Role of the Premotor Cortex in Recovery From Middle Cerebral Artery Infarction

Rüdiger J. Seitz, MD; Patrick Höflich, MS; Ferdinand Binkofski, MD; Lutz Tellmann, BS; Hans Herzog, PhD; Hans-Joachim Freund, MD

Objective: To study the mechanisms underlying recovery from middle cerebral artery infarction in 7 patients with an average age of 53 years who showed marked recovery of hand function after acute severe hemiparesis caused by their first-ever stroke.

Interventions: Assessment of motor functions, transcranial magnetic stimulation, somatosensory evoked potentials, magnetic resonance imaging, and positron emission tomographic measurements of regional cerebral blood flow during finger movement activity.

Results: The infarctions involved the cerebral convexity along the central sulcus from the Sylvian fissure up to the hand area but spared the caudate nucleus, thalamus, middle and posterior portions of the internal capsule, and the dorsal part of the precentral gyrus in each patient. After recovery (and increase in motor function score of 57%, $P<.001$), the motor evoked potentials in the hand and leg muscles contralateral to the infarctions were normal, whereas the somatosensory evoked potentials from the contralateral median nerve were reduced. During fractionated finger movements of the recovered hand, regional cerebral blood flow increases occurred bilaterally in the dorsolateral and medial premotor areas but not in the sensorimotor cortex of either hemisphere.

Conclusions: Motor recovery after cortical infarction in the middle cerebral artery territory appears to rely on activation of premotor cortical areas of both cerebral hemispheres. Thereby, short-term output from motor cortex is likely to be initiated.

Arch Neurol. 1998;55:1081-1088

MECHANISMS influencing clinical recovery from hemiparesis in brain infarction involve hemodynamic, biochemical, neurophysiological, and neuropsychological factors that we are only beginning to understand.1,2 Evidence based on large clinical cohorts indicates that approximately 45% of patients with hemiplegic stroke suffer from persistent hemiparesis,3,4 whereas the larger proportion of patients recover mostly during the first 4 weeks after stroke.5 As demonstrated by neurophysiological and morphometric studies, the severity of pyramidal tract damage appears to be a major predictor of outcome.6 Accordingly, in patients with striatocapsular stroke, initial hemiplegia may regress completely when the posterior part of the internal capsule is spared7 or when the magnetic evoked motor potentials are preserved.8 Activation studies with positron emission tomography (PET) in such patients showed that the sensorimotor cortex is recruited when the recovered hand is moved.9,10 Against this background, the additional bilateral premotor cortical activations not seen in normal subjects during the same motor tasks11 seemed to participate in rather than substitute motor cortex activity.

The aim of the present study was to examine which cortical areas become engaged in patients with infarctions of the middle cerebral artery (MCA) territory including the motor cortex hand representation or its underlying white matter. Based on a preceding study in patients with suprathalamic hemiparetic stroke,12 we predicted an enhanced activation in the supplementary motor area (SMA). The SMA is known to possess relatively high numbers of corticospinal neurons projecting to the cervical spinal cord.13-15 We also predicted ectopic activations in the spared motor cortex adjacent to the infarct lesion, since such activation patterns were observed in patients with precentral brain tumors.16 Here, we report that recovery from MCA infarction results in motor cortical reorganization with bihemispheric recruitment of premotor cortical areas.

RESULTS

CLINICAL DATA

All patients had a first brain infarction that was localized in the cortical MCA territory (Figure 1). The lesions differed in location and size among the patients but spared the caudate nucleus, thalamus, the middle and posterior portions of the internal capsule,
PATIENTS AND METHODS

PATIENTS

Seven patients with a mean (±SD) age of 53.9 ± 8.0 years were consecutively entered into the study during a period of 3 years (Table 1). Patients were referred to our clinic because of their first completed ischemic stroke. Inclusion criteria for this study were acute hemiplegia or severe hemiparesis with complete loss of fractionated movements of the affected hand and presence of only 1 brain lesion, as evident from magnetic resonance (MR) images. Some patients additionally exhibited hemianesthesia, hemineglect, or aphasia (Table 1). Patients with only moderate or slight hemiparesis and those who did not recover were excluded from the study. The study was approved by the Ethics Committee of the Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany. Motor impairment was assessed by a multifactorial score that was specifically designed for examining arm and hand function by separate assessment of various components contributing to the motor disturbance. They included maximal grip force, dexterity, apraxia, motor hemineglect, limb sensation, and muscle tone. Scores ranged from 0 (complete loss of functions on 1 side of the body) to 4 (normal), summing up to 24 at maximum. Testing was performed before the PET scan in the acute stage (1-3 days) and within 2 days before or after PET scanning. All patients showed severe motor impairment in the acute stage with scores within the range of 0 to 11 (mean, 4.6 ± 3.3). At PET scanning, the mean score was 18.3 ± 4.2, which corresponded to an improvement of 57.2% over the pre-PET scores (P < .001, Mann-Whitney test).

Patients received medical treatment including high-dose heparin treatment, antihypertensive medication, or antiarrhythmic medication according to their requirements. Medication did not include long-term sedation. In addition, each patient received physiotherapy that was continued after discharge from the hospital.

LESION LOCATION AND VOLUME

The MR images were recorded with a 1.5-T imager (Siemens Magnetom, Erlangen, Germany) within 3 days before or after the PET scan by means of a volumetric fast low-angle shot sequence. This sequence provides 128 sagittal images with a thickness of 1.17 to 1.51 mm and a pixel size of 1 × 1 mm. The proton-weighted MR images were spatially aligned with the templates of the Talairach and Tournoux atlas, and the chronic lesions were plotted on the corresponding templates. Additionally, the lesions of each patient were evaluated morphometrically to determine the lesion size and were superimposed on each other to create a mean lesion map (Figure 1).

EVOKED POTENTIALS

Magnetic evoked motor potentials (MEPs) were studied within 3 days before or after PET scanning. The MEPs were recorded on both sides from the first dorsal interosseus (FDI) and the anterior tibial (TA) muscles. A Magnestim 200 (Madaus, Freiburg, Germany) and a conventional coil with an outer diameter of 12 cm for FDI and an angulated figure-8 coil for TA were used. Stimulation strength was set to 1.5-fold of the threshold for responses in the relaxed FDI and TA on the side contralateral to the stimulated intact hemisphere. This ensured comparable MEP amplitudes on both sides, as discussed in detail elsewhere. For evoking MEPs in FDI, the 12-cm circular coil was centered over the vertex; for evoking TA muscle response, the crossing of the windings of the angulated figure-8 coil was placed over the vertex. The MEPs were recorded with self-adhesive surface electrodes, the active lead placed over the muscle belly, the neutral one over the tendon. Facilitation was induced by tonic voluntary contraction (20% to 30% of maximal isometric power) of the FDI and TA on either side to obtain reproducible MEPs. Central motor conduction times were calculated by subtracting the peripheral conduction time after magnetic root stimulation from the fastest of 5 cortically evoked responses. On both sides, MEP amplitudes were calculated as the percentage of the largest MEP in relation to the maximal M-waves (evoked muscle potentials) obtained by supramaximal electrical stimulation of the ulnar and peroneal nerves. The MEP amplitude ratio was assessed as the percentage of the MEP amplitude on the affected side compared with the MEP amplitude on the unaffected side. The M-wave-related MEP amplitude on the intact side was set to 100%.

Somatosensory evoked potentials (SSEPs) were elicited by cutaneous electrodes over the median and tibial nerves at a 3-Hz stimulation frequency. Recording from the scalp was averaged over 200 responses. The median nerves were stimulated with bipolar surface electrodes at the wrist; the tibial nerves, at the ankles. The intensity of the 0.1-millisecond square-wave pulse was adjusted to 4 mA above the motor threshold. The SSEPs of median nerve stimulation were recorded 8 cm lateral to the midline and 3 cm behind the vertex (C3, C4); SSEPs of tibial nerve stimulation were recorded at the midline 2 cm behind the vertex (Cz). The latencies and base-to-peak amplitudes of the N20 potential after median nerve stimulation and of the P40 potential after tibial nerve stimulation were measured.

SENSORIMOTOR ACTIVATION TECHNIQUES

The patients were blindfolded and underwent 4 sequential regional cerebral blood flow (rCBF) measurements, with intermissions of 15 minutes while lying in the PET scanner. In one scan, the subjects had to perform finger movements required for execution of sequential thumb-finger oppositions and somatosensory discrimination of parallelepipeds. The MEP amplitudes recorded from the contralateral FDI and TA muscles were slightly reduced, while the latencies were not affected (Table 2). The SSEPs showed a significant amplitude reduction of the contralateral median nerve. However, there were no changes in the latencies of the SSEPs after median or tibial nerve stimulation (Table 2). There was no correlation of the motor score with the MEPs of the FDI, and the dorsolateral part of the precentral gyrus even in the patient with the largest stroke lesion. At the time of admission, the patients were hemiparetic with complete loss or severe impairment of hand function (Figure 2). During the subsequent weeks, however, the patients recovered significantly (P < .001). At the time of PET scanning, i.e., 6 months after stroke on average (Table 1), the motor score of hand function had improved by 57%. Thus, the patients were ambulatory and could use their affected hand for everyday activities again. They were able to perform individual finger movements.
of tasks was randomized across the patients. One of us observed the subjects and registered the number of finger movements during the finger movement sequences and the correctly identified cubes in the tactile exploration task, respectively.

PET MEASUREMENTS

An 8-ring PET camera (PC4096 plus; GE/Scanditronix, Uppsala, Sweden) was used to measure the rCBF after intravenous bolus injection of butanol labeled with oxygen 15. This PET camera had an optimal spatial resolution of 4.9 mm in plane and a slice distance of 6.4 mm. The axial field of view is 105 mm and in this study was positioned to cover the entire extent of the motor cortex. Thus, rCBF measurements of the cerebellum were not made in all patients. A transmission scan using a rotating germanium 68 pin source was obtained before the emission to correct for attenuation. The 15 PET image slices were reconstructed with a Hanning filter to an effective image resolution (full width half maximum) of 9 mm.

The PET scanning started at the time of the intravenous bolus injection of 1480 MBq of $^{15}$O]butanol into the right brachial vein, which was flushed with 10 mL of saline. The local tissue concentration was sampled in list mode from which frames of 2 seconds each were calculated. The rCBF was measured with a combined dynamic-autoradiographic approach with the use of a common look-up table that was normalized to a global mean of 50 mL in the reference plane.

DATA ANALYSIS

Because of the homogeneous lesion location among our patients, we attempted to identify common areas of activation for the patient group by means of the new version of the computerized brain atlas. As detailed elsewhere, the rCBF images were transformed into standard brain anatomy by means of transformation parameters determined for each individual. Standardization yielded 21 axial image slices that were 6.43 mm apart with a matrix of 128 × 128 pixels, each measuring 2.55 × 2.55 mm. Image standardization compensated for minimal misalignments between the PET scans. After image standardization, subtraction of rest from the activation condition, mean images across the subjects, maps of the local variance, and descriptive t-maps of the rCBF changes were calculated pixel by pixel. In this omnibus testing, the mean rCBF changes compared with “rest” were set to a threshold of 12.4. To correct for the autocorrelation of adjacent pixels that is limited by the spatial resolution (full width half maximum) of the reconstructed PET images, only clusters of at least 17 spatially contiguous suprathreshold pixels in the PET image slices were accepted, corresponding to P < .05. This descriptive analysis is similar to theoretical cluster analysis approaches that incorporate the degree of smoothness in the images. Since stimulation-induced rCBF changes have been shown to vary considerably between patients, individual data analysis was also performed. In this empirical method that was validated by phantom simulations, a 2-parameter probability estimation was performed to identify the areas of maximal, task-related rCBF change in each subject. Briefly, regions of interest (ROIs) were drawn at a 30% isocontour level of the maximal activity in the 15 transaxial slices of the individual subtraction images. Gamma-distributions for spatial extent of and maximal rCBF increase in all ROIs were estimated according to the cumulative density functions of these parameters. The ROI values that were above a critical threshold of 0.01 for each of these parameters were considered significant. For the maximal number of ROIs in 1 set of 21 PET image slices, this meant accepting 0.65 ROI by chance alone in a 2-tailed analysis.

The rCBF changes were localized in each subject by coregistration of the PET image with the subject’s MR image by means of a spatial alignment algorithm and the anatomical structures derived from the database of the computerized brain atlas. For presentation of the significant mean rCBF changes, the MR image of the patient with the largest brain lesion was used and transformed into standard anatomy of the computerized brain atlas. The stereotactic coordinates were determined for the peak values in the descriptive t-maps by means of the computerized brain atlas.

STATISTICS

The differences of the motor score at the acute and chronic stage were assessed by the Mann-Whitney test. Evoked potentials of the affected side were compared with those of the contralateral side by the paired 2-tailed Student t-test. The relations of motor scores, evoked potentials, lesion volumes, and rCBF changes were calculated by parametric and nonparametric statistics (Spearman rank correlation). The differences of the motor score at the acute and chronic stage were assessed by the Mann-Whitney test. Evoked potentials of the affected side were compared with those of the contralateral side by the paired 2-tailed Student t-test. The relations of motor scores, evoked potentials, lesion volumes, and rCBF changes were calculated by parametric and nonparametric statistics (Spearman rank correlation).
During sequential finger movements of the recovered hand, the mean rCBF increased in premotor cortical areas of both cerebral hemispheres (Table 3). The activation in the ipsilesional frontomesial cortex probably included the SMA but may have extended ventrally also into the closely adjacent cingulate motor area. As evident from overlay with the anatomy of the corresponding MR image, the mean rCBF increases in the premotor cortex (PMC) occurred in its dorsolateral part along the posterior bank of the precentral sulcus in the ipsilesional hemisphere and along the anterior bank of the precentral sulcus in the contralateral hemisphere (Figure 3, top). In addition, significant mean rCBF increases were observed in abnormal locations including the ipsilesional anterior cingulate, prefrontal cortex, and contralateral hippocampal formation (Table 3). Sequential finger movements of the unaffected ipsilesional hand induced mean rCBF increases in contralesional motor, premotor, somatosensory, and parietal cortex as well as in SMA (Figure 3, top). This contrasted to the finger movements of the recovered hand, where there were no mean rCBF increases in the motor and somatosensory cortex.
somatosensory cortex (Table 3). Also, in the individual data, no activation was observed in motor cortex of the damaged or contralesional cerebral hemisphere during finger movements of the contralesional hand. This was even the case when no cutoff threshold was applied in group and individual image analysis. Structurally, the dorsolateral part of the precentral gyrus was spared in all patients, whereas in 4 patients the adjacent part of the postcentral gyrus was included in the infarction, as illustrated in Figure 3.

We wished to examine the patterns of rCBF increases related to finger movements after recovery from hemiparetic infarction in the MCA territory. When motor cortex is damaged, recovery can be mediated by the remaining cortical parts—possibly by reorganization of body map circuitries or by recruitment of nonprimary motor output modules in either hemisphere. We observed activations of lateral and medial premotor cortical areas when the patients performed fractionated finger movements with their recovered hand as used in simple motor sequences as well as in object exploration (Figure 3). The PMC activations occurred in the cortex lining the precentral sulcus at the level of the motor hand area. The activation of its posterior wall in the affected hemisphere and of its anterior wall in the contralesional hemisphere probably corresponded to the dorsal premotor area that in the monkey has been shown to contain neurons engaged in forelimb movements. This premotor area and the medial wall motor areas including the SMA and cingulate motor area accommodate corticospinal neurons, giving rise to a cortical-reticulospinal route that is bilaterally organized. If these cortical areas are homologous in the human to those in subhuman primates, their output projections should pass through the midportion of the internal capsule. Since the greater part of the internal capsule including the midportion was spared in our patients, these premotor cortical ar-

Table 3. Significant Sensorimotor Activations After Recovery From Middle Cerebral Artery Infarction*  

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>Coordinates</th>
<th>rCBF Increases, %</th>
<th>Volume, mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sequential Finger Movements With Recovered Hand</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premotor cortex IL</td>
<td>−31</td>
<td>−3</td>
<td>47</td>
</tr>
<tr>
<td>Premotor cortex CL</td>
<td>28</td>
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<td>47</td>
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<tr>
<td>Supplementary motor area IL</td>
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<td>1</td>
<td>47</td>
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<tr>
<td>Anterior cingulate IL</td>
<td>−9</td>
<td>16</td>
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<tr>
<td>Lateral prefrontal IL</td>
<td>−24</td>
<td>50</td>
<td>11</td>
</tr>
<tr>
<td>Hippocampus CL</td>
<td>34</td>
<td>−48</td>
<td>−1</td>
</tr>
<tr>
<td><strong>Sequential Finger Movements With Unaffected Hand</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Motor cortex CL</td>
<td>48</td>
<td>−12</td>
<td>47</td>
</tr>
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<td>Sensory cortex CL</td>
<td>47</td>
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<td>Supplementary motor area CL</td>
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<td>5</td>
<td>43</td>
</tr>
<tr>
<td>Anterior inferior cingulate CL</td>
<td>3</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Cuneus CL</td>
<td>12</td>
<td>−80</td>
<td>13</td>
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<tr>
<td><strong>Tactile Exploration With Recovered Hand</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premotor cortex IL</td>
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<td>−12</td>
<td>52</td>
</tr>
<tr>
<td>Supplementary motor area CL</td>
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<td>9</td>
<td>47</td>
</tr>
<tr>
<td>Frontal operculum CL</td>
<td>35</td>
<td>25</td>
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<tr>
<td>Postcentral gyrus CL</td>
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<td>−15</td>
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</tr>
<tr>
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<td>43</td>
</tr>
<tr>
<td>Precuneus CL</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Mesial prefrontal CL</td>
<td>3</td>
<td>25</td>
<td>35</td>
</tr>
</tbody>
</table>

* Listed are all significant mean regional cerebral blood flow (rCBF) changes compared with the resting state. Locations of the peak changes in coordinates (in millimeters) of the stereotactic space are given. IL indicates ipsilesional; CL, contralesional.
the normal motor activation pattern induced by the ipsilesional premotor cortical areas. This contrasted with the ipsilesional, unaffected hand, fine motor performance of the recovered hand may not have become “automatic.” That is, the dorsolateral prefrontal cortex is engaged a more complex involvement in learning-associated plasticity. That is, the dorsolateral prefrontal cortex was probably related to a more complex involvement in learning-associated plasticity. That is, the dorsolateral prefrontal cortex was probably related to a more complex involvement in learning-associated plasticity.

Although our patients showed a good clinical recovery (Figure 2), they clearly retained residual deficits, such as a reduced finger movement rate and slowed tactile exploration. Both deficits can be ascribed to reduced performance consistency and automaticity of sensorimotor control as recently observed by detailed kinematic analysis in clinically completely recovered stroke patients.57 Compared with the ipsilesional, unaffected hand, fine motor performance of the recovered hand may not have become “automatic,” which, therefore, necessitated the recruitment of prefrontal and premotor cortical areas. This contrasted with the normal motor activation pattern induced by the ipsilesional, clinically unaffected hand.41 However, performance of the finger movement sequence by even this hand was below normal, which was in accordance with recent observations by Winston and Pohl.58

In contrast to purely subcortical striatocapsular infarctions,9,10 there was no rCBF increase in the structurally preserved dorsolateral and dorsal portion of the motor cortex in the damaged hemisphere when the patients moved the fingers of their recovered hand, as evident both from group and individual data analysis. This observation was in accordance with the lack of activation in the left temporoparietal junction after recovery from Wernicke aphasia caused by cortical stroke.39 By contrast, electrophysiological mapping studies in monkeys have shown that after focal ischemia, cortical motor representations expand into adjacent areas in relation to behavioral recovery.66 Similar to the use-dependent changes in motor cortical representations in healthy monkeys,67,68 Also, human rCBF PET studies of slowly growing brain tumors of the precentral gyrus, subcortical lesions of the motor output system, and motor neuron diseases demonstrated motor cortical activations of abnormal topography within the precentral gyrus.68,69 Nevertheless, the lack of activation in the ipsilesional motor cortex in our MCA stroke patients was not caused by arbitrary statistical thresholds.

Our seemingly contradictory observations may find explanation and compatibility with recent results of MEP studies in patients with brain infarction. Typically, the MEPs are absent or severely abnormal in the acute phase after infarction but normalize in proportion to clinical recovery.70-72 Indeed, on PET scanning, MEPs of small hand muscles could be elicited from the affected cerebral hemisphere in our patients, indicating that the corticospinal output system was functional again. Classen et al68 demonstrated that in the acute stage after brain infarction there may be a significant increase of the silent period of electromyographic activity after transcranial magnetic stimulation of the affected motor cortex despite a formally normal MEP. Moreover, during the silent period, the cortex was refractory to a second cortical stimu-
lus that probably was the electrophysiological counterpart to the motor deficit and the irregular electromyographic activity.68 Presumably, the lack of motor cortical excitability and the silent period resulted from enhanced inhibition in motor cortex.69,70 We, therefore, suggest that the lack of an rCBF increase in ipsilesional motor cortex in our patients may be the hemodynamic or metabolic equivalent of this enhanced inhibition. That is, ischemia appeared to have damaged the neuronal machinery in motor cortex in the sense that it remained impaired for sustained activation as used in PET scanning.71 However, in correspondence to the structurally intact dorsolateral part of the precentral gyrus in MR imaging (Figures 1 and 3), the motor cortical output system was functional in our recovered patients, as evident from the MEP studies (Table 2). It is therefore suggested that input from the premotor cortical areas could elicit descending volleys from the motor cortex during movements.

In addition to the somewhat artificial finger movement sequences, we also wished to investigate the cerebral activation pattern during the natural tactile exploration of geometric objects with the recovered hand. We observed rCBF increases, in addition to the premotor areas, also in the contralateral parietal lobe. In normal subjects this task has been shown to involve the somatosensory cortex and the superior parietal lobule.27,72,73 In our patients, these portions of the parietal and somatosensory cortex were included in the ischemic brain lesion, probably causing reduced SSEPs and a lack of stimulation-related rCBF changes. Instead, we found the contralateral anterior parietal cortex activations in regions that in normal subjects seem to participate in consciously controlled movement activity.33,74 Therefore, this activation possibly did not reflect an abnormal reorganization of the somatosensory system, but rather enhanced control to meet the task demands of the task. Indeed, there is kinematic evidence showing that patients with parietal cortex lesions show abnormal finger movements when required to explore macrogeometric objects.75 Also, the coding of force is impaired in stroke patients.76

There is increasing evidence that the extent of sparing of the motor cortex and its corticospinal output tract correlates with the degree of motor recovery.77,78 Others have reported that recovery from aphasia after stroke correlated with the resting metabolism in the left inferior frontal cortex.79-80 However, recovery of motor function was demonstrated not to correlate with the recovery of somatosensory function.12 In this study we found that motor recovery in terms of fractionated finger movements was quite advanced, whereas stereognostic discrimination remained markedly impaired, so that sensory recovery did not seem to be a prerequisite for motor recovery. At the time of PET scanning, our patients did not show associated movements of the unaffected hand, which have been described after striatocapsular infarction.81-83 Correspondingly, there was no activation in the contralateral motor cortex. An unmasking of the corticospinal projections in the contralateral hemisphere, as demonstrated by electromyographic and MEP recordings, does not appear to correlate with motor recovery.80,82,86 Instead, motor recovery was shown by kinematic analysis to result from stereotypic and active training of self-initiated movements.81-86 Since self-initiation of movement is associated with increased activation of the SMA,75-79 and there is an enhanced functional interaction of the SMA within the spared cerebellomedullar motor loop in patients who have recovered from brain infarction,12 the SMA activation in this study seemed to underline the importance of voluntary initiation of movement in motor recovery after brain infarction.

In conclusion, our results suggest that in patients who have recovered from MCA infarction, movement-related activity in bilateral PMC and SMA initiated a short-term motor cortical drive for movement generation that was too subtle to be picked up by rCBF measurements.

Accepted for publication January 5, 1998.

This study was supported by grant number SFB 194 of the Deutsche Forschungsgemeinschaft, Bonn, Germany. We thank W. Hamkens, Institute of Nuclear Chemistry, Research Center Jülich, Jülich, Germany, for skillful tracer production. The help of Mrs Erika Rädisch for MR imaging is gratefully acknowledged. We thank Nina Azari, PhD, for helpful comments on the manuscript.

Reprints: R. J. Seitz, MD, Department of Neurology, Heinrich-Heine-University Düsseldorf, PO Box 10 10 07, D-40001 Düsseldorf, Germany (e-mail: Seitz@neurologie.uni-duesseldorf.de).

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