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Longitudinal Changes of Resting-State Functional Connectivity During Motor Recovery After Stroke

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Background and Purpose—Functional MRI (fMRI) studies could provide crucial information on the neural mechanisms of motor recovery in patients with stroke. Resting-state fMRI is applicable to patients with stroke who are not capable of proper performance of the motor task. In this study, we explored neural correlates of motor recovery in patients with stroke by investigating longitudinal changes in resting-state functional connectivity of the ipsilesional primary motor cortex (M1).

Methods—A longitudinal observational study using repeated fMRI experiments was conducted in 12 patients with stroke. Resting-state fMRI data were acquired 4 times over a period of 6 months. Patients participated in the first session of fMRI shortly after onset and thereafter in subsequent sessions at 1, 3, and 6 months after onset. Resting-state functional connectivity of the ipsilesional M1 was assessed and compared with that of healthy subjects.

Results—Compared with healthy subjects, patients demonstrated higher functional connectivity with the ipsilesional frontal and parietal cortices, bilateral thalamus, and cerebellum. Instead, functional connectivity with the contralesional M1 and occipital cortex were decreased in patients with stroke. Functional connectivity between the ipsilesional and contralesional M1 showed the most asymmetry at 1 month after onset to the ipsilesional side. Functional connectivity of the ipsilesional M1 with the contralesional thalamus, supplementary motor area, and middle frontal gyrus at onset was positively correlated with motor recovery at 6 months after stroke.

Conclusions—Resting-state fMRI elicited distinctive but comparable results with previous task-based fMRI, presenting complementary and practical values for use in the study of patients with stroke. **(*Stroke*. 2011;42:1357-1362.)**

Key Words: functional connectivity ■ motor recovery ■ resting-state fMRI ■ stroke

Functional MRI (fMRI) has played an integral role in defining the neural substrates and mechanisms underlying recovery after brain disease such as stroke at the system level of the brain. Cortical reorganization has been characterized by observation of changes in brain activation during motor recovery after stroke.[1–6] fMRI studies using motor activation tasks have been conducted for investigation of the effects of specific therapeutic interventions, including constraint-induced movement therapy,[7] treadmill training,[8] and repetitive transcranial magnetic stimulation[9]; these studies focused on recovery mechanisms associated with these interventions.

On the other hand, longitudinal studies have been conducted for assessment of changes in brain activation that are related to recovery after stroke. The initial contralesional shift of activation and evolution to later ipsilesional activation,[1,2] recruitment of additional regions that are not activated in healthy subjects,[10] and importance of ipsilesional surviving regions[11] during motor recovery have been demonstrated using task-based fMRI. However, these reports showed certain variability in brain activation results; one reason for this diversity originated from use of diverse activation paradigms, which prevent adequate comparison between results, although passive movement[4] and motor imagery[5] have been proposed as alternative methods. In addition, longitudinal studies using task-based fMRI are limited in their application for patients with stroke with severe impairment, and results may be confounded by changes in performance during recovery as well.

Resting-state fMRI is a recently evolving method from which functional connectivity between distant brain regions is extracted based on low-frequency fluctuations. Although the meaning of the resting-state fMRI signal has been debated since its initial trial,[12] evidence has suggested that resting fluctuations correspond to neuronal activation during task

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performance.[13] The methodological advantage of resting state is that it can be performed without an overt task or external input; therefore, it is applicable to unconscious patients, infants,[14] and even to experimental animals.[15]

In healthy subjects, resting-state fMRI has shown remarkable consistency in functional connectivity[16,17]; however, significant differences were observed within the aged population[18] or after interventions such as acupuncture.[19] Resting-state fMRI has demonstrated unique changes in patients with various neurological disorders, including Alzheimer disease,[20] attention deficit hyperactivity disorder,[21] depression,[22] and schizophrenia.[23]

For patients with stroke with severe motor impairment who could not perform the fMRI activation task at the early stage of onset, it is expected to be achieved through long-term follow-up by use of resting-state fMRI. Therefore, in this study, we aimed to carry out long-term follow-up of resting-state fMRI in patients with stroke for delineation of the neural substrates of motor recovery after stroke. We analyzed functional connectivity of the ipsilesional primary motor cortex (M1) in patients with stroke and compared it with that of healthy subjects. To propose a plausible underlying mechanism for successful stroke recovery, we also investigated neural correlates associated with long-term motor recovery at 6 months after stroke.

Methods

Subjects

A total of 51 patients who had their first-ever stroke were assessed for their eligibility. Inclusion criteria were as follows: (1) <2 weeks from the onset of ischemic stroke; (2) unilateral supratentorial lesions; (3) moderate to severe motor deficits of the contralesional upper and lower extremities; and (4) age >18 years and <75 years. Exclusion criteria were as follows: (1) any clinically significant or unstable medical disorder; (2) any neuropsychiatric comorbidity other than stroke; and (3) any contraindication to MRI. Twenty-five patients out of 51 were excluded and 26 patients were enrolled in this study. Fourteen patients dropped out during the follow-up period. Finally, 12 patients with ischemic stroke (5 males and 7 females, 58.4±6.9 years) with supratentorial lesions completed longitudinal fMRI experiments, and their image data were included in the analysis (Figure 1; Table 1). Also, 11 healthy subjects (3 males and 8 females, 52.1±9.4 years) who reported no history of psychiatric or neurological problems were included as an age-matched control group. Experiments were conducted with the understanding and written consent of each participant, and ethics approval was provided by the Institutional Review Board.

Experimental Design

This study was designed as a longitudinal observational study for conduct of repeated fMRI experiments. A cross-sectional controlled study design was also applied for comparison of data from patients with stroke with those of healthy subjects.

fMRI Data Acquisition

Resting-state fMRI data were longitudinally acquired 4 times over a period of 6 months in patients with stroke. Patients participated in the first session of fMRI shortly after onset (10.5±4.3 days) and thereafter in subsequent sessions at 1, 3, and 6 months after onset. In healthy subjects, we obtained one time resting-state fMRI data.

During the resting state, subjects were instructed to keep their eyes closed and to remain motionless. fMRI data were acquired using a Philips ACHIEVA MR scanner (Philips Medical Systems, Best, The Netherlands) operating at 3 T. At each session, a total of 100 whole-brain images was collected using a T2*-weighted gradient-echo echoplanar imaging sequence (repetition time=3000 ms, echo time=35 ms, number of slices=35, slice thickness=4 mm, matrix size=128×128, field of view=220×220 mm).

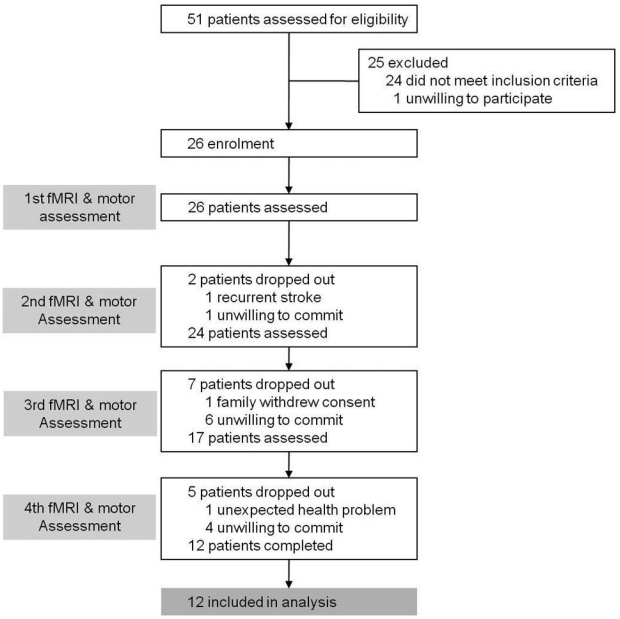

Figure 1. Patient enrollment process for a longitudinal observational study conducting repeated functional MRI (fMRI) experiments. A total of 51 patients with first-ever stroke were assessed for their eligibility. Twenty-five patients were excluded and 14 patients dropped out during the follow-up fMRI experiments. Finally, 12 patients with ischemic stroke completed longitudinal fMRI experiments. Acquisition of resting-state fMRI data, accompanied by behavioral assessment using Fugl-Meyer assessment, was performed within 2 weeks after onset and then at 1, 3, and 6 months after onset.

Behavioral Assessment

Degree of motor impairment was scored using the Fugl-Meyer assessment for upper and lower extremities[24] on the same day as fMRI data acquisition.

fMRI Data Analysis

fMRI data were preprocessed using SPM8 (Wellcome Trust Centre for Neuroimaging, University College London, London, UK) and AFNI (Scientific and Statistical Computing Core, National Institute of Mental Health, Bethesda, MD) software. Preprocessing steps included spatial realignment to the mean volume of a series of images, normalization into the same coordinate frame as the MNI template brain, band-pass filtering between 0.01 and 0.08 Hz, and smoothing using a Gaussian filter of 8 mm full width at half maximum.

Correlation analysis between the reference time course of the M1 and the time course of every voxel in the brain was performed for acquisition of a map of correlation coefficients that revealed functional connectivity of the M1. The reference time course was extracted from the ipsilesional M1 in patients with stroke and the left M1 in healthy subjects. M1 was defined to include voxels covering approximately the caudal half of the precentral gyrus along the anterior wall of the central sulcus. Correction of time courses was made by regressing out the time courses that corresponded to head motions and global fluctuations.

A map of correlation coefficients was converted to a map of Gaussian distributed values through Fisher z-transformation defined by $z=\tanh^{-1} r$ or $z=(1/2)\ln[(1+r)/(1-r)]$, where r is a correlation coefficient, z is an approximately Gaussian distributed value, $\tanh^{-1}$ is the inverse hyperbolic tangent function, and ln is the natural logarithm function.[25] The lesion side of the correlation map was set

Table 1. Patient Characteristics and Motor Function

Patient No.	Gender	Age, Years	Lesion	FMA Scores				FMA Change
				Onset	1 Month	3 Months	6 Months	
1	F	66	L MCA infarction	8	8	19	27	19
2	F	61	L MCA infarction	20	22	27	33	13
3	F	55	R MCA infarction	30	55	70	73	43
4	M	74	L CR infarction	16	22	17	21	5
5	F	58	L MCA infarction	36	42	52	52	16
6	F	47	L MCA infarction	44	59	100	100	56
7	M	55	L ACA infarction	19	42	60	73	54
8	M	62	L MCA infarction	19	22	52	57	38
9	M	59	R MCA infarction	24	24	24	24	0
10	F	52	R CR infarction	52	52	99	99	47
11	M	57	L MCA infarction	13	13	52	52	39
12	F	55	R SC infarction	9	9	34	34	25
Mean±SD	M=5; F=7	58.4±6.9		24.2±13.8	30.8±18.3	50.5±28.5	53.8±27.7	29.6±19.1

FMA indicates Fugl-Meyer assessment; F, female; M, male; L, left; R, right; MCA, middle cerebral artery; CR, corona radiata; ACA, anterior cerebral artery; SC, striatocapsular; FMA change, FMA total scores at 6 months−FMA total scores at onset.

to the left side by flipping the map from right to left about the midsagittal line for patients with lesions on the right side.

Fisher z-transformed and flipped correlation maps were used for random-effects analysis. Two-sample t tests were performed to find areas that showed significant differences in functional connectivity between patients and healthy subjects. Also, to search for brain regions correlated with motor improvement, correlation maps of patients at onset were regressed with increases in the Fugl-Meyer assessment score at 6 months after stroke. We determined the significance using height (uncorrected $P<0.001$ at the voxel level) and extent (uncorrected $P<0.05$ at the cluster level) thresholds.

Lateralization Index

As a quantitative measure of functional connectivity, the lateralization index (LI) was calculated for each correlation map. The LI was introduced for the purpose of providing a specific description of the asymmetry of functional connectivity between the ipsilesional and contralesional M1 according to the following definition: (number of connected voxels in the ipsilesional M1/total number of voxels in the ipsilesional M1)−(number of connected voxels in the contralesional M1/total number of voxels in the contralesional M1). If functional connectivity of the ipsilesional M1 with any voxel had a value >95th percentile of the Gaussian distribution when considering all Gaussian distributed values in a map, the voxel was determined to be connected. This approach yielded LIs that ranged between −1 and 1, in which −1 referred to contralesional connectivity only, 1 ipsilesional connectivity only, and values close to 0 referred to symmetrical connectivity. The LI of patients was assessed at each time point and compared with that of healthy subjects.

Results

Differences in Connectivity Between Patients and Healthy Subjects

Correlation analysis of data acquired from 11 healthy subjects demonstrated the discrete network, namely sensorimotor network (SMN), which is displayed in Figure 2A. SMN of healthy subjects included motor–sensory-related regions such as the primary sensorimotor cortex, premotor cortex, supplementary motor area (SMA), cingulate motor area, secondary somatosensory cortex, cerebellum, basal ganglia, thalamus, frontal and parietal cortices, and striate and extrastriate cortices. SMN in patients with stroke showed asymmetrical involvement, and other regions were additionally included throughout a period of 6 months. Figure 2B shows comparisons of connectivity between patients with stroke and healthy subjects at 4 time points. Significant differences of connectivity in the SMN are summarized (Supplemental Table I, http://stroke.ahajournals.org). Pa-

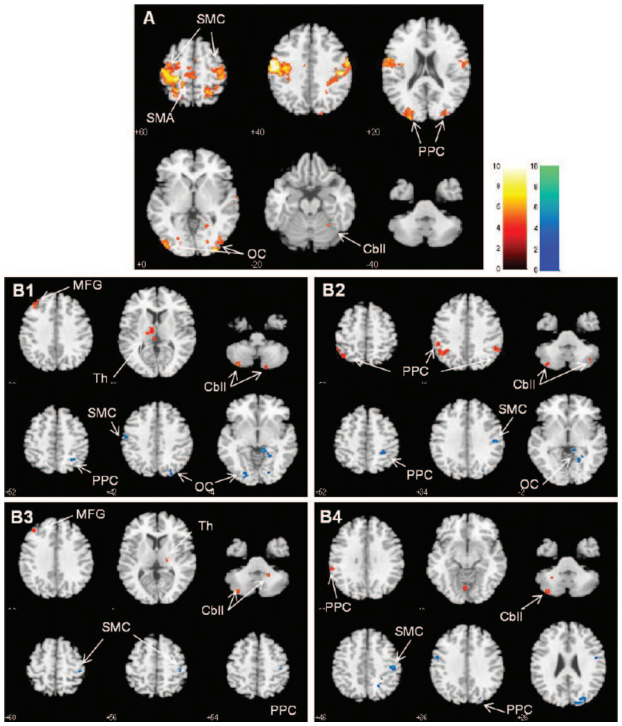

Figure 2. A, Sensorimotor networks acquired by resting-state functional connectivity of the ipsilesional primary motor cortex in healthy subjects. **B**, Significant differences in resting-state functional connectivity between patients and healthy subjects over 4 time points of onset (B1), 1 month (B2), 3 months (B3), and 6 months (B4) after onset. Red–yellow blobs and blue–green blobs indicate increased and decreased functional connectivity in patients compared with healthy subjects, respectively. The left side of the brain is the ipsilesional hemisphere. SMC indicates sensorimotor cortex; SMA, supplementary motor area; PPC, posterior parietal cortex; OC, occipital cortex; Cbll, cerebellum; MFG, middle frontal gyrus; Th, thalamus.

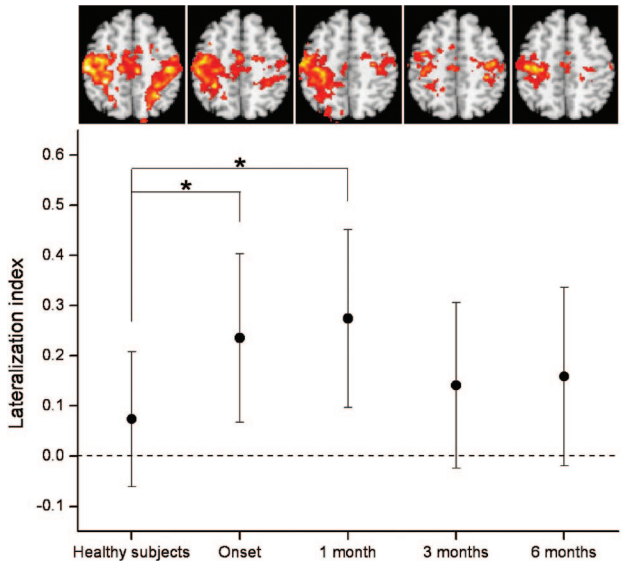

Figure 3. Time-dependent changes in resting-state functional connectivity. Quantitative changes were exhibited by the lateralization index (LI) and corresponding maps of functional connectivity were also displayed. The LI was compared between patients and healthy subjects over 4 time points, including onset, 1 month, 3 months, and 6 months after onset. In the graph of the LI, points represent means, error bars represent SDs, and stars represent significant differences between patients and healthy subjects at a threshold of $P<0.05$.

tients with stroke displayed decreased connectivity of the ipsilesional M1 with the sensorimotor cortex, occipital cortex, middle frontal gyrus (MFG), and posterior parietal cortex since onset. On the other hand, patients with stroke showed increased connectivity of the ipsilesional M1 with the cerebellum, thalamus, MFG, and posterior parietal cortex since onset. In particular, decreased connectivity with the sensorimotor cortex and increased connectivity with the cerebellum persisted throughout a period of 6 months after onset. In general, it is conceivable that connectivity of the ipsilesional M1 increased within ipsilesional brain regions, whereas it decreased within contralesional brain regions.

Time-Dependent Changes in Connectivity

Figure 3 shows time-dependent changes in the LI together with corresponding maps of functional connectivity. The LI of patients was larger at onset and even larger at 1 month after onset compared with that of healthy subjects. At 3 months and 6 months after onset, the LI of patients had decreased so that it did not differ significantly from that of healthy subjects. Corresponding maps of functional connectivity also showed that asymmetry of functional connectivity between ipsilesional and contralesional M1 increased until 1 month after onset and then decreased.

Correlation of Connectivity at Onset With Later Motor Improvement

Figure 4 shows brain regions in which functional connectivity at onset was positively correlated with later motor improvement, as measured by increases in the Fugl-Meyer assessment score at 6 months after onset. Brain areas demonstrating significant correlation with Fugl-Meyer assessment changes are summarized in Table 2. Connectivity of the ipsilesional M1 with the contralesional thalamus, SMA, and MFG showed positive correlation with later motor improvement. R^2 statistics were 0.8400, 0.7821, and 0.7111 for the thalamus, SMA, and MFG, respectively, in linear regression analysis or partial correlation coefficients were 0.8998, 0.8822, and 0.8311 for the thalamus, SMA, and MFG, respectively, in partial correlation analysis with control of Fugl-Meyer assessment scores at onset.

Discussion

In the current study, we investigated (1) differences in resting-state functional connectivity between patients and healthy subjects during the period after stroke; and (2) a prognostic value of initial resting-state functional connectivity for assessment of later motor improvement. Our results demonstrated characteristic asymmetry of resting-state functional connectivity of the ipsilesional M1 in patients with stroke, which lasted until 6 months after onset. Connectivity with subcortical SMN areas such as the cerebellum and thalamus increased at the early stage of stroke. On the other hand, connectivity with ipsilesional cortical areas increased and connectivity with contralesional cortical areas decreased. Preservation of connectivity with the contralesional thalamus, SMA, and MFG at an early stage of stroke was meaningful for later motor recovery in these patients.

If resting-state fMRI activity reflects neuronal baseline activation, changes in resting-state connectivity may be

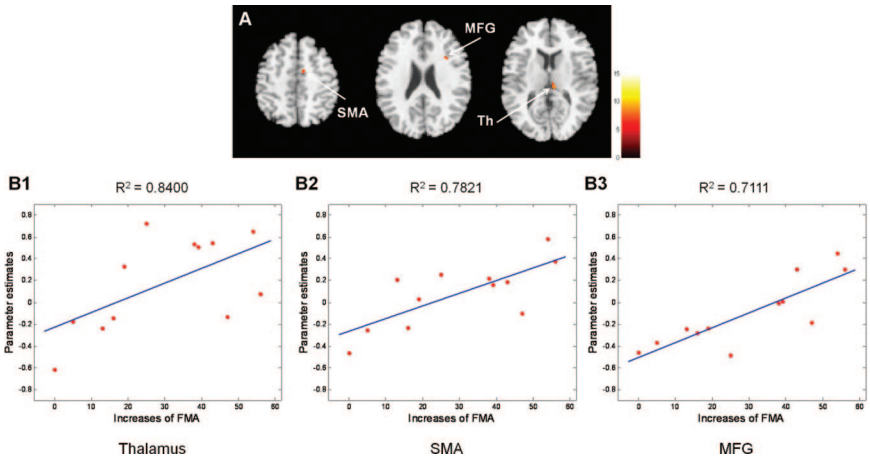

Figure 4. A, Significant positive correlations of patients' resting-state functional connectivity at onset with later motor improvement, as indexed by changes in the Fugl-Meyer assessment score for 6 months after onset. **B**, Linear regression of functional connectivity in the thalamus (B1), SMA (B2), and MFG (B3) on increases in the Fugl-Meyer assessment score. The goodness of fit for each linear regression was given by the R^2 statistic. Th indicates thalamus; SMA, supplementary motor area; MFG, middle frontal gyrus.

Table 2. Cluster Maxima Showing a Significant Positive Correlation Between Patients' Resting-State Functional Connectivity at Onset and Later Motor Improvement as Indexed by Changes in the Fugl-Meyer Assessment Score for 6 Months After Onset

			Peak MNI Coordinates, mm					
Brain Region	BA	Side	x	y	z	Voxel Count	Z-Score	*P*
Thalamus		C	8	−26	12	18	3.7726	0.0001
SMA	6	C	10	−6	54	15	3.5941	0.0002
MFG	48	C	34	16	26	16	3.1698	0.0008

MNI indicates Montreal Neurological Institute; BA, Brodmann area; SMA, supplementary motor area; MFG, middle frontal gyrus; C, contralesional.

related to functional changes in the brain. Previous studies using resting-state fMRI have demonstrated differences in the default-mode network in Alzheimer disease[20] and connectivity of the dorsal anterior cingulate cortex in attention deficit hyperactivity disorder,[26] implying pathophysiology of disease. Correspondence of the regions involved in the current resting-state connectivity study with previous motor task activation studies implies that stroke also influences resting-state connectivity in reference to functional impairment. In previous task-based fMRI studies, activation of the contralesional sensorimotor cortex showed an initial increase and then decreased or vanished in correspondence with functional restoration of the perilesional cortex and the ipsilesional M1.[2] In the current study, decreased connectivity between the ipsilesional M1 and contralesional hemispheric cortex was demonstrated after unilateral ischemic injury of the motor network. This finding implies that breakdown of harmonious interaction between two hemispheres at resting state may lead to alteration of the activity of the contralesional hemisphere in response to ipsilesional M1 activity.

Specifically, breakdown of harmonious interaction between both M1 could be quantitatively characterized in terms of the LI. Patients' functional connectivity between the ipsilesional and contralesional M1 was more highly lateralized to the ipsilesional M1 at onset, compared with healthy subjects, and showed the greatest asymmetry at 1 month after onset. Restoration of relatively symmetrical connectivity since 3 months after onset may be achieved after widespread reorganization in the sensorimotor system. That is, in the process of recovery after stroke, increased asymmetry in functional connectivity between both hemispheres in resting-state fMRI is considered to correspond to rearrangements of activation over the bihemispheric sensorimotor system in task-based fMRI.

Changes in connectivity of the ipsilesional M1 with the nonprimary SMN regions such as the frontal and parietal cortices and occipital cortex were observed; these may reflect plastic changes to compensate for impaired connectivity with the contralesional hemisphere or response to disconnection of transcallosal inhibition. These findings coincide with previous task-based fMRI studies that reported increased activation of the frontoparietal cortex[10] and other nonmotor brain areas such as the occipital cortex[6] in association with motor tasks in patients with stroke. Changes in involvement of the cerebellum and thalamus after stroke have also been demonstrated in previous task-based fMRI studies of motor recovery.[2,6,10] In particular, activation of the cerebellum was correlated with later motor recovery.[27] Taken together, resting-state SMN connectivity appears to reflect abnormalities of motor network interaction after stroke as well as plastic changes in response to motor network impairment. In addition, these changes appear to have an association with changes in brain activation provoked by performance of overt motor tasks.

In addition, regression analysis showed that preservation of connectivity of the ipsilesional M1 with the contralesional thalamus, SMA, and MFG at an early stage of stroke was positively correlated with later motor improvement at 6 months after stroke. The crucial role of the SMA in motor recovery has been demonstrated in previous task-based fMRI studies of patients with stroke in which early involvement of the SMA in the process of stroke recovery[2] and correlation of initial activation of the SMA with motor recovery[28] were described. The MFG is not regarded as a primary SMN region; however, recruitment of the MFG may be helpful in reinforcement of the management of cognitive load required for motor performance.[10] In the case of the thalamus, despite its important contribution to processing and relay of sensorimotor information, the role of the thalamus in recovery of motor function has not yet been established. Strong recruitment of regions related to sensory integration such as the thalamus at an early stage of stroke, as shown in the current study, may suggest a beneficial effect of sensory-related areas on later motor restoration in patients with stroke. For detailed clarification of the role of those regions, further investigation should be invited.

With a view that motor recovery corresponds to reorganization of surviving neuronal networks over the bihemispheric sensorimotor system, overall patterns of use of neuronal resources should be examined with respect to functional specialization and integration. Results of the current study are distinctive; however, they are comparable with those of previous task-based fMRI studies by a plausible association between resting-state connectivity and motor task activation.

Despite its novel results, the current study has some limitations in presenting results that cover various patterns of stroke recovery. Due to a high dropout rate in long-term follow-up over a period of 6 months, we only had final resting-state fMRI data for 12 patients. Most dropouts were due to patients' circumstances. Still, with resting-state fMRI, recruitment of different subgroups of patients with uniform characteristics and careful control during follow-up appear to be requirements for successful explanation of different stroke recovery patterns.

Another limitation is that, in the current study, we did not specifically measure physiological noise such as cardiac and

respiratory cycles. It has previously been proclaimed that cardiac[29] and respiratory[30] cycles can obscure detection of low-frequency fluctuations in resting-state fMRI and, thus, induce changes in resting-state connectivity, although resting-state connectivity cannot be explained by cardiorespiratory effects alone.[31] Therefore, investigation of resting-state connectivity corrected for cardiorespiratory effects would provide us with better information and is recommended for future study.

Conclusions

Stroke recovery might be time-dependent and affected according to task parameters. In this study, we attempted to overcome these critical issues through longitudinal resting-state fMRI. Although the implications of resting-state fMRI are still under dispute, systematic assessment of initial resting-state functional connectivity may provide prognostic insight for later motor recovery. In addition, practical values of the resting-state fMRI study, free from a number of confounds that are associated with task performances, may enable thorough long-term follow-up in patients with severe motor impairment at onset of stroke.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL.

Supplemental Table. Cluster maxima showing the significant differences in resting-state functional connectivity between patients and healthy subjects.

Time	Brain region	BA	Side	Peak MNI coordinates (mm)			Voxel count	Z-score	p-value
				x	y	z			
Onset	*Patients > healthy subjects*								
	MFG	9, 45, 46	I	-38	48	18	251	4.3523	0.0000
	Thalamus		I	-16	-18	10	111	4.3705	0.0000
	Cerebellum		I	-36	-78	-44	78	4.6893	0.0000
			I	-18	-80	-34	58	3.9953	0.0000
			C	18	-82	-48	68	3.6710	0.0001
	Patients < healthy subjects								
	Occipital cortex	27, 30, 37	C	10	-38	-4	143	4.6346	0.0000
		18, 19	I	-34	-86	8	67	4.2580	0.0000
		19, 37	I	-30	-60	-18	36	3.9377	0.0000
		18	I	-24	-82	-6	81	3.8865	0.0001
		19	C	28	-80	26	123	3.7013	0.0001
		18	C	22	-86	-8	30	3.5099	0.0002
	PPC	7, 40	C	28	-54	52	39	3.8708	0.0001
	SMC	3, 4	I	-52	-12	42	31	3.5819	0.0002
1 month	*Patients > healthy subjects*								
	PPC	7, 39, 40	I	-46	-56	38	316	4.6086	0.0000
		39, 40, 48	C	56	-50	40	155	4.1949	0.0000
		7, 40	I	-40	-62	56	62	3.7263	0.0001
	Cerebellum		I	-38	-78	-40	35	4.0493	0.0000
			C	44	-70	-36	41	3.6536	0.0001
	Patients < healthy subjects								
	Occipital cortex	19, 37	C	22	-52	4	88	4.4688	0.0000
		27, 30, 37	C	12	-36	-2	99	4.3705	0.0000
		18, 19	C	36	-86	16	63	4.1732	0.0000
		19	C	18	-86	46	43	3.8681	0.0001
		7, 19	C	26	-74	42	30	3.7282	0.0001
	SMC	3, 4, 48	C	52	-20	34	70	4.2323	0.0000
	PPC	2, 3, 40	C	30	-42	52	60	3.8407	0.0001
	MFG	11, 38, 48	C	24	20	-20	58	4.6086	0.0000
		10	I	-8	64	4	33	3.7786	0.0001
		10, 11	I	-8	50	-14	57	3.6305	0.0001
3 months	*Patients > healthy subjects*								
	Cerebellum		C	26	-58	-54	40	4.2989	0.0000
			C	20	-48	-40	48	4.2593	0.0000
			I	-34	-78	-40	39	4.1426	0.0000
			C	16	-80	-50	60	4.1243	0.0000

SUPPLEMENTAL MATERIAL.

			I	-20	-34	-48	77	4.0609	0.0000
			I	-42	-54	-52	29	3.7547	0.0001
	MFG	9, 46	I	-38	38	36	35	3.5571	0.0002
	Thalamus		C	18	-18	8	33	4.3602	0.0000
	Temporal cortex	37, 39	I	-52	-64	16	26	3.7334	0.0001
	Patients < healthy subjects								
	SMC	3	C	42	-30	60	27	3.7876	0.0001
6 months	*Patients > healthy subjects*								
	Cerebellum		I	-36	-78	-40	101	4.2081	0.0000
			I	-2	-72	-10	33	3.9546	0.0000
			I	-28	-52	-42	26	3.7464	0.0001
	PPC	22, 40, 48	I	-66	-40	22	74	4.1617	0.0000
	Patients < healthy subjects								
	MFG	10, 11	I	-10	50	-14	474	4.7508	0.0000
		11, 38, 48	C	22	18	-20	37	4.3602	0.0000
	SMC	2, 3, 4	C	48	-20	46	189	4.3543	0.0000
		6, 43, 48	C	50	-2	20	39	4.1862	0.0000
		4, 6	I	-50	-2	36	37	3.8871	0.0001
	Occipital cortex	18, 19	C	18	-90	26	178	4.5855	0.0000
		18, 19	C	36	-88	12	37	4.0220	0.0000
	PPC	5, 7, 40	C	22	-58	50	160	3.6941	0.0001

BA, Brodmann's area; MNI, Montreal Neurological Institute; MFG, Middle frontal gyrus; PPC, Posterior parietal cortex; SMC: sensorimotor cortex; I, Ipsilesional; C, Contralesional

Full Article

脳卒中後の運動回復過程における MRI 安静時機能的結合の長期的変化

Longitudinal Changes of Resting-State Functional Connectivity During Motor Recovery After Stroke

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背景および目的：機能的 MRI（fMRI）検査により，脳卒中患者における運動回復の神経メカニズムに関する重要な情報を得ることができる。安静時 fMRI は，運動課題を正しく遂行できない脳卒中患者に適用できる。本研究では，病変と同側の一次運動野（M1）の安静時機能的結合の長期的変化を調べることにより，脳卒中患者における運動回復の神経系相関を探索した。

方法：12 例の脳卒中患者を対象に，fMRI を反復した縦断的観察研究を実施した。安静時 fMRI データを 6 カ月間に 4 回取得した。患者は発症後間もなく最初の fMRI セッションに参加し，その後，発症から 1 カ月，3 カ月，6 カ月の時点でセッションに参加した。病変と同側の M1 の安静時機能的結合を評価し，健康被験者と比較した。

結果：健康被験者と比べて，患者は，病変と同側の前頭皮質および頭頂皮質，両側視床，および小脳との高い機能的結合を示した。一方，病変の対側の M1 および後頭皮質との機能的結合は脳卒中患者で低かった。同側と対側の M1 の間の機能的結合は，発症後 1 カ月で同側との非対称性が最も高かった。発症時における同側の M1 と対側の視床，補足運動野，および中前頭回との機能的結合は，脳卒中から 6 カ月後における運動回復と正の相関を示した。

結論：安静時 fMRI の結果は特有のものであるが，従来の課題ベースの fMRI と類似しており，脳卒中患者の研究における補完的かつ実用的な価値が示された。

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KEYWORDS 機能的結合，運動回復，安静時 fMRI，脳卒中

機能的 MRI（fMRI）は，脳のシステムレベルにおける脳卒中などの脳疾患後の回復の根底をなす神経基質およびメカニズムを明確にするうえで不可欠な役割を果たしてきた。皮質の再構築は，脳卒中後の運動回復期に脳活動の変化が観察されることを特徴とするとされている[1-6]。運動賦活課題を用いた fMRI 検査は，強制誘導運動療法[7]，トレッドミル訓練[8]，反復経頭蓋磁気刺激[9]などの，特定の治療的介入の効果を調べるために行われている。これらの検査は，こうした介入に関連する回復のメカニズムに焦点をあてたものである。

一方，脳卒中後の回復に関連した脳活動の変化を評価するための縦断的研究が行われている。脳活動は当初，病変の対側に移行し，その後，病変と同側の活動に進展すること[1,2]，健康被験者では賦活されない領域も動員されること[10]，また，運動回復期には同側の生存領域が重要であることが[11]，課題ベースの fMRI により証明されている。しかし，これらの報告では，脳の賦活結果に一定のばらつきが認められる。受動的運動[4]や運動イメージ[5]が代替法として提唱されているが，このばらつきの 1 つの理由は，多様な賦活パラダイムの使用が結果の適切な比較を妨げることによる。さらに，課題ベースの fMRI を用いた縦断的研究は，重度の障害を有する脳卒中患者に対してはその適用が限られ，また，回復中の課題処理能力の変化も結果と交絡する可能性がある。

安静時 fMRI は最近発展をみせている方法であり，離れた脳領域間の機能的結合が低周波変動に基づいて抽出される。安静時の fMRI 信号の意義については最初の試み以来議論がなされているが[12]，安静時の変動は課題遂行中の神経細胞活動に対応していることがこれまでのエビデンスから示唆されている[13]。安静状態の方法論的利点は，明白な課題や外部からの入力なしに実施できることである。このため，意識不明の患者，乳幼児[14]，さらには実験動物[15]にさえ適用できる。

健康被験者においては，安静時 fMRI は機能的結合について顕著な整合性を示すが[16,17]，高齢集団内や[18]，鍼治療[19]などの介入後には有意な差が認められた。安静時

fMRI はアルツハイマー病[20]，注意欠陥多動性障害[21]，うつ病[22]，統合失調症[23]など，さまざまな神経障害を有する患者において独特な変化を示している。

重度の運動障害を有し発症の初期段階で fMRI の賦活課題を遂行できなかった脳卒中患者の場合でも，安静時 fMRI の使用によって長期追跡調査が実施可能になると予想される。このため，本研究では，脳卒中後における運動回復の神経系基盤を描くため，脳卒中患者を対象に安静時 fMRI の長期追跡調査を行うことを目的とした。脳卒中患者における病変と同側の一次運動野（M1）の機能的結合を解析し，健康被験者と比較した。また，脳卒中からの回復の根底となるメカニズムとして可能性の高い提案をするため，脳卒中から 6 カ月後の長期的な運動回復に関連する神経系相関を検討した。

方　法

被験者

初発脳卒中を発症した合計 51 例の患者について適格性を評価した。選択基準は以下の通りとした：(1) 虚血性脳卒中の発症から 2 週未満である；(2) 一側性のテント上病変；(3) 病変と対側の上下肢の中等度から重度の運動障害；(4) 年齢 18 歳超かつ 75 歳未満。除外基準は以下の通りとした：(1) 臨床的に重要な，もしくは不安定な医学的状態；(2) 脳卒中以外の精神神経系併存疾患；(3) MRI の禁忌。51 例中 25 例の患者が除外され，26 例が本研究に登録されたが，14 例が追跡調査期間中に脱落した。最終的に，テント上病変を有する 12 例の虚血性脳卒中患者（男性 5 例，女性 7 例，58.4 ± 6.9 歳）が縦断的 fMRI 検査を完了し，これらの患者の画像データを解析に組み入れた（図 1，表 1）。また，精神医学的または神経学的に問題となる既往歴の報告がない 11 例の健康被験者（男性 3 例，女性 8 例，52.1 ± 9.4 歳）を，年齢が一致した対照群として組み入れた。研究は各参加者の理解と同意書を得て行われ，治験審査委員会から倫理的承認を得た。

実験デザイン

本研究は，反復 fMRI 実験の実施のための縦断的観察研究としてデザインされた。また，脳卒中患者のデータと健康被験者のデータを比較するための横断的比較試験デザインも適用した。

fMRI データの取得

脳卒中患者において，安静時 fMRI データを 6 カ月間に 4 回，長期的に取得した。患者は発症後間もなく（10.5 ± 4.3 日）最初の fMRI セッションに参加し，その後，発症から 1 カ月，3 カ月，6 カ月の時点でさらにセッションに参加した。健康被験者については，安静時 fMRI データを 1 回取得した。

安静状態時に，目を閉じて動かずにいるように被験者に指示した。3 T で動作する Philips ACHIEVA MR スキャナー（Philips Medical Systems, オランダ，ベスト市）を用いて fMRI データを取得した。各セッションで，T2* 強調グラディエントエコー・エコープラナーイメージングシーケンス（繰り返し時間＝ 3,000 ms，エコー時間＝ 35 ms，スライス数＝ 35，スライス厚＝ 4 mm，マトリックスサイズ＝ 128 × 128，視野＝ 220 × 220 mm）を用いて合計 100 枚の画像を撮影した。

行動評価

fMRI データの取得と同じ日に，上肢および下肢の Fugl-Meyer 評価[24]を用いて運動障害の程度のスコアをつけた。

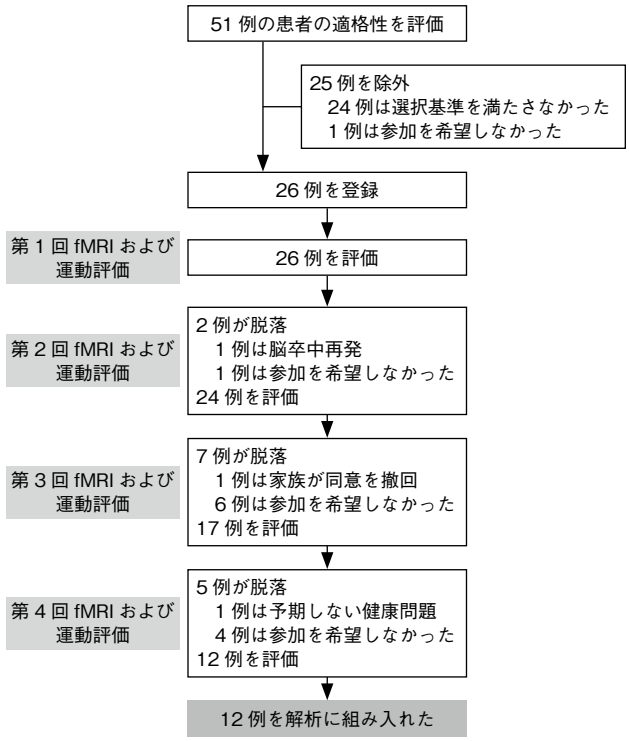

図 1　反復機能的 MRI（fMRI）検査を行う縦断的観察研究の患者登録プロセス。初発の脳卒中を発症した合計 51 例の患者について適格性を評価した。51 例中 25 例の患者が除外され，14 例がフォローアップ fMRI 検査中に脱落した。最終的に，12 例の虚血性脳卒中患者が縦断的 fMRI 検査を完了した。安静時 fMRI データの取得は，Fugl-Meyer 評価を用いた行動評価とともに発症から 2 週間以内に実施し，その後は発症から 1 カ月，3 カ月，6 カ月の時点で実施した。

表 1 患者背景および運動機能

患者番号	性別	年齢（歳）	病変	FMA スコア 発症	1 カ月	3 カ月	6 カ月	FMA の変化
1	F	66	L MCA 梗塞	8	8	19	27	19
2	F	61	L MCA 梗塞	20	22	27	33	13
3	F	55	R MCA 梗塞	30	55	70	73	43
4	M	74	L CR 梗塞	16	22	17	21	5
5	F	58	L MCA 梗塞	36	42	52	52	16
6	F	47	L MCA 梗塞	44	59	100	100	56
7	M	55	L ACA 梗塞	19	42	60	73	54
8	M	62	L MCA 梗塞	19	22	52	57	38
9	M	59	R MCA 梗塞	24	24	24	24	0
10	F	52	R CR 梗塞	52	52	99	99	47
11	M	57	L MCA 梗塞	13	13	52	52	39
12	F	55	R SC 梗塞	9	9	34	34	25
平均値± SD	M＝5; F＝7	58.4 ± 6.9		24.2 ± 13.8	30.8 ± 18.3	50.5 ± 28.5	53.8 ± 27.7	29.6 ± 19.1

FMA：Fugl-Meyer 評価，F：女性，M：男性，L：左，R：右，MCA：中大脳動脈，CR：放射冠，ACA：前大脳動脈，SC：線条体内包，FMA の変化：6 カ月時の FMA 総スコアー発症時の FMA 総スコア。

fMRI データの解析

fMRI データは SPM8（ウェルカムトラスト神経画像センター，ユニヴァーシティ・カレッジ・ロンドン，英国ロンドン）および AFNI（Scientific and Statistical Computing Core，米国国立精神保健研究所，メリーランド州ベセスダ）ソフトウェアを用いて前処理した。前処理の手順には，一連の画像の平均容積への空間再構成，MNI テンプレート脳と同じ座標フレームへの標準化，0.01 ～ 0.08 Hz のバンドパスフィルタリング，半値全幅 8 mm のガウスフィルターを用いた平滑化が含まれた。

M1 の機能的結合を明らかにする相関係数のマップを取得するため，基準となる M1 の経時的推移と脳のすべてのボクセルの経時的推移との相関解析を行った。基準となる経時的推移は，脳卒中患者の病変と同側の M1 および健康被験者の左 M1 から抽出した。M1 は，中心溝の前壁に沿った中心前回の尾側半分をほぼカバーするボクセルを含むものと定義した。頭部の動きと全体的変動に対応する経時的推移を回帰推定することにより，経時的推移の修正を行った。

$z = \tanh^{-1} r$ または $z = (1/2)\ln[(1+r)/(1-r)]$（$r$：相関係数，$z$：近似的なガウス分布の値，$\tanh^{-1}$：逆双曲正接関数，ln：自然対数関数）で定義される Fisher の z 変換により，相関係数マップをガウス分布の値のマップに変換した[25]。右側に病変を有する患者については正中矢状線を中心にして右から左へマップを反転させることにより，相関マップの病変側を左側に設定した。

Fisher の z 変換を行い反転させた相関マップを使用して変量効果解析を行った。二標本 t 検定を行い，患者と健康被験者との間で機能的結合に有意差が認められる領域を探した。また，運動の改善と相関した脳領域を探すため，発症時の患者の相関マップを脳卒中から 6 カ月後の Fugl-Meyer 評価スコアの上昇により回帰推定した。有意性の決定には，高さ（ボクセルレベルで未補正の $p < 0.001$）および程度（クラスタレベルで未補正の $p < 0.05$）の閾値を使用した。

Lateralization Index

機能的結合の定量的尺度として，各相関マップについて Lateralization Index（LI：優位側の指標）を算出した。LI を取り入れたのは，（病変と同側 M1 の結合ボクセル数 / 病変と同側 M1 の総ボクセル数）－（対側 M1 の結合ボクセル数 / 対側 M1 の総ボクセル数）という定義に従い，同側と対側の M1 間の機能的結合の非対称性を明確に記述するためである。同側 M1 と評価するボクセルとの機能的結合が，マップ内のすべてのガウス分布の値を考慮した時にガウス分布の 95 パーセンタイルを超える場合，そのボクセルは結合されていると判断した。この方法により得られた LI は－1 から 1 の範囲であり，ここでは－1 は対側の結合のみを表し，1 は同側の結合のみを表し，0 に近い値は対称的な結合を表す。患者の LI を各時点で評価し，健康被験者の LI と比較した。

結　果

患者と健康被験者との結合の差

11 例の健康被験者から取得したデータの相関解析の結

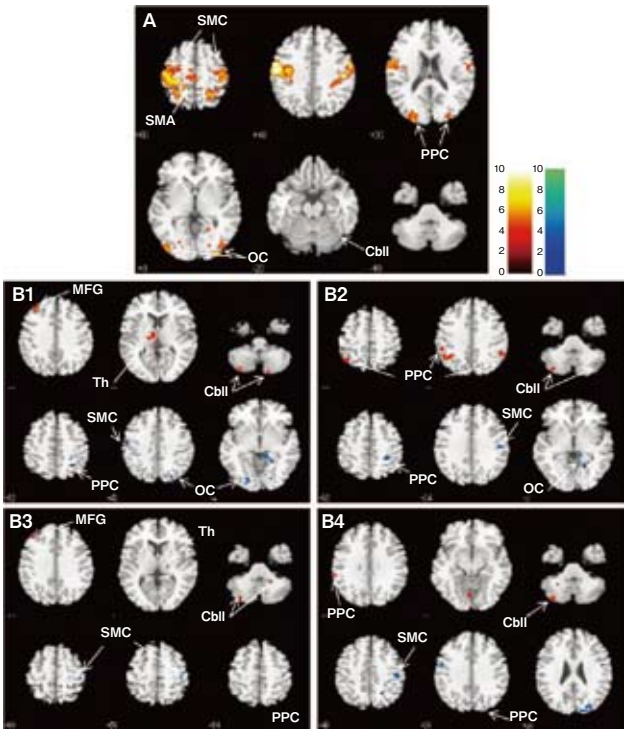

図 2　A，健康被験者における病変と同側の一次運動野の安静時機能的結合により得られた感覚運動ネットワーク。B，発症時（B1），発症から 1 カ月後（B2），3 カ月後（B3），6 カ月後（B4）の 4 つの時点における患者と健康被験者の安静時機能的結合の有意な差。赤 - 黄色の小塊は健康被験者と比較して患者の機能的結合が高いことを示し，青 - 緑色の小塊は健康被験者と比較して患者の機能的結合が低いことを示す。脳の左側が病変と同側の半球である。SMC：感覚運動野，SMA：補足運動野，PPC：後頭頂皮質，OC：後頭皮質，CbII：小脳，MFG：中前頭回，Th：視床。

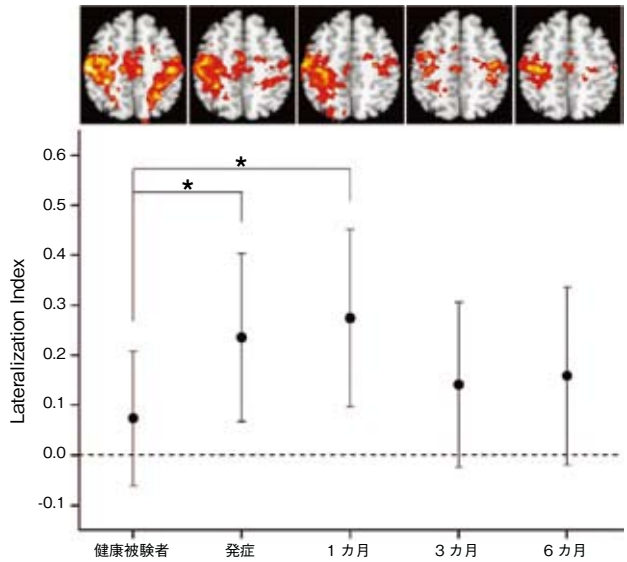

図 3　安静時機能的結合の経時的変化。Lateralization Index（LI）による定量的変化と，対応する機能的結合のマップを示す。発症時，発症から 1 カ月後，3 カ月後，6 カ月後の 4 つのタイムポイントで患者と健康被験者の LI を比較した。この LI のグラフの丸印は平均値を表し，エラーバーは標準偏差を，星印は $p < 0.05$ の閾値での患者と健康被験者との有意差を表す。

果は分散したネットワーク，すなわち感覚運動ネットワーク（sensorimotor network：SMN）を示した。これを図 2A に示す。健康被験者の SMN には，一次感覚運動野，運動前野，補足運動野（supplementary motor area：SMA），帯状皮質運動野，二次体性感覚皮質，小脳，基底核，視床，前頭皮質および頭頂皮質，線条皮質および外線条皮質などの運動 - 感覚に関連した領域が含まれた。脳卒中患者の SMN は非対称的な関与を示し，6 カ月の期間全体を通じてその他の領域がさらに含まれた。図 2B に，4 つの時点での脳卒中患者と健康被験者の結合の比較を示す。SMN における結合の有意差は supplement に要約している（補足の表 I，http://stroke.ahajournals.org）。脳卒中患者は発症以降，病変と同側の M1 と感覚運動野，後頭皮質，中前頭回（middle frontal gyrus：MFG），後頭頂皮質との結合の減少を示した。その一方で，脳卒中患者は発症以降，病変と同側の M1 と小脳，視床，MFG，後頭頂皮質との結合の増加を示した。特に，感覚運動野との結合の減少と小脳との結合の増加は発症後 6 カ月間の期間全体を通して持続した。全般に，同側の M1 の結合は同側の脳領域内で増加し，病変と対側の脳領域内で減少したと考えられる。

結合の経時的変化

図 3 に，LI の経時的変化と，対応する機能的結合のマップを示す。患者の LI は健康被験者と比べて発症時に高く，発症から 1 カ月後にはさらに高かった。発症から 3 カ月後および 6 カ月後には患者の LI は低下し，健康被験者との有意差はなくなった。対応する機能的結合のマップでも，発症から 1 カ月後までは病変と同側および対側の M1 間の機能的結合に非対称性が増加し，その後減少した。

発症時の結合とその後の運動改善との相関

図 4 に，発症から 6 カ月後の Fugl-Meyer 評価スコアの上昇を指標として，発症時の機能的結合とその後の運動の改善との間に正の相関が認められた脳領域を示す。Fugl-Meyer 評価の変化と有意な相関を示す脳領域を表 2 に要約する。病変と同側の M1 と対側の視床，SMA，MFG との結合は，その後の運動の改善と正の相関を示した。線形回帰分析での R^2 統計量は視床，SMA，MFG についてそれぞれ 0.8400，0.7821，0.7111 であり，また，発症時の Fugl-Meyer 評価スコアを対照とした偏相関分析での偏相関計数は視床，SMA，MFG についてそれぞれ 0.8998，0.8822，0.8311 であった。

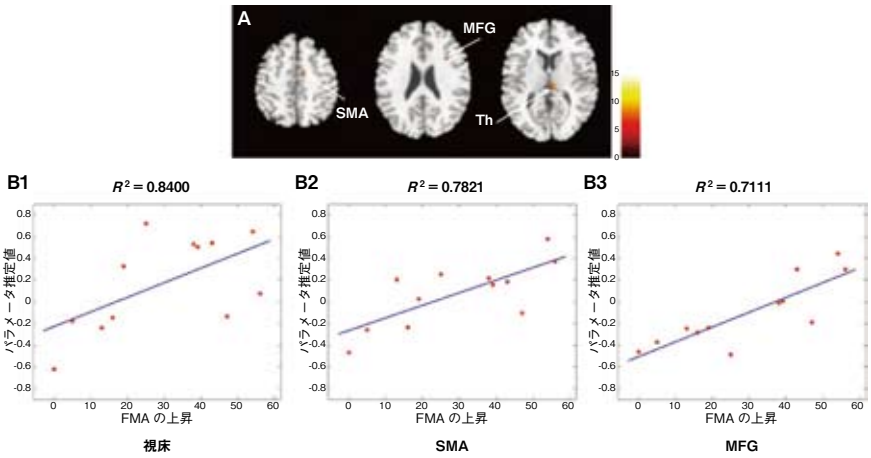

図 4 A，発症から 6 カ月間の Fugl-Meyer 評価スコアの変化を指標とする，発症時の患者の安静時機能的結合とその後の運動の改善との有意な正の相関。B，Fugl-Meyer 評価スコアの上昇に対する視床（B1），SMA（B2），MFG（B3）における機能的結合の線形回帰。各線形回帰の適合度を R^2 統計量により示した。Th：視床，SMA：補足運動野，MFG：中前頭回。

考　察

本研究では，(1) 脳卒中後の期間中の患者と健康被験者との安静時機能的結合の差，および (2) その後の運動改善を評価するための初期の安静時機能的結合の予後予測能を調べた。本研究の結果，脳卒中患者において病変と同側の M1 の安静時機能的結合に特徴的な非対称性が示され，これは発症から 6 カ月後まで持続した。小脳や視床などの皮質下 SMN 領域との結合は，脳卒中の初期段階で増加した。他方，病変と同側の皮質領との結合は増加し，対側の皮質領との結合は減少した。脳卒中の初期段階における対側の視床，SMA，MFG との結合の保持は，これらの患者におけるその後の運動回復にとって意味をもったものであった。

安静時 fMRI 活動が神経細胞のベースラインの活動を反映しているならば，安静時機能的結合の変化は脳の機能的変化に関連している可能性がある。安静時 fMRI を用いたこれまでの研究から，アルツハイマー病におけるデフォルト・モード・ネットワーク[注)]の差や [20]，注意欠陥多動性障害における背側前帯状皮質の結合 [26] の差が示され，疾患の病態生理が示唆されている。本研究における安静時の結合に関する領域が，以前の研究における運動課題の脳賦活に関する領域と対応していることから，脳卒中は機能障害に関しても安静時の結合に影響を及ぼすことが示唆される。課題ベースの fMRI を用いた以前の研究では，病変と対側の感覚運動野の活動が最初は上昇し，続いて，病変周囲の皮質および病変と同側の M1 の機能回復に対応して低下または消失した [2]。本研究では，運動ネットワークの一側性虚血傷害後に，同側の M1 と対側大脳半球皮質の間に結合の減少が示された。この所見は，安静状態における 2 つの大脳半球間の調和した相互作用が途絶えると，同側 M1 の活動に呼応して対側大脳半球の活動が変化する可能性があることを示唆している。

特に，両側 M1 間の調和した相互作用の途絶は，LI に関して定量的に特徴付けることができると思われる。患者において同側と対側の M1 間の機能的結合は，健康被験者と比べて，発症時には同側 M1 がより優位であり，発症から 1 カ月後に最大の非対称性を示した。発症後 3 カ月以降の比較的対称的な結合の回復は，感覚運動系の広範な再構築の後で達成されると思われる。すなわち，脳卒中後の回復過程で，安静時 fMRI にみられる両半球間の機能的結合の非対称性の増加は，課題ベースの fMRI におけ

表 2 発症から 6 カ月間の Fugl-Meyer 評価スコアの変化を指標とする，発症時の患者の安静時機能的結合とその後の運動の改善との有意な正の相関を示すクラスター最大値。

脳領域	BA	側面	ピーク MNI 座標，mm			ボクセル数	Z スコア	*p* 値
			x	y	z			
視床		C	8	− 26	12	18	3.7726	0.0001
SMA	6	C	10	− 6	54	15	3.5941	0.0002
MFG	48	C	34	16	26	16	3.1698	0.0008

MNI：モントリオール神経学研究所，BA：ブロードマン領野，SMA：補足運動野，MFG：中前頭回，C：病変の対側。

注：本論文で紹介されている Resting-State Functional Connectivity には，その概念が生まれた初期から Resting-State Network や Default Mode Network という用語も用いられている。

る両半球の感覚運動系活動の再構築に対応していると考えられる。

病変と同側の M1 と，前頭皮質と頭頂皮質や後頭皮質などの非一次 SMN との結合の変化が認められた。これらは，病変と対側の大脳半球との結合の低下を補うため，あるいは経脳梁抑制の断絶に対応するための可塑的変化を反映したものと思われる。これらの所見は，脳卒中患者における運動課題と関連して前頭頭頂皮質[10]や後頭皮質などのその他の非運動野[6]の活動の上昇を報告した課題ベースの fMRI を用いた以前の研究と一致している。脳卒中後の小脳および視床の関与の変化も，運動回復に関する課題ベースの fMRI を用いた以前の研究で示されている[2,6,10]。特に，小脳の活動はその後の運動回復と相関していた[27]。これらを総合すると，安静時の SMN の結合は，脳卒中後の運動ネットワークの相互作用の異常ならびに運動ネットワークの障害に反応した可塑的変化を反映していると思われる。さらに，これらの変化は，明白な運動課題の遂行により誘発される脳活動の変化と関連があると思われる。

さらに，回帰分析の結果，脳卒中の初期段階における病変と同側の M1 と対側の視床，SMA，MFG との結合の保持は，脳卒中から 6 カ月後の運動の改善と正の相関を示した。脳卒中患者を対象とした課題ベースの fMRI を用いた以前の研究では，脳卒中回復のプロセスへの SMA の早期の関与[2]および初期の SMA の活動と運動回復との相関[28]が観察され，運動回復における SMA の重要な役割が示されている。MFG は一次 SMN 領域とはみなされない。しかし，MFG の動員は運動遂行に必要な認知的負荷の管理を強化するのに役立つ可能性がある[10]。視床の場合，感覚運動情報の処理および中継への重要な貢献にもかかわらず，運動機能の回復における視床の役割は確立されていない。本研究で示されたように，脳卒中の初期段階における視床などの感覚統合に関連した領域の強い動員は，脳卒中患者におけるその後の運動回復に対する感覚関連領域の有益な影響を示唆する可能性がある。これらの領域の役割を詳細に解明するため，さらなる研究が推奨される。

運動回復は両側大脳半球にまたがった感覚運動系の残存神経ネットワークの再構築に対応すると考えると，存在する神経細胞を使う全体的パターンを機能の分化と統合に関して検討するべきである。本研究の結果は他と一線を画すものであるが，安静時結合と運動課題の脳賦活との間の妥当と思われる関連性の点では，課題ベースの fMRI を用いた以前の研究と類似している。

斬新な結果にもかかわらず，本研究は脳卒中回復のさまざまなパターンに対応した結果を提示する点では限界がある。6 カ月間にわたる長期追跡調査での脱落率が高かったため，12 例の患者についてのみ最終的な安静時 fMRI データが得られた。ほとんどの脱落例は患者の事情によるものであった。やはり，安静時 fMRI では，均一な特徴をもつさまざまなサブグループの患者を集め，追跡調査中は綿密に管理することが，脳卒中回復のさまざまなパターンを説明するための要件と思われる。

もう 1 つの限界として，本研究では，心拍周期や呼吸周期などの生理的ノイズを特に測定しなかったことである。安静時結合は心呼吸系の影響のみで説明することはできないが[31]，これまでに心拍周期[29]および呼吸周期[30]は安静時 fMRI での低周波変動の検出を不明瞭にする可能性があり，このため，安静時結合の変化を誘発する可能性があることが明らかにされている。したがって，心呼吸系の影響について補正した安静時結合によってよりすぐれた情報が得られると思われ，将来の研究での補正が推奨される。

結　論

脳卒中の回復は時間依存性であり，課題パラメータの影響を受ける可能性がある。本研究では，縦断的な安静時 fMRI により，これらの重要な問題を克服しようと試みた。安静時 fMRI の意味するところについては依然として議論があるが，初期の安静時機能的結合の系統的評価により，その後の運動回復に対する予後的な洞察が得られる可能性がある。さらに，安静時 fMRI 検査の実用的な価値は，課題処理能力に関連したいくつかの交絡因子とは関係なく，脳卒中発症時に重度の運動障害を有する患者における詳細な長期追跡調査を可能にするかもしれない。

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情報開示

なし。

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