Reorganization of Sensory and Motor Systems in Hemiplegic Stroke Patients
A Positron Emission Tomography Study

Gereon Nelles, MD; Gregor Spiekermann, PhD; Markus Jueptner, MD; Georg Leonhardt, MD; Stefan Müller, MD; Horst Gerhard, MD; H. Christoph Diener, MD

Background and Purpose—Cortical reorganization of motor systems has been found in recovered stroke patients. Reorganization in nonrecovered hemiplegic stroke patients early after stroke, however, is less well described. We used positron emission tomography to study the functional reorganization of motor and sensory systems in hemiplegic stroke patients before motor recovery.

Methods—Regional cerebral blood flow (rCBF) was measured in 6 hemiplegic stroke patients with a single, subcortical infarct and 3 normal subjects with the [15O]H2O injection technique. Brain activation was achieved by passive elbow movements driven by a torque motor. Increases of rCBF comparing passive movements and rest were assessed with statistical parametric mapping. Significant differences were defined at \( P < 0.01 \).

Results—In normal subjects, significant increases of rCBF were found in the contralateral sensorimotor cortex, supplementary motor area, cingulate cortex, and bilaterally in the inferior parietal cortex. In stroke patients, significant activation was observed bilaterally in the inferior parietal cortex and in the contralateral sensorimotor cortex, ipsilateral prefrontal cortex, supplementary motor area, and cingulate cortex. Significantly larger increases of rCBF in patients compared with normal subjects were found bilaterally in the sensorimotor cortex, stronger in the ipsilateral, unaffected hemisphere, and in both parietal lobes, including the ipsilateral precuneus.

Conclusions—Passive movements in hemiplegic stroke patients before clinical recovery elicit some of the brain activation patterns that have been described during active movements after substantial motor recovery. Changes of cerebral activation in sensory and motor systems occur early after stroke and may be a first step toward restoration of motor function after stroke. (Stroke. 1999;30:1510-1516.)

Key Words: hemiplegia ■ somatosensory cortex ■ stroke ■ treatment outcome
restorative mechanisms of the brain. Early neuroplastic changes may form the basis for restitution of motor function after stroke, when severe hemiparesis or hemiplegia persists despite regression of edema and reperfusion of the ischemic penumbra. Knowledge of these adaptive structural and functional rearrangements may also be helpful in defining more effective therapeutic strategies for hemiplegic stroke patients.

In a PET study comparing active and passive elbow movements in normal subjects, nearly identical increases of regional cerebral blood flow (rCBF) in location, amount, and extent were found between both conditions.8 Passive elbow movements may thus serve as a performance-independent paradigm to study reorganizational patterns of the brain in patients without sufficient motor control to perform voluntary movements.

In this study we sought to investigate patterns of brain activation during passive movements in patients with a single, subcortical, ischemic stroke. Subcortical lesions were selected because in these patients the morphological structure of the cortex is preserved. We hypothesized that patterns of brain activation during passive movements early after stroke onset are different from those seen in normal subjects and that reorganization of sensory and motor systems can be found before any return of neurological function occurs.

Subjects and Methods

rCBF was measured as an index of neuronal activity in 6 stroke patients and 3 control subjects. Stroke patients were identified from the Stroke Service of the University Hospital and the Neurological Therapy Center, an outpatient rehabilitation facility for stroke patients. Inclusion criteria for stroke patients were as follows: (1) first ischemic stroke causing hemiplegia defined as National Institutes of Health Stroke Scale (NIHSS)9 question 5 score ≥3; (2) no prior stroke with sensory or motor deficits; and (3) no signs or history of other neurological or psychiatric diseases. Exclusion criteria were defined by the following NIHSS questions: decreased level of consciousness (questions 1a, 1b, 1c; each score >0); aphasia (question 9; score ≥2), or neglect (question 11; score ≥2). All patients received poststroke rehabilitation therapy consisting of physical and occupational therapy once daily. Stroke location was identified by CT or MR images of the brain. Three age-matched control subjects (2 female) were recruited through local advertisements. All control subjects were healthy volunteers with no history of neurological or psychiatric disease. Neurological examinations were conducted immediately before PET scanning. During clinical evaluation, the Fugl-Meyer score (motor component for upper extremity) was obtained for each subject (range, 0 to 66; normal score=66).10 The Fugl-Meyer scale is a standardized, reliable scale used to assess the neurological status of hemiplegic stroke patients.11 Handedness was evaluated according to the Edinburgh Handedness Inventory.12 All patients gave written informed consent. The study was approved by the Ethics Committee of the University of Essen.

PET Image Acquisition

Increases of radioactivity in specific brain regions correlate with rCBF,13 which in turn reflects synaptic activity.14 rCBF was measured with the [15O]H2O bolus injection technique (700 MBq in 10 to 20 mL of 0.9% sodium chloride solution per application over 50 seconds) with an ECAT 953-15 Siemens PET scanner (CTI, Inc.). Head movements were minimized with foam rubber pads on each side of the head. The plegic arm (right arm in control subjects) was abducted at the shoulder level to 70° and placed in a forearm brace that was connected to a torque motor (Jace Systems). Wrists were kept in a neutral position. The torque motor generated passive movements of the brace, resulting in flexion and extension of the elbow between 0° and 90° at a frequency of 0.5 Hz. Consecutive measurements of rCBF were performed during rest (condition A) and during passive elbow movements (condition B). Three scans for each condition were obtained in alternating order (ABABAB). Subjects kept eyes closed at all times during measurements. Measurement of rCBF during each scan lasted 90 seconds and started only shortly before the rise of the head curve. Given the restricted axial field of view of our PET camera (5.4 cm), a region 20 mm above the anterior commissure/posterior commissure line scanning the upper part of the brain was chosen. Fifteen contiguous slices, oriented parallel to the anterior commissure/posterior commissure line, were obtained. Attenuation correction was achieved with a transmission scan. The attenuation-corrected emission data were reconstructed by filtered back projection with the use of a cutoff frequency of 0.5 cycles per pixel (1.96-mm pixel size), resulting in a full width at half maximum (FWHM) resolution of 9 to 10 mm in the reconstructed image.

Image Analysis

Images were realigned with each other (statistical parametric mapping; SPM 96), transformed into the standard anatomic space corresponding to the atlas of Talairach and Tournoux,15,16 and filtered (low-pass gaussian filter: 15×15×9 mm at FWHM). Assessment of significant rCBF changes was performed with the use of statistical parametric mapping. Global flow differences were normalized voxel by voxel to a mean of 50 mL·d L−1·min−1 by ANCOVA with whole brain activity as covariate.

Statistical Analysis

All statistical analyses are based on group effects. Because the majority of patients had a right-sided infarct, all lesions were assigned to the right side of the brain. Two patients with a left-sided lesion were inverted about the mid sagittal plane. Thus, the hemispheric arm was always on the left for analytical purposes. Voxel-by-voxel comparison with the use of the general linear model and t statistics calculated differences of rCBF between passive movements and rest in patients and normal subjects (group study). The same model was used for comparisons between groups (multigroup study). The t statistic for every voxel was transformed into a unit normal distribution such that f(Z)=y(t), where f(Z) is the standard normal cumulative density function and y(t) is the Student’s t distribution, with the appropriate degrees of freedom given by the experimental design. The resulting statistical parametric map SPM(Z) is subsequently used to assign P values (to voxels and also to clusters), which are corrected for multiple, nonindependent comparisons.16 In this study significant differences were defined at P<0.01. Results are displayed as statistical parametric maps, showing areas of significant increases of rCBF. Small patches of activation, which are expected to appear by random fluctuations, were excluded by setting an additional cluster extent level of inference at P<0.3.

Results

Clinical and demographic data of patients are summarized in Table 1. All stroke and control subjects were right-handed. The mean±SEM age was 62±9.4 years in control subjects and 65±3.0 years in patients. All patients had a small-vessel, subcortical infarct affecting either the striatocapsular region or the pons. The time between stroke and PET imaging was 19.0±7.3 days. In all patients the infarct caused a dense flaccid hemiplegia for proximal and distal arm motor function. At time of PET imaging, the mean±SEM NIHSS and Fugl-Meyer scores of patients were 9.0±0.7 and 10.1±0.8, respectively. All but 1 patient (patient 6) had recovered voluntary control of shoulder elevation and abduction, but none was able to move the forearm or distal parts of the upper extremity. Sensory modalities such as pinprick, light touch, and proprioceptive function were intact in all patients. No
Areas that were significantly more activated in stroke patients and normal subjects

Comparisons of rCBF Between Stroke Patients and Normal Subjects

Areas that were significantly more activated in stroke patients than in normal subjects were identified by subtracting increases of rCBF during passive movements versus rest in normal subjects from those in patients (patients versus controls, multigroup study analysis). Significant increases of rCBF were found in the sensorimotor cortex bilaterally; these were stronger in the ipsilateral, unaffected hemisphere (Z=3.9). The focus of maximum activation of the ipsilateral sensorimotor cortex was centered on the posterior bank of the central sulcus. This cluster of activation also extended into the ipsilateral inferior parietal cortex (Brodmann area 40). In the contralateral sensorimotor cortex, the increase of rCBF was less strong, with the maximum activation again located in the postcentral gyrus. A strong increase of rCBF also occurred in the contralateral superior parietal lobe and ipsilateral precuneus (bilateral Brodmann area 7). Comparison of increases of rCBF between stroke patients and normal subjects showing activation of the ipsilateral sensorimotor cortex are illustrated in the bottom row of the Figure. Table 3 summarizes the exact anatomic localization, with Z scores and number of activated voxels of regions significantly more activated in patients than in normal subjects.

Areas that were significantly more activated in normal subjects than in stroke patients were identified by subtracting increases of rCBF during passive movements versus rest in patients from those in normal subjects (normal subjects versus patients, multigroup study analysis). In this analysis, no areas of activation above threshold were found.

Discussion

In this pilot study, PET was used to evaluate patterns of brain activation in nonrecovered, hemiplegic stroke patients. Previous functional imaging studies have focused on patients with almost complete recovery after hemiparetic stroke and used active movement paradigms such as finger tapping or sequential finger-to-thumb opposition to evaluate patterns of functional reorganization. Here we used passive elbow movements to study the functional reorganization of the brain during the early, postacute period after stroke before clinical recovery had occurred.

In normal subjects, passive movements produced activation in the contralateral sensorimotor cortex, cingulate gyrus, supplementary motor area, and bilateral inferior parietal cortex. Although the number of control subjects is low, this pattern of activation confirms the result of a previous PET study using the same paradigm of passive elbow movements in a larger sample of normal subjects. Very similar patterns of activation were also reported in a recent fMRI experiment.
during passive index finger movements of normal subjects.\textsuperscript{17} In our study we did not use electromyographic recordings of biceps and triceps muscles to demonstrate the absence of voluntary muscular activity during passive movements, but subjects were closely monitored during the experiment for any active movements of the right elbow. The maximum of sensorimotor cortex activation in normal subjects covered the precentral and postcentral gyrus. Activation on both sides of the central sulcus in normal subjects has been described with the use of active motor tasks\textsuperscript{18} as well as somatosensory discrimination tasks,\textsuperscript{19} suggesting that afferent synaptic activity may have a major significance for the PET signal in the primary sensorimotor cortex.

Several mechanisms may explain the precentral and postcentral activation. First, it is possible that the distance between the precentral and postcentral gyrus is smaller than the effective spatial resolution in the Z maps. However, we used a smoothing kernel of $15 \times 15 \times 9$ mm at FWHM to obtain Z maps that have sufficient spatial resolution to differentiate between the precentral and postcentral gyrus in the Talairach space.\textsuperscript{8,15} Second, earlier studies of active hand movements in stroke patients and normal subjects using fMRI described activation of the ipsilateral sensorimotor cortex on both sides of the central sulcus.\textsuperscript{15,16} These observations may indicate a marked rostral-caudal variability in the localization of cortical representation within the primary sensorimotor system. In a study of epilepsy patients who underwent implantation of subdural grid electrodes, electric stimulation was used to map motor and sensory responses in the primary sensorimotor cortex.\textsuperscript{20} Hand motor and sensory responses occurred in both precentral and postcentral regions, suggesting that motor and sensory hand cortices overlap and are not

Increases of rCBF during passive movements (passive movements vs rest, group study; $P<0.01$). Top row, Increases of rCBF during passive movements of the right elbow in normal subjects. a, Surface view of statistical parametric maps. Intersecting lines show activation of (b) contralateral sensorimotor cortex ($-16, -28, 64$) and (c) inferior parietal cortex ($-64, -34, 28$). Middle row, Increases of rCBF during passive movements of the plegic (left) arm in stroke patients (passive movements vs rest, group study). All lesions were assigned to the right side of the brain. Two patients with a left-sided lesion were inverted about the midsagittal plane. d, Surface view of statistical parametric maps. Intersecting lines show activation of (e) ipsilateral inferior parietal cortex ($-56, -42, 32$) and of (f) contralateral inferior parietal cortex ($44, -28, 26$). Bottom row, Increases of rCBF during passive movements, showing areas that were more activated in stroke patients than in normal subjects ($P<0.01$). These areas were identified in a multigroup study analysis by subtracting increases of rCBF during passive movements vs rest of normal subjects from those of patients. g, Surface view of statistical parametric maps. Intersecting lines show activation of (h) contralateral superior parietal lobe ($26, -42, 50$) and of (i) ipsilateral sensorimotor cortex ($-56, -12, 30$).
strictly divided by the central sulcus. Third, both precentral and postcentral regions are heavily interconnected, and both are sites of origin of pyramidal tract fibers. Taken together, the observation of precentral and postcentral activation during active as well as during passive movements suggests a less strict segregation of sensory and motor cytoarchitecture between the precentral and postcentral gyrus. This hypothesis receives additional support from animal experiments in which tight anatomic coupling between somatosensory input and motor output in the sensorimotor cortex has been found. These studies have shown that afferent neurons from spindles of a passively stretched muscle project to distinct cortical areas in which excitation of motor neurons produces contraction of the same muscle. Forwarded connections from the postcentral gyrus to the motor system may explain the activation of premotor and supplementary motor areas. These structures may also receive direct somatosensory input from subcortical structures involved in sensory function such as the thalamus.

Sensory systems play an important role in central motor control. Severe sensory loss can result in functional disability similar to that of paresis and often predicts poor recovery of motor function. Asanuma and Keller found highly specific projections from the sensory cortex to the motor cortex, with each sensory column projecting to only a few motor output areas. They suggested that these corticocortical projections may provide the necessary feedback to modulate the learning of new motor tasks. The sensory feedback in mediating motor control has also been suggested by PET studies that demonstrate altered CBF to the motor cortex after transient induced anesthesia of the forearm. Furthermore, ample evidence of sensory cortex reorganization in response to brain injury

<table>
<thead>
<tr>
<th>Region</th>
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<th>Z Scores</th>
<th>Size of Activated Area, voxel</th>
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| Stroke patients Contralateral activations | | | | |
| Inferior parietal cortex | 40 | 44, -28, 26 | 4.4 | 2212 |
| Sensorimotor cortex | 38, 0, 20 | 3.0 | 224 |
| Ipsilateral activations | | | | |
| Inferior parietal cortex | 40 | -56, -42, 32 | 4.7 | 1116 |
| Lateral prefrontal cortex | 9 | -10, 64, 28 | 3.7 | 69 |
| Premotor cortex | 6 | -32, 8, 36 | 3.2 | 86 |
| Cingulate cortex | 24 | -14, -10, 24 | 3.7 | 201 |

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BA indicates Brodmann area. Anatomic areas indicated on statistical parametric maps show increases of CBF during passive movements of the right arm in normal subjects and hemiplegic (left) arm in stroke patients (group study; P<0.01). Talairach coordinates are in millimeters and correspond to the stereotaxic conventions of the atlas of Talairach and Tournoux. Z scores reflect signal intensity.

*Identical numbers because of 1 coherent block of activated voxels.
exists. Small experimental lesions in the sensory cortex of monkeys induce changes in the representational fields of fingers. More recently, the plasticity of the somatosensory cortex, paralleling recovery of motor skills after stroke, has also been demonstrated in the same animal model. In hemiplegic stroke patients, a distributed activation of bilateral parietal lobes and sensorimotor cortices was seen compared with normal subjects. Subcortical lesions of hemiplegic patients may cause decrease of metabolism and blood flow in remote cortical areas such as the prefrontal and premotor cortex and the supplementary motor area. Cortical hypoperfusion, however, is unlikely to explain the increases of rCBF in patients versus controls found in this study, because possible differences of cerebral blood flow were normalized voxel by voxel to a mean of 50 mL · min⁻¹ · 100 g⁻¹ by ANCOVA.

The sensorimotor cortex was more active in the ipsilateral hemisphere (Table 3; Figure), with the maximum increase of rCBF in the postcentral gyrus. The increase of rCBF in these structures suggests recruitment of ipsilateral sensory and motor pathways during the early, postacute phase after stroke. The ipsilateral sensorimotor cortex activation resembles brain activation patterns seen during active motor tasks in stroke patients after almost complete recovery. Recruitment of the ipsilateral, unaffected sensorimotor cortex is a well-known mechanism in recovered stroke patients who regained sufficient motor skills to perform fine finger movements with the formerly paretic hand and has been demonstrated in studies using various techniques, including single-photon emission CT, PET, and fMRI. Increased synaptic activity of the ipsilateral corticospinal tract may have a restorative function after focal brain damage. Under normal conditions, approximately 15% of the corticospinal tract descend undecussated. Approximately 40% of the pyramidal cells of the ipsilateral, unaffected sensorimotor cortex of hemiplegic patients may cause decrease of metabolism and blood flow in remote cortical areas such as the prefrontal and premotor cortex and the supplementary motor area. Cortical hypoperfusion, however, is unlikely to explain the increases of rCBF in patients versus controls found in this study, because possible differences of cerebral blood flow were normalized voxel by voxel to a mean of 50 mL · min⁻¹ · 100 g⁻¹ by ANCOVA.

The parietal lobes, including bilateral Brodmann areas 7 and 40, and the ipsilaterial precuneus were also significantly more activated in stroke patients than in controls (Table 3). Brodmann area 7 may be involved in multimodal sensory integration and may provide somatosensory representation of external space. Previous PET studies in normal subjects have shown that Brodmann area 7 participates in processing of multimodal sensory information. By ANCOVA.

The bilateral inferior parietal cortex (Brodmann area 40) was active during passive movements in both groups. However, more activation was found in patients than in normal subjects (Table 3). The inferior parietal cortex has rich connections to the motor system. It projects directly to the supplementary motor area (area 6), which in turn is connected to area 4. The inferior parietal cortex also sends projections to the medial parts of the insula. The insula and parietal cortex (Brodmann area 40) showed covariation of rCBF with primary and premotor cortices of the same side in normal subjects during active finger movements, suggesting that the parietal cortex, insula, and premotor cortex constitute a functional network of normal motor control. The increases of rCBF in bilateral inferior parietal cortex and sensorimotor cortex of hemiplegic patients suggest that these areas may play an important role in the reorganization of sensory and motor systems preceding restoration of neurological function.

In conclusion, passive movements in hemiplegic stroke patients before clinical recovery elicited some of the brain activation patterns found in other studies of stroke patients during active movements after substantial recovery had occurred. This analogy between activation patterns of passive and active movements highlights the contribution of afferent synaptic activity for central motor control. Our data further indicate that reorganization of sensory and motor systems occurs early after stroke. These early changes of cerebral activation may be critical for return of voluntary motor control. Serial studies of functional brain imaging will help to clarify the temporal evolution of reorganization processes paralleling clinical recovery. Such studies may also be helpful in examining the efficacy of rehabilitative interventions targeting restoration of motor function after stroke.

Acknowledgments

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References


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