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

Chang-hyun Park, PhD; Won Hyuk Chang, MD; Suk Hoon Ohn, MD; Sung Tae Kim, MD; Oh Young Bang, MD, PhD; Alvaro Pascual-Leone, MD, PhD; Yun-Hee Kim, MD, PhD

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 stimulation9; 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 regions11 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 movement4 and motor imagery5 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
performance. 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, and even to experimental animals.

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

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) 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 functional MRI (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. Participants included 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 ACHEVA 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).

Behavioral Assessment

Degree of motor impairment was scored using the Fugl-Meyer assessment for upper and lower extremities 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. The lesion side of the correlation map was set...
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 contralateral 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 contralateral M1/total number of voxels in the contralateral 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 contralateral 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](http://stroke.ahajournals.org/)

**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; Cbl, cerebellum; MFG, middle frontal gyrus; Th, thalamus.

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Mean ± SD  M = 5; F = 7  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.
Patients 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
related to functional changes in the brain. Previous studies using resting-state fMRI have demonstrated differences in the default-mode network in Alzheimer disease20 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 contralateral 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 contralateral 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 cortex10 and other nonmotor brain areas such as the occipital cortex 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 recovery2 and correlation of initial activation of the SMA with motor recovery28 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 respiratory 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. 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.

References

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
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**SUPPLEMENTAL MATERIAL.**

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

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

Chang-hyun Park, PhD; Won Hyuk Chang, MD; Suk Hoon Ohn, MD; Sung Tae Kim, MD; Oh Young Bang, MD, PhD; Alvaro Pascual-Leone, MD, PhD; Yun-Hee Kim, MD, PhD

1 Samsung Biomedical Research Institute, Samsung Medical Center, Seoul, Korea; 2 Departments of Physical and Rehabilitation Medicine, Diagnostic Radiology and Imaging Science, and Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; 3 Department of Physical Medicine and Rehabilitation, Hallym University College of Medicine, Seoul, Korea; and 4 Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Boston, MA

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、運動課題を正確に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額頭皮質、両側小脳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。

Keywords:機能的結合、運動回復、安静時fMRI、脳卒中

[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]

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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。
fMRI はアルツハイマー病, 注意欠陥多動性障害, うつ病, 統合失調症など, 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。本研究では, 脳卒中後における運動回復と神経系基盤を検討し, 脳卒中患者の病変と対側の一次運動野 (M1) の機能的結合を解析し, 健康被験者を比較した。また, 脳卒中からの回復の根拠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 例の患者について選択基準を満たしたものについて選択基準を満たした被験者を評価した。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) 一侧のテント上病変; (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 歳から 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, または心臓的および神経系併存疾患; (2) 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) が選択的 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, 治験審査委員会に倫理的承認を得た。

実験デザイン

本研究は, 反復 fMRI 実験の実施のための繰返し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用いた。

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 4 回, 長期間に取得した。患者は発症後も少なくなく (10.5 ± 4.3 日) 初めて 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。fMRI 検査を行う繰返し観察研究の患者は通常, 虚血性脳卒中の発症を診断された後, fMRI の使用を考慮した。以下に fMRI の使用を確認した。Fugl-Meyer 実験を行った行動評価とともに, 脳卒中 2 週以内に実施し, その後は 1 カ月, 3 カ月, 6 カ月の時点で実施した。
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）の閾値を用いた。

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対称性の値を用いた。

Fisherのz変換を用い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、患者と健康被験者の間で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）の閾値を用いた。

### 結果

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<td>12</td>
<td>F</td>
<td>55</td>
<td>R SC梗塞</td>
<td>9</td>
<td>9</td>
<td>34</td>
<td>34</td>
<td>25</td>
</tr>
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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

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

続きした。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。

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図4に示す。発症時と同側および対側のM1の結合と機能的結合に非対称性が増加し、その後減少した。特に、発症時と対側のM1の結合と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

発症時とその後の運動改善との相関において、発症時と対側のM1の結合と機能的結合に非対称性が増加し、その後減少した。特に、発症時と対側のM1の結合と機能的結合に非対称性が増加し、その後減少した。

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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。小脳や視床などの被験下 SMN 領域との結合は、脳卒中発症初期段階で増加した。他方、病変と同側の皮質領域との結合は減少し、対側の皮質領域との結合は減少した。脳卒中発症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では、病変と対側の感覚運動野の活動が最初には上昇し、続いて、変化段階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。脳卒中の初期段階における対側の視床、SMA、MFG との結合の保有は、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では、アルツハイマー病における Default Mode Network 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と被験者の領域が、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機能的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には上昇し、続いて、変化段階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。脳卒中の初期段階における対側の視床、SMA、MFG との結合の保有は、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。

特に、両側 M1 間の調和した相互作用の途絶は、L1 に関しても定期的に特徴付けることができると考えられる。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1カ月以降の比較的対称的な結合の回復は、運動障害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 に示唆される。
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

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 MRI 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 MRI 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 MRI 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。
References