Cortical reorganization in patients with subcortical hemiparesis: neural mechanisms of functional recovery and prognostic implication

YUKIHKO FUJII, M.D., PH.D., AND TSUTOMU NAKADA, M.D., PH.D.

Center for Integrated Human Brain Science, Brain Research Institute, University of Niigata, Japan

Object. A systematic investigation on cortical reorganization in patients with hemiparesis of a subcortical origin, with special emphasis on functional correlates, was conducted using functional magnetic resonance (fMR) imaging performed on a 3-tesla system specifically optimized for fMR imaging investigation.

Methods. The study group included 46 patients with hemiparesis (25 with right and 21 with left hemiparesis) and 30 age-matched healthy volunteers as controls. All study participants were originally right handed. The characteristics of the lesion were putaminal hemorrhage in 19 patients, thalamic hemorrhage in 10 patients, and striatocapsular bland infarction in 17 patients.

Functional recovery in subcortical hemiparesis showed two distinct phases of the recovery process involving entirely different neural mechanisms. Phase I is characterized by the process of recovery and/or reorganization of the primary system. Successful recovery of this system is typically achieved within 1 month after stroke onset. Its clinical correlate is a rapid recovery course and significant recovery of function within 1 month of stroke onset. Failure of recovery of the primary system shifts the recovery process to Phase II, during which reorganization involving the ipsilateral pathway takes place. The clinical correlate of Phase II is a slow recovery course with variable functional outcome.

Conclusions. Effective functional organization of the ipsilateral pathway, as identified by linked activation of the ipsilateral primary sensorimotor cortex and contralateral anterior lobe of the cerebellum, is correlated with a good prognostic outcome for patients in the slow recovery group. A high degree of connectivity between supplementary motor areas, bilaterally, appears to influence functional recovery adversely.

Key Words • motor reorganization • stroke • hemiparesis • functional magnetic resonance imaging • high-magnetic field

There is no doubt that cortical plasticity and conncational reorganization play an essential role in the functional recovery following stroke. Thus far, however, the precise mechanisms of functional reorganization remain to be elucidated. One of the key factors governing the recovery processes in hemiparesis is believed to be the participation of the hemisphere ipsilateral to the side of the hemiparesis. Activation studies have repeatedly demonstrated prominent activation of the ipsilateral motor cortex associated with motion of the paretic hand.6,10,21,43 These observations are further supported by studies, performed with transcranial magnetic stimulation, in patients with hemiparesis who were shown to elicit muscle action potentials in ipsilateral as well as contralateral limbs, clearly demonstrating the physiological connectivity of the ipsilateral hemisphere.7,31,33 Nevertheless, to date, no definitive role of the ipsilateral hemisphere in the process of functional recovery, especially in relation to functional prognosis, has been identified.

One unique advantage of fMR imaging over other functional imaging modalities, especially when it is performed using a high-field system, is its capability of providing highly reproducible, high-resolution activation maps for an individual patient, without the necessity of applying artificial standardized maps of brain anatomy.24,28,29 This advantage is especially germane to clinical investigations of pathological conditions in which individual factors are certain to play a role. In this study we performed a systematic investigation of cortical reorganization in patients with hemiparesis of subcortical origin, with special emphasis on functional correlates, by using activation maps obtained using a 3-tesla MR imaging system.

Clinical Material and Methods

Patient Population

The study group comprised 46 patients (mean age 60 years, range 45–75 years), all of whom were right handed prior to stroke onset. Twenty-five patients had right hemiparesis and 21 had left hemiparesis. Thirty age-matched healthy, right-handed volunteers served as a control group.
The characteristics of the lesion causing paresis were putaminal hemorrhage in 19 patients, thalamic hemorrhage in 10 patients, and striatocapsular bland infarction in 17 patients. Each participant’s stated handedness was confirmed during focused interviews in which the Edinburgh inventory was used. Motor function of the paretic hand was evaluated and graded according to a modified Brunnstrom classification (Table 1). Subsequently, patients were classified into the three groups based on serial ratings of functional recovery, which was evaluated during a period lasting at least 3 months from the time of onset of stroke by examiners blinded to the fMR imaging results (Fig. 1). The first group was composed of patients with the rapid, good recoveries. Patients in this group attained good functional recoveries (Stage 5 or 6 of the modified Brunnstrom classification) within 1 month after stroke onset. The second group was composed of patients with slow, good recoveries. These patients had severe residual hemiparesis (Stages 1–4) 1 month after stroke onset, but this improved to good recovery (Stage 5 or 6) by the end of the 3rd month after stroke onset. The third group was composed of patients with slow, poor recoveries. Patients in this category had severe residual hemiparesis (Stages 1–4) 1 month after stroke onset, and continued to display significant deficits (Stages 1–4) at the end of the 3rd month poststroke. Patients were examined and rated at weekly intervals for the first 4 weeks after stroke onset and at 2 to 3-week intervals thereafter for a total of at least 3 months. All patients were treated using a similar rehabilitation protocol.

Data Acquisition

A research MR imaging system (Signa; General Electric Medical Systems, Waukesha, WI) with a superconductive magnet operated at 3 tesla (Magnex, Yarnton, UK) was used to perform all imaging studies. To ensure that patients had reached maximum functional recovery, fMR imaging studies were performed 3 to 6 months after stroke onset. Studies were performed in compliance with the human research guidelines of the internal review board of the University of Niigata. For evaluation of motor cortical function, the self-paced grasp task was chosen to minimize effort on the part of the study participants. The participants were instructed to perform self-paced grasps at a rate of approximately one grasp per second. If this rate resulted in great effort, the participants were told to adjust their grasp rate. Once the rate (adjusted if necessary) was established, the participants were asked not to change the rate within and between sessions. Study participants underwent several trial runs both inside and outside the magnet before the fMR imaging studies were performed to ascertain the patients’ and volunteers’ proper understanding and performance. Their performance during fMR imaging studies was monitored using a charge-coupled device camera and the grasp rate was recorded for each session. Participants who exhibited more than a 10% difference in rate within or between sessions, compared with the mean, repeated the session. No mirror movements (associated contralateral hand movements) were observed in any patient. Each session consisted of multiple 30-second epochs. A total of nine 30-second epochs were organized in a boxcar configuration with an RMRMRMR sequence, in which R and M indicated rest and motion, respectively. Gradient-echo echo–planar images were obtained using the following parameter: field of view 40 × 20 cm, matrix 128 × 64, slice thickness 5 mm, and TR 1 second. Spatial resolution was approximately 3 × 3 × 5 mm. To obtain high-field homogeneity, each slab was restricted to 30 mm. Four consecutive 5-mm slices with an interslice gap of 2.5 mm were obtained during a single session. Sessions that demonstrated brain motion exceeding 0.6 mm were repeated to avoid pixel misalignment being mistaken for activation.

Statistical Analysis

Statistical analysis of the data was conducted at two levels. First, task-related activation was evaluated on an individual basis. Subsequently, the data from each participant were incorporated into a second-level analysis of group effects. This multiparticipant analysis was performed on the basis of the activation frequency in the motor areas by using a multiple comparison method.

Individual Analysis. Functional MR imaging time series data, consisting of consecutive echo–planar images for each slice, were analyzed using appropriate computer software (SPM99; Wellcome Department of Cognitive Neurology, London, UK). Data smoothing was accomplished using a 3-mm full width at half maximum kernel. Statistical analysis was performed using a delayed boxcar hemodynamic
model function in the context of the general linear model, used by the SPM99 software. To minimize the effects of physiological noise, a high-pass filter and global normalization (proportional scaling) were applied within the design matrix. Signals were proportionally scaled by setting the whole-brain mean value to 100 arbitrary units. Specific effects were tested by applying appropriate linear contrasts to the parameter estimates for each condition, yielding a t statistic for each and every voxel. These t statistics, which were transformed to Z statistics, constituted an activation map (fMR images). Functional maps were presented as the contrast between two specified conditions and demonstrated activated areas that conformed to the statistical criteria of significance (p < 0.0001). Data were analyzed and reproducibility was confirmed for each participant individually. Anatomical identification of activated areas was performed on an individual basis by mapping sites of activation onto high-resolution anatomical images obtained in the same individual by using identical coordinates. All individual activation patterns were determined using fMR imaging studies performed 3 to 6 months after stroke onset.

**Multipaticipant Analysis.** The activation was defined as positive if the cluster of activation at the given volume of
Cortical reorganization

**Results**

Based on the serial functional ratings described in *Clinical Material and Methods*, three distinct time courses of functional recovery rates were identified and are schematically shown in Fig. 1. Representative fMR images of individuals (healthy volunteers and patients with right or left hemiparesis) are shown in Fig. 2. The results of the multiparticipant analysis are summarized in Tables 2 through 4 and key findings are schematically presented in Figs. 3 through 5. In these figures, the size of each circle provides a relative indication of the number of participants in whom activation of the indicated anatomical site was observed.

### Multiparticipant Analysis

The data sets containing individual activation maps and their activation frequencies were statistically analyzed from both temporal (Table 2) and functional (Table 3) standpoints.

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (%) of cortical activation associated with hand motion in 30 healthy volunteers and 46 patients with hemiparesis who attained rapid or slow functional recoveries*</td>
</tr>
<tr>
<td>Motor Areas</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Grasp Side</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

* All patients who suffered strokes were right handed before injuries. Abbreviations: ACL = anterior cerebellar lobe; pts = patients.
† Significantly different (p < 0.05) from healthy volunteers (Ryan multiple comparison).
‡ Significantly different (p < 0.05) from patients with rapid recoveries (Ryan multiple comparison).

### Motor Cortical Function and Recovery Time

To evaluate associations between the changes in motor cortical function and the time interval from stroke onset to recovery, the frequency of activation associated with the hand-motor task was statistically assessed in healthy volunteers, patients with rapid recoveries, and patients with slow recoveries. In the rapid-recovery patient group, regardless of the side of the stroke, almost no significant difference was observed in activation frequency compared with the healthy volunteer group (Table 2 and Figs. 3 and 4). The frequency of activation associated with motion of the paretic hand in the slow-recovery patient group was significantly higher in the ipsilateral SM1 and SMA and the contralateral anterior cerebellum than in corresponding sites in healthy volunteers. Regardless of final clinical outcome, the slow-recovery patient group exhibited a significantly higher frequency of ipsilateral hemispheric activation compared with healthy volunteers. The frequency of paradoxical ipsilateral SM1 activation associated with motion of the nonparetic hand increased significantly during left-hand motion in patients with right hemiparesis, but not during right-hand motion in patients with left hemiparesis. (Recall that all stroke patients were right handed before onset of hemiparesis.)
with patients who did not regain significant functional recovery and those who eventually displayed significant recovery. The ipsilateral SM1 and contralateral anterior cerebellum was involved much more and with a higher frequency of activation associated with motion of the paretic hand than patients who made rapid recoveries. Patients with slow, poor recoveries, and those with slow, good recoveries were evaluated statistically (Table 3 and Fig. 5). Patients with slow, poor recoveries (14 patients) and slow, good recoveries (16 patients) demonstrated a higher frequency of ipsilateral (SM1 and SMA) activation and coactivation of the ipsilateral SM1 and the contralateral anterior cerebellum than patients who made rapid recoveries; and slow, good recoveries were further assessed using principal component analysis in stroke patients.

### Motor Cortical Function and Functional Recovery

To assess associations between changes in motor cortical function and functional recovery, the activation frequencies among patients with rapid recoveries, those with slow, poor recoveries, and those with slow, good recoveries were evaluated statistically (Table 3 and Fig. 5). Patients with slow, good recoveries exhibited a significantly higher frequency of ipsilateral (SM1 and SMA) activation and coactivation of the ipsilateral SM1 and the contralateral anterior cerebellum associated with motion of the paretic hand than patients who made rapid recoveries. Patients with slow, poor recoveries also demonstrated a higher frequency of ipsilateral SM1 activation associated with motion of the paretic hand than those with rapid, good recoveries. The frequency of ipsilateral hemispheric activation and coactivation of ipsilateral SM1 and contralateral anterior cerebellum was even higher in patients who eventually displayed significant functional recovery (slow, good recovery group) compared with patients who did not regain significant functional recovery (slow, poor recovery group).

### Functional Correlation Analysis

The interrelations between motor cortical areas in patients who attained rapid, good recoveries; slow, poor recoveries; and slow, good recoveries were further assessed statistically by application of univariate and multivariate methods (Table 4) in an attempt to understand the mechanisms underlying the observed changes in motor cortical function after stroke. Correlation analysis revealed that activation of the ipsilateral and contralateral SMAs was significantly coupled in the slow, poor recovery group, whereas the ipsilateral SM1 and contralateral anterior cerebellum, and the ipsilateral and contralateral anterior cerebellum were significantly coupled in the slow, good recovery group (Table 4). In the patients with rapid, good recoveries, no significant correlation between motor areas was found.

### Discussion

#### Rapid Compared With Slow Recovery Processes

The rapid and slow recovery patient groups demonstrated a clear difference in activation patterns. Although the former group were found to have activation indistinguishable from that of the healthy volunteer group, the latter patient group showed significant involvement of the hemisphere ipsilateral to the paretic hand. Moreover, good functional recovery of the paretic hand within 1 month post-stroke did not significantly trigger motor reorganization involving the hemisphere ipsilateral to the paretic hand. These observations indicate that there is a critical time period that determines involvement of the hemisphere ipsilateral to the paretic hand in the process of functional recovery. Furthermore, the observations strongly indicate that the process of functional recovery is not a single continuous process. Rather, it has two separate phases. Phase I represents the process of recovery and/or reorganization of the original system. Patients who attained good functional recovery within 1 month demonstrated only Phase I of the recovery process. Patients who did not achieve significant recovery of the original system within 1 month entered Phase II of the recovery process, as later evidenced by the fMR imaging activation pattern. Phase II involves reorganization of the secondary system in the hemisphere ipsilateral to the paretic hand.

Electrophysiological support for the findings of the cur-
rent study is provided by Netz, et al.\textsuperscript{31} In their study, in which transcranial magnetic stimulation was used, these authors reported that ipsilateral responses were recorded after stimulation of the unaffected hemisphere only in stroke patients who had poor functional recoveries, but not in patients who attained good recoveries. Because their study was based on patients who recovered early, their good- and poor-recovery groups correspond to the rapid- and slow-recovery patient groups in our study, respectively.

Our findings have important implications for clinical practice. Because it appears that recovery is a bimodal process, entry into Phase II should be considered to be another beginning in the functional recovery process. Rehabilitation efforts need to distinguish between the two phases, namely, the rapid recovery of the original system of Phase I and the slower recovery with secondary system reorganization of Phase II, and apply treatment strategies appropriate for the particular phase. Prognostic judgment should also be adjusted once a patient enters Phase II of the recovery process.

Because the current study was designed for a multipar- ticipant analysis, it is difficult to make specific comments regarding individual prognosis. It can be inferred, however, that bihemispheric activation in subcortical hemiparesis has a differential clinical significance, depending on how soon it is observed after stroke onset. The observation of bihemispheric activation early in the period of recovery is a relatively poor prognostic sign because it signifies nonrecovery of the original system and entry into Phase II, in which

---

**Fig. 4.** Schematic summary of multipar-ticipant analysis of stroke patients. The size of each circle provides a relative indica- tion of the number of patients in whom activation of the specified anatomical site was observed relative to that of healthy volunteers. \textit{Asterisk} indicates a significant increase; \textit{dagger} indicates a significant decrease in the frequency of acti- vation in the patient group compared with healthy volunteers. \textit{Arrow} indicates lesion.
functional recovery depends on successful cortical reorganization involving the ipsilateral hemisphere.

Prognostic Factors for Patients With Slow Recoveries

Correlation analysis demonstrated that activation of two major components of the secondary system, namely the ipsilateral SM1 and the contralateral anterior cerebellum, demonstrated significant linkage in patients who showed slow but good recoveries. It is highly plausible that the observed coactivation of the ipsilateral SM1 and contralateral anterior cerebellum indicates a linked functionality of these two areas and the successful reorganization of motor circuitry from the primary to the secondary system. Hence, the coactivation of the ipsilateral SM1 and contralateral anterior cerebellum is also expected to be the prognostic indicator for functional recovery.

An intriguing finding is the significantly correlated coactivation of the contralateral and ipsilateral SMAs in the slow, poor recovery group. Whether this coactivation is an epiphenomenon or adversely influences the proper reorganization process is unclear. Nevertheless, this observation may potentially lead to new treatment modalities for those patients who fail to show significant functional recovery within the first 3 months. Bilateral interruption of the interhemispheric connections of the SMAs may facilitate cortical reorganization and effective functional recovery.

Dominant Compared With Nondominant Hand

All patients in this study had been right handed before stroke onset. Our findings demonstrated that the activation pattern associated with motion of the unaffected hand was significantly different, depending on whether the paretic hand was the dominant or nondominant hand. Although the motion of the intact right hand in patients with left hemiparesis did not produce significant activation of the hemisphere ipsilateral to the moving hand (the right hemi-
Cortical reorganization

.. suggests the importance of an uncrossed corticospinal tract for motor compensation. In a report on experiments in monkeys, Lawrence and Kuypers\(^3\) have suggested the importance for recovery of uncrossed corticoreticulospinal pathways as alternative pathways of the crossed corticospinal tract. Several lines of evidence indicate that an interhemispheric functional disinhibition of the contralateral motor cortices is important for recruiting the ipsilateral pathway as an alternative pathway.\(^18,36,44\) Our findings are consistent with these reported observations.

**Role of the SMA in Functional Recovery**

Despite the efforts of a number of investigators, the function of the human SMA remains unclear.\(^4,37,39,41\) Increased activity in the SMA has been reported to be associated with initiation, programming, selection, learning, and responsiveness to internal cuing of movements, or to the selection of the appropriate neuronal populations necessary to execute a movement. In monkeys, neural activity in the SMA increases after recovery from lesions of the primary motor cortex.\(^1\) Increased SMA activity in motor reorganization of stroke patients has also been observed on functional imaging studies.\(^10,21,44\) Findings of the present study suggest a more complex role of the SMA in motor reorganization and functional recovery.

Following the standard concept that the SMA represents a part of the hemispheric motor control system, the increased activation of ipsilateral SMA in the slow-recovery patient group would simply imply motor reorganization of an ipsilateral motor pathway. Intriguingly, activation of the ipsilateral SMA and SM1 did not demonstrate significant correlation with good functional outcome in the slow-recovery patient group as did linked activation of the ipsilateral SM1 and contralateral anterior cerebellum. Furthermore, even though physiological, bilateral connectivity of the SMA is well known,\(^41\) activation of the ipsilateral and contralateral SMAs showed significant correlation with poor functional outcomes in the slow, poor recovery patient group. Future investigation on the specific role of the SMA in functional reorganization is clearly warranted.

**Task Performance and Motor Demand**

There have been several publications on the relationship between task performance and motor demand. Authors of positron emission tomography studies have reported that increased effort is likely to lead to recruitment of more motor areas.\(^3,38,39\) Gerloff, et al.,\(^39\) found that the internal pacing of movement posed higher demands on the motor system than external pacing movements, resulting in an increase in the chances of both medial and ipsilateral activations. Therefore, prudence dictates the cautious interpretation of activation maps in patients with severe hemiparesis because such patients may exert different degrees of absolute force and different degrees of effort. In the present study we used a self-paced grasp task to minimize the patient’s effort. Furthermore, the performance of the patient was monitored and controlled to the extent feasible. Despite the lack of difference in motor function between patients who attained slow, good recoveries and those with rapid, good recoveries, significant differences in cortical function were observed between these two groups. It is therefore likely that the ob-
served differences in motor cortical function between the two groups reflect functional reorganization rather than a consequence of higher applied force or increased effort in some patients.

Conclusions

Functional recovery in patients with hemiparesis originating subcortically showed two distinct phases of the recovery process involving entirely different neural mechanisms. Phase I is characterized by the process of recovery and/or reorganization of the primary system. Successful recovery of this system is typically reached within 1 month after stroke onset. Its clinical correlate is a rapid recovery course and significant recovery of function within 1 month after stroke onset. Failure of recovery of the primary system shifts the recovery process to Phase II, during which reorganization involving the ipsilateral pathway, takes place. The clinical correlate of Phase II is a slow recovery course with variable functional outcome. Effective functional organization of the ipsilateral pathway, as identified by linked activation of the ipsilateral SMA and contralateral anterior cerebellum, is correlated with good prognostic outcome of patients in the slow recovery group. The degree of connectivity between the bilateral SMAs appears to influence prognosis, in that a tight connectivity may adversely affect functional recovery.

Acknowledgments

We thank Dr. Ingrid L. Kwee (University of California at Davis) for her critical reading of the manuscript and Drs. Masato Watanabe (Kuwana Hospital) and Hiroyuki Arai (Niigata Neurosurgical Hospital) for their help with patient recruitment.

References


Y. Fujii and T. Nakada

Cortical reorganization


Manuscript received April 11, 2002.
Accepted in final form August 27, 2002.
This work was supported by grants from the Ministry of Education, Culture, Sports, Science, and Technology in Japan.
This manuscript was previously presented in part at the Second International Workshop on Biomedical Imaging, Fukui, Japan, November 2000.
Address reprint requests to: Tsutomu Nakada, M.D., Ph.D., Center for Integrated Human Brain Science, Brain Research Institute, University of Niigata, 1 Asahimachi, Niigata 951-8585, Japan.
email: tnakada@bri.niigata-u.ac.jp.