Functional MRI Detects Posterior Shifts in Primary Sensorimotor Cortex Activation After Stroke Evidence of Local Adaptive Reorganization?

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Background and Purpose—Further recovery from stroke can occur late, long after the end of the apparent evolution of pathological changes. This observation and evidence obtained from functional imaging for altered patterns of activation after brain injury suggest that cortical reorganization may contribute to recovery. Here, we have tested for potentially adaptive reorganization in the primary sensorimotor cortex.

Methods—We used functional MRI to study brain activation with dominant hand movement in right-handed healthy control subjects (n=20) and in patients after subcortical ischemic infarcts causing mild to moderate right hemiparesis (n=8). The numbers of pixels activated above threshold and the geometric centers of activation clusters were determined.

Results—Although random-effects analysis identified some differences in activation maxima, similar regions of the brain were activated with sequential finger tapping in the patient and control groups. However, consistent with the heterogeneity in the locations, sizes, and times after the infarcts, patterns and magnitudes of activation showed some heterogeneity between patients. Nonetheless, for the group as a whole, there was a decreased motor cortex lateralization index (−0.1±0.7 in patients and 0.7±0.3 in control subjects, P=0.05). The geometric center of activation of the primary sensorimotor cortex activation cluster contralateral to the affected hand in patients was also shifted posteriorly (mean 12 mm, P<0.04) relative to that of the control subjects. To confirm the latter observation, the activation response with a simple hand-tapping task was examined in some of the subjects. With this task, there was also a trend (mean 10 mm, P=0.07) toward a more posterior activation in patients.

Conclusions—These results confirm altered patterns of activation in the contralateral and ipsilateral primary sensorimotor cortices after recovery from strokes causing hemiparesis. These (and other changes) suggest that modulation of widely distributed parts of the cortical network for motor control may contribute to adaptations leading to functional recovery after stroke. (Stroke. 2001;32:1134-1139.)

Key Words: magnetic resonance imaging  motor activity  motor cortex  rehabilitation  stroke

Spontaneous recovery after stroke can be prolonged well past the period of the evolution of acute structural changes secondary to infarction. This suggests that mechanisms other than simply reperfusion or resolution of the injury response (eg, edema and inflammation) may contribute to recovery. Consistent with this, recent rehabilitation interventions initiated well past the time of the ischemic stroke have led to functional gains. The mechanisms for these long-term changes remain uncertain. They could represent compensatory responses with differences in task performance. However, although compensatory strategies seem to be an important mechanism, particularly for more severe injury, it is not clear that differences in strategy account for all of the observed recovery. Therefore, a second possibility is that maladaptive altered local and distant cortical excitability may resolve over time, leading to functional gains. Finally, there may be a direct compensatory cortical reorganization in response to the injury. This could involve the “unmasking” of parallel pathways or functional changes in the cortex with alterations in synaptic strength or the formation of new synapses.

Functional imaging and magnetic stimulation studies in humans have emphasized the long-distance changes with descriptions of enhanced ipsilateral motor cortex activation and changes in activation in additional regions in the motor cortex, including the supplementary motor area. However, studies of animals after focal brain lesions have emphasized the potential importance of local reorganization in response to injury. Recent studies involving brain tumors or multiple sclerosis have extended the latter observations to humans,
with demonstrations of local shifts of the centers of activation in the primary sensorimotor cortex (SMC) after injury.14,15 Of particular interest has been the observation that these shifts show a consistent posterior direction even with different mechanisms of injury. There is some evidence that such changes may occur after stroke as well.16,17 The notion that local changes in the primary SMC may contribute to recovery is consistent with studies of motor learning in humans. For example, the work of Karni et al18 has shown that with improved performance on a complex motor task, there is an expansion of the representation for finger movements in the primary SMC.

In the present study, we describe functional MRI (fMRI) studies of motor cortex activation with simple hand movements in patients who have shown good recovery from small subcortical ischemic strokes. We wished to test for functional reorganization of the primary SMC, particularly contralateral to the hand moved.

Subjects and Methods

Patients

Patients were recruited from outpatient clinics after a first-ever ischemic stroke resulting in a relatively pure motor deficit on the right side (Table 1). The patients were examined at variable periods after their strokes: 1 patient in the acute period (1 day), 2 in the subacute period (7 to 14 days), and 5 in the chronic period (45 to 660 days) after infarct. All had lacunar infarcts (diameters of 2 to 5 mm) were estimated from T2-weighted MRI in the left hemispheric white matter. Patients with cortical or hemorrhagic stroke, primarily sensory or ataxic symptoms or signs, other coexistent neurological disease or cognitive impairment (as assessed by medical history or Mini-Mental State Examination), or contraindications to MRI were excluded. Healthy control volunteers who had not previously suffered from recognized neurological disease were recruited. To determine whether there are significant age-dependent effects, we studied 2 distinct populations in the control group: 10 younger subjects (mean age 28 years, range 22 to 38 years, 1 woman and 9 men) and 10 older subjects (mean age 67 years, range 56 to 83 years, 5 women and 5 men), who were better matched to the ages of the patients studied. Ethical approval was obtained from the Central Oxford Ethics Committee, and informed consent was obtained before all studies.

Functional Assessment

Functional assessments were carried out at the time of each scan visit. Specific measures of motor function obtained were the motricity index, the 9-hole peg test, and the maximum tapping rate of all 4 fingers moving together at the metacarpal-phalangeal joints. The maximum tapping rate was tested while the patients wore hand splints (available commercially for the treatment of repetitive strain injury), which prevented flexion at the wrist joint. The maximum finger-tapping rate has been found to be a sensitive measure of damage to the descending motor tracts.19

Motor Paradigm

Subjects were required to place their hands onto a flat plastic hand rest, which defined both the base and the maximum excursion for movements. One of 2 tasks was given. The first task, sequential finger-tapping, involved lifting each finger from the surface serially, starting with the index finger and ascending to the little finger, whereupon the sequence was reversed until the index finger was reached again, and the process was recommenced. The task was cued visually at 1 Hz by use of a schematic representation of the hand. The second task involved hand tapping: the 4 fingers were raised and lowered alternately with the arm and palm of the hand resting on the support. The task was visually cued at 75% of the maximum rate for each individual (mean 4.5 Hz, range 2.5 to 5.5 Hz for control subjects; mean 2.9 Hz, range 1.8 to 4.5 Hz for patients).

The paradigms were organized into an ABAB pattern, in which A indicates rest and B indicates movement, with each lasting 30 seconds. There were a total of 6 rest periods and 6 movement periods. The tasks were performed once with each hand.

Before the subjects entered the magnet, they were shown the visual cues and were trained to perform the task in time with the cue. All subjects were monitored during task performance either directly or via a camera positioned at the entrance to the magnet bore.

Imaging and Analysis

Data were acquired with a Siemens/Varian 3T MRI scanner with a custom-made head radiofrequency transmitter-receiver coil (E. Barberi, University of Western Ontario, London, Ontario, Canada). Blood oxygenation level–dependent multishot echo-planar images were obtained continuously in a transverse orientation by using the following acquisition parameters: repetition time 3.0 seconds, echo time 30 ms, 6-mm slice thickness, 21 slices, field of view 256×256 mm, and 64×64 matrix.

Image processing and statistical analysis were carried out by using an in-house modification of MEDx software (version 3.0, Sensor Systems, Inc). Motion correction was performed by using the SPM (Functional Imaging Laboratory) realignment procedure with adjustment for movement as implemented in MEDx, and spatial smoothing (full width at half maximum 5 mm), intensity normalization, and temporal filtering were applied before statistical analysis. Activation maps were calculated by using a Student parametric unpaired t test, and cluster detection was performed on all voxels above t=2.3 to determine clusters significantly activated (P<0.01). A high-resolution (1.0×1.0×6-mm3 voxel size) structural MRI acquired by using a standard T1-weighted sequence was coregistered to the functional image to define the neuroanatomic localization of activation. Activation images then were linearly transformed into a common stereotactic space (the Montreal Neurological Institute 305 brain as incorporated in MEDx software) by use of an in-house registration tool (FLIRT, which is described online at www.fmrib.ox.ac.uk/fsl). The geometric center of the activation cluster was determined and expressed in Talairach coordinates in the average brain space. Group statistical analysis of activation images in the common stereotactic space was performed by using a random-effects model.20

Generating the ROI Masks

To define quantitatively the numbers of pixels showing significant activation in different areas of the brain in response to a task, we defined various regions of interest (ROIs) on each subject’s structural scan and then applied these to the activation maps after transformation of the functional scans into the individual’s own structural scan space. ROIs were defined on the individual brains to

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**TABLE 1. Clinical Characteristics of Ischemic Stroke Patients and Their Disabilities**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Time to Scan, d</th>
<th>Affected Side</th>
<th>Motricity Index</th>
<th>Lacune Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>M</td>
<td>450</td>
<td>Right</td>
<td>100</td>
<td>Corona radiata</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td>M</td>
<td>660</td>
<td>Right</td>
<td>100</td>
<td>Corona radiata</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>F</td>
<td>7</td>
<td>Right</td>
<td>92</td>
<td>Internal capsule</td>
</tr>
<tr>
<td>4</td>
<td>51</td>
<td>M</td>
<td>14</td>
<td>Right</td>
<td>100</td>
<td>Corona radiata</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>F</td>
<td>70</td>
<td>Right</td>
<td>100</td>
<td>Internal capsule</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>M</td>
<td>45</td>
<td>Right</td>
<td>100</td>
<td>Corona radiata</td>
</tr>
<tr>
<td>7</td>
<td>75</td>
<td>F</td>
<td>1</td>
<td>Right</td>
<td>84</td>
<td>Corona radiata</td>
</tr>
<tr>
<td>8</td>
<td>71</td>
<td>F</td>
<td>420</td>
<td>Right</td>
<td>76</td>
<td>Corona radiata</td>
</tr>
</tbody>
</table>

All infarcts were lacunar (estimated sizes, 2–5 mm), involving only white matter in the left hemisphere in the regions defined. Patient 5 had 2 additional lacunes in white matter of the right hemisphere.
preserve their precise neuroanatomic definition, given the structural variations between individual brains. To generate the individual ROIs, the structural scans from each patient were loaded into the DISPLAY software package (Brain Imaging Center, Montreal Neurological Institute) within MEDx. For each brain, the following regions were defined for each hemisphere as described previously21 with minor modifications: (1) the primary SMC (including the premotor cortex), which involves the paracentral lobule, the anterior two thirds of the postcentral gyrus, the precentral gyrus, and adjacent lateral cortex extending 1 cm anteriorly from the precentral sulcus, and (2) the supplementary motor area, which involves the medial cortex dorsal to the cingulate sulcus and anterior to the paracentral lobule up to the genu of the corpus callosum, including the caudal half of the medial aspect of the superior frontal gyrus.

**Lateralization Index**
The lateralization index for the SMC (LI) was defined as follows: $LI = \frac{SMC_{ipsilateral}}{SMC_{contralateral}}$ ($SMC_{ipsilateral}$/$SMC_{contralateral}$), where the individual values were numbers of significantly activated pixels for the designated anatomic regions. The LI is a threshold-dependent index. In preliminary work, a range of thresholds from $z=2$ to 13 was tested. Although the LI showed continuous variation (as long as the chosen threshold did not exceed maximum $z$ scores for activated voxels in either hemisphere), the relative differences between the patients and control subjects remained similar. We also tested whether the LI might be more consistently measured from the numbers of pixels showing a mean difference change from rest exceeding 0.8%. A range of thresholds from 0.5% to 20% was tested. Again, the exact value of the LI showed threshold dependence, although the relative difference in signal intensity between control subjects and patients was maintained. However, because this measure did not appear to offer any advantages in the stability of the measurement over the $z$-thresholded value, the latter was used (for $z>7$).

Comparisons of values obtained from control subjects and patients were made by using a 2-tailed Wilcoxon test with a significance threshold of $P<0.05$ (SPSS, version 9).

**Results**
Eight right-handed patients (4 men and 4 women, median age 70 years, range 51 to 78 years) were studied by using fmRI after lacunar strokes in the white matter of the left hemisphere, which causes right hemiparesis (Table 1). Although the time after stroke was variable (Table 1), all patients were clinically stable. All showed good recovery at the time of the study (motricity index: median 100, range 76 to 100). Direct observation confirmed that all patients performed the required tasks in the magnet. Mirror movements were not evident. Comparisons were made with healthy control subjects ($n=20$, median age 42, range 22 to 83 years).

All subjects performed the sequential finger-tapping task for fmRI. The pattern of activation in an individual control subject was similar to that described in previous studies, with the most significant clusters of activation in the contralateral and ipsilateral primary SMC (typically including the not-well-resolved, more anterior activation in the region of the premotor cortex) and supplementary motor cortex, the ipsilateral cerebellum, and contralateral parietal cortex (in some cases). The patients showed activation in the same regions generally, but the extent of activation in the individual regions was more variable, as has been described previously after stroke (Figure 1). With the use of identical thresholds for patients and control subjects, random-effects analysis demonstrated differences between the control and patient groups. There was bilateral activation in the secondary sensory cortex for the patients (mean Talairach coordinates: left $-35, 4, 10$; right $44, 9, 7$) but not for the control subjects; also, there was activation in the thalamus for the control subjects but not for the patients (mean coordinates: $x=\pm 4, y=1, z=7$) and a shift in the bilateral basal ganglia activation from maxima in the globus pallidus in control subjects (mean coordinates: left $-26, -5, -2$; right $26, -4, 2$) to maximum activations in the caudate nuclei in the patients (mean coordinates: left $-22, -13, 5$; right $21, -9, 5$) (Figure 1).

Quantitative analysis of volumes of SMC activation from individual subjects was performed. Although more variable than for the control subjects, activation of the SMC was more bihemispheric overall in the patients as a group than in the control subjects (for patients, LI=$-0.1 \pm 0.7$; for control subjects, LI=$0.7 \pm 0.3$; $P=0.05$) (Figure 2A). There was greater activation in the ipsilateral than in contralateral SMC cortex in 3 of 8 patients. This pattern was not found in any of the control subjects (Figure 2B).
The geometric center of the contralateral SMC activation cluster was determined for each of the control subjects and for 6 of the 8 patients who showed activation above threshold during sequential finger movements (Table 2). A posterior shift was found for the patient group (mean shift 12 mm, P=0.04). This corresponds anatomically to a position for the cluster center in the anterior wall of the postcentral rather than the precentral gyrus. The mean y coordinate for the older (mean age 67 years, range 56 to 83 years) healthy control subjects (mean y=25±4) was similar to that for the younger (mean age 28 years, range 22 to 38 years) healthy control subjects (mean y=27±6); thus, age alone does not account for the differences between the localization of the geometric center of the activation cluster in the control and patient groups. When the activation coordinates for individual patients were considered, no relationship was found between the extent of the posterior shift and either the size of the lesion or the degree of functional impairment as assessed from the motricity score (data not shown).

To test whether a posterior shift in the geometric center of the SMC is more generally associated with hand movements by the stroke patients, activation coordinates were determined for the 10 older healthy control subjects and for 4 of the patients during a different hand-tapping task (Figure 3). The mean coordinates for activation with this task (which involves flexion/extension of the 4 fingers grouped together) were not significantly different from those for the sequential individual finger movements (Table 2). Direct comparison between patients and control subjects showed a trend (P=0.07) for a similar posterior shift of the center of activation for patients relative to control subjects (mean shift 12 mm).

**Discussion**

The present study has demonstrated potentially adaptive differences between the patterns of brain activation during hand movements for patients after lacunar strokes in the white matter that caused mild to moderate hemiparesis. Most novel was evidence of a significant posterior shift in the geometric center of activation in the contralateral primary SMC. A similar shift was found both with a sequential finger-tapping task and a grouped 4-finger flexion/extension task (although there was only a trend for the latter, which was tested by using a smaller group of subjects). The magnitude of the shift implies relatively enhanced activation in the postcentral gyrus. A similar observation has been made in patients after corticospinal tract injury from tumors or multiple sclerosis.14,15 Preliminary data from a few patients have suggested that this might also occur in stroke.16,17

There did not appear to be a relationship between the degree of functional deficit and the extent of the posterior shift in the geometric center of the SMC activation cluster,
suggesting that the shift was not simply a consequence of weakness in the affected limb. However, the range of functional impairments studied and patient numbers were too small for this conclusion to be very meaningful. Similarly, although there did not appear to be a relationship between lesion size and the extent of the shift, lesion volumes could not be precisely defined on the relatively thinly sliced structural scans, and both patient numbers and the range of lesion sizes were small. Thus, defining the relationship between the lesion burden or functional impairment and the magnitude of the posterior shift demands further study.

Segmentation of functional regions contributing to the activation within the SMC was not performed because smaller distinct clusters of activation were not identified in this larger region. With overlapping activations, the apparent contributions from each neuroanatomic structure would thus be determined most directly by the chosen neuroanatomic borders rather than by the underlying functional data. In addition, in the absence of direct cytoarchitectural information, the accuracy of the segmentation would be limited, particularly given the anticipated variability between the subjects.22

Although the postcentral gyrus is generally identified functionally as a primary somatosensory cortical area, there are neurons in the somatosensory cortex of rodents that project directly to spinal or bulbar motor neurons in rats.23 Therefore, increased learned use (ie, a compensatory strategy) or adaptive recruitment of similar cortical motor neurons in humans for the control of hand movement after injury in the corticospinal tract is an attractive hypothesis to explain the posterior shift observed.

However, there are alternative interpretations. It is possible, for example, that the increased postcentral gyrus activation reflects an enhanced somatosensory response in patients with stroke relative to the normal control subjects. Recently, we have confirmed that increased attention enhances activation in the primary as well as the secondary somatosensory cortex.24 Enhanced attention could be part of a compensatory strategy for movements after brain injury. The finding of significant activation in the secondary sensory cortex in the patient group (and not in the control group) would be consistent with this hypothesis.

The independent significance of this posterior shift for functional recovery is difficult to assess for 2 reasons. First, association studies based on functional brain imaging alone cannot establish that activated regions are either necessary or sufficient for a particular aspect of recovery behavior. Second, the imaging data provide evidence for other changes in the patterns of activation in the patients relative to control subjects. As described in previous studies of patients after strokes,7,9,10,12 this patient group also showed decreased motor cortex LI. Parallel ipsilateral motor pathways have been suggested by previous functional imaging studies (eg, after stroke7,9) to contribute to recovery after corticospinal tract injury. In our patients, there was also more frequent activation in additional areas, including the parietal cortex (data not shown), as also suggested in another recent report.12

Patients with more severe deficits after motor cortex infarct may use more anterior premotor pathways for recovery of limb motor functions.25 Although they are less important for inferences concerning long-distance activations (as in measurement of the LI), there are some technical considerations that can confound the interpretation of local spatial shifts measured by fMRI. The spatial resolution of the technique is limited fundamentally by the acquisition parameters and the associated point-spread function, as well as the spatial smoothing, which is used for optimization of signal to noise in data analysis. Therefore, shifts of under \( \approx 5 \) mm would not be anticipated to be able to be discerned by using the data acquisition parameters chosen for the present study. Additional potential uncertainty in localization arises from the physiology. The blood oxygenation level–dependent fMRI signal arises from blood oxygenation changes that occur both in the brain parenchyma and in the draining veins.26 Signal changes in draining veins do not precisely localize the cortical region activated, although brain parenchymal signal changes may be able to localize cortical activation to regions as small as a single-activated cortical column by using a difference-mapping procedure.27 The use of a higher-field (3-T) magnet theoretically contributes to an increased ability to localize precisely relative to lower field systems, because the relative contribution of signal from brain parenchyma relative to draining veins rises as magnetic field strength increases.26

If this local posterior shift in the center of the primary sensory motor cortex activation results from an intrinsic adaptive local change in the functional organization of the motor cortex, it could arise as a consequence of locally decreased inhibition.28 Decreased GABA expression is found after peripheral nerve transaction leading to local cortical reorganization.29 Animal studies have also demonstrated that local circuits can be expanded even acutely with GABA-ergic antagonism.30 Regulation of local circuitry by such inhibitory mechanisms may contribute to motor learning in the normal brain. Consistent with this notion, Karni et al18 have demonstrated that SMC activation enhances local representations with the learning of a complex motor task. Taken together, these observations raise the question of whether pharmacological modulation of inhibitory circuits may contribute to functional recovery. However, with such an approach, the timing of the administration of inhibitory blockade potentially could be critical, because in the subacute stages of infarct evolution, inhibitory circuits may contribute to minimizing damage via excitotoxic mechanisms.31

**Acknowledgments**

P.M.M. gratefully acknowledges support from the Medical Research Council (UK) for program and ROPA grant support and the
European Commission BIOMED II program supporting the MICRODAB collaboration. We particularly thank Dr Steve Smith, Head of Image Analysis in the Centre for Functional Magnetic Resonance Imaging of the Brain, for software tools used for the present study. H.J.B. is the recipient of a Wellcome studentship.

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