Altered Topological Properties of the Cortical Motor-Related Network in Patients With Subcortical Stroke Revealed by Graph Theoretical Analysis

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Abstract: Cerebral neuroplasticity after stroke has been elucidated by functional neuroimaging. However, little is known concerning how topological properties of the cortical motor-related network evolved following subcortical stroke. In the present study, we investigated 24 subcortical stroke patients with only left motor pathway damaged and 24 matched healthy controls. A cortical motor-related network consisting of 20 brain regions remote from the primary lesion was constructed using resting-state functional MRI datasets. We subsequently used graph theoretical approaches to analyze the topological properties of this network in both stroke patients and healthy controls. In addition, we divided the stroke patients into two subgroups according to their outcomes in hand function to explore relationships between topological properties of this network and outcomes in hand function. Although we observed that the cortical motor-related network in both healthy controls and stroke patients exhibited small-world topology, the local efficiency of this network in stroke patients is higher than and global efficiency is lower than those in healthy controls. In addition, striking alterations in the betweenness centrality of regions were found in stroke patients, including the contralesional supplementary motor area, dorsolateral premotor cortex, and anterior inferior cerebellum. Moreover, we observed significant correlations between betweenness centrality of regions and Fugl-Meyer assessment scores. A tendency for the cortical motor-related network to be close to a regular configuration and altered betweenness centrality of regions were demonstrated in patients with subcortical stroke. This study provided insight into functional organization after subcortical stroke from the viewpoint of network topology. *Hum Brain Mapp* 35:3343–3359, 2014. © 2013 Wiley Periodicals, Inc.

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INTRODUCTION

Numerous studies have revealed cerebral reorganization underlying functional recovery after stroke. Through task-based functional neuroimaging, overactivation of the ipsilesional primary sensorimotor cortex (S1M1), bilateral secondary motor cortex, and even certain non-motor areas has been observed [Calautti and Baron, 2003; Chollet et al., 1991; Cramer et al., 1997; Weiller et al., 1993]. Longitudinal studies have indicated less overactivation in a number of primary and non-primary motor regions following functional recovery after stroke [Calautti et al., 2001; Sun et al., 2013; Ward et al., 2003]. Additionally, Marshall et al. [2000] described that the ratio of contralateral to ipsilateral S1M1 activity during movement of the paretic hand significantly increased over time as the paretic hand regained function. Moreover, Sharma et al. [2009] used structural equation modeling to investigate cortical motor network connectivity in patients with subcortical stroke while either imaging or executing a finger-thumb opposition sequence and indicated that neuroplasticity can manifest itself as differences in connectivity among cortical regions remote from the infarct, rather than in the degree of regional activation. Recently, with increasing attention on resting-state functional magnetic resonance imaging (fMRI) [Biswal et al., 1995; Fox and Raichle, 2007], longitudinal changes in resting-state functional connectivity of the ipsilesional primary motor cortex (M1) with contralesional S1M1, frontal cortex, parietal lobe, thalamus, and cerebellum during motor recovery have also been reported [Park et al., 2011]. Our recent studies, using a cross-sectional design, revealed that the two subgroups of subcortical stroke patients with different outcomes in hand function displayed substantially distinct patterns of both cortical functional connectivity and regional homogeneity compared with healthy controls [Yin et al., 2012, 2013a]. However, little is known concerning how the topological properties of the cortical motor-related network evolved in response to subcortical motor pathway stroke, knowledge of which can further help us understand functional reorganization remote from the primary lesion following stroke.

Graph theoretical approaches have been popularly used to investigate topological properties of a remarkable variety of social, economic, and biological networks, which can be represented graphically by a collection of nodes (or vertices) and edges (or links) [Sporns et al., 2000; Sporns and Zwi, 2004; Strogatz, 2001]. Watts and Strogatz [1998] first proposed a mathematical model called the “small-world” network, corresponding to an intermediate state between a regular network (i.e., all nodes are only related

to their nearest neighbors) and a random network (i.e., all nodes are related randomly). Small-world topology can be quantitatively described as having a higher local efficiency and a comparable global efficiency compared with the matched random networks with the same number of nodes, edges, and degree distribution [Achard et al., 2006; Humphries et al., 2006; Latora and Marchiori, 2001; Shu et al., 2011; Watts and Strogatz, 1998]. Therefore, small-world networks are considered to be an efficient connectivity system because the combination of high clustering and short path length confers capability for both specialized (or modular) processing in local neighborhoods and integrated (or distributed) processing over the entire network [Bassett and Bullmore, 2006; Kaiser, 2011; Sporns and Zwi, 2004]. The human brain has been demonstrated to be a large, sparse, and complex network characterized by small-world property at the level of both anatomical (e.g., diffusion tensor imaging or cortical thickness) and functional networks (functional connectivity or effective connectivity) [Bullmore and Sporns, 2009; Gong et al., 2009; He et al., 2007; Liao et al., 2011; Rubinov and Sporns, 2010; Salvador et al., 2005; Sporns et al., 2004; Wang et al., 2010a].

In recent years, altered topological properties of brain networks have been shown in a wide range of psychiatric or neurological disorders by graph theoretical approaches [Liao et al., 2010; Liu et al., 2008; Supekar et al., 2008; Wang et al., 2009b]; however, these approaches mainly focused on the whole brain network (e.g., functional connectivity between 90 regions from the AAL template). By contrast, researchers have increasingly focused on a specific functional network to characterize the sensitivity of the neuronal network in response to development [Fair et al., 2008, 2009] and diseases [Church et al., 2009; De Vico Fallani et al., 2007], leading to better understanding of pathophysiological changes. Regarding stroke studies, one pilot study [Wang et al., 2010bb] with a longitudinal design employed graph theory to analyze dynamic functional reorganization of the motor execution network, which was constructed by functional connectivity between 21 regions of interest (ROIs) in patients with subcortical stroke. However, the motor execution network included subcortical ROIs (i.e., basal ganglia and thalamus) that were directly involved in the infarct in a portion of stroke patients, possibly influencing their results, due to heterogeneity of the network. In addition, the frontal cortex has been demonstrated to play an important role in functional reorganization after stroke [Park et al., 2011; Sharma et al., 2009; Ward et al., 2003; Yin et al., 2012], which was not addressed in that study. Moreover, topological properties of the motor execution network varying with the threshold

of sparsity were not well-studied. Previous studies commonly described topological properties of the brain network as a function of cost (sparsity or degree) [Achard and Bullmore, 2007; He et al., 2008; Wu et al., 2012] or correlation threshold [Achard et al., 2006; He et al., 2007] because there currently is no definitive way to select a single threshold.

In our study, we mainly focused on cortical motor-related regions remote to the site of the lesion. Thus, we can better control homogeneity of the network, which was not directly attacked by lesion in any stroke patient. We subsequently used graph theoretical approaches to investigate topological properties of the cortical motor-related network over a range of thresholds in both stroke patients and healthy controls. In addition, we divided the stroke patients into two subgroups according to their outcomes in hand function because relationships between topological properties of the cortical motor-related network and outcomes in hand function remain unclear. We hypothesized that topological properties of the cortical motor-related network were altered in subcortical stroke patients compared with healthy controls. Moreover, the differences in topological properties of the cortical motor-related network can be displayed between the two subgroups.

MATERIALS AND METHODS

Participants

We collected 25 subcortical stroke patients with only left motor pathway damage and 24 age-, gender-, and handedness-matched healthy controls. Inclusion criteria were as follows: (1) first-onset stroke, (2) pure motor deficits, (3) right-handedness, (4) sufficient cognitive abilities (Mini-Mental State Examination [Folstein et al., 1975], MMSE > 24), (5) examination time greater than 3 months from stroke onset, and (6) aged 45 to 80 years old. Exclusion criteria were as follows: (1) contraindication to MRI, (2) quadriplegia, (3) prior history of neurological and psychiatric disorders, (4) diabetes, (5) previous hand dysfunctions, and (6) severe aphasia, neglect and sensory disturbances. Their clinical characteristics and demographic data are summarized in Table I. The T2-weighted images show the lesion with the maximum area in each stroke patient (Fig. 1).

We also divided the stroke patients into two subgroups (partially paralyzed hands (PPH) group, consisting of 12 patients (case 01–12 in Table I)), and completely paralyzed hands (CPH) group, consisting of 12 patients (case 13–24 in Table I)). We identified CPH and PPH using Paralyzed Hand Function Assessment [Yin et al., 2012], which involves five practical actions of hand in daily life. All those who could not complete any action were regarded as CPH, and those who could complete at least one of the five actions were regarded as PPH.

Data Acquisition

All images were acquired on a Siemens Trio 3.0 Tesla MRI scanner (Siemens, Erlangen, Germany) at the Shanghai Key Laboratory of Magnetic Resonance, East China Normal University. The protocol for this prospective study was approved by the Institutional Ethics Committee of East China Normal University (Shanghai, China), and all participants or their guardians signed informed written consent. Resting-state fMRI data of the whole brain were acquired using an echo-planar imaging (EPI) sequence: 30 axial slices, thickness = 4 mm, gap = 0.8 mm, matrix = 64×64 , repetition time = 2,000 ms, echo time = 30 ms, flip angle = 90° , and field of view = $220 \text{ mm} \times 220 \text{ mm}$. T1-weighted images covering the entire brain were obtained in a sagittal orientation employing a magnetization-prepared rapid gradient echo sequence (MPRAGE): 192 slices per slab, thickness = 1 mm, gap = 0.5 mm, repetition time = 1,900 ms, echo time = 3.42 ms, inversion time = 900 ms, field of view = $240 \text{ mm} \times 240 \text{ mm}$, flip angle = 9° , and matrix = 256×256 . To identify the location and size of the lesion, T2-weighted images were also collected using a turbo-spin-echo sequence: 30 axial slices, thickness = 5 mm, no gap, repetition time = 6,000 ms, echo time = 93 ms, field of view = $220 \text{ mm} \times 220 \text{ mm}$, flip angle = 120° , and matrix = 320×320 . During EPI data acquisition, the participants were instructed to remain awake, relaxed with their eyes closed, and motionless without thinking about anything in particular. Each scan lasted for 8 min and 6 s; however, the first 6 s was consumed by a dummy scan. Thus, we collected 240 image volumes in total.

Lesion Volume

Lesion volume of each patient was determined by an experienced neuroradiologist who manually outlined the signal abnormality on T2-weighted images slice by slice using the software MRIcron (www.mricro.com). And, the lesion overlap across stroke patients is also exhibited (Fig. 2).

Preprocessing of the Resting-State fMRI Data

Preprocessing of the resting-state fMRI data was performed using Statistical Parametric Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>). We discarded the first 10 volumes of the dataset for each participant to allow for magnetization equilibrium, leaving 230 volumes for further analysis. The images were corrected for delay in slice acquisition and were later co-registered to the first image for correction of rigid-body head movement. Excessive motion was defined as more than 2.5 mm of translation or greater than a 2.5° rotation in any direction. One stroke patient was excluded due to excessive motion. Thus, there were 24 patients included in the final analysis. Subsequently, the individual three-dimensional T1-weighted

TABLE I. Clinical and demographic data of 24 stroke patients enrolled in this study

Case	Gender	Age (yr)	Location of lesion	Time poststroke (mo)	Lesion volume (ml)	FMA score (hand + wrist)
01	M	56	L,IC,BG,Th	14	25.1	23
02	M	60	L,IC,Th ^a	53	35.3	12
03	F	48	L,IC,BG	23	9.4	6
04	M	76	L,IC	21	62.2	22
05	M	60	L,IC,BG	36	16.5	6
06	M	71	L,IC,Th ^a	22	17.6	11
07	M	63	L,IC,BG,Th	3	22.1	13
08	M	54	L,IC,Th ^a	3	12.4	23
09	M	60	L,BG,Th ^a	11	27.0	23
10	M	65	L,IC,Th	12	8.9	23
11	M	53	L,IC,BG,Th ^a	22	125.1	15
12	M	65	L,IC,BG ^a	6	81.8	20
13	M	62	L,BG,IC,Th	6	19.2	4
14	M	56	L,IC	7	10.6	6
15	M	56	L,BG,IC,Th ^a	21	86.9	1
16	M	57	L,IC,Th	19	23.7	0
17	F	75	L,IC,CR	24	7.8	4
18	M	63	L,BG,IC,Th ^a	16	61.5	1
19	F	65	L,IC,Th	17	29.6	1
20	F	68	L,BG,IC,Th ^a	62	25.5	0
21	M	68	L,IC,Th ^a	47	32.7	1
22	M	53	L,BG,IC,Th ^a	86	55.5	1
23	F	50	L,BG,IC,Th ^a	13	18.7	0
24	M	61	L,IC,BG	6	9.7	4

^aThe character of the lesion is hemorrhage, others are ischemia.

M = male; F = female. L = left; R = right; BG = basal ganglia; IC = internal capsule; Th = thalamus; CR = coronal radiata; FMA = Fugl-Meyer Assessment.

image was co-registered to the mean functional image, which was generated by SPM in the preprocessing step of alignment, after motion correction using a linear transformation. Each co-registered image was then segmented into gray matter, white matter, and cerebrospinal fluid using a unified segmentation algorithm [Ashburner and Friston, 2005]. After motion correction, the functional images were spatially normalized to the Montreal Neurological Institute (MNI) space and resampled to 3 mm isotropic voxels using the normalization parameters estimated during unified segmentation. Finally, the normalized images were spatially smoothed using an isotropic Gaussian filter at full width at a half maximum (FWHM) of 4 mm.

Regions of Interest in the Cortical Motor-Related Network

In our study, we mainly focused on the cortical motor-related network remote from the primary lesion. We selected 17 cortical ROIs (including the cerebellum) from the motor execution network proposed by a previous study [Wang et al., 2010b]. To eliminate potential confusion from the lesion, four subcortical ROIs (bilateral basal ganglia and thalamus) in the motor execution network

were excluded in our study. A previous study [Park et al., 2011] and our recent study [Yin et al., 2012] have demonstrated altered organization of connectivity of the middle frontal gyrus in patients with subcortical stroke, reflecting the role of the frontal lobe in higher order planning of movement. Therefore, bilateral middle frontal gyri were recruited. In addition, we added a ROI from the ipsilesional postcentral gyrus because dysfunctional connectivity of the ipsilesional postcentral gyrus with both ipsilesional M1 and contralesional M1 were observed in patients with subcortical stroke [Yin et al., 2012]. Thus, a total of 20 cortical ROIs remote from the primary lesion were obtained by creating 10-mm diameter spheres around the predefined MNI coordinates, and the node distribution of the cortical motor-related network was visualized with BrainNet Viewer [Xia et al., 2013] (Fig. 3 and Table II).

Construction of the Cortical Motor-Related Network

Following preprocessing, the smoothed images were further processed using the free software Resting-State fMRI Data Analysis Toolkit (REST, <http://restfmri.net>)

Figure 1.

T2-weighted images show lesion (red arrow) of each stroke patient at the axial cross-section with the largest area. Arabic numbers denote the case numbers of the stroke patients. L = left, R = right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

[Song et al., 2011]. First, we removed the linear trend and applied the temporal filter (0.01–0.08 Hz) to reduce low-frequency drift and high-frequency respiratory and cardiac noise [Fox and Raichle, 2007]. Second, the time series of all voxels in each predefined ROI were extracted and averaged to obtain a representative mean time series. Several nuisance covariates, including the signals from white matter, cerebrospinal fluid, and global mean for the entire brain, as well as six parameters of head motion (three for translation and three for rotation), were removed from the mean time series using a multiple linear regression model. The residuals of this regression were later used to substitute for the raw mean time series of the corresponding regions. Third, Pearson's correlation analysis was performed between the residual time series of all possible pairs of the 20 ROIs, to produce a 20×20 symmetric correlation matrix (i.e., functional connectivity) for each subject. Finally, the resulting correlation coefficients were transformed into z-scores using Fisher's z-transformation so that their distributions could better

satisfy normality [Hampson et al., 2002]. Mean z-score matrices for healthy controls and stroke patients were shown in Figure 4.

For threshold selection, a previous study [He et al., 2008] suggested that, when the same correlation threshold was applied to the correlation matrices of patients and controls groups, the resulting graphs would comprise a different number of edges because of discrepancies in the low-level correlations. Thus, between-group differences in network parameters would not purely reflect the alterations in topological organization. To control this effect, the network sparsity (i.e., connection density) defined as the number of existing connections divided by all possible connections, was commonly used as a threshold to produce a graph, ensuring that both patients and controls groups have the same number of edges or wiring cost [Achard and Bullmore, 2007; He et al., 2008; Stam et al., 2007; Wang et al., 2009b]. Following previous studies, we adopted the network sparsity as a threshold to yield a binary graph. Moreover, because there is currently no definitive way to select a

Figure 2.

Lesion overlap across stroke patients. After spatial normalization of T2-weighted images to the MNI space, individual lesion masks were drawn manually using MRIcron. Then, the lesion overlap was obtained by averaging the individual lesion masks, and superimposed on a canonical template as provided by MRIcron. Color

coding indicates the percentage of lesion overlap. Z-axis from $Z = -1$ to $Z = 41$ in MNI coordinates, with an incremental interval of 5. R = right, L = left, MNI = Montreal Neurological Institute. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

single threshold, we therefore investigated topological properties of the cortical motor-related network over a range of sparsity. We identified the range of sparsity as follows.

First, to assure that functional connectivity actually existed between the ROIs, we performed a two-tailed one-sample t -test ($P < 0.05$, Bonferroni corrected) on the correlation

Figure 3.

The node distribution of the cortical motor-related network was visualized with BrainNet Viewer (<http://www.nitrc.org/projects/bnv/>) [Xia et al., 2013]. A total of 20 ROIs remote from the primary lesion were selected for constructing the cortical motor-related network. Each ROI was obtained by a 10-mm diameter

sphere with predefined MNI coordinates in Table II. We carefully examined the location of ROIs and no overlap was observed between any pair of ROIs. ROIs = regions of interest, MNI = Montreal Neurological Institute. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE II. Regions of interest in the cortical motor-related network

ID	Regions	Abbreviation	Side	MNI coordinate		
				<i>x</i>	<i>y</i>	<i>z</i>
1	Middle frontal cortex	MFC	L	-39	18	57
2	Middle frontal cortex	MFC	R	30	33	48
3	Supplementary motor area	SMA	L	-5	-4	57
4	Supplementary motor area	SMA	R	5	-4	57
5	Dorsolateral premotor	PMd	L	-22	-13	57
6	Dorsolateral premotor	PMd	R	28	-10	54
7	Ventrolateral premotor	PMv	L	-49	-1	38
8	Ventrolateral premotor	PMv	R	53	0	25
9	Primary motor cortex	M1	L	-38	-22	56
10	Primary motor cortex	M1	R	38	-22	56
11	Postcentral gyrus	PCG	L	-37	-34	53
12	Postcentral gyrus	PCG	R	37	-34	53
13	Superior parietal lobule	SPL	L	-22	-62	54
14	Superior parietal lobule	SPL	R	16	-66	57
15	Superior cerebellum	SCb	L	-25	-56	-21
16	Superior cerebellum	SCb	R	16	-59	-21
17	Dentate nucleus	DN	L	-28	-55	-43
18	Dentate nucleus	DN	R	19	-55	-39
19	Anterior inferior cerebellum	AICb	L	-22	-45	-49
20	Anterior inferior cerebellum	AICb	R	16	-45	-49

The regions were selected from a previous study (Wang *et al.*, 2010b) and our recent study (Yin *et al.*, 2012).

matrices of all subjects and found 87 significant connections. According to the formula of sparsity, $K_{\text{cost}} = E/(N(N-1)/2)$ (where E is the number of existed edges, and N is the number of nodes in a graph), we identified the sparsity $K_{\text{cost}} = 0.46$ as the upper bound value. Second, previous studies have demonstrated that brain functional networks have economic small-world properties at relatively low cost (or sparsity) [Achard and Bullmore, 2007; Bassett and Bullmore, 2006]. However, the minimum sparsity must also assure that each network is fully connected with N nodes. Therefore, the degree K of the resulting graph must be more than $\ln(N)$ (i.e., $K > \ln(20) \approx 3$ in our current study) [Achard *et al.*, 2006; Watts and Strogatz, 1998]. Here, degree K of a graph is the average number of edges per node. Thus, the lower bound of sparsity should be $K_{\text{cost}} = N \times K/(N(N-1)/2) \approx 0.32$. To summarize, we identified the sparsity $0.33 \leq K_{\text{cost}} \leq 0.46$ as a range of the threshold, with an incremental interval of 0.01, to construct cortical motor-related networks.

Graph Theoretical Analysis

An $N \times N$ ($N = 20$ in the present study) binary graph G , consisting of nodes (brain ROIs) and edges (functional connectivity) can be constructed by applying a threshold of

sparsity. We defined subgraph G_i as the set of nodes that are the direct neighbors of the i th node (i.e., directly connected to the i th with an edge). The degree of the i th node (K_i) is defined as the number of nodes in the subgraph G_i . The total number of edges in a graph, divided by the maximum possible number of edges is called the cost of the network:

$$K_{\text{cost}} = \frac{1}{N(N-1)} \sum_{i \in G} K_i$$

which measures sparsity or how expensive it is to build the network.

We employed a network efficiency measure to quantify the small-world property of the cortical motor-related network. This efficiency metric can deal with disconnected graphs and provides a clear physical meaning for the topological characterization of the networks. The global efficiency (GE) of graph G can be calculated as [Latora and Marchiori, 2001]:

$$GE = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{L_{ij}},$$

where L_{ij} is the shortest path length between node i and j in graph G (i.e., the minimal number of edges that has to be traveled to go from the node i to j).

The local efficiency (LE) of graph G is measured as [Latora and Marchiori, 2001]:

$$LE = \frac{1}{N} \sum_{i \in G} GE(G_i)$$

where G_i denotes the subgraph composed of the nearest neighbors of node i .

Practically, a network can be categorized as small-world network if GE is slightly less than and LE is much greater than the matched random networks with the same number of nodes, edges, and degree distribution. For comparison purposes, we generated random networks using the random rewiring procedure that preserves degree distribution as the real network [Maslov and Sneppen, 2002]. Thus, a small-world network should meet the following criteria: $LE(\text{real})/LE(\text{random}) > 1$, and $GE(\text{real})/GE(\text{random}) \approx 1$ [Wang *et al.*, 2009a]. To explore small-world efficiency, we also calculated the normalized $GE = GE(\text{real})/GE(\text{random})$ and normalized $LE = LE(\text{real})/LE(\text{random})$.

In the present study, we were also interested in nodal characteristics of the cortical motor-related network. To this end, we considered betweenness centrality of nodes, which is defined as the number of shortest paths between any two nodes that run through node i [Freeman, 1977]:

$$B_i = \sum_{j,k \in N, j \neq k} \frac{n_{j,k}(i)}{n_{j,k}}$$

where $n_{j,k}(i)$ is number of shortest paths between nodes j and k that run through node i and $n_{j,k}$ is all shortest paths

Figure 4.

Mean z-score matrices for healthy controls and stroke patients. Each figure shows a 20×20 square matrix, where the x and y axes correspond to the ROIs listed in Table II, and where each entry indicates the mean strength of the functional connectivity between each pair of ROIs. The diagonal running from the upper left to the lower right is intentionally set to zero. The z score of the functional connectivity is indicated with a gray bar. ROI = region of interest.

between nodes j and k . We then calculated the normalized betweenness centrality $BC_i = B_i / \langle B \rangle$, where $\langle B \rangle$ is the averaged betweenness across all nodes [He et al., 2008]. As a global centrality measure, BC_i captures the influence of a node over information flow between other nodes in the network.

Statistical Analysis

We performed statistical comparisons of GE, LE, normalized GE, normalized LE, and BC_i , between stroke patients and healthy controls using a general linear model with considering age and gender as covariates for each metric over a range of sparsity. Because the comparisons of betweenness centrality metric were performed on the 20 brain regions separately, corrections for multiple comparisons were carried out ($P < 0.05$, FDR corrected). In addition, the comparison of functional connectivity between stroke patients and healthy controls was performed using a two-tailed two-sample t -test ($P < 0.01$).

To explore whether the differences in topological properties of the cortical motor-related network can be displayed between the two subgroups, we also performed statistical comparisons of GE, LE, normalized GE, normalized LE, and BC_i between the two subgroups using a general linear model with considering age, gender, and lesion volume as covariates for each metric over a range of sparsity, as well as between each subgroup with healthy controls using a general linear model with considering age

and gender as covariates. We used a statistical significance level of $P < 0.05$.

In addition, to explore the relationships between topological properties of the cortical motor-related network and clinical outcomes in hand function, we further performed a two-tailed Spearman correlation (nonparametric) between topological properties (GE, LE, normalized GE, normalized LE, and BC_i) and FMA scores (hand + wrist) over a range of sparsity. We used a statistical significance level of $P < 0.05$.

RESULTS

Clinical Statistics

We found no significant differences between stroke patients and healthy controls in age (patients, mean $\pm$ SD = 61.0 ± 7.3 years; healthy controls, mean $\pm$ SD = 61.6 ± 9.8 years; $P > 0.1$, was obtained by two-tailed two-sample t -test) and gender (patients, 19 males; healthy controls, 14 males; $P > 0.1$, obtained by Pearson χ^2 analysis). Between the two subgroups of stroke patients, no significant differences were observed in age (PPH, mean $\pm$ SD = 60.9 ± 7.8 years; CPH, mean $\pm$ SD = 61.2 ± 7.2 years; $P > 0.1$), gender (PPH, 11 males; CPH, 8 males; $P > 0.1$), time post-stroke (PPH, mean $\pm$ SD = 18.8 ± 14.5 months; CPH, mean $\pm$ SD = 27.0 ± 25.1 months; $P > 0.1$), and lesion volume (PPH, mean $\pm$ SD = 36.9 ± 35.4 ml; CPH, mean $\pm$ SD = 31.8 ± 24.2 ml; $P > 0.1$). Instead, we found a significant difference in FMA scores (hand + wrist) between

Figure 5.

Mean local efficiency (A) and normalized local efficiency (B) of the cortical motor-related network as a function of sparsity for stroke patients (red circles) and healthy controls (green squares). Error bars correspond to standard error of the mean. Black stars indicate where the difference between the two groups is statistically significant ($P < 0.05$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Mean global efficiency (C) and normalized global efficiency (D) of the cortical motor-related network as a function of sparsity for stroke patients (red circles) and healthy controls (green squares). Error bars correspond to standard error of the mean. Black stars indicate where the difference between the two groups is statistically significant ($P < 0.05$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the two subgroups (PPH, mean $\pm$ SD = 16.4 ± 6.7 ; CPH, mean $\pm$ SD = 1.9 ± 2.0 ; $P < 0.01$).

Direct Comparisons of Topological Properties between Stroke Patients and Healthy Controls

We observed that the normalized local efficiency is much greater than and normalized global efficiency is slightly less than 1 at a wide range of sparsity in both healthy controls and stroke patients, indicating the local efficiency is much higher than and global efficiency is slightly lower than the matched random networks. Furthermore, we found that both the local efficiency and nor-

malized local efficiency are higher in stroke patients than in healthy controls and reach statistical significance at relatively low thresholds of sparsity. In contrast, both the global efficiency and normalized global efficiency in stroke patients are lower than those in healthy controls, however, both coefficients do not reach the level of statistical significance (Fig. 5).

The betweenness centrality, a measure of nodal characteristics of a network, was also calculated for all the nodes in the cortical motor-related network. We found that the betweenness centrality of the contralesional SMA and anterior inferior cerebellum are significantly increased in stroke patients compared with healthy controls. By contrast, the betweenness centrality of the contralesional dorsal premotor

Figure 6.

Mean betweenness centrality of regions as a function of sparsity for stroke patients (red circles) and healthy controls (green squares). Error bars correspond to standard error of the mean. Black stars indicate where the difference between the two groups is statistically significant ($P < 0.05$, FDR corrected). R =

right (contralateral), SMA = supplementary motor area, PMd = dorsolateral premotor cortex, AICb = anterior inferior cerebellum. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

cortex was significantly decreased in stroke patients compared with that in healthy controls (Fig. 6).

Altered Functional Connectivity in Stroke patients Compared With Healthy Controls

Several altered functional connectivity between the ROIs were detected in stroke patients compared with that in healthy controls. Significantly increased connectivity was found between the left middle frontal cortex and right anterior inferior cerebellum and between the left ventrolateral premotor cortex and left primary motor cortex, left postcentral gyrus, and right postcentral gyrus. In addition, we observed significantly decreased connectivity between the left middle frontal cortex and left ventrolateral premotor cortex; between the right middle frontal cortex and left

primary motor cortex; and between the left postcentral gyrus and right postcentral gyrus (Fig. 7 and Table III).

Topological Properties for the Two Subgroups of Stroke Patients

Although no significant differences were found in both local efficiency and global efficiency between the two subgroups, the two subgroups showed remarkable differences in betweenness centrality of the regions. We found that the betweenness centrality of the contralateral SMA and anterior inferior cerebellum in both CPH and PPH groups was greater than that in healthy controls, and the betweenness centrality in the CPH group was the greatest. Inversely, the betweenness centrality of the contralateral dorsolateral premotor cortex in both the CPH and PPH

Figure 7.

Altered functional connectivity in stroke patients compared with healthy controls. Both significantly increased functional connections (yellow lines, row 1) and decreased functional connections (blue lines, row 2) were observed ($P < 0.01$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

groups were smaller than those in healthy controls, and the betweenness centrality in the CPH group was the smallest. The betweenness centrality of the ipsilesional middle frontal cortex and superior parietal lobule in CPH group was greater than observed that in healthy controls. By contrast, this centrality is smaller in the PPH group than in healthy controls. The betweenness centrality of the ipsilesional dorsolateral premotor cortex in the CPH group is smaller than that in both the PPH group and healthy

controls, and it is similar between the PPH group and healthy controls (Fig. 8).

Correlation between Topological Properties of the Cortical Motor-Related Network and Clinical Variable

Correlation analysis between topological properties and FMA scores (hand + wrist) was performed over a range

TABLE III. Altered cortical connectivity in subcortical stroke patients compared with healthy controls ($P < 0.01$)

Region	Region	<i>t</i> -value	<i>P</i> value	Signs
Increased functional connectivity				
Left middle frontal cortex	Right anterior inferior cerebellum	4.39	<0.001	(-, +)
Left ventrolateral premotor cortex	Left primary motor cortex	2.87	0.006	(+, +)
Left ventrolateral premotor cortex	Left postcentral gyrus	2.94	0.005	(+, +)
Left ventrolateral premotor cortex	Right postcentral gyrus	2.91	0.005	(+, +)
Decreased functional connectivity				
Left middle frontal cortex	Left ventrolateral premotor cortex	-2.75	0.008	(+,-)
Right middle frontal cortex	Left primary motor cortex	-3.34	0.002	(-,-)
Left postcentral gyrus	Right postcentral gyrus	-3.23	0.002	(+, +)

The signs denote the connectivity changes from positive (or negative) to positive (or negative) correlations. For example, (-, +) denotes the connectivity changes from negative to positive correlations after stroke.

Left = ipsilesional, right = contralesional.

Figure 8.

Mean betweenness centrality of regions as a function of sparsity for CPH patients (red asterisks), PPH patients (blue circles), and healthy controls (green squares). Error bars correspond to standard error of the mean. Black, carmine, and cyan stars indicate where the difference between CPH and PPH patients, between CPH patients and HCs, and between PPH patients and

HCs is statistically significant respectively ($P < 0.05$). SMA = supplementary motor area, PMd = dorsolateral premotor cortex, AICb = anterior inferior cerebellum, MFC = middle frontal cortex, SPL = superior parietal lobule, L = left (ipsilesional), R = right (contralesional). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of sparsity in stroke patients. We observed a significant negative correlation between the betweenness centrality of the contralesional SMA, contralesional anterior inferior cerebellum, ipsilesional middle frontal cortex, and ipsilesional superior parietal lobule and FMA scores. By contrast, a significant positive correlation was found between the betweenness centrality of the bilateral dorsolateral premotor cortex and FMA scores (Fig. 9). No significant correlations were found between both local efficiency and global efficiency and FMA scores.

DISCUSSION

In this study, we employed graph theoretical approaches to investigate the topological properties of the cortical motor-related network in patients with subcortical stroke, and all of the ROIs in this network were remote from the primary lesion. We adopted a cross-sectional design, and many confounding factors (e.g., age, gender, handedness, and location, side, and size of lesion) were

well-controlled. The altered topological properties of the cortical motor-related network can be considered to be cortical reorganization in response to the subcortical motor pathway stroke. To comprehensively investigate the topological properties of the cortical motor-related network, we analyzed multiple frequently used network parameters (i.e., global efficiency, local efficiency, and betweenness centrality) over a range of sparsity, reflecting the capability of a network in both specialized (or modular) processing in local neighborhoods and integrated (or distributed) processing over the entire network, as well as the hubs of regions [Bassett and Bullmore, 2006; He et al., 2008; Kaiser, 2011; Sporns and Zwi, 2004; Watts and Strogatz, 1998].

Direct Comparisons of Small-World Efficiency Between Stroke Patients and Healthy Controls

In an experimental stroke study, van Meer et al. found the bilateral cortical sensorimotor network shifts from subacutely increased small-worldness toward a baseline

Figure 9.

Correlation between betweenness centrality of regions and FMA scores over a range of sparsity. r denotes correlation coefficient. Black stars indicate where the correlation is statistically significant ($P < 0.05$). SMA = supplementary motor area, PMd = dorsolateral premotor cortex, AICb = anterior inferior cere-

bellum, MFC = middle frontal cortex, SPL = superior parietal lobule, L = left (ipsilesional), R = right (contralesional). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

small-world topology, optimal for global information transfer and local processing at chronic stages [van Meer et al., 2012]. In our study, we focused on the cortical motor-related network that was not directly attacked by lesions and found the local efficiency is much higher than and global efficiency is slightly lower than the matched random networks at a wide range of sparsity in both healthy controls and stroke patients. This result suggests that the cortical motor-related network in both healthy controls and stroke patients exhibits economical small-world topology. Furthermore, we observed that the local efficiency in stroke patients is significantly higher than that observed in healthy controls at relatively low thresholds of sparsity. Instead, the global efficiency in stroke patients is slightly lower than that in healthy controls. This finding suggests that the configuration of the cortical motor-related network shifts toward a configuration of regular network. Previous study indicated that the higher the local efficiency of a network, the larger fault tolerance was the network facing the external attack [Latora and Marchiori, 2001]. We can interpret that the higher local efficiency of the cortical motor-related network observed in stroke patients might be a kind of defense mechanism

in response to the subcortical motor pathway deficits. Furthermore, De Vico Fallani et al. [2007] compared the cortical motor networks in patients with spinal cord injury with those in healthy controls. Significant increases in the local efficiency but not in the global efficiency were shown in patients with spinal cord injury compared with healthy controls, suggesting that the cortical motor networks in patients with spinal cord injury tend to have regular configuration. Our finding not only further validates previous reports regarding the existence of cortical reorganization following stroke but also is compatible with previous study on the shift of network configuration due to remote effect of lesions on brain functional networks.

By contrast, Wang et al. [2010b] revealed a significant decrease in the normalized clustering coefficient γ during the recovery process but not in the normalized path length λ following stroke, suggesting that the motor execution network in stroke patients tend to have random configuration. Moreover, a significant correlation was found between restoration of function and γ values over time, indicating that the restoration of function was accompanied by a shift toward a nonoptimal network configuration. It is possible that the apparent discrepancy of the

shift of network configuration is attributed to different selections of ROIs. In a study by Wang et al., the motor execution network included subcortical ROIs (i.e., basal ganglia and thalamus), which were directly damaged by lesions in a portion of subcortical strokes. Thus, the tendency for the motor execution network to be a non-optimal network configuration might occur as a result of a direct attack from a lesion. However, all ROIs selected in our study and De Vico Fallani et al.'s study [2007] for constructing the cortical motor-related network were remote from the primary lesion. Therefore, it is very important to consider whether or not a network is directly attacked by lesions and to well control the homogeneity of networks across subjects. Our results, showing reorganization of the cortical motor-related network that is remote from the primary lesion, can further complement Wang et al.'s findings.

Altered Functional Connectivity in the Cortical Motor-Related Network After Subcortical Stroke

A number of studies have reported disruptions in functional connections to areas remote to the site of the lesion following stroke. For instance, previous study [Carter et al., 2010] has demonstrated that disruption of inter-hemispheric functional connectivity in the somatomotor network was significantly correlated with upper extremity impairment after stroke. However, intrahemispheric functional connectivity within intact or damaged hemispheres was not correlated with performance in the somatomotor network. In addition, Park et al. revealed that stroke patients displayed decreased connectivity of the ipsilesional M1 with the contralesional middle frontal gyrus, and the connectivity showed positive correlation with later motor improvement [Park et al., 2011]. Corresponding to previous studies, we found decreased connectivity between the ipsilesional M1 and contralesional middle frontal gyrus and between ipsilesional postcentral gyrus and contralesional postcentral gyrus in stroke patients. Our result further validates disruption of inter-hemispheric functional connectivity remote from the primary lesion.

Meanwhile, we observed increased local connectivity of the ipsilesional ventrolateral premotor cortex with ipsilesional M1 and bilateral postcentral gyri in stroke patients. It is possible that the increased local connections contribute to the enhanced local efficiency observed in stroke patients. Particularly, we observed an increased long-range connection between the ipsilesional middle frontal gyrus and contralesional anterior inferior cerebellum. Previous studies have demonstrated that small-world topology is an attractive model for brain network organization because it could support both segregated/modular and integration/distributed information processing and confer resilience against pathological attack [Achard et al., 2006; Bassett and Bullmore, 2006; Sporns and Zwi, 2004]. Moreover, Achard et al. [2006] and Achard and Bullmore [2007] sug-

gested that economical models of brain function might have been competitively selected to minimize cost efficiency and parallel information processing in large-scale networks. Not only with the selection pressures driving brain evolution has been minimization of costs, favoring a high density of short-range local connections but also the expectation to favor selection of a few long-range connections mediating efficient information transfer between spatial distributed regions. Therefore, we speculate that preservation of high global efficiency of the cortical motor-related network in stroke patients might be attributed to the increased long-range connection between the ipsilesional middle frontal gyrus and contralesional anterior inferior cerebellum, although decreased inter-hemispheric connections were shown.

Importantly, although existence of functional connectivity network related to motor function in the resting brain, it should be noted that the functional connectivity during resting state can considerably differ from that during movement state. For example, previous study [Jiang et al., 2004] has demonstrated that the connectivity degree of contralateral M1 and premotor cortex dramatically increased during movement state compared with resting state, whereas the connectivity degree of contralateral superior cerebellum had a significant decrease. Moreover, the connectivity of cortical motor network is also modulated by different motor tasks (e.g., motor imagery vs. motor execution) and conditions (e.g., stroke patients vs. healthy controls) [Sharma et al., 2009].

Direct Comparisons of Betweenness Centrality of Regions Between Stroke Patients and Healthy Controls

The regions with high value of betweenness centrality are considered hubs of a network, and group differences in betweenness centrality of nodes reflect effects of the disease on the global roles of regions in the network [He et al., 2008; Rubinov and Sporns, 2010]. Previous studies have demonstrated that the pre-existing uncrossed corticospinal tract pathways originating from the contralesional hemisphere were recruited to compensate for the damage to the crossed motor pathways [Ago et al., 2003; Thomas et al., 2005]. Moreover, increased recruitment of the contralesional hemisphere was most commonly observed in patients following stroke [Chollet et al., 1991; Gerloff et al., 2006; Tombari et al., 2004; Ward et al., 2003; Weiller et al., 1992]. Consistently, we found that the betweenness centrality of the contralesional SMA and anterior inferior cerebellum in stroke patients was significantly greater than that in healthy controls. Furthermore, dramatically negative correlations were observed between the betweenness centrality of the contralesional SMA and anterior inferior cerebellum and FMA scores. This finding indicates that the contralesional SMA and anterior inferior cerebellum play a key role in reorganization of the cortical motor-

related network in response to subcortical insult, and the more they were recruited, the poorer the recovery in hand function. In addition, we observed significantly reduced betweenness centrality of the contralesional dorsolateral premotor cortex in stroke patients compared with that in healthy controls. Moreover, a significantly positive correlation was observed between the betweenness centrality of the contralesional dorsolateral premotor cortex and FMA scores in stroke patients. Johansen-Berg et al. [2002] reported that disruption of the contralesional premotor cortex activity affected the movement ability of the paretic hand, particularly in patients with poor recovery. Our result suggests that reduced betweenness centrality of the contralesional dorsolateral premotor cortex implies poor outcomes in hand function and also further supports previous findings from the viewpoint of network topology.

Different Topological Properties of the Cortical Motor-Related Network for the Two Subgroups

Our previous studies revealed different patterns of functional reorganization in both cortical connectivity and regional homogeneity for the two subgroups of stroke patients with different outcomes in hand function [Yin et al., 2012, 2013a]. To further explore the relationships between topological properties of the cortical motor-related network and outcomes in hand function, we divided the stroke patients into two subgroups. Although a tendency of shift toward regular network configuration was observed in stroke patients compared with healthy controls, no significant differences of both the local efficiency and global efficiency were detected between the two subgroups. Furthermore, we found no striking correlations between both local efficiency and global efficiency and FMA scores. It is possible that the outcomes in hand function is less pronounced for the global characterization of the cortical motor-related network in stroke patients.

Instead, we detected significant differences in betweenness centrality of the ipsilesional dorsolateral premotor cortex, middle frontal cortex, and superior parietal lobule between the two subgroups, however, no significant differences in betweenness centrality of any of these regions were observed by direct comparisons of stroke patients with healthy controls. Furthermore, striking correlations were observed between the betweenness centrality of the three ipsilesional regions and FMA scores. Obviously, the reason for the lack of difference in betweenness centrality of the three ipsilesional regions detected by direct comparisons of stroke patients and healthy controls is that their betweenness centralities in the CPH and PPH groups were inconsistently greater or lower than those in healthy controls. This result suggests that we can obtain more detailed information about functional reorganization from subgroup analysis.

In particular, previous studies have revealed that recovery of motor function after stroke is associated with

enhanced activation in the ipsilesional dorsolateral premotor cortex [Carey et al., 2002; Mima et al., 2001; Seitz et al., 1998; Weiller et al., 1993]. Fridman et al., through disruption of activity in the ipsilesional premotor cortex with transcranial magnetic stimulation, also indicated that the ipsilesional dorsolateral premotor cortex participates as a substrate mediating the functional recovery of executive motor function in patients with focal lesions [Fridman et al., 2004]. In line with previous studies, we found that the betweenness centrality of the ipsilesional dorsolateral premotor cortex in the CPH group was dramatically lower than that in both the PPH group and healthy controls, and no difference was found between the PPH group and healthy controls. Our finding further suggests that reduced betweenness centrality of the ipsilesional dorsolateral premotor cortex hints at poor outcomes in hand function. Therefore, our study evidences that alterations in region centrality play a vital role in functional recovery after stroke.

Limitations of our Study

Several issues need to be further addressed in our study. First, in keeping with most resting-state fMRI studies, we cannot eliminate the effects of physiological noise because we used a relatively low sampling rate ($TR = 2$ s) for multislice acquisitions. Under this sampling rate, respiratory and cardiac fluctuations may still be present in the fMRI time series, although band-pass filtering in the range of $0.01 < f < 0.08$ Hz was used to reduce them. Second, previous studies have suggested that low-frequency fluctuations measured by BOLD fMRI most likely reflect underlying anatomic connectivity of the cortex [Achard et al., 2006; Salvador et al., 2005]. For example, Gong et al. revealed topological architectures of human brain anatomical networks underlying functional states by diffusion tensor tractography [Gong et al., 2009]. By diffusion tensor imaging, we have demonstrated secondary degeneration in widespread regions of the motor system remote from the primary lesion in patients with subcortical stroke, and the degree of degeneration was related to the functional recovery [Yin et al., 2013b]. In future studies, it would be important to further investigate the topological properties of anatomical networks using diffusion tensor tractography. Third, as discussed in the method section, a wide range of sparsity thresholds were employed to investigate the topological properties of the cortical motor-related network because no definitive approach is available to determine a single threshold so far. For this exploratory study, the results were reported without corrections for multiple comparisons on a wide range of thresholds. Moreover, for the subgroup analysis, we did not perform corrections for multiple comparisons because the sample size for each subgroup was relatively small. The use of a larger sample size of stroke patients is important to increase statistical power.

CONCLUSIONS

In summary, the present study using graph theoretical approaches investigated topological properties of the cortical motor-related network in response to subcortical motor pathway stroke. A tendency for the cortical motor-related network to be close to a regular configuration was demonstrated in patients with subcortical stroke. Moreover, the alterations in betweenness centrality of regions in both ipsilesional and contralesional hemispheres were detected in association with outcomes in hand function. The present study provided insight into functional organization after subcortical stroke from the perspective of network topology.

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