Longitudinal Study of Motor Recovery After Stroke
Recruitment and Focusing of Brain Activation

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Background and Purpose—The goal of this study was to characterize cortical reorganization after stroke and its relation with the site of the stroke-induced lesion and degree of motor recovery using functional MRI (fMRI).

Methods—Fourteen stroke patients with an affected upper limb were studied longitudinally. Three fMRI sessions were performed over a period of 1 to 6 months after stroke. Upper limb recovery, Wallerian degeneration of the pyramidal tract, and responses to transcranial magnetic stimulation were assessed.

Results—Two main patterns of cortical reorganization were found. Pattern 1 was focusing, in which, after initial recruitment of additional ipsilateral and contralateral areas, activation gradually developed toward a pattern of activation restricted to the contralateral sensorimotor cortex in 9 patients. Five patients were found to have pattern 2, persistent recruitment, in which there was an initial and sustained recruitment of ipsilateral activity. Occurrence of recruitment or focusing seemed to depend mainly on whether the primary motor cortex (M1) was lesioned; persistent recruitment was observed in 3 of 4 patients with M1 injury, and focusing was seen in 8 of 10 patients with spared M1. These patterns had no relation to the degree of recovery; in particular, focusing did not imply recovery. However, there was a clear relation between the degree of recovery and the degree of Wallerian degeneration.

Conclusions—These results suggest that ipsilateral recruitment after stroke corresponds to a compensatory corticocortical process related to the lesion of the contralateral M1 and that the process of compensatory recruitment will persist if M1 is lesioned; otherwise, it will be transient. (Stroke. 2002;33:1610-1617.)

Key Words: magnetic resonance imaging ■ motor activity ■ movement ■ rehabilitation ■ stroke, ischemic

The initial deficit and the degree of motor recovery after ischemic stroke vary greatly and are related to such factors as lesion type, topography, and size. However, neither the plasticity occurring in the brain after stroke nor the relation between plasticity and functional recovery is fully understood.

Brain imaging (positron-emission tomography [PET] or functional MRI [fMRI]) has revealed a cortical “reorganization” in patients with complete or partial upper limb recovery. These studies showed activation not only of the contralateral but also of the ipsilateral sensorimotor cortex (SMC) and other cortical regions such as the premotor areas, supplementary motor area (SMA), and parietal cortex, suggesting the involvement of a widespread network in recovery.1–6

However, single fMRI or PET sessions with various delays after stroke have shown a large variety of functional cortical reorganization.7 For example, divergent results were reported in terms of the relative involvement of affected8 (contralateral) compared with unaffected9 (ipsilateral) cortical structures in recovery. In some cases, stroke patients activated the same contralateral or bilateral motor regions as control subjects but to a larger extent, whereas other patients had predominantly ipsilateral activations in primary and nonprimary motor cortices.

In this debate, the time point of investigation seems crucial and may in part explain the observed differences. Cortical plasticity is a long-term process that can last several months, even longer in cases of tumors.8 One way to overcome these differences is to track the time course of cortical activation during recovery. Recently,9 8 stroke patients were studied with 2 successive fMRIs. Compared with the nonparetic hand, the ratio of contralateral to ipsilateral SMC activity during movement of the paretic hand increased over time as the paretic hand regained function. A PET study of 5 stroke patients showed similar results.10 These results suggest a dynamic bihemispheric reorganization and emphasize the necessity of longitudinal studies.

Another important point is the reorganization of the descending motor pathways after stroke. We used 2 methods to evaluate deficits in the corticospinal system. First, transcra-
nial magnetic stimulation (TMS) was used to evoke electromyogram (EMG) responses on the affected and nonaffected sides.11 Second, the degree of Wallerian degeneration (WD) of the corticospinal tract was assessed from anatomic MRI images.12

Another critical point in assessing the relationship between cortical plasticity and recovery is the degree of the initial deficit and the degree of subsequent recovery. Usually, patients with relatively mild motor symptoms and good recovery have been investigated, which a priori limits the scope of the findings.7

Taking the above points into account, the aim of the present work was to use a more refined longitudinal approach with 3 fMRI sessions per patient to study a larger sample of patients with a greater variety of lesions and a larger spectrum of recovery. The objective was to measure changes in the functional cortical activation over time and to assess its relationship with several factors: (1) the impact of the lesion on the primary motor cortex (M1), (2) the degree of WD of the pyramidal tract, (3) responses to TMS, and (4) the degree of motor recovery of the arm and hand.

Materials and Methods

Patients

Fourteen stroke patients (inpatients in a rehabilitation center) who suffered from hemiplegia (n=13) or severe paresis (n=1; strength=1/5) resulting from an ischemic stroke in the middle cerebral artery (MCA) territory volunteered for this study, which was approved by the local ethics committee. Subject’s consent was obtained according to the declaration of Helsinki. Entry criteria included the following: (1) an initial hemiplegia or severe paresis persisting for at least 1 week after the stroke, (2) no prior stroke with sensorimotor deficits, (3) age from 30 to 70 years, and (4) an MCA infarct. Exclusion criteria were (1) multiple cerebral lesions, (2) no prior stroke with hemiplegia or severe paresis, (3) prior cerebrovascular disease, (4) preexisting neurological or psychiatric disorders, (5) deafness and/or blindness, (6) current or previous alcohol or drug abuse, (7) entry to the rehabilitation center more than 1 week after the stroke, (8) no adequate recovery (Rpoor) if FAT was ≤3, BBT was ≤30 blocks, 9HP was ≤100 seconds, and grip force was ≤50% of unaffected side; (9) poor recovery (Rpoor) if FAT was <3, BBT was <30 blocks, 9HP was ≤100 seconds, and grip force was ≤50%; and (10) moderate recovery (Rmod) if neither Rgood nor Rpoo. Based on multiple tests, the robustness of this criterion is below that of a single test but provides a more accurate behavioral description.

Evaluation and Follow-Up of the Upper Limb Deficit

At the time of the imaging experiments, an upper limb evaluation was performed with the Frenchay Arm Test (FAT), the Box and Block Test (BBT), the 9-Hole Peg Test (9HP), and a grip force assessment. Patients were classified into 3 grades of recovery: good recovery (Rgood) if FAT was ≥3, BBT was ≥30 blocks, 9HP was ≤100 seconds, and grip force was ≥50% of unaffected side; poor recovery (Rpoor) if FAT was <3, BBT was <30 blocks, 9HP was ≥100 seconds, and grip force was <50%; and moderate recovery (Rmod) if neither Rgood nor Rpoo. Based on multiple tests, the robustness of this criterion is below that of a single test but provides a more accurate behavioral description.

MEP Mapping

TMS was performed through a circular coil (8-cm diameter, MAG-STIM 200, Dyfed). Stimulations (80% maximal output) were applied at 6 sites: 3 sites 4 cm left of midline (at vertex and 4 cm rostral and caudal to it) and 3 sites symmetrical to the right of midline. Single shock stimulations (50 stimuli) were performed at rest and during tonic bilateral contractions of the finger flexors (fist). Motor evoked potentials (MEPs) were recorded from the left and right first dorsal interossei with surface EMG electrodes.

Task for fMRI

We used the following motor tasks: for patients capable of executing hand movements (n=10), self-paced closing and opening of the hand, ie, making a fist repetitively; and for patients unable to perform hand movements, repetitive flexion/extension of the elbow (n=2) or repetitive abduction/adduction of the shoulder (n=2).

Movement amplitude and rate were determined by the experimenter, who visually monitored accuracy. The amplitude (small or large) and rate (0.5 or 1.0 Hz) but not the movement task were included in the analysis. Demonstration of adequate recovery (Rgood) if FAT was ≥3, BBT was ≥30 blocks, 9HP was ≤100 seconds, and grip force was ≥50% of unaffected side; poor recovery (Rpoo) if FAT was <3, BBT was <30 blocks, 9HP was ≥100 seconds, and grip force was ≤50%; and moderate recovery (Rmod) if neither Rgood nor Rpoo. Based on multiple tests, the robustness of this criterion is below that of a single test but provides a more accurate behavioral description.

Acquisition Sequence

Images were obtained with a 1.5-T scanner. The scanning session included anatomic images of the whole brain using spin-echo T1- and T2-weighted images. Functional blood oxygen level–dependent contrast images consisted of single-shot echo-planar imaging.
gradient-echo images (repetition time, 3000 ms; echo time, 50 ms; slice thickness, 7 mm; in-plane resolution, 3 mm²; 10 contiguous slices covering the supratentorial brain; 50 images per slice in 150 seconds; 30-second periods of rest-task-rest-task-rest). This procedure was repeated twice during a session. Each patient had 3 fMRI sessions at 1 to 2 months, 2 to 4 months, and 4 to 6 months after stroke.

Analysis of Anatomical Images

Lesions
Patients were classified into 2 categories: M1normal, in which stroke lesions spared the upper precentral gyrus (hand representation of M1) but affected the periventricular white matter, ie, the internal capsule or the corona radiata (Figure 1), and M1lesioned, in which stroke lesions affected the upper precentral gyrus (M1, Figure 1) as a result of a cortical atrophy or a lesion extended into the precentral gyrus. WD of the pyramidal tract was assessed from previous descriptions of signal intensity changes. The classifications (Table 1) were as follows: absent (0), subtle (1; moderate hyperintensity, limited peduncle involvement), medium (2; frank hyperintensity, partial peduncle involvement), and severe (3; bright extensive area, whole peduncle).

Analysis of Functional Images

Data analysis consisted of motion correction, statistical analysis of activated voxels, and calculation of activated voxels in specific cortical regions of interest (ROI). Statistical parametric maps were generated voxel by voxel with Student’s t test (task versus rest).

ROIs for SMC, SMA, superior parietal cortex, and frontal cortex anterior to M1 were defined (Figure 1) by use of standard neuroanatomical criteria. Infarcted tissue was excluded from ROIs. The same threshold for the 3 fMRI sessions per subject was used (0.0001 < P < 0.001). The evolution of activation between the 3 sessions was quantified with 2 indexes (which are independent of topological variations of activity within an ROI) of relative spatial extent of activation in ROIs: IndexSMC, activation of contralateral SMC divided by total activation of all ROIs (1 = activation exclusively situated in contralateral SMC, 0 = no activity in contralateral SMC), and IndexHEM, difference between the 4 ROIs of the contralateral (HEMc) and ipsilateral (HEMi) hemisphere [IndexHEM = (actiHEMc - actiHEMi)/(actiHEMc + actiHEMi); 1 = purely contralateral, −1 = purely ipsilateral activation].
Results

Categorization of Anatomical Lesions and Recovery

Anatomical Lesions

All 14 patients had a stroke in the MCA territory with chronic ischemic areas. No mass effect was observed. From the anatomical MRI images, patients were classified into 2 groups. In 10 M1normal patients (Table 1, top; patients 1 through 10), stroke lesions spared the upper precentral gyrus (Figure 1) but affected underlying white matter. In 4 M1lesioned patients (Table 1, bottom; patients 11 through 14), stroke lesions affected the gray matter of the upper precentral gyrus (Figure 1, arrow). The SMA and the parietal cortex were spared in all patients.

WD of the pyramidal tract was present and increased over time in all 14 patients, sometimes accompanied by an atrophy of the midbrain (brainstem shrinkage in 9 patients). At the last of the 3 sessions, the WD was graded (see Materials and Methods) as subtle in 3, medium in 9, and severe in 2 patients (Table 1).

Relation Between Motor Recovery, M1 Lesion, and WD of the Pyramidal Tract

From a combined criterion of FAT, BBT, and 9HP scores, as well as a grip force assessment (see Materials and Methods), the degree of motor recovery of the patients at a given time was classified (Table 1). Among the 14 patients, 5 were classified as Rgood, 5 as Rmod, and 4 as Rpoor at the end of the evaluation period. Importantly, there was no significant relation between the type of lesion (M1normal, M1lesioned) and the degree of recovery (Rgood, Rmod, or Rpoor; Table 2; Fisher’s exact test, $P>0.23$). In contrast, the degree of WD was related to the degree of functional recovery; among the 5 patients with good recovery, none had a severe pattern, and among the 4 patients with poor recovery, none had a subtle pattern of WD (Table 2; Fisher’s exact test, $P<0.01$).

TMS and Relation to WD and Recovery

We compared responses to TMS applied to the affected and unaffected hemispheres (usually at the time of the second fMRI session). All 11 tested patients showed contralateral responses after TMS over the unaffected hemisphere at normal latencies for first dorsal interosseous (20 to 25 ms). TMS over the affected side evoked no contralateral responses in 3 patients and delayed responses in 8 patients (3- to 12-ms delay compared with the nonaffected side). There was no clear relation between the latency of the evoked EMG response and the degree of WD at the time of the test. A trend was found between TMS response and the degree of final recovery: The clear majority of patients (7 of 8) with either good or moderate recovery had TMS responses on the affected side; only 1 of 3 patients with poor recovery showed such a response (Table 2; Fisher’s exact test, $P>0.18$).

fMRI Activation After Stroke

We compared the cortical activations during use of the affected and unaffected hands. For each patient, the undamaged hemisphere was used as control. The cortical activation for the control task always involved the contralateral SMC, with little or no variation within and between sessions (Figure 2). In most of the 14 patients, bilateral activation of the SMA was present during performance of the control task, although with more variability than the SMC activation.

The pattern of activation for the affected hand, measured with the same statistical threshold used for the control task, could be quite different, as illustrated in Figure 2 for an M1lesioned, Rgood patient. The activity for the unaffected hand is focused on the contralateral SMC, whereas there is an extensive recruitment of additional areas for the affected hand, including ipsilateral SMC, SMA, and frontal premotor cortex.

When there was a marked difference between the affected and unaffected hands (Figure 2), the activation usually involved the SMC (contralateral and ipsilateral), frontal...
Assessment of Longitudinal fMRI Activation Patterns

Patterns of Evolution

We found 3 distinctive patterns of evolution over time and illustrate here some representative cases. Pattern 1 was initial focusing. Figure 3A shows the evolution for patient 3-PAQ with a lesion sparing M1 and good recovery (M1normal, Rgood). At stroke onset, she experienced right hemiplegia but recovered rapidly. The activation produced by movements of her paretic (right) hand was centered on the contralateral (left) SMC and remained focused in this region, as in normal subjects. Pattern 2 was progressive focusing. Figure 3B shows the evolution for patient 1-POI with a lesion sparing M1 and progressive recovery (M1normal, Rgood). At stroke onset, he experienced right hemiplegia but had a progressive recovery over a 3-month period. Longitudinal analysis revealed a progressive focusing of activation on the contralateral SMC across sessions. In the first session, the activation involved the SMC on both sides and other ipsilateral regions (SMA, premotor, and prefrontal); in the second session, only the contralateral SMC and the SMA were active; and in the third session, activation was seen exclusively in the contralateral SMC. Pattern 3 was persistent recruitment. Figure 3C shows a rather different pattern of evolution for patient 11-HEM with a lesion affecting M1 and progressive recovery (M1lesioned, Rgood). In the first session, based on hand movements, there was clear bilateral activation of the motor cortex. Activation at 3 and 4 months remained bilateral, with a predominance of the ipsilateral SMC.

Relation to Recovery and M1 Lesion

In our population, no clear relation could be established between the degree of recovery and activation pattern (Table 3); initial or progressive focusing on contralateral SMC and recruitment were equally distributed among patients with good, moderate, or poor recovery (Fisher’s exact test, \( P>0.5 \)). Neither could an association between the degree of WD and activation pattern be established (Table 3; Fisher’s exact test, \( P>0.9 \)).

However, there was a trend for a relation between the 2 different patterns of evolution and the type of cortical lesion (Fisher’s exact test, \( P<0.09 \)). In the M1normal group, more patients with lesions sparing M1 than expected (8 of 10 patients) showed a pattern of focusing (either initial or progressive) on the contralateral SMC (Table 3). In the M1lesioned group, persistent recruitment was predominant (3 of 4 patients).

Threshold-Independent Comparison Between Ipsilateral and Contralateral Activation

In patients with either initial or progressive focusing, the quantitative measurements of activation showed that con-

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**TABLE 3. Comparison Between Clinical Variables and fMRI Evolution**

<table>
<thead>
<tr>
<th>fMRI Evolution</th>
<th>Recovery, n</th>
<th>M1 Lesion, n</th>
<th>WD, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good</td>
<td>Moderate</td>
<td>Poor</td>
</tr>
<tr>
<td>Focusing</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Recruitment</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
Recruitment

Recruitment for the use of the affected hand gives rise to an extension of activation into areas not activated by movements of the unaffected hand such as the ipsilateral SMC, SMA, and frontal premotor and superior parietal areas. These initially recruited areas may persist across sessions, ie, over several months, especially in patients with lesions of M1. These activation patterns are similar to those reported by previous studies based on single exams. However, persistent recruitment was observed in cases of good and poor recovery.

Focusing

The main result is that in some patients recruitment tends to decrease over time. This focusing process is observed mainly in patients with lesions sparing M1 who showed an initial recruitment of activity, followed by a more and more focused activation, ultimately restricted to the contralateral SMC. As with recruitment, focusing was observed in cases of good and poor recovery.

Except for 2 recent studies in which the ratio of contralateral to ipsilateral SMC activity during movement of the paretic hand (in M1-normal patients) increased significantly over time as the hand regained function, such a focusing process had not been reported previously because of a lack of longitudinal observations. Because our patients were first tested 1 month after stroke, those with initial focusing could have shown recruitment in the first days after stroke.

Cortical Reorganization and WD of the Pyramidal Tract

All patients had an increase in WD over time as previously observed, and the degree of WD was inversely related to the degree of recovery (Table 2). This could explain why 4 patients without an M1 lesion did not recover; they all had a severe or intermediate WD, indicating a weak corticospinal link. A similar but predictive relation between WD and recovery was recently demonstrated.

In parallel with this observation, the great majority of patients with good recovery also showed clear, although delayed, responses to TMS over the lesioned side, which was not the case for patients with poor recovery. A similar prognostic trend has now been established for TMS applied shortly after stroke.

Cortical Reorganization and Lesion of the Primary Motor Cortex

The data in Table 3 indicate that the evolution of activation patterns was related to the severity of the M1 injury but not to the degree of recovery or the degree of WD. There was a
focusing of activation toward the contralateral SMC when M1 was unaffected, as well as a more persistent recruitment of other areas when M1 was affected by the stroke lesion. This association has not been previously reported because of a lack of longitudinal studies taking into account a sufficient diversity of lesions. Previous studies of capsular stroke\(^1\) suggested that the initial ipsilateral activation could be a transient phenomenon. Our results confirm and qualify this suggestion. Although our data may seem to contradict earlier observations\(^1\) in which bilateral activation (ie, recruitment) was found in patients with striatocapsular strokes (ie, M1normal), they do not; half of those patients had synkinetic movements of the “unaffected” hand, and the other half had activated ipsilateral areas outside SMC. Furthermore, one should keep in mind that focusing (which does not exclude an ipsilateral activation) and recruitment are expressed by indexes in a given range and represent an evolution rather than a classification based on a single examination.\(^5,6\)

Our results are compatible with the previous conclusion based on TMS\(^11\) and on lesions in primate M1\(^17\) that ipsilateral M1 and its corticospinal connections alone are not sufficient for recovery of normal hand functions. However, ipsilateral M1 may contribute to recovery via its interhemispheric\(^18\) or corticocortical connections.\(^19,20\) Our M1normal patients with poor recovery demonstrate that contralateral M1, if its descending connections are nonfunctional, is not sufficient for recovery either. The 1 patient with M1normal and good recovery should not lead to the conclusion that M1 contralateral is not necessary for recovery. This patient had only a partial lesion of M1, and although his recovery was good (according to criteria), it was not at normal levels.

**Functional Hypothesis**

Assuming that deep white matter lesions sparing M1 (M1normal) primarily affect the corticospinal interaction whereas superficial gray matter lesions (M1lesioned) of M1 strongly impair the corticocortical interactions and that recruitment and focusing mutually depend on the balance between corticocortical excitation and inhibition.\(^1,21\) we suggest the following functional hypothesis (Figure 5): Persistent recruitment (usually seen in M1lesioned patients) may be due to a decrease in inhibition (disinhibition) caused by the lesion in M1 and the underlying reciprocal corticocortical connections from M1 to the secondary motor areas, leading to more extensive ipsilateral and contralateral activation (Figure 5, stippled trace). Preexisting excitatory intracortical connections have been unmasked in rats by application of a GABA-antagonist blocking cortical inhibition,\(^22\) and in some stroke patients, interhemispheric inhibition from the affected toward the unaffected side was decreased.\(^18,23\)

Focusing, ie, inhibition of formerly recruited areas over time (usually seen in M1normal patients), may be due to a gradually exerted inhibition by M1 over initially recruited motor areas. In the case of initial focusing, activation may remain contralateral from the very beginning (Figure 5, thin trace) or, after initial recruitment, may focus back on SMC in case of progressive focusing (Figure 5, thick trace).

Thus, recruitment and focusing could be adaptive mechanisms of the central nervous system to the injury caused by stroke. First, recruitment may increase the population of potentially available neurons to counteract the loss of control induced by the lesion, and later, focusing may select those neurons that potentially improve the efficiency of the impaired motor command relayed by the corticospinal tract. As has been shown by TMS\(^11,14,16\) and an MRI study relating infract location to the topology of the corticospinal fibers,\(^24\) recovery depends on the functionality of the corticospinal tract, consistent with our finding of a relation between the degree of WD (involving axons originating from M1) and recovery.

Our results indicate that functional recovery does not depend on the type of plasticity. Why is that? We hypothesize that the efficacy of recruitment or focusing in terms of recovery of hand function depends itself on the amount of remaining fibers in the impaired corticospinal tract; if insufficient numbers of crossed corticospinal axons are left, cortical plasticity, whether focusing or recruitment, will remain ineffective.

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