$).

significant correlations for D→ E and C ⇒F for both healthy controls and stroke patients. For healthy controls only, we found connectivity for C ⇒D and E ⇒C, while we found connectivity in stroke patients only for D→ B, B ⇒C, E ⇒A, A ⇒F, F→ D, A→ G, B→ A, F→ B and B ⇒E.

From the results, we found compensatory connection loop in the functional network of stroke patients. For example, we found that the correlations C→ D and E ⇒C only existed in healthy controls. There were no direct connections in stroke patients between components C and D, or components E and C.

However, there was an indirect connection between components C and D in stroke patients through component F with the path: C ⇒F ⇒D. There was also an indirect connection in stroke patients between components E and C through component A with the path: E ⇒A→ G.

Discussion

In this paper, functional network connectivity was used to study functional connectivity during rehabilitation following stroke and was used to explore the differences between stroke patients and healthy controls.

Previous studies have shown that independent component analysis is one of the most effective methods for fMRI dataset analysis[29, 34-35]. Independent component analysis and functional network connectivity can be used to distinguish the difference between patients with schizophrenia and controls[26], and can also be used to study the temporal sequence of hemispheric network activation during semantic processing[32]. We studied changes in the functional network connectivity of stroke patients during movements using independent component analysis and the functional network connectivity method. Our results illustrated that the functional network connectivity of stroke patients was more complex than that of healthy controls.

In addition, a compensatory connection loop existed in the functional network of stroke patients. These results illustrate that the changes in functional network connectivity can be explored by the dual methods of independent component analysis and functional network connectivity.

The independent component analysis method is a data-driven method for preprocessing fMRI datasets. Many fMRI datasets have been decomposed in this way in a large number of recent studies. Independent component analysis can decompose the fMRI datasets into mutually independent components in the spatial domain, and a single component of time synchronization. This method has been used in different studies and has obtained good results[30-31]. In this study, the fMRI datasets of stroke patients and healthy controls were first preprocessed using the independent component

Table 3 The details of activated regions for each component

Region	Brodmann area	MNI coordinate (*X*, *Y*, *Z*)
Component A		
Frontal lobe	9, 8, 6, 10, 13	42, 32, 38
Middle temporal gyrus	39	–40, –68, 22
Parietal lobe	40, 39	40, –56, 40
Precuneus	31, 7	2, –68, 28
Cingulate gyrus	23	4, –20, 28
Parietal lobe	40	–50, –48, 34
Frontal_Mid_L	9, 8	–36, 30, 40
Cingulate gyrus	31	2, –30, 40
Paracentral gobule	4, 5	0, –40, 64
Medial frontal gyrus	6	–2, –8, 74
Component B		
Frontal lobe	46, 9	–40, 12, 26
Inferior parietal lobule	40, 7	30, –60, 42
Temporal lobe	2, 39, 31, 4	45, –60, 28
Middle frontal gyrus	6, 8	34, 16, 52
Superior frontal gyrus	6, 8	0, 18, 60
Component C		
Culmen		6, –38, –26
Cerebellum anterior lobe		14, –36, –16
Limbic lobe	23	0, –60, 12
Insula	13, 41	44, –26, 16
Precuneus	31, 7, 18	–2, –76, 30
Paracentral lobule	6, 5, 7, 4, 3, 31, 40	0, –44, 60
Superior frontal gyrus	8, 6	2, 26, 58
Component D		
Cerebellum anterior lobe		–6, –46, –18
Occipital lobe	19, 18	–26, –70, –18
Temporal lobe	18, 13	–48, –52, 4
Sub-lobar	8, 4, 7	2, –14, 10
Insula	13, 40	56, –34, 18
Cingulate gyrus	24	0, 8, 38
Precuneus	7	–4, –58, 46
Frontal lobe	6, 8, 4, 5, 3	0, –14, 74
Component E		
Declive	19, 18	–28, –70, –18
Culmen		–14, –32, –16
Frontal lobe	32, 9, 10, 24, 46, 13, 33, 47, 45	–36, 42, 16
Occipital lobe	18, 17	–16, –84, 12
Middle temporal gyrus	39, 22	–40, –70, 14
Parietal obe	6, 4, 3, 9, 13, 40, 43	–58, –18, 22
Superior frontal gyrus	6	–20, 12, 64
Paracentral lobule	4, 5	–4, –40, 64
Component F		
Parahippocampa gyrus	19	–30, –48, –6
Corpus Callosum		0, –46, 8
Middle temporal gyrus	39, 19, 22	44, –62, 16
Parietal lobe	7, 31, 5, 4	0, –54, 48
Inferior frontal gyrus	9, 6	44, 4, 32
Superior frontal gyrus	6	–18, 12, 64

Component A mainly includes frontal lobe, medial frontal gyrus, and superior frontal gyrus. Component B includes frontal lobe and temporal lobe. Component C includes paracentral lobule, culmen, and cerebellum anterior lobe. Component D includes superior frontal gyrus, occipital lobe and inferior frontal gyrus. Component E includes the covarying regions in limbic lobe and anterior cingulate. Component F includes parietal lobe and precuneus.

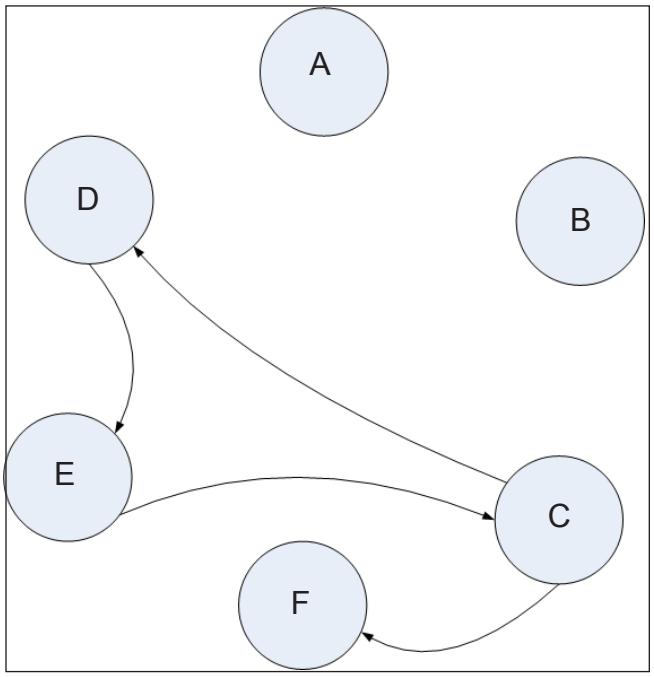

Figure 2 Functional network connectivity model for the healthy controls.
Components A–F represent the independent component analysis components that were selected for establishing the functional network (the regions comprising each component are shown in Table 3). The links indicate that there was a correlation between the two components, and the direction of the arrow describes the lag relationship between the two linked components. For example, C→F means that component C precedes component F according to the group lag average.

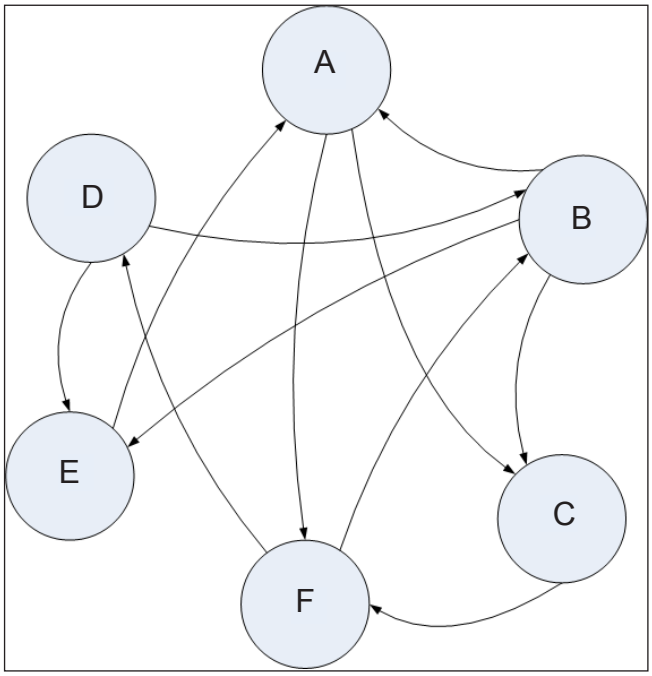

Figure 3 Functional network connectivity model for the stroke patients.
Components A–F represent the independent component analysis components that were selected for establishing the functional network (the regions comprising each component are shown in Table 3). The links indicate that there was a correlation between the two components, and the direction of the arrow describeds the lag relationship between the two linked components. For example, C→F means that component C preceded component F according to the group lag average.

analysis method.

In this study, the functional regions involved in component A include the supplementary motor cortex and premotor cortex. These regions have been shown to play a crucial role in motor control[22, 36-37]. Component B mainly represents primary somatosensory cortex[38]. These regions of component C are generally associated with the recognition of human beings[39]. They are also considered to have a relationship with the motor cortex. Component D may be related to sensory systems[40].

Component E has been shown to be involved in directing attention in space both when an individual makes movements and while imaging or preparing the movements[41]. From the selected components, we can find that many of the areas of movement were found by the independent component analysis method, although we did not obey the previous seed-voxel method. The results show the feasibility of selecting components with this method, and provide a theoretical basis for future research.

Previous studies on stroke have demonstrated that cortical activation is increased in stroke patients in comparison with healthy controls in the contralesional primary sensorimotor cortex during the performance of movement[42]. It also has been suggested that the disorganization of the motor network after stroke is increased, notably including more bilateral involvement of BA4p[43]. This result indicates that the neurovascular coupling may be affected by infarct lesions in patients[44-46].

Wang et al.[19] found from analysis of the whole brain network that the connectivity of patients was much more complex than that of healthy controls. The result was consistent with our hypothesis. The same results were also found in a study by Jafri et al.[26]. Thus, the optimal structure of the brain may change during disease, which is also consistent with a previous study of brain injury[47].

The network connections in the healthy controls were simple and of good group consistency, which may imply a simple but efficient network. For stroke patients, we could interpret their complex connectivity as evidence that plenty of new connections were produced to compensate for the damaged or injured connections and nerves[48-49]. Although the network connections in stroke patients may be less stable and efficient than those in controls, this solution evolved after the stroke and does work[50-51].

Previous studies have suggested that the functional networks of patients with brain disease were more complex than those of healthy controls[52] and our study also demonstrated this fact, which could help us to comprehend the mechanism of neurological rehabilitation after stroke. These results have very important theoretical and clinical significance for stroke.

The analysis of functional network connectivity could also be used to obtain the functional connectivity of various other brain regions and the temporal relationships among the identified components[26]. Theoretically, the time lag between the two components could be due to temporal differences

in blood supply to different brain regions[32, 53-54]. Results from this study showed that the significant correlations D Ē and C Ē existed in both healthy controls and stroke patients, which suggests that these connections, including correlations and temporal relationships, existed after stroke in patients, and still worked during performance of movements.

From our results, we also found some connections which were found in healthy controls disappeared in the stroke patients, while these components can be connected through other components. This shows that some cerebral regions play an important role as a bridge to connect damaged connections, such as component F or component D. Thus, it suggests that although some connections were damaged after stroke, indirect connections were produced and functional compensation may be achieved through such new indirect connections or neural circuits[55-56].

Generally, the studies illustrated that the human brain has a strong robustness[57], and that the function of the injured brain regions could be compensated for by their peripheral regions or nerves that have similar functions. This may be due to the long-term evolution of the brain. In this study, a loop existed in the functional network connectivity of stroke patients although small components were selected. This conclusion further demonstrates the robustness of the brain, and confirms the reliability of the previous studies. At the same time, it illustrates that functional compensation plays a very important role in functional rehabilitation for stroke patients.

It should be mentioned here that there are several limitations to this study. The sample set is not large enough, and the behavioral data have not been included in the network connectivity analysis. In future research, it may be meaningful to combine the behavioral data and functional network connectivity analysis to explore the possible correlations between them after stroke.

In conclusion, differences in functional network connectivity between stroke patients and healthy controls were explored in this paper. Six spatially independent components highly correlated to the experimental paradigm were extracted using independent component analysis to find the nodes of the network. The results of network modeling illustrated that functional network connectivity in stroke patients was much more complex than that in healthy controls. This result suggests that many new connections are produced to compensate for the damaged connections and nerves after stroke.

Furthermore, it also has been found that some damaged connections may be compensated for by new indirect connections or circuits produced after stroke, which implies that functional network reorganization plays a very important role in the process of rehabilitation after stroke.

Subjects and Methods

Design

A case-control study.

Time and setting

This study was performed at the Laboratory of Nuclear Magnetic Resonance, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China between April 2010 and November 2010.

Subjects

Each subject was recognized as having had a stroke using a T1 image. The patients were recruited by the Department of Rehabilitation, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China. All participants were stroke patients who received treatment in Tongji Hospital and came from Hubei Province, China.

All stroke patients fulfilled the following inclusion criteria: (1) first-ever ischemic stroke; (2) within 2 weeks after stroke; (3) showing motor deficits with acute unilateral loss of hand strength (grade 4 on the Medical Research Council (MRC) scale (0–5, the higher the score, the greater the muscle strength, a score of 5 = normal))[58]; (4) good hand motor function.

Exclusion criteria for stroke patients were as follows: (1) language or cognitive deficits that would impair cooperation in fMRI examination; (2) significant somatosensory (light touch or proprioception) deficits in the stroke-affected hand; (3) mirror movements; and (4) contraindication to magnetic resonance imaging.

In this study, healthy controls (4 male; age range: 40–58 years; mean: 53 years) with a similar age and education to the patients with stroke (5 male; age range: 17–65 years; mean: 41.5 years) were selected. Healthy controls were recruited by the Department of Rehabilitation, Tongji Hospital, and all of them came from Hubei Province. All healthy controls fulfilled the following inclusion criteria: (1) No previous history of brain injury; (2) no history of mental illness; (3) normal motor function. Exclusion criteria for the healthy controls were as follows: (1) contraindication to MRI; (2) the subjects could not complete the experiment.

This study was approve by the Ethics Committee of Tongji Hospital, Tongji Medical college, Huazhong Unversity of Science and Technology, China, all subjects gave their informed consent before being submitted to fMRI examination.

The clinical characteristics of the stroke patients are summarized in Table 2. All six patients had a subcortical stroke encompassing the left basal ganglia or the left frontal cortex (Table 1), and the illustration of the lesion location is shown in red in Figure 4. For all stroke patients, the localization of infarct was almost the same.

Methods

Experimental paradigm

All the subjects were instructed to execute alternating unilateral finger-to-thumb opposition movements at a frequency of 1 Hz in a block-design fMRI paradigm.

The task occurred in 20-second blocks of movements alternated with 20-second intervals as rest periods: Rest – Movements (Left) – Rest – Movements (Right) – Rest – Movements (Left) – Rest – Movements (Right) – Rest – Movements (Left) – Rest – Movements (Right) – Rest. It lasted for a total of 260 seconds as shown in Figure 5.

During the fMRI procedure, the subjects kept their eyes open, and their head was kept motionless. Prior to scanning,

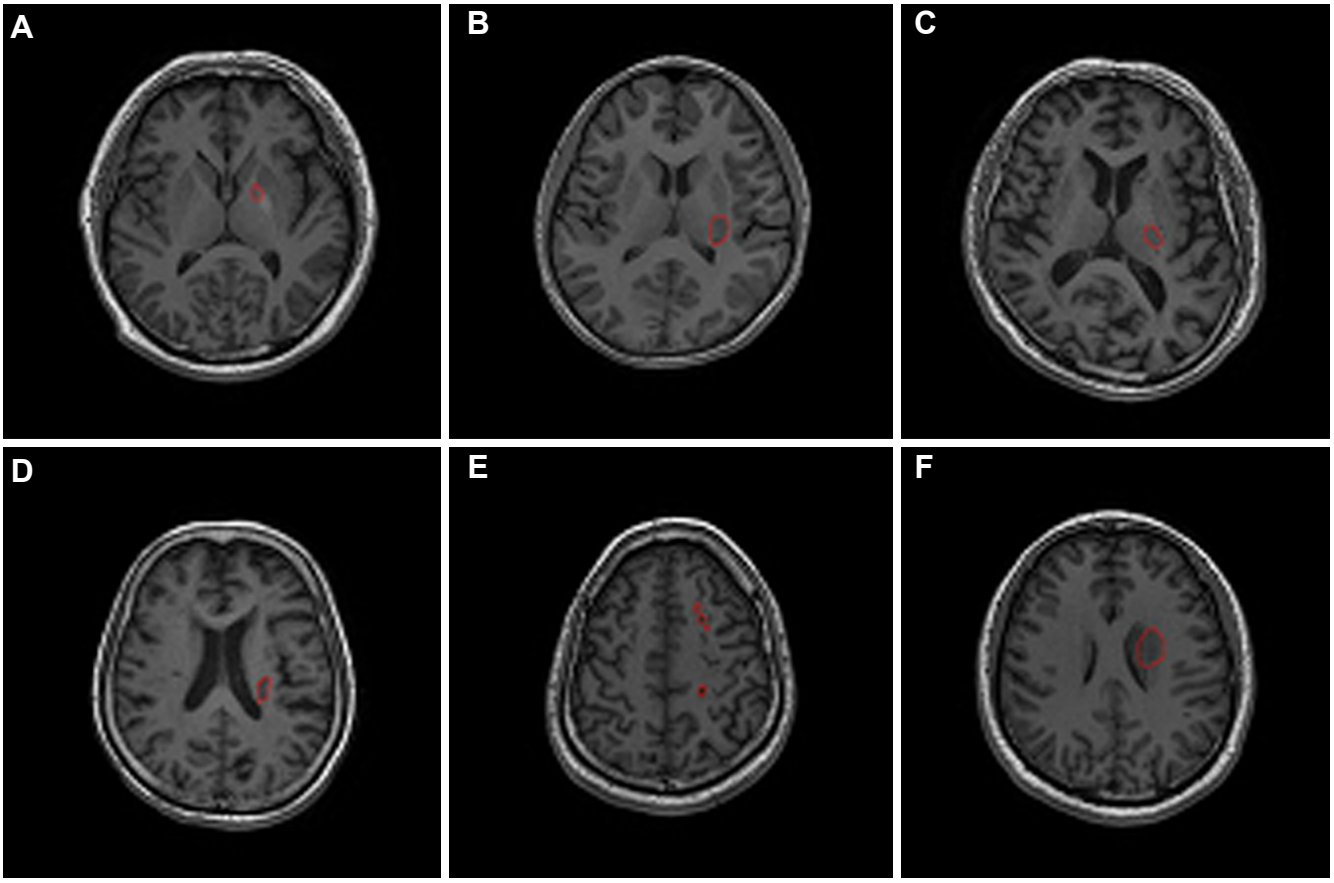

Figure 4 Illustration of lesion location in red for each patient.
A–F indicate the six stroke patients in the experiment. The red circled area in the figure is the position of the lesion.

the subjects were instructed and trained until they fully understood the task and were able to adequately follow the cues and instructions.

Parameters of fMRI and data acquisition

MRI scans were acquired on a 3.0T GE Signaxs scanner (Signa HDxt, GE Healthcare, Fairfield, CT, USA) with a custom-built head coil. A high resolution T1-weighted spoiled grass gradient recalled (SPGR) inversion recovery three-dimensional MRI sequence was performed for each subject with the following parameters: inversion time = 400 ms; repetition time = 6.5 ms; echo time = 2.1 ms; flip angle = 15 degrees; field of view = 25.6 cm; 132 slices in coronal plane; matrix = 256 × 256; number of excitations = 1; acquired resolution = 1.5 mm × 0.9 mm × 1.1 mm.

BOLD signal was collected with a T2-weighted gradient echo spiral in-out pulse sequence[59] with the following parameters: repetition time = 2,000 ms; echo time = 30 ms; flip angle = 90 degrees; 1 interleave; field of view = 24 cm; 64 × 64 matrix. A total of 32 axial slices (5.0 mm thickness, 0 mm skip), which were parallel to the AC-PC line and covered the whole brain, were obtained with a temporal resolution of 2 seconds. For the whole task, 120 images were obtained for a total duration of 4 minutes. Structural and functional scans were acquired in the same scan session.

Preprocessing of fMRI data

The fMRI datasets were preprocessed using SPM8 software (www.fil.ion.ucl.ac.uk/spm). First, the dicom dataset was converted into *.img/*.hdr document. Then, all image volumes were realigned to the mean volume. The subjects whose head displacements were more than 2 mm in the *X*, *Y*, *Z* direction or whose head rotation exceeded 1° were excluded (two patients were excluded for this reason and are not shown in Table 1).

Using the unified segmentation approach[60], functional images were normalized to the MNI template (voxel 3 mm × 3 mm × 3 mm). In order to decrease spatial noise, volumes were smoothed by a 4-mm full-width half maximum Gaussian kernel.

Independent component selection

The procedure of component identification and selection described by Jafri et al.[26] was followed in this study. First, the preprocessed data of all twelve participants (six stroke patients and six healthy controls) were decomposed using the group spatial independent component analysis. Then, 36 independent components were obtained using the GIFT toolbox (http://icatb.sourceforge. net/). The rules of component selection should include the principles described as follows.

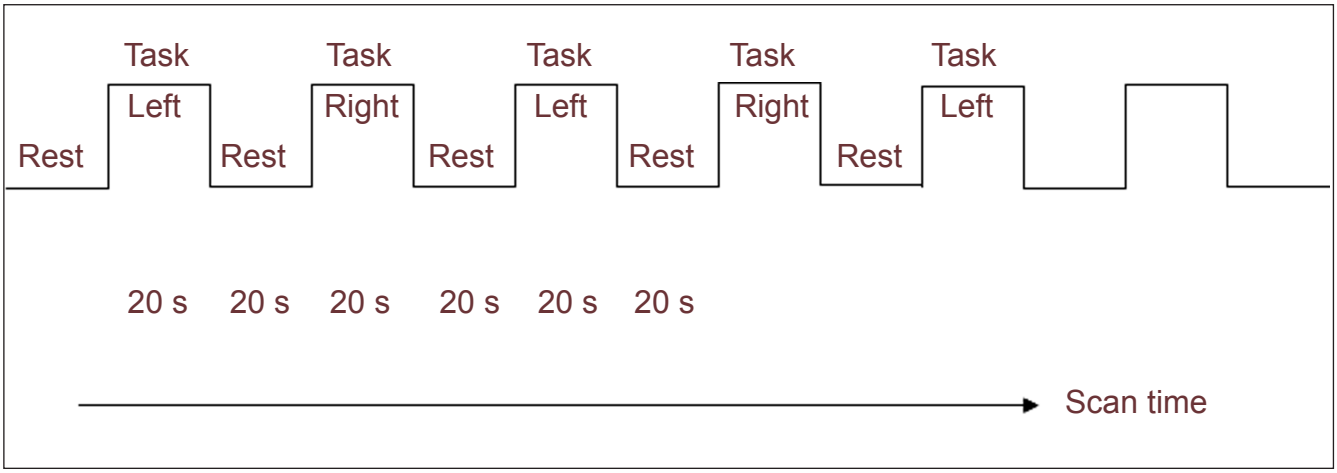

Figure 5 The movement paradigm of the subjects in the magnetic field.
The task occurred in 20-second (20 s) blocks of movements alternated with 20 s intervals as rest periods: Rest – Movements (Left) – Rest – Movements (Right) – Rest – Movements (Left) – Rest – Movements (Right) – Rest – Movements (Left) – Rest – Movements (Right) – Rest.

First, only those components highly correlated to gray matter would be chosen, as the activation of those components always represent significant hemodynamic change[27]. Second, different from prior studies in which M1, S1 and PMd regions of interest were extracted from the template[2], only those components highly correlated to our experimental paradigm would be chosen. In standard general linear model analysis, the canonical hemodynamic response function obtained from SPM8 software was convolved with the experimental paradigm time course to get the BOLD time courses. Then, GIFT was used to obtain the association coefficients between the time courses of components and our experimental paradigm. GIFT is a software package that includes different independent component analysis methods.

In this study, the information algorithm was used in the preprocessing of the fMRI datasets. The independent components whose correlation coefficients were greater than 0.15 between the activation of independent component and the task were chosen.

Establishing the functional network connectivity model

In this study, six spatially independent component analysis components were selected. However, according to their temporal properties, there were correlations between them. A constrained maximal lagged correlation between every pairwise combination of time courses of the independent component analysis components selected was computed by a functional network connectivity toolbox (http://mialab.mrn.org/software).

Theoretically, there should be a maximum of 15 connections among the six components. The statistical analysis was performed using SPSS 13.0 software (SPSS, Chicago, IL, USA). The connections between any two components were first calculated, and then an independent sample *t*-test was used to test the significance of any connection. If the *P* value was < 0.05, the connection was established. The group average of the lag was evaluated for two groups (stroke patients and healthy controls). For more detail on this method, refer to Jafri et al.[26].

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Author contributions: *Li W conceived and designed this study, conducted data analysis, revised the manuscript and guided the study. Li YP conducted data analysis and wrote the manuscript. Zhu WZ collected experimental data. Chen X participated in statistical analysis and manuscript revision. All authors approved the final version of the paper.*

Conflicts of interest: *None declared.*

Peer review: *The present findings confirm that the functional network connectivity of motor areas in stroke patients is more complex than that in healthy controls, and that some damaged connections can be compensated by new indirect connections or circuits produced after stroke. These findings provide theoretical and clinical significance for brain rehabilitation and nerve regeneration after stroke.*

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