RESEARCH ARTICLE

Differences in motor network dynamics during recovery between supra- and infra-tentorial ischemic strokes

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Most previous stroke studies have been performed in heterogeneous patient populations. Moreover, the brain network might demonstrate different recovery dynamics according to lesion location. In this study, we investigated variation in motor network alterations according to lesion location. Forty patients with subcortical ischemic stroke were enrolled. Patients were divided into two groups: 21 patients with supratentorial stroke (STS) and 19 patients with infratentorial stroke (ITS). All patients underwent resting-state functional magnetic resonance imaging and behavioral assessment at 2 weeks and 3 months poststroke. Twenty-four healthy subjects participated as a control group. To compare altered connectivity between groups, measures used in previous studies to evaluate interhemispheric balance and global network reorganization were investigated and the relationship between network measures and motor functions were examined. Cortico-cerebellar connectivity was also extracted to investigate its relationship with interhemispheric connectivity. In the STS group, measures related to interhemispheric balance were disrupted compared to the control group 2 weeks poststroke, while this was not found in the ITS group. During recovery, measures related to global network reorganization in the STS group and measures related to interhemispheric balance in the ITS group demonstrated significant changes, respectively. Moreover, motor functions were correlated with altered network measures in both groups. There was an interactive relationship between cortico-cerebellar and interhemispheric cortical connectivity only in the ITS group. Different changes in the motor network were observed depending on the location of stroke lesions. These results might originate from differences in the interactions between cortico-cerebellar and interhemispheric connectivity.

KEYWORDS

brain connectivity, infratentorial stroke, motor network, resting-state fMRI, supratentorial stroke

1 | INTRODUCTION

Stroke occurs in various brain regions and often results in motor deficits. The lesion location provides important information for managing stroke patients because it can indicate symptoms and recovery patterns (Feng et al., 2015; Ganesan, Ng, Chong, Kirkham, & Connelly, 1999; Meyer et al., 2016). On the basis of lesion location, strokes can be classified as cortical and subcortical or as supratentorial and infratentorial (Abend et al., 2011). The supratentorial compartment includes the cerebral hemispheres and the diencephalic regions, which are located above the tentorium cerebelli, whereas the infratentorial

compartment includes the brainstem regions and cerebellum, which are located below the tentorium cerebelli. Supratentorial stroke (STS) frequently occurs, while infratentorial stroke (ITS) comprises approximately 15–20% of all strokes (Diringer, 1993; Lekic et al., 2011). Damage to the sensorimotor pathways by stroke induces motor deficits; recovery of these pathways is related to dynamic network changes for recovery of motor function, and serves as a neuroimaging biomarker (Lee et al., 2017; Puig et al., 2013; Schulz, Braass, et al., 2015; Schulz, Frey, et al., 2015; Schulz et al., 2012). The sensorimotor pathways comprise the cortico-cortical, cortico-spinal, and cortico-cerebellar pathways. Among these pathways, damage to the

cortico-cerebellar pathways may be particularly variant according to STS and ITS. The cortico-cerebellar pathways include the cortico-ponto-cerebellar and cerebello-thalamo-cortical pathways. These pathways reciprocally connect motor-related regions and the cerebellum, and form closed loops of descending and ascending projections (Palesi et al., 2017; Proville et al., 2014). The cortico-ponto-cerebellar pathway connects motor-related cortical regions with the contralateral cerebellum passing through the pontine nucleus and middle cerebellar peduncle. The cerebello-thalamo-cortical pathway connects the cerebellum with the contralateral motor cortex passing through the superior cerebellar peduncle, contralateral red nucleus, and thalamus (Palesi et al., 2017; Ramnani, 2006). Decussation of the cerebello-thalamo-cortical pathway occurs through the superior cerebellar peduncle and is located at the level of the inferior colliculi. Therefore, this pathway may be preserved in cases of pontine and medullary infarction in ITS. A few studies have compared the characteristics of STS and ITS and reported differences in functional outcomes during rehabilitation depending on lesion location (De Haan, Limburg, Van der Meulen, Jacobs, & Aaronson, 1995; Gialanella, Bertolinelli, & Santoro, 2008; Turney, Garraway, & Whisnant, 1984; Van Straten, Reitsma, Limburg, Van den Bos, & De Haan, 2001). In previous neuroimaging studies, interhemispheric interaction and balance were reportedly disrupted by stroke onset (Carter et al., 2012; Murase, Duque, Mazzocchio, & Cohen, 2004; Siegel et al., 2016). Recovery of interhemispheric interaction and balance, as well as occurrence of global network reorganization, have also been reported during stroke recovery (Calautti & Baron, 2003; Carter et al., 2010; Park et al., 2011). However, these previous studies were performed in heterogeneous populations or only in patients with STS. Unfortunately, no studies have used neuroimaging to compare brain network changes during the recovery phase between STS and ITS.

Therefore, in this study, we hypothesized that motor networks demonstrate different dynamics in recovery and the relationships between cortico-cortical connectivity and cortico-cerebellar connectivity probably differ depending on lesion location because of differences in structural damage to the cortico-cerebellar pathways. To validate our hypothesis, motor networks were constructed from resting-state functional magnetic resonance imaging (MRI) obtained 2 weeks and 3 months after stroke onset, and changes in motor network connectivity during recovery were compared between STS and ITS groups.

2 | MATERIALS AND METHODS

2.1 | Participants

Forty patients were enrolled 2 weeks after onset of first-ever ischemic stroke according to the following inclusion and exclusion criteria. Inclusion criteria were; (a) first-onset unilateral subcortical cerebral stroke, (b) aged 19 years old or older. Patients were excluded if they presented with any clinically significant or unstable medical conditions, any neuropsychiatric comorbidity other than stroke, or any contraindication to MRI. Patients were divided into two groups based on the location of stroke lesion: STS (12 males and 9 females, mean age

57.8 ± 11.2 years, range 33–77 years) and ITS (13 males and 6 females, mean age 59.7 ± 12.0 years, range 33–79 years). All patients underwent MRI 2 weeks (T1) and 3 months (T2) after stroke onset, and residual motor function was measured using Fugl-Meyer assessment (FMA) scores on the same day as MRI acquisition (Fugl-Meyer, Jääskö, Leyman, Olsson, & Steglind, 1974). The FMA score is a stroke-specific and performance-based impairment index ranging from 0 to 100, with a lower score indicating greater motor impairment. Demographic characteristics such as age, sex, lesion side, time post-stroke, and initial FMA did not differ significantly between groups. Participant characteristics are summarized in Table 1. Lesions were manually drawn on T1-weighted structural MRI with lesion mapping software (MRIcro software <http://www.cabiatl.com/micro/micro/index.html>). The lesions were normalized to the standard Montreal Neurological Institute (MNI) space and overlaid on a template in the MNI space. Lesion maps of both groups were visualized with the xjView toolbox (<http://www.alivelearn.net/xjview>) (Figure 1). The lesions were flipped to the right side to visualize the distribution for patients with lesions on the left side. All lesions were overlaid on the right side in the MNI space. Twenty-four healthy subjects (14 males and 10 females, mean age 58.4 ± 10.4 years, range 34–77 years) with no reported history of psychiatric or neurological disorders were enrolled as age-matched controls. They also underwent MRI. The experimental procedures were explained, and informed consent was provided by all participants. This study was approved by the Institutional Review Board of Samsung Medical Center, Seoul, Republic of Korea.

2.2 | Data acquisition

Participants including patients and healthy subjects underwent resting-state fMRI scanning. They were instructed to keep their eyes

TABLE 1 Patient characteristics and motor function

Group	STS	ITS
Age (years)		
Mean ± SD (range)	57.8 ± 11.2 (33–77)	59.7 ± 12.0 (33–79)
Sex (n)		
Male	12	13
Female	9	6
Lesion side (n)		
Right	12	9
Left	9	10
Bilateral	0	0
Time post stroke (days)		
T1, mean ± SD	12.4 ± 3.9	14.7 ± 7.0
T2, mean ± SD	94.3 ± 8.0	94.8 ± 16.1
NIHSS at T1		
Mean ± SD (range)	6.8 ± 3.9 (2–14)	5.9 ± 2.6 (2–11)
Fugl-Meyer assessment scores		
T1, mean ± SD (range)	44.5 ± 19.7 (11–83)	44.8 ± 22.1 (12–75)
T2, mean ± SD (range)	66.8 ± 25.1 (24–100)	71.7 ± 25.4 (26–100)

STS = supratentorial stroke; ITS = infratentorial stroke; SD = standard deviation; T1 = 2 weeks poststroke; T2 = 3 months poststroke; NIHSS = National Institutes of Health Stroke Scale.

FIGURE 1 Lesion maps. The images were flipped for patients with lesions on the left side. All lesions were overlaid on the right side in the MNI space. The color bar indicates the number of patients

closed and remain motionless during the scan. The resting-state fMRI was acquired with a Philips ACHIEVA[®] MR scanner (Philips Medical Systems, Best, The Netherlands) operating at 3T. One hundred whole-brain images were collected with a T2*-weighted gradient echo-planar imaging sequence with the following metrics: 35 axial slices, slice thickness = 4 mm, no gap, matrix size = 128 × 128, repetition time = 3,000 ms, echo time = 35 ms, flip angle = 90°, and field of view = 220 × 220 mm. T1-weighted images were acquired with the following settings: 124 axial slices, slice thickness = 1.6 mm, no gap, matrix size = 512 × 512, repetition time = 13.9 ms, echo time = 6.89 ms, flip angle = 8°, and field of view = 240 × 240 mm for lesion segmentation and atlas transformation.

2.3 | Data preprocessing

Preprocessing of the resting-state fMRI data included slice timing correction; spatial realignment to correct head motion; spatial normalization to the MNI space and resampled to 2-mm isotropic voxels; and spatial smoothing with a 6-mm full-width half-maximum Gaussian kernel. All processes were performed with the SPM8 package (Wellcome Trust Centre for Neuroimaging, University College London, London, United Kingdom). Nuisance signals were removed with a linear regression of 22 parameters including 6 head motion parameters, 6 first-order temporal derivatives of the head motion parameters, and 5 temporal parameters for each of the white matter and ventricle signals obtained from principal component analysis (Chai, Castañón, Öngür, & Whitfield-Gabrieli, 2012). Band-pass filtering between 0.009 and 0.08 Hz was performed to remove constant offsets and linear trends. These processes were performed with MATLAB (Mathworks, Natick, MA).

2.4 | Network construction

The motor network was constructed with 24 predefined ROIs (regions of interest) (Table 2 and Supporting Information Figure S1). The ROIs were obtained from a previous meta-analysis (Rehme, Eickhoff, Rottschy, Fink, & Grefkes, 2012). The meta-analysis was performed with 54 experimental contrasts for movement of the paretic upper limb (472 patients, 452 activation foci) and 20 experiments comparing

activation between patients and healthy controls (177 patients, 113 activation foci) from 36 neuroimaging studies of stroke patients. The motor network was constructed by calculating Pearson's correlation for the mean time course of each ROI (Lee et al., 2017). The extended motor network was also constructed to investigate the relationship between cortico-cortical connectivity and cortico-cerebellar connectivity depending on lesion location. The network included 18 cerebellar regions in the automated anatomical labeling (AAL) template (Tzourio-Mazoyer et al., 2002), instead of the two cerebellar regions in the 24 predefined ROIs. As a result, the extended motor network was constructed from 40 cortical and cerebellar regions. In the study, 18 cerebellar regions include crus I, crus II, lobule III, lobule IV and V, lobule VI, lobule VIIb, lobule VII, lobule IX, and lobule X of left and right cerebellar hemispheres. The AAL atlas was coregistered to the normalized fMRI data space with SPM8 and then analyzed.

2.5 | Network measures

2.5.1 | Correlation matrix distance (network distance)

The correlation matrix distance was used to measure the similarity between ipsilesional and contralesional networks (Herdin, Czink, Ozcelik, & Bonek, 2005).

$$\text{Distance} = 1 - \frac{\text{trace}(R1 \cdot R2)}{\text{norm}(R1) \cdot \text{norm}(R2)}$$

where $R1$ and $R2$ are ipsilesional and contralesional hemispheric connectivity adjacency matrices, trace is the sum of the elements on the main diagonal of a rectangular matrix, and norm is the Frobenius norm. If the $R1$ and $R2$ matrices are equal, the distance becomes zero. The measure was used to investigate the network balance between bilateral hemispheres of stroke patients by measuring the similarity between the ipsilesional and contralesional hemispheric networks (Lee et al., 2017).

2.5.2 | Strength of connectivity

The strength of interhemispheric connectivity in the motor network was measured by averaging the strength of connections between homotopic regions in bilateral hemispheres. The strength of cortico-cerebellar connectivity was obtained by averaging the strength of the

TABLE 2 Regions of interest in the motor networks of stroke patients

No. Region	Side	MNI coordinates		
		x	y	z
1 Precentral gyrus (M1)	IL	-38	-24	58
2 Precentral gyrus (M1)	CL	42	-14	52
3 Medial superior frontal gyrus (SMA)	IL	-4	-6	54
4 Medial superior frontal gyrus (SMA)	CL	4	-6	54
5 Postcentral gyrus (S1)	IL	-36	-30	60
6 Postcentral gyrus (S1)	CL	40	-28	52
7 Cerebellum (lobule VI)	IL	-24	-60	-22
8 Cerebellum (lobule V and VI)	CL	20	-50	-22
9 Medial superior frontal gyrus (pre-SMA)	IL	-2	6	54
10 Medial superior frontal gyrus (pre-SMA)	CL	2	2	56
11 Dorso-lateral precentral gyrus/sulcus (PMd)	IL	-42	-10	58
12 Dorso-lateral precentral gyrus/sulcus (PMd)	CL	42	-6	56
13 Ventro-lateral precentral gyrus/sulcus (PMv)	IL	-46	-10	48
14 Ventro-lateral precentral gyrus/sulcus (PMv)	CL	42	-6	48
15 Parietal operculum (S2)	IL	-48	-18	22
16 Parietal operculum (S2)	CL	50	-28	28
17 Inferior frontal gyrus (IFG)	IL	-48	6	6
18 Inferior frontal gyrus (IFG)	CL	48	6	6
19 Inferior frontal sulcus (IFS)	IL	-50	8	34
20 Inferior frontal sulcus (IFS)	CL	50	8	34
21 Rostral cingulate zone (RCZ)	IL	-8	14	36
22 Rostral cingulate zone (RCZ)	CL	8	14	36
23 Anterior intraparietal sulcus (aIPS)	IL	-42	-40	50
24 Anterior intraparietal sulcus (aIPS)	CL	42	-40	50

IL = ipsilesional side; CL = contralesional side.

connections between cortical ROIs in a hemisphere and contralateral ROIs in the cerebellum.

2.5.3 | Network efficiency

Network efficiency is inversely related to path length in a graph theoretical analysis (Achard & Bullmore, 2007; Latora & Marchiori, 2001; Sporns & Zwi, 2004). For reference, the path length (number of connections between regions) is the minimum number of connections required to travel from one node to another. In other words, the network efficiency is a measure of how efficiently information is exchanged in the network structure. This measure is defined as follows:

$$E_{\text{global}} = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} (d_{ij}^w)^{-1}}{n-1}$$

where n is the number of regions, and d_{ij}^w is the shortest path length between region i and region j . Network efficiency is an important measure of brain function (Langer et al., 2012; Langer, von Bastian, Wirz, Oberauer, & Jäncke, 2013; van den Heuvel, Stam, Kahn, & Pol, 2009).

2.6 | Clustering coefficient

The clustering coefficient quantifies how well-connected the neighbors of a specific node in a network are (Watts & Strogatz, 1998). The clustering coefficient of region i is defined as:

$$C_i = \frac{1}{k_i(k_i-1)} \sum_{j,h \in N} a_{ij}a_{ih}a_{jh}$$

where k_i is the degree (number of connections) of region i and a_{ij} is the connection between region i and region j . The average clustering coefficient of a network with n regions is defined as

$$C = \frac{1}{n} \sum_{i \in N} C_i$$

where N is the set of all regions in the network, and n is the number of regions.

2.7 | Characteristic path length

The characteristic path length is the average number of minimum connections that must be taken to join one region to another (Watts & Strogatz, 1998). This measure is defined as:

$$L = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}}{n-1}$$

where d_{ij} is the shortest path length between regions i and j . In other words, it represents the minimum number of connections between regions i and j .

2.8 | Network randomization

The randomness of a network is measured based on changes in the normalized clustering coefficient and characteristic path length. As the randomness of the network increases, the normalized clustering coefficient and characteristic path length decrease (Watts & Strogatz, 1998). The occurrence of network randomization during recovery in neurological diseases including stroke has been reported in previous studies (Lee, Lee, Kim, & Kim, 2015; Nakamura, Hillary, & Biswal, 2009; Stam et al., 2009; Wang et al., 2010). The normalized clustering coefficient and characteristic path length were obtained by comparing the value calculated from a motor network and the value calculated from the surrogate random network derived from the motor network (Lee et al., 2015; Maslov & Sneppen, 2002; Sporns & Zwi, 2004).

2.9 | Statistical analysis

The Shapiro-Wilk normality test was used to test data for a normal distribution. The null hypothesis was rejected in all cases. Repeated measures ANOVA was performed to identify significant differences in network measures between groups (STS and ITS) and times (T1 and T2). A paired t -test was conducted to evaluate significant changes over time within a group. One-way ANOVA was used to identify differences in network measures between the patient and healthy control groups. Post hoc tests (Tukey's test) were used to examine specific differences between the patient and control groups. Cohen's d was used to investigate effect size relative to differences between groups and alterations during recovery. To investigate the relationship between network measures and motor function and between interhemispheric cortical and cortico-cerebellar connectivity, a linear regression model was used. All statistics were performed with the *ranova*, *ttest*, *anova1*, *multcompare*,

and *fitlm* functions in the statistics toolbox of MATLAB R2014b. The statistical significance was set at $p < .05$ in this study.

3 | RESULTS

3.1 | Comparison of lesion maps

Lesion maps of the STS and ITS groups are displayed in Figure 1. All lesions were flipped to the right side to visualize the distribution at a glance and were overlaid on the MNI space. The STS group included 12 right-sided and 9 left-sided lesions, and the ITS group included 9 right-sided and 10 left-sided lesions. Mean lesion volumes of the STS and the ITS groups were 6.55 ± 6.91 mL and 0.94 ± 0.77 mL.

3.2 | Disruption of interhemispheric balance caused by stroke

To investigate interhemispheric balance, the network distance and strength of interhemispheric connectivity were measured. Network distance and strength of interhemispheric connectivity 2 weeks after stroke in the STS and ITS groups were compared with those of the healthy control group to investigate disruptions of these measures caused by stroke (Figure 2). Network distance in the STS group was significantly higher than in the control group ($d = 0.80$, $p = .0298$). The strength of interhemispheric connectivity in the STS group was also significantly lower than in the control group ($d = -1.00$, $p = .0037$). On the other hand, there were no differences between these network measures in the control group and the ITS group. These meant that disruption of interhemispheric balance was obvious in the STS group, while it was relatively minimal in the ITS group. Details of the statistical results are reported in Supporting Information Table S1.

3.3 | Alterations in network measures during the recovery period

Changes in network distance and strength of interhemispheric connectivity during recovery were investigated to assess network balance and interaction between the ipsilesional and contralesional hemispheres (Figure 3a,b). Network distance tended to decrease and the strength of interhemispheric connectivity increased significantly in the ITS group ($d = 0.72$, $t = 2.61$, $p = .0177$). However, neither measure changed in the STS group. Changes in network efficiency, normalized clustering coefficient, and characteristic path length were investigated to assess global network reorganization during recovery (Figure 3c,d). Network efficiency significantly increased ($d = 0.59$, $t = 2.21$, $p = .0389$) and the normalized clustering coefficient decreased ($d = -0.63$, $t = -2.14$, $p = .0449$) in the STS group. On the other hand, no measures related to global network reorganization changed in the ITS group during recovery. Therefore, global network reorganization was characteristic findings of STS during the recovery phase, while improved interhemispheric balance was evident in ITS. Detailed statistical results are reported in Supporting Information Table S2.

3.4 | Relationship between network measures and motor functions

Relationships between network measures and motor functions were investigated (Figure 4). Changes in network distance were correlated with changes in motor function score during recovery in the ITS group ($r = -.52$, $p = .0219$). As the network distance between bilateral hemispheric networks decreased during recovery, motor function improved in the ITS group. In other words, as interhemispheric balance improved during recovery, motor function improved in the ITS group. In the STS group, network efficiency was correlated with motor function scores 3 months poststroke ($r = .64$, $p = .0018$). Higher network efficiency correlated with better motor function in the STS group.

FIGURE 2 Comparison of network distance and interhemispheric connectivity between the healthy control and stroke groups 2 weeks after stroke. Network distance and interhemispheric connectivity were significantly disrupted in the STS group compared to healthy controls 2 weeks after stroke, while the ITS group did not differ from healthy controls (* $p < .05$; ** $p < .01$, respectively)

FIGURE 3 Changes in (a) network distance, (b) interhemispheric connectivity, (c) global efficiency, (d) normalized clustering coefficient, and (e) normalized characteristic path length during recovery. Network distance decreased and interhemispheric connectivity increased only in the ITS group. Measures of global network reorganization, such as network efficiency and normalized clustering coefficient, decreased significantly during recovery only in the STS group (* $p < .05$)

3.5 | Interrelationship between interhemispheric cortical connectivity and cortico-cerebellar connectivity depending on lesion location

There was a significant variation in which network measures were altered during recovery between groups. Measures related to interhemispheric balance were restored in the ITS group, while the same was not seen in the STS group. Cortico-cerebellar connectivity was additionally examined

to determine the cause of the variation in network alterations between groups. Relationships between interhemispheric cortical connectivity and cortico-cerebellar connectivity were investigated in the extended motor network (Figure 5). Changes in the strength of interhemispheric connectivity during recovery were positively associated with changes in cortico-cerebellar connectivity between the contralesional cerebellum and ipsilesional motor-related regions during recovery only in the ITS group

FIGURE 4 Relationship between network measures and motor function scores. A change in network distance and a change in FMA score during recovery in the STS (A1) and the ITS (A2) groups. Network efficiency and FMA scores 3 months post stroke in the STS (B1) and ITS (B2) groups. Network distance correlated with motor function in the ITS group (A2, $r = -.52$, $p = .0219$) and network efficiency correlated with motor function in the STS group (B1, $r = .64$, $p = .0018$). $\Delta\text{FMA} = \text{FMA (T2)} - \text{FMA (T1)}$; T1, 2 weeks poststroke; T2, 3 months poststroke

($r = .56$, $p = .0127$). As affected cortico-cerebellar connectivity, which indicates connections between ipsilesional cortical regions and contralateral cerebellar regions, increased during recovery, the increase in interhemispheric cortical connectivity was higher in the ITS group. However, unaffected cortico-cerebellar connectivity was not significantly related to interhemispheric cortical connectivity in the ITS group, and cortico-cerebellar connectivity was also not significantly related to interhemispheric connectivity in the STS group. Cortico-cerebellar connectivity interacted with interhemispheric cortical connectivity only in the ITS group. Therefore, it was assumable that, after ITS, cortico-cerebellar connectivity might play a role in restoring interhemispheric connectivity and contribute to recovery of interhemispheric balance.

4 | DISCUSSION

In this study, changes in network measures during recovery were investigated and compared between the STS and ITS groups. Network

distance and interhemispheric connectivity related to interhemispheric balance were significantly disrupted in the STS group compared to the healthy control group 2 weeks after stroke, while this was not observed in the ITS group. During recovery, measures related to interhemispheric balance, such as network distance and the strength of interhemispheric connectivity, were restored only in the ITS group. Motor recovery also correlated with the recovery of this network distance in the ITS group. Measures related to global network reorganization, such as network efficiency and normalized clustering coefficient, were significantly altered only in the STS group. Network efficiency significantly increased and normalized clustering coefficient decreased in the STS group. Motor function correlated with this network efficiency measure in the STS group. In summary, the ITS group exhibited interhemispheric balance recovery while the STS group predominantly underwent global network reorganization.

In previous stroke studies, interhemispheric balance has reportedly been disrupted by stroke onset (Carter et al., 2012; Murase et al., 2004; Siegel et al., 2016). Recovery of interhemispheric balance has

FIGURE 5 Relationship between change in interhemispheric cortical connectivity and change in cortico-cerebellar connectivity: (a) affected cortico-cerebellar connectivity; (b) unaffected cortico-cerebellar connectivity) in the STS (A1, B1) and the ITS (A2, B2) groups. Affected cortico-cerebellar connectivity indicates connections between ipsilesional cortical regions and contralesional cerebellar regions. Unaffected cortico-cerebellar connectivity indicates connections between contralesional cortical regions and ipsilesional cerebellar regions. Change in interhemispheric connectivity was correlated with change in affected cortico-cerebellar connectivity only in the ITS group (A2, $r = .56$, $p = .0127$). Cx, cerebral cortex; Cb, cerebellum; IH, interhemispheric connectivity; $\Delta IH = IH$ (3 months) – IH (2 weeks); CC, cortico-cerebellar connectivity; $\Delta CC = CC$ (3 months) – CC (2 weeks)

also been investigated after stroke onset (Calautti & Baron, 2003; Carter et al., 2010; Park et al., 2011). Previous brain network studies in stroke patients have reported an increase in network randomness caused by network reorganization during recovery. Network reorganization was investigated as a decrease in the normalized clustering coefficient or characteristic path length (Lee et al., 2015; Wang et al., 2010). However, previous studies were performed in heterogeneous populations or in patients with STS. Our study assessed a homogeneous stroke population with subcortical ischemic stroke and no cerebellar stroke. We investigated whether existing results might differ depending on the stroke location.

Differences in results between groups may result from differences in stroke-related damage to the cortico-cerebellar pathway. Several motor pathways, such as the cortico-spinal and cortico-cortical pathways exist. Damage to the corticospinal tract (CST), a representative tract in the cortico-spinal pathway, is closely related to residual motor function in stroke patients (Schaechter et al., 2009; Stinear et al., 2007; Stinear & Ward, 2013). Therefore, the CST is the primary focus of motor function studies in stroke patients. The CST begins in motor-related regions of the cerebral cortex, passes through the internal capsule and pons, and enters the medulla (Wakana, Jiang,

Nagae-Poetscher, Van Zijl, & Mori, 2004). The risk of damage to the tract is similar for STS and ITS because lesions occur around the internal capsule in STS and around the pons and medulla in ITS. Cortico-cortical pathways were not as likely to be damaged in either group because only subcortical stroke was included. Therefore, differences between groups in related to the cortico-spinal and cortico-cortical pathways may be small. However, the risk of damage to the cortico-cerebellar pathways might differ between groups. The cortico-cerebellar pathways comprise the cortico-ponto-cerebellar and cerebello-thalamo-cortical pathways. These pathways reciprocally connect motor-related regions and the cerebellum, and form closed loops of descending and ascending projections (Palesi et al., 2017; Proville et al., 2014). The cortico-ponto-cerebellar pathway connects motor-related cortical regions with the contralateral cerebellum passing through the pontine nucleus and middle cerebellar peduncle (Palesi et al., 2017; Ramnani, 2006). Therefore, the risk of damage to this pathway was similar between groups. However, the risk of damage to the cerebello-thalamo-cortical pathway differed between groups. The cerebello-thalamo-cortical pathway connects the cerebellum with the contralateral motor cortex passing through the superior cerebellar peduncle, red nucleus, and thalamus (Palesi et al., 2017;

Ramnani, 2006). This pathway can easily be damaged in STS. However, this pathway is likely preserved in ITS because it passes through the superior cerebellar peduncle, which is located in the top of the pons, and into the mesencephalon (Schulz, Frey, et al., 2015). Therefore, cortico-cerebellar connectivity seems to have an interactive relationship with cortical connectivity in the ITS group only in our study.

The cerebellum communicates with the sensorimotor cortex through a closed-loop circuit (Kelly & Strick, 2003; Proville et al., 2014; Ramnani, 2006), and interhemispheric interactions occur between sensorimotor regions in both hemispheres (Carter et al., 2010, 2012; Grefkes, Eickhoff, Nowak, Dafotakis, & Fink, 2008; Murase et al., 2004). In addition, interhemispheric connectivity between motor-related regions and the integrity of the cortico-cerebellar tract are positively related to residual motor function in stroke patients (Carter et al., 2010; Schulz, Frey, et al., 2015). Motor cortical excitability is reduced in cerebellar stroke patients (Liepert et al., 2004). Therefore, cortico-cerebellar connectivity and interhemispheric cortical connectivity might interact. The relationship between cortico-cerebellar connectivity and interhemispheric cortical connectivity in the ITS group was evidenced by differences in cortico-cerebellar connectivity between the contralesional cerebellum and ipsilesional motor regions that were likely preserved. According to functional connectivity studies, several connections between ipsilesional motor-related regions and contralesional cerebellar regions positively contribute to residual motor function, and most connections that are positively correlated with motor function are interhemispheric cortical connections (Wang et al., 2010). Increased activity in contralesional cerebellar regions and ipsilesional motor-related regions was important to residual motor function in a meta-analysis of motor-related neural activity after stroke (Rehme et al., 2012). These previous results reflect the importance of cortico-cerebellar connectivity. This connectivity interacted with interhemispheric cortical connectivity in the ITS group.

In our study, disruption of interhemispheric balance was relatively small and improved during recovery in the ITS group. These results may indicate that interhemispheric balance is preserved and recovers due to an interactive relationship with affected cortico-cerebellar connectivity. The cortico-cerebellar connectivity that is likely preserved in the ITS group might compensate for disrupted interhemispheric interactions caused by stroke and contribute to interhemispheric recovery. On the other hand, interhemispheric cortical connectivity and cortico-cerebellar connectivity were not related in the STS group. Recovery of interhemispheric balance was rare, and instead the motor network globally reorganized in the STS group. According to existing studies, global network reorganization results from non-optimized connections during recovery that are impaired by the stroke lesion (Lee et al., 2015; Wang et al., 2010). Recovery might have been better in the ITS group than in the STS group because wiring costs required for recovery were lower in the motor network of the ITS group, which did not require global reorganization. Previous studies have also reported better recovery in ITS than in STS (De Haan et al., 1995; Gialanella et al., 2008; Turney et al., 1984). In our study, the ITS group tended to exhibit improvement that was five points higher on average compared with the STS group, although this difference was not statistically significant.

There are some limitations to this study. While both groups were well matched in demographic characteristics and severity of initial motor function, the degree of structural damage of motor pathways in the subacute stage was not examined or matched in this functional neuroimaging study. Further studies related to structural connectivity using diffusion tensor imaging should be performed in the future. The network measure was well correlated with motor function 3 months poststroke in the STS group, but there was no correlation between changes in the network measure and motor function during recovery. Improvement in motor function related to changes in a specific network measure might have been related to interindividual variability and not be a linear relationship. Motor recovery after stroke can be influenced by a combination of biomarkers related to motor function. Therefore, the relationship between changes in a specific network measure and changes in motor function may not always be significant.

5 | CONCLUSION

We compared changes in network measures during recovery from subcortical ischemic stroke in STS and ITS patients. Stroke onset significantly disrupted interhemispheric balance in only the STS group. During recovery, measures related to interhemispheric balance were restored significantly in the ITS group, whereas measures related to global network reorganization were significantly altered in the STS group, with network efficiency increasing and the normalized clustering coefficient decreasing. The altered network measures in each group were correlated with motor function. Affected cortico-cerebellar connectivity interacted with interhemispheric cortical connectivity only in the ITS group. In conclusion, our results revealed that changes in the motor network and recovery-related network measures differ according to lesion location. Recovery after ITS occurred through restoration of interhemispheric balance contributed by the cortico-cerebellar connectivity. In contrast, recovery after STS occurred through global network reorganization. These findings may indicate that characteristic motor network dynamics during recovery phase of stroke result from different interactions between cortico-cortical and cortico-cerebellar connectivity dependent to lesion location. These may also give an implication for establishing neurorehabilitation strategies in terms of target site determination by noninvasive brain stimulation. Rebalancing strategy or cerebellar stimulation by NBS will be differently applied according to lesion location and this can be one of the background knowledge for individually tailored rehabilitation strategy. Also, this study may suggest the need for stratification analysis regarding lesion location when investigating recovery-related biomarkers and predicting motor recovery after stroke are performed.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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