Motor Cortex Organization After Stroke Is Related to Side of Stroke and Level of Recovery

Anna C. Zemke, BS; Patrick J. Heagerty, PhD; Christopher Lee, BA; Steven C. Cramer, MD

Background and Purpose—The present study hypothesized that side of stroke and level of recovery influence motor system organization after stroke.

Methods—Functional MRI was performed on 14 control subjects and 21 patients with chronic stroke during index finger tapping (control subjects, right; patients, recovered side).

Results—On functional MRI, stroke patients with right arm involvement showed (1) significantly smaller activation in contralateral motor cortexes compared with control subjects; (2) smaller ipsilateral (nonstroke) premotor and larger contralateral (stroke-side) sensorimotor activation compared with patients with left arm involvement, although electromyogram across groups was similar; and (3) 2.7-fold–larger contralateral sensorimotor cortex activation, ventrally, in those with full recovery compared with those with partial recovery, despite similar tapping force, frequency, range of motion, and electromyogram between groups. Supplementary motor area activation was unrelated to level of recovery.

Conclusions—After stroke that causes mild to moderate initial impairment and mild residual hand weakness, cortical organization varies with side of injury and with final motor status. The findings may have implications for treatment after stroke.

Key Words: brain mapping • neuronal plasticity • recovery of function

Limited data are available relating level of final motor status after stroke to features of functional imaging brain activation maps. One goal of this study was to test the hypothesis that functional MRI (fMRI) motor activation maps vary in relation to final motor status.

Nondominant hand movements normally have different cortical organization than dominant hand movements, the former being more bilaterally organized in dextrals. However, functional imaging studies have not examined whether motor system reorganization after stroke differs when nondominant compared with dominant hand movements are affected. When side of stroke influences poststroke physiotherapy, it is usually on the basis of associated cognitive symptoms, but theoretically, differences in motor reorganization related to stroke side might also be important. The present study addressed the hypothesis that nondominant hand movements are organized differently than dominant hand movements chronically after stroke.

Materials and Methods

Subject Selection and Evaluation
Twenty-five patients with stroke >10 weeks previously that was associated with arm sensorimotor deficits and 14 control subjects gave informed consent. There were no differences in age or sex. Patients and control subjects were all right handed (Edinburgh Inventory). fMRI head motion eliminated 4 patients. Language or attention deficits were uncommon (1 of 21) and were unrelated to fMRI performance. Review of acute stroke records showed mostly mild strokes; only 6 patients had complete hand function loss. Affected muscles improved by fMRI.

Each subject spent <5 minutes practicing tapping just before fMRI, during which surface electromyograph (EMG) measured 5 right and 5 left arm muscles.

Image Acquisition
fMRI was acquired as described previously, with 5 cycles of rest alternating with tapping. Control subjects tapped their right index fingers; patients tapped their stroke-affected side on top of a force transducer. Wrist splints restricted metacarpophalangeal flexion and extension to 25°. An in-room examiner verified tapping performances. Subjects tapped at 50% of the maximum rate (2-Hz limit).

Data Analysis
Data were analyzed as described previously. Significantly (Z>3) activated voxels were counted in precentral gyrus, postcentral gyrus, supplementary motor area (SMA), premotor cortex, parietal operculum, frontal operculum, and remaining parietal lobe. Contralateral precentral gyrus signal change was measured (1% and 0.5% threshold). A >10% difference in pegboard performance (normal right-left
### Key Clinical and fMRI Results

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Time After Stroke, days</th>
<th>Stroke Volume, cm³</th>
<th>Fugl-Meyer Score</th>
<th>Pegboard Score</th>
<th>Tap Rate, Hz</th>
<th>% Signal Change (1% Threshold)</th>
<th>Premotor Cortex Activation, voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td>14</td>
<td>...</td>
<td>...</td>
<td>66</td>
<td>0.93</td>
<td>2.0</td>
<td>1.89</td>
<td>21, 9</td>
</tr>
<tr>
<td>Left hand affected</td>
<td>10</td>
<td>136</td>
<td>68</td>
<td>62.0</td>
<td>0.67</td>
<td>1.5</td>
<td>1.73</td>
<td>11, 21</td>
</tr>
<tr>
<td>Right hand affected</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire group</td>
<td>11</td>
<td>127</td>
<td>36</td>
<td>63.5</td>
<td>0.86</td>
<td>1.8</td>
<td>1.74</td>
<td>9, 5</td>
</tr>
<tr>
<td>Full recovery</td>
<td>6</td>
<td>99</td>
<td>31</td>
<td>65.3</td>
<td>1.06</td>
<td>1.9</td>
<td>1.76</td>
<td>8, 6</td>
</tr>
<tr>
<td>Partial recovery</td>
<td>5</td>
<td>157</td>
<td>38</td>
<td>61.4</td>
<td>0.62</td>
<td>1.7</td>
<td>1.71</td>
<td>10, 3</td>
</tr>
</tbody>
</table>

Values are mean, except stroke volume and time after stroke (median). Pegboard score is number of pegs in Purdue Pegboard during separate 30-second trials for each hand, expressed as (affected hand)/(nonstroke hand); for controls, (left)/(right). Internal carotid artery narrowing (3/10 left-hand vs 3/11 right-hand involvement), deep stroke (2/10 vs 3/11), and prior stroke radiologically (3/10 vs 5/11) were evenly distributed among patient groups.

**Figure 1.** Individual patient activation maps. In a, bilateral brain activation was accompanied by unilateral EMG activity. Large arrows indicate contralateral (stroke-side) sensorimotor cortex activation; small arrows, ipsilateral (not stroke-side) motor-premotor cortex.
asymmetry) between affected and unaffected hands separated right-hand–affected patients into full or partial recovery. Group maps were generated in stereotaxic space and then contrasted pairwise by use of the 2-sample test statistic to reduce impact of different group sizes. Group and group contrast maps were then probed for significant \((Z>4)\) activation clusters; Wilcoxon signed-rank test compared continuous measures. An all motor area–laterality index \(^2\) was calculated.

**Results**

**Effect of Stroke**

No EMG leads showed significant differences between control subjects and right-arm–affected patients. Voxel counting found larger activation in control subjects within contralateral premotor cortex \((P<0.03)\). When contrasting group maps, we found that control subjects showed significantly larger contralateral precentral gyrus and SMA activation.

**Effect of Stroke Side**

Patients who were right arm affected had no significant clinical differences compared with those who were left arm affected: smaller wrist extensor EMG on resting side \((0\% \text{ versus} 19\%, \, P<0.01)\), which was minute compared with active side \((610\% \text{ versus} 498\%, \, P=\text{NS})\); smaller voxel counts within nonstroke \((\text{ipsilateral})\) premotor cortex \((P<0.05, \text{the Table and Figure} \, 1)\); higher motor-laterality index \((\text{more contralateral}, \, P<0.05)\); and when group maps were contrasted, significantly larger contralateral sensorimotor and smaller ipsilateral premotor plus SMA activation \((\text{Figure 2})\).

**Effect of Recovery Level**

Right-arm–affected patients with full recovery showed no clinical differences compared with those experiencing partial recovery, apart from pegboard results: in group maps, 2.7-fold–larger contralateral sensorimotor activation, with negligible differences in SMA; no differences in tapping force \((1.03 \text{ versus} 1.2 \text{ N}, \, P=\text{NS})\) or EMG; and when group maps were contrasted, a significant contralateral sensorimotor cortex focus ventrally at Talairach \((30, -20, 45)\). Correlation analysis \((\text{SPM99})\), limited by the small sample size \((n=11)\), did not find a linear relationship between activation and pegboard performance.
Reanalysis with threshold $Z=4$ (voxel counting) or $Z=3$ (cluster detection) minimally affected results. Contralateral percent signal change results did not differ between groups at either threshold and were not influenced by arterial disease. Negative activation maps showed no significant foci.

Discussion

Side of stroke and final motor status are related to motor system organization after stroke. Measurement of prescan EMG plus in-scan tapping force suggests that findings are related to changes in brain function rather than divergent movement performances.

Side of stroke influenced results, a finding relevant to occupational therapy. Greater ipsilateral premotor cortex recruitment is normally seen with left compared with right hand movement. Such ipsilateral recruitment increases after stroke.2 3 4 7 Ipsilateral recruitment varies according to stroke side (see Figures 1 and 2). Conclusions would be stronger if control left tapping data were available.

The best return of motor function after dominant-hemisphere stroke is related to preservation of function in affected hemisphere sensorimotor cortex, especially ventrally.5 Results are consistent with transcranial magnetic stimulation studies,8 which suggest that neurophysiological integrity of the affected hemisphere corticospinal tract is important to motor outcome. The basis for smaller activation with lesser recovery, despite movements similar to those of patients with full recovery, may relate to activity of subcortical areas not imaged.9

A previous functional imaging study found that stroke topography influences motor system reorganization.10 Present results indicate that stroke side and final motor status are also important. Restorative therapy trials, as with acute and preventative trials, might reduce variance and increase power if patients are enrolled or stratified on the basis of clinical and physiological assessments relevant to recovery processes.

References


Editorial Comment

Functional MRI: A Potential Physiologic Indicator for Stroke Rehabilitation Interventions

A patient recovering from a modest hemiparesis from stroke alternates between rest and tapping the affected index finger or gripping a transducer with visual feedback about the force exerted during functional MRI (fMRI). Do the evoked patterns of cerebral activity reveal the reorganization and rehabilitation of the motor mind? They may, if considered within the context of potentially confounding technical, statistical, anatomical, experiential, and task-dependent factors.3 4

What Are the General Determinants of fMRI Patterns of Activation Induced By a Movement? Maps of functional anatomy obtained using the blood-oxygen–level-dependent (BOLD) technique depend on the spatial extent of metabolic and hemodynamic changes induced by local synaptic activity and local field potentials, but do not precisely correlate with such activity.5 Localization and spatial resolution of neuronal activity may be confounded by a range of signal-dependent factors. These include BOLD-dependent capillary density and draining veins, perfusion of hemodynamically compromised tissue, links between one active population of neurons to others,6 possible differences in the BOLD signal caused by presynaptic inhibition compared with excitation, and fine differences between subjects in the location of regions of interest.7 fMRI methods are not a done deal. Some controversy and room for error accompany every aspect of data acquisition and analysis. Choices are made about the MR sequences for scans, data smoothing and correction schemes, registration of activations onto anatomical space especially when an infarct distorts morphology, modeling choices for the statistics represented by colored voxels of activity, statistical inferences, and approaches to individual subject versus group analyses. In addition, physiological factors such as sleep deprivation and estrogen levels
and drugs such as caffeine may alter the BOLD signal from one day to another in the same subject. Any agent or injury that affects neurotransmitters, especially widely projecting neuromodulators such as dopamine, acetylcholine, noradrenaline, and serotonin may alter large-scale synaptic excitability and, in turn, the BOLD response.

The primary sensory (S1) and motor cortex (M1) is the most common region of interest studied. Other sensorimotor areas, some of which project bilaterally, also contribute to the corticospinal control of movement (Table). Some or all regions are activated by a motor task, more so as task demands increase. A hemiparesis will add to task difficulty. Performance, then, depends in part on the relative sparing of the nodes included in the Table in relation to task requirements. Greater knowledge about spared sensorimotor projections would help put activations into the context of structure and function. The integrity of descending and ascending projections of parallel fiber arrays may come to be better appreciated using diffusion tensor imaging algorithms that estimate the anatomical connectivity between the cortex and subcortical white matter tracts. The colorful maps of activity, however, may not offer predictable patterns, even if the volume of spared neurons can be estimated. Gains in motor skills and fMRI activity also depend on the subject’s history of practice, as well as handedness, sex, education, motivation, age-related prior brain and biomechanical adaptations, and genetic differences, along with various adaptive and sensory drives for movement. The limitations of the BOLD signal and analytic techniques mean that signals from reticulospinal inputs to propriospinal premotoneurons for control of a synergistic grasp and rubrospinal contributions to individuated finger and feeding movements will not be detected. Patterns of activation, then, seem to ride on the individual subject’s ability to recruit residual portions of a bilateral motor network, driven in part by residual sensory feedback related to task performance.

**What Conclusions Can Be Drawn From Movement-Related Activation Studies After Stroke?**

In studies of patients who regain most of their ability to tap fingers or open the hand, fMRI reveals a ventral expansion of neuronal assemblies in S1M1 representing the hand toward those for the face. For ankle dorsiflexion, the representation expands toward the proximal leg and back muscles. These activations may later decrease with behavioral gains. Activation is often prominent along the rim of a cortical infarct, which may be a bastion for long-term potentiation soon after stroke.

Animal and human studies of cerebral reorganization with fMRI also reveal a shift of activation to the contralateral cortex soon after a stroke, somewhat in parallel to the extent of tissue loss. As functional use of the hand improves, activity shifts more to ipsilesional S1M1, if it is relatively spared. At least for subcortical stroke, worse behavioral outcomes for the hand correlate with a shift in the balance of activation toward the contralateral S1M1 with greater ipsilesional M1 injury. In this issue of *Stroke*, Zemke and colleagues find that reorganization within S1M1 and premotor areas differs, depending on the side of the stroke and whether minimal or mild impairments persist. The investigators controlled their motor task for force, range of joint motion, speed, muscles activated, and attention, so the data are especially likely to reflect a change in cortical function, rather than reflect a different movement strategy. Other studies reveal that less premotor activity and higher contralateral activation in the cerebellar hemisphere correlate with greater motor control, consistent with sparing of corticopontocerebellar projections. A posterior extension of peak activation in S1M1 of uncertain relevance to behavioral gains has been noted in some subjects but may reflect a compensatory sensory drive for movement. The limitations of the BOLD signal and analytic techniques mean that signals from reticulospinal inputs to propriospinal premotoneurons for control of a synergistic grasp and rubrospinal contributions to individuated finger and feeding movements will not be detected. Patterns of activation, then, seem to ride on the individual subject’s ability to recruit residual portions of a bilateral motor network, driven in part by residual sensory feedback related to task performance.

**Can We Improve on Our Understanding of Activation Patterns?**

Theory-driven, experimental evidence is rapidly improving fMRI acquisition and analytical methodologies. Correlations between representational or network changes and behavior require continuing careful study. Learning-dependent plasticity is a function of the novelty, intensity, duration, and specificity of the movement skill that is practiced. As rehabilitation practice proceeds after stroke, fMRI could be used to reveal both the capacity and progress of experience-dependent changes in the interactive nodes of the motor network. That would increase our understanding of the meanings of patterns of activity over time. Indeed, a great value of fMRI for rehabilitation could be to serially monitor functional anatomical changes over the course of a physical, cognitive, pharmacologic, or, one day, biologic repair intervention. Pushing the potential for gains after stroke by continuing a specific therapy, until no further behavioral improvements and no further evolution in the activity of regions of interest result, may also ensure that the interven-
tion has been maximized and that the reorganizational potential of the regions studied has peaked, at least as far as fMRI can discern. Used this way, fMRI patterns may provide a physiological indicator to monitor and eventually to predict the utility of a rehabilitative intervention for patients.

Acknowledgments

Support was provided by NIH grants HD39629 and HD07479. I thank my colleagues at the Brain Mapping Center at UCLA.

References

Motor Cortex Organization After Stroke Is Related to Side of Stroke and Level of Recovery
Anna C. Zemke, Patrick J. Heagerty, Christopher Lee and Steven C. Cramer

Stroke. 2003;34:e23-e26; originally published online April 3, 2003;
doi: 10.1161/01.STR.0000065827.35634.5E

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/34/5/e23

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/