Motor Impairment and Recovery in the Upper Limb After Stroke
Behavioral and Neuroanatomical Correlates

Leeanne M. Carey, PhD; David F. Abbott, PhD; Gary F. Egan, PhD; Julie Bernhardt, PhD; Geoffrey A. Donnan, MD

Background and Purpose—Motor recovery after stroke is associated with cerebral reorganization. However, few studies have investigated the relationship directly, and findings are equivocal. We therefore aimed to characterize the relationship between motor impairment, motor recovery, and task-related changes in regional cerebral blood flow (ΔrCBF) longitudinally.

Methods—We obtained a profile of motor impairment and recovery in the upper limb and conducted positron emission tomography motor activation studies using a simple finger-tapping task in 9 stroke patients 2 to 7 weeks after stroke and 6 months later. For correlation analysis, mean images of task-related ΔrCBF for each individual were linearly regressed with motor impairment scores. Motor recovery was correlated with longitudinal ΔrCBF images.

Results—Patients (7 males; 72.0±9.8 years) demonstrated a wide range of impairment severity and variable recovery. Upper-limb motor function was linearly correlated with task-related ΔrCBF. Importantly, sites of correlated ΔrCBF differed over time. Subacutely correlated ΔrCBF was observed in supplementary motor area (SMA), bilateral cingulate, and contralesional insula with a small area in ipsilesional primary sensorimotor cortex (SM1). Conversely, at the 6-month study, correlated ΔrCBF was primarily in ipsilesional SM1, extending to the cingulate gyrus. Better motor recovery was correlated with reduction in contralesional activity and increase in ipsilesional SM1.

Conclusions—Upper-limb motor function and recovery are correlated with ΔrCBF in SMA, cingulate, insula, and SM1, highlighting the role of these areas in the recovery process. The dynamic nature of the relationship suggests ongoing adaptation within motor networks. (Stroke. 2005;36:625-629.)

Key Words: brain mapping ▪ cerebrovascular accident ▪ neuronal plasticity ▪ recovery of function ▪ upper extremity

Development of restorative approaches to neurorehabilitation requires integration of research into behavioral outcomes and mechanisms of neural plasticity and repair. Evidence of changes in sites of task-related brain activation, mostly in recovered stroke patients, is identified relative to healthy controls and over time.

Presumably, these changes are adaptive and related to behavioral recovery. However, limited range in severity of motor impairment and recovery in most studies impacts on the ability to adequately test these propositions. Further, only a few studies have correlated behavioral outcome with relative cerebral blood flow or blood oxygenated level–dependent signal change, and findings are equivocal. Moreover, the temporal aspects of the relationship need to be established, given evidence of dynamic changes.

Adaptive versus maladaptive brain reorganization reported in animals is possibly related to compensatory motor strategies. Therefore, it is important that neural correlates of motor recovery are established relative to functionally and clinically relevant motor recovery. Yet, the scanning environment dictates sampling of restricted movements such as finger tapping, gross grasp, or passive elbow movement. It is unclear how well these surrogate markers of recovery correlate with motor function in the upper limb.

To address these issues, we characterized the nature of impaired motor function in the upper limb after stroke and investigated the relationship between motor impairment, motor recovery, and changes in regional cerebral blood flow (ΔrCBF) longitudinally. Specifically, we hypothesized that: (1) upper limb function would be highly correlated with finger-tapping ability; (2) task-related ΔrCBF in primary and nonprimary motor areas would correlate with level of impairment on the Action Research Arm Test (ARAT); and (3) longitudinal changes in ΔrCBF would correlate with change in ARAT (recovery) over time.
TABLE 1. Motor Impairment and Recovery of Stroke-Affected Hand at Initial and 6-Month Studies

<table>
<thead>
<tr>
<th>Subject/Hand Affected</th>
<th>Percent Reduction in Deficit ARAT (57)</th>
<th>ARAT (/57)</th>
<th>Range Finger Flex/Extension (degrees)</th>
<th>Rate of Finger Tapping (Hz)</th>
<th>Finger Control (at 0.5 Hz)</th>
<th>Force-Finger Extension (VAS/100)</th>
<th>Normality (VAS/100)</th>
<th>Perceived Effort (VAS/10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>07 R</td>
<td>100 24 57</td>
<td>60.0</td>
<td>85.7</td>
<td>1.02</td>
<td>1.38</td>
<td>0.46</td>
<td>0.72</td>
<td>0.04</td>
</tr>
<tr>
<td>01 R</td>
<td>97.1 22 56</td>
<td>7.3</td>
<td>45.5</td>
<td>1.05</td>
<td>1.40</td>
<td>0.04</td>
<td>0.76</td>
<td>0.00</td>
</tr>
<tr>
<td>06 R</td>
<td>96.7 26 56</td>
<td>51.1</td>
<td>85.1</td>
<td>1.52</td>
<td>1.58</td>
<td>0.81</td>
<td>0.82</td>
<td>0.08</td>
</tr>
<tr>
<td>02 R</td>
<td>86.3 35 54</td>
<td>81.5</td>
<td>91.5</td>
<td>1.32</td>
<td>1.32</td>
<td>0.26</td>
<td>0.69</td>
<td>0.13</td>
</tr>
<tr>
<td>10 L</td>
<td>76.9 18 48</td>
<td>7.5</td>
<td>64.1</td>
<td>0.40</td>
<td>1.03</td>
<td>0.04</td>
<td>0.16</td>
<td>0.06</td>
</tr>
<tr>
<td>04 R</td>
<td>35.1 0 20</td>
<td>23.3</td>
<td>55.5</td>
<td>0.72</td>
<td>0.67</td>
<td>0.04</td>
<td>0.71</td>
<td>0.07</td>
</tr>
<tr>
<td>03 L</td>
<td>20 1 11</td>
<td>7.5</td>
<td>53.2</td>
<td>0.20</td>
<td>0.70</td>
<td>0.10</td>
<td>0.21</td>
<td>0.00</td>
</tr>
<tr>
<td>09 L</td>
<td>14 0 8</td>
<td>6.5</td>
<td>42.4</td>
<td>0.42</td>
<td>0.60</td>
<td>0.09</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>08 L</td>
<td>8.7 0 5</td>
<td>2.6</td>
<td>6.5</td>
<td>0.15</td>
<td>0.16</td>
<td>0.02</td>
<td>0.16</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Healthy controls
Mean 57 88.8 1.53 0.89 0.16 86.4 3.5 3.3
SD 0.0 15.5 0.13 0.09 0.05 13.82 2.4 2.2

R indicates right; L, left.
*Minimum force production, unable to reliably rate trace from graph.

Methods

Subjects
Nine stroke patients with first-episode cortical or subcortical infarcts of middle cerebral artery (MCA) origin participated after giving written informed consent. They were medically stable, could comprehend simple instructions, and were right-hand dominant. Infarct site was identified using structural magnetic resonance (MR) or computed tomography (CT) scans and classified using clinicoradiological criteria. Patients with brain stem infarcts, previous neurological dysfunction, history of impaired hand function, or history that precluded positron emission tomography (PET) scanning were excluded. The study was approved by the local ethics and radiation safety committees.

Experimental Design
Quantitative measures of upper limb function and finger-tapping ability were obtained on 2 occasions, 2 to 7 weeks after stroke and 6 months later. Brain activation during performance of a simple finger-tapping movement was obtained within 48 hours of the end of the PET session using a VAS. A second, whole-body video was recorded for subsequent analysis. Average amplitude and rate of finger tapping were calculated for initial and 6-month studies.

Quantification of Motor Impairment and Recovery
Our primary index of motor outcome, the ARAT, comprises reach and grasp movements, has good reliability, and is able to detect clinically relevant recovery after stroke. Individual item rating (0 to 3) is based on item completion and clinical judgment of normality, with a maximum possible score of 57.

PET Activation Protocol
Regional cerebral blood flow (rCBF) was measured using 15O-labeled water during task and rest conditions using a Siemens/CTI 951/31R PET scanner, as described previously. Briefly, the task involved a simple, repetitive finger-tapping movement of the index finger of the hand contralateral to the lesioned hemisphere for 100 seconds. Four pairs of tasks and rest conditions were presented in a within-pair-randomized order. The hand and forearm were supported in an individually molded splint, allowing freedom of movement of the index finger. Patients were briefly trained to move the MCP joint of the index finger at an attempted rate of 1.5 Hz (cued by a metronome), using their "near-maximum comfortable" range of movement.

Data Analysis
Impairment scores for the ARAT and each of the parameters of finger-tapping ability were calculated for initial and 6-month studies. Correlation between measures was tested using Spearman ρ (for ARAT) or Pearson’s coefficient. Improvement in upper limb function over time
right, large 1). One patient (S08) had severe hemianesthesia, and 7 had mildly reduced touch sensation at the fingertips, with minimal change over time. Patients received standard clinical management followed by 1 to 3 months of inpatient rehabilitation (n=8), outpatient therapy (n=7), or both (n=6).

Motor Impairment and Recovery
Impairment scores are reported in Table 1. Upper limb function (ARAT) correlated highly with range, rate, control, and overall normality of the finger-tapping movement at initial and 6-month studies (Table 2). Correlations with force were moderate initially, whereas effort showed negative, low-moderate correlations. Range, rate, control, and normality were also highly correlated with each other at initial and 6-month studies (r≥0.7), except range was only moderately correlated with control (r=0.6) and normality (r=0.6) at 6 months. Force had moderate correlations (0.4 to 0.6) with rate, control, and normality initially and moderate to high correlations (0.6 to 0.8) at 6 months. Performance on the ARAT was significantly different between initial and 6-month studies (P=0.004).

Neural Correlates of Motor Impairment
ARAT scores for the contralesional hand at the initial study correlated significantly with the corresponding ΔrCBF, involving clusters in supplementary motor area (SMA), bilateral cingulate gyrus (posterior to vertical anterior commissure [VAC] plane), contralesional insula (extending to middle frontal gyrus), and ipsilesional primary sensorimotor cortex (SM1; Figure 1; Table 3). In contrast, at the 6-month study, the major region of correlated ΔrCBF was in the hand area of ipsilesional SM1, extending to the cingulate gyrus. The correlation plots at sites of maximum correlation in each cluster demonstrated a linear relationship (Figure 2).

Neural Correlates of Motor Recovery Over Time
Improvement in upper limb function over the 6-month interval of recovery was correlated with a reduction in contralateral activity (204 voxels) in the middle frontal gyrus (22, 20, 28; Z=4.46) and insula (22, 28, 8; Z=4.16) regions, identified at the initial study, and increased activity (121

TABLE 2. Correlation of Scores on ARAT With Parameters of Finger-Tapping Ability and Effort

<table>
<thead>
<tr>
<th>Measure</th>
<th>Initial</th>
<th>6-Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>0.76</td>
<td>0.72</td>
</tr>
<tr>
<td>Rate</td>
<td>0.78</td>
<td>0.93</td>
</tr>
<tr>
<td>Control</td>
<td>0.71</td>
<td>0.82</td>
</tr>
<tr>
<td>Force (extension)</td>
<td>0.55</td>
<td>0.71</td>
</tr>
<tr>
<td>Normality</td>
<td>0.92</td>
<td>0.93</td>
</tr>
<tr>
<td>Effort</td>
<td>−0.30</td>
<td>−0.58</td>
</tr>
</tbody>
</table>

Correlations using Spearman ρ. Range, rate, control, and force (extension) were measured outside the scanner. Normality of movement and effort are based on task performance during scanning.

Results
Nine patients were tested on 2 occasions. Patients (mean age 72; SD=9.8 years; 7 males) had initial moderate-to-severe paresis. Sites of infarct were: left internal capsule, single-perforator-artery territory (n=2); internal watershed (left 1; right 1); paraventricular, single-perforator-artery territory (left 1; right 1); superior division MCA territory (left, partial 1; right, partial 1;...
voxels) in the ipsilesional postcentral gyrus (−44, −38, 60, Z=3.70; −48, −26, 44, Z=3.47).

Discussion
We have shown that upper limb function (measured using the ARAT) is linearly correlated with brain activity (ΔrCBF) in primary and nonprimary motor areas in patients with a wide range of clinical impairment. Moreover, sites of correlated ΔrCBF differed at initial and 6-month studies. Recovery in upper limb function was also related to longitudinal changes in ΔrCBF. These findings provide evidence that sites of correlated ΔrCBF change with time after stroke, according to degree of impairment and recovery, suggesting adaptation in motor networks recruited to perform the simple movement task.

Relationship Between Upper Limb Function and Parameters of Finger Movement
Detailed characterization of motor function across patients with a wide range of impairment and recovery was central to the study. The impairment and recovery observed was consistent with larger behavioral studies. Interestingly, we observed some sparing of fractionated finger movement even in patients with very severe motor impairment.

Rate, range, control, and normality of finger-tapping ability were highly correlated with the ARAT. This suggests concomitant improvement in finger-tapping parameters and functional tasks involving grasp and release and supports use of finger-tapping as a surrogate marker of functional recovery in neuroimaging studies. Perceived effort had a relatively low and negative correlation, consistent with our design in which effort of movement at the time of imaging was at least partially controlled. The need to interpret findings relative to the nature of the deficit and paradigm used is highlighted.

Neural Correlates of Motor Impairment
Better upper limb function at the initial time after stroke was associated with greater ΔrCBF in nonprimary motor areas (ie, SMA, bilateral cingulate, and contralesional insula). Only a relatively small area of correlated ΔrCBF was observed in ipsilesional SM1. In contrast, at the time of recovered function (6 months), better upper limb function was correlated with activity in SM1 of the lesioned hemisphere.

Investigation of the potential relationship between movement outcomes and brain activity is still in its infancy. Whereas some studies report different patterns of activation in subgroups of good and poor recoverers, findings from the few studies that have correlated signal change with behavioral outcomes vary in relation to the type of relationship (linear or nonlinear) and the sites involved.

A cross-sectional functional MRI (fMRI) study of patients with moderate to mild motor impairment at 3 months (ARAT 10 to 57) reported a negative correlation with degree of task-related activation in SMA, cingulate cortex, premotor cortex, posterior parietal cortex, and cerebellum. Although some sites were similar to those identified in our study, the relationship was negative, such that patients with poorer outcome showed greater activity in these regions. This apparent difference may in part be explained by differences in time studied and impairment levels because patients with better recovery at 2 to 6 weeks in our study still had moderate impairment, consistent with poorer recoverers studied by Ward et al at 3 months. Thus, involvement of additional motor regions appears to be associated with partial recovery of motor ability, subacutely and at 3 months after stroke.

Differences in the motor paradigm used (ie, variation in peak force exerted in a gross grasp versus constant force but variable rate during finger tapping) may also have contributed to the different findings. Evidence of dissociated impairment of force and control and lower correlations between force and motor abilities in our study highlight the potential for differential involvement of the motor network in the 2 tasks.

Correlated activity in SMA, bilateral cingulate, and contralesional insula subacutely may have predictive significance after stroke. SMA proper and cingulate (posterior to VAC) have direct connections with spinal motoneurons, particularly of the wrist and fingers, consistent with use of alternate and parallel motor pathways. The correlated activity we observed in SMA and cingulate was posterior to VAC, areas typically linked with

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**TABLE 3. Brain Regions Correlated With Upper Limb Function Impairment at Initial and 6-Month Studies**

<table>
<thead>
<tr>
<th>Cluster of correlated ΔrCBF</th>
<th>I/C</th>
<th>BA</th>
<th>Talairach coordinate x, y, z</th>
<th>Z score</th>
<th>Size of cluster (voxels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA and cingulate g</td>
<td>6</td>
<td>24</td>
<td>0, −16, 48</td>
<td>4.87</td>
<td>399</td>
</tr>
<tr>
<td>Insula</td>
<td>C</td>
<td>24</td>
<td>8, −14, 40</td>
<td>4.07</td>
<td>399</td>
</tr>
<tr>
<td>Initial Study</td>
<td>I</td>
<td>24</td>
<td>−10, −12, 40</td>
<td>3.87</td>
<td>399</td>
</tr>
<tr>
<td>SM1</td>
<td>I</td>
<td>4</td>
<td>−32, −18, 52</td>
<td>4.12</td>
<td>91</td>
</tr>
<tr>
<td>6-Month Study</td>
<td>I</td>
<td>4</td>
<td>−32, −24, 60</td>
<td>3.98</td>
<td>91</td>
</tr>
<tr>
<td>3, 1, 2</td>
<td>−30, −36, 60</td>
<td>3.87</td>
<td>91</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clusters of correlated ΔrCBF are significant at the cluster-level threshold of P<0.05 (corrected). The 3 most significant sites of correlated ΔrCBF within each cluster (all with a voxel-level threshold of P<0.001, uncorrected) are reported.

Size of cluster indicates No. of connected voxels in region at P<0.01. I, ipsilesional; C, contralesional; BA, Brodmann’s area; g, gyrus.
movement execution on the basis of structural and functional evidence.16,17 Correlated activity in SMA, cingulate, and insula may also be associated with increased attention to the task,18 use of alternate strategies for executing the movement, or an increased planning demand, as if finger tapping was a more complex movement.17 Further, the transient nature of the initial correlated ΔrCBF may represent dynamic motor learning on the basis of observations of early increased activation in SMA followed by a reduction when the task was learned.19 Reduced ability to change direction of movement quickly (control) observed is consistent with time delays incurred in accessing contralesional and nonmotor primary areas.

At the 6-month study, an association between almost-normal performance and activity in ipsilesional SM1 is consistent with a relative lack of additional nonprimary activation4 and increased activation in ipsilesional SM113 in patients with almost full recovery. It also indicates a more typical involvement of the primary motor cortex,9,17 which has a greater excitatory effect and more dense corticospinal projections.20

Neural Correlates of Motor Recovery Over Time

The magnitude of motor recovery over time was also correlated with change in ΔrCBF, involving relative reduction in activity in vicinity of contralesional insula and increase in ipsilesional SM1. The dynamic nature of change observed is consistent with ongoing recovery of motor function and highlights the role of the ipsilesional SM1 region in final recovery.

Findings from longitudinal studies are equivocal. Change from distributed contralesional activation subacutely to more focal, ipsilesional activation at the recovered stage is described.2,3,14,21 This change in laterality was associated with recovery for some14 but not others.2,21 Small et al reported a weak nonlinear relationship in ipsilateral cerebellum but not with ipsilesional or contralesional SM1.2 Ward et al reported a negative correlation, involving decreased activity in primary motor cortex, premotor cortex, SMA, cingulate, and other motor areas of both hemispheres with good recovery.2 In our study, correlated activity in SMA, cingulate, and contralesional insula initially, followed by reduction in contralesional activity and increase in ipsilesional SM1, provides converging evidence in support of a “focusing” of activation and return to activation patterns observed in healthy controls2 in those with good recovery.1 Importantly, convergence of results is evident despite different imaging modalities (ie, PET and fMRI).

Although only 9 subjects were studied longitudinally, we detected linear correlations with impairment and recovery in support of our hypotheses. Further investigation of infarct site on recovery and neural outcomes13 is indicated.

Acknowledgments

This work was supported by the National Health and Medical Research Council Australia (grant 960285), the Austin Medical Research Foundation, and the Centre for Positron Emission Tomography, Austin Health. We thank participants and therapists who assisted with recruitment.

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Stroke. 2005;36:625-629; originally published online January 27, 2005;
doi: 10.1161/01.STR.0000155720.47711.83
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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