

# The Role of Diaschisis in Stroke Recovery

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**Background and Purpose**—Recovery from hemiparesis after stroke has been shown to involve reorganization in motor and premotor cortical areas. However, whether poststroke recovery also depends on changes in remote brain structures, ie, diaschisis, is as yet unresolved. To address this question, we studied regional cerebral blood flow in 7 patients (mean±SD age, 54±8 years) after their first hemiparetic stroke.

**Methods**—We analyzed imaging data voxel by voxel using a principal component analysis by which coherent changes in functional networks could be disclosed. Performance was assessed by a motor score and by the finger movement rate during the regional cerebral blood flow measurements.

**Results**—The patients had recovered ( $P<0.001$ ) from severe hemiparesis after on average 6 months and were able to perform sequential finger movements with the recovered hand. Regional cerebral blood flow at rest differentiated patients and controls ( $P<0.05$ ) by a network that was affected by the stroke lesion. During blindfolded performance of sequential finger movements, patients were differentiated from controls ( $P<0.05$ ) by a recovery-related network and a movement-control network. These networks were spatially incongruent, involving motor, sensory, and visual cortex of both cerebral hemispheres, the basal ganglia, thalamus, and cerebellum. The lesion-affected and recovery-related networks overlapped in the contralesional thalamus and extrastriate occipital cortex.

**Conclusions**—Motor recovery after hemiparetic brain infarction is subserved by brain structures in locations remote from the stroke lesion. The topographic overlap of the lesion-affected and recovery-related networks suggests that diaschisis may play a critical role in stroke recovery. (*Stroke*. 1999;30:1844-1850.)

**Key Words:** brain mapping ■ hemiparesis ■ infarction ■ neuronal plasticity ■ tomography, emission computed

In 1914, von Monakow<sup>1</sup> established the concept of diaschisis as a principle for recovery from brain lesions. Accordingly, functional changes in brain structures remote from the site of a focal brain damage, ie, diaschisis, were conceptualized as processes underlying functional recovery. The role of diaschisis, however, has remained elusive. Modern neuroimaging studies have provided first clues to the existence of diaschisis by revealing that focal brain lesions are accompanied by widespread metabolic changes involving the affected cerebral hemisphere but extending into brain areas supplied by contralateral and cerebellar arteries.<sup>2</sup> More recently, such remote metabolic changes have been shown to be lesion-specific in terms of cerebral topography and the related clinical deficits.<sup>3,4</sup> Corresponding findings in experimental models of ischemia further support the concept that these remote abnormalities are brought about acutely by neurotransmitter changes and chronically by degeneration of fiber tracts.<sup>5</sup> However, evidence that diaschisis is also related to recovery of function is virtually lacking.

In this study we tested the hypothesis that lesion-induced, remote metabolic abnormalities share a selective topographic territory with recovery-related activity in patients who have

recovered from hemiparesis. We demonstrate this type of topographic overlap by evaluating the patterns of networks expressed in regional cerebral blood flow (rCBF) data obtained with positron emission tomography (PET). For this purpose, we used a principal component analysis (PCA), which estimates the tendency of signals to covary at all possible pairs of voxels. Orthogonal spatial covariance patterns are then identified that capture the greatest variance in the data.<sup>6</sup> This statistical approach is advantageous compared with other methods that assess connectivity patterns<sup>7,8</sup> in that PCA does not rely on a priori assumptions. This particular aspect of PCA suggests that such an analytic approach to functional imaging data would conform well with the clinical observation that the locus of a brain lesion cannot accurately be determined directly by the pattern of deficits, as is the case in the so-called disconnection syndromes,<sup>9,10</sup> because the lesion interrupts connections between macroscopic loci required to perform a psychomotor task. In essence, PCA combines the complementary principles of connectionism and localization such that the brain regions involved in a given psychomotor function may be widely distributed, and thus the brain activity required to perform a given task may be

Received February 2, 1999; final revision received May 10, 1999; accepted June 4, 1999.

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the coherent activity in multiple macroscopic loci or distinct brain systems.

## Subjects and Methods

### Subjects

Seven patients (age range, 41 to 66 years; mean  $\pm$  SD age,  $54 \pm 8$  years; 1 woman, 6 men) were referred to our clinic because of their first completed ischemic stroke. Inclusion criteria for this prospective and exploratory 5-year 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 MR images. Five patients had right hemispheric infarctions, and 2 had left hemispheric infarctions. Because of the large extent of the infarctions in the middle cerebral artery territory, aphasia was present in the 2 patients with left hemispheric infarction, while hemineglect and hemianopia were present in 3 patients with right-sided infarctions. Furthermore, 5 patients also suffered from hemihypesthesia. However, none of the patients had signs of microangiopathy. The contrast, high-resolution MR images were taken at the chronic stage after infarction (3 days before or after PET scanning) with a 1.5-T Magnetom (Siemens). All patients were right handed as assessed with the Edinburgh questionnaire.<sup>11</sup> Patients with only moderate or slight hemiparesis and those who did not recover were excluded from the study. 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.<sup>12</sup> In the present study, the score values for arm and leg force as well as for dexterity (eg, the ability to perform individual and fractionated finger movements) were considered. The scores ranged from 0 to 4, as follows: 0, loss of function; 1, severe impairment; 2, moderate impairment; 3, slight impairment; and 4, normal function. Testing was performed in the acute stage (1 to 3 days after stroke) and within 2 days before or after PET scanning.

Controls were 7 healthy, right-handed volunteers (age range, 26 to 29 years; 1 woman, 6 men) without neurological abnormality on history and examination. Although younger than the patients, controls were chosen because at this age they had no neurological abnormality, and they presented with normal MRI and rCBF scans.

The study was approved by the ethics committee of the Heinrich-Heine University Düsseldorf.

### PET Imaging of rCBF

PET scanning was performed after significant recovery, which was on average 6 months ( $23 \pm 14$  [SE] weeks) after brain infarction. As described in detail elsewhere,<sup>13,14</sup> an 8-ring PC4096 plus PET camera (GE/Scanditronix) was used to measure the rCBF after intravenous bolus injection of 40 mCi [<sup>15</sup>O]butanol. PET scanning started at the time of injection into the right brachial vein. The 15 PET image slices had a slice distance of 6.5 mm.<sup>15</sup> A transmission scan using a rotating <sup>68</sup>Ge pin source was obtained before the emission scans to correct for attenuation. The PET images were reconstructed with a Hanning filter to an effective image resolution (full width at half maximum) of 8 mm.

During the rCBF measurements, patients and controls were blindfolded. In 1 rCBF scan, the patients performed finger movement sequences of the recovered hand as accurately and as fast as they could. The control subjects performed the finger movement sequences with the right hand. Before they were scanned, patients and controls were instructed to sequentially touch the index, long, ring, and little fingers with the thumb of the recovered and right hands, respectively. All subjects were trained until they understood the directions. In a second scan, the patients performed the same sequence but with the unaffected ipsilesional hand. A third scan, under resting conditions, was taken as either the first or the last scan for both patients and controls. The sequence of tasks was randomized across the subjects. One investigator observed the subjects and registered the number of finger movements. None of the patients had associated movements of the unaffected hand.

### rCBF Data Analysis

Quantification of rCBF was performed with a combined dynamic-autoradiographic approach that involved arterial blood sampling and PET scanning in list mode.<sup>16,17</sup> The rCBF images were then spatially standardized, as detailed elsewhere.<sup>13,14</sup> Standardization is highly accurate (<3 mm) for the brain surface, yielding 21 axial image slices that were 6.43 mm apart with a matrix of 128  $\times$  128 voxels, each of 2.55  $\times$  2.55 mm.<sup>18</sup> In these standardized images, all brains were oriented such that the stroke lesions were on the same (left) side.

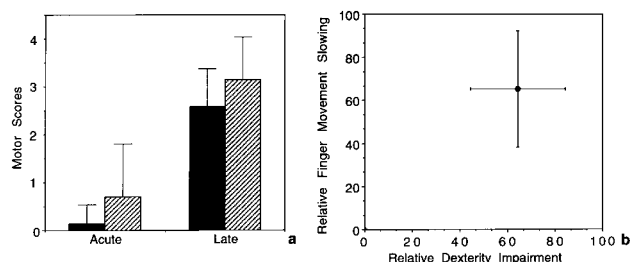
Since correlated changes in complex functional networks of the human brain cannot be assessed by categorical comparisons, we subjected the imaging data to a PCA.<sup>6</sup> The PCA is a data reduction technique that was applied to the rCBF data of the patients and controls voxel by voxel. The data were first normalized across groups and conditions, which standardized the variances across the PET images. For normalization, the infarcted area was excluded from the calculation by thresholding. During the subsequent PCA, however, all voxels representing the brain were included in the calculation. The PCA extracted the important features of the covariance matrix in terms of principal components (PCs) or eigenvectors without requiring a priori assumptions. The eigenvectors are linear combinations that account for independent (or orthogonal) amounts of variance in the observed data. Normally, the number of orthogonal PCs required to adequately represent the data to a specified level of accuracy is much smaller than the original dimensions of the data.<sup>19</sup> Thus, PCA may be more powerful than categorical analysis methods by virtue of its potential for data reduction, capturing overall patterns of voxel-pair relationships. In terms of functional connectivity, a PC represents a distributed brain system or network within which there are strong intercorrelations.<sup>6</sup> Because any single PC is orthogonal to the remaining, these networks are functionally independent of each other.<sup>6</sup> The degree of expression of each PC or network in each subject is given by a single number, the factor score or PC value.

Since each individual subject in the present study had a numerical value for each PC, groups and conditions were formally compared to make statistical inferences about the PCs, as was proposed recently.<sup>20</sup> Specifically, we tested the hypothesis ( $H_0$ ) that the PCs were not differently expressed in rest and activation in the patients and controls (independent 2-tailed *t* test,  $P < 0.05$ , uncorrected for multiple comparisons). Of 8 PCs that accounted for 80% of the variance, only PC1, PC3, and PC8 showed significant group differences. In addition, linear regressions between the individual patient PC values and external measures were calculated; *r* denotes the regression coefficient; probability values correspond to testing if the slope was different from zero.

In the PET image matrix, the coupling of a single brain voxel with a PC can be expressed by a number, the PC load, which is similar to a correlation coefficient. While mapping of the PCA components is not possible, mapping of the PC loads can be done for the voxel matrix.<sup>6,19</sup> Thus, local expression of functional connectivity networks could be visualized as an image in which each voxel showed the PC load. Since PCA was calculated over the entire voxel matrix of brain space, we assessed formally in which voxels the PC load significantly correlated with the corresponding PC. With the use of standard tables of normal distribution and Fisher's *Z* transformation,<sup>21,22</sup> thresholds were set for constituting core areas for each PC at the absolute value of loading factor  $> 0.63$  ( $P < 0.05$ ). The suprathreshold voxels were superimposed onto the spatially standardized MRI of the patient with the largest stroke lesion. This procedure is admittedly descriptive, but it focused the resulting image on those areas that strongly correlated with each PC. Thereby, it became possible to compare the lesion extent with the connectivity patterns and to identify those cerebral areas that participated in different PCs. These brain structures were localized in stereotaxic coordinates.<sup>23</sup>

### Assessment of Lesion Volume

The high-contrast MR images with a thickness of 1.17 to 1.51 mm and a voxel size of 1  $\times$  1 mm were spatially aligned with the templates of the Talairach and Tournoux atlas<sup>23</sup> in each patient. In



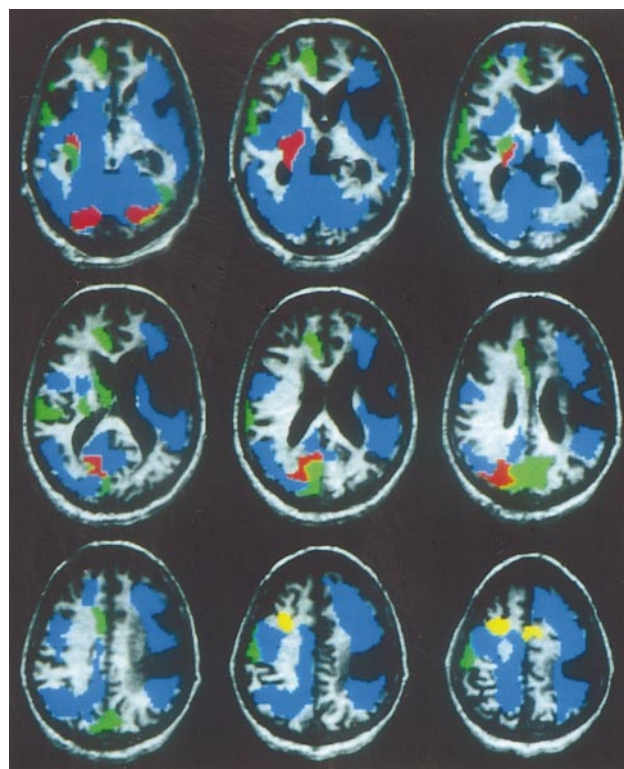
**Figure 1.** Recovery-associated changes. a, Recovery ( $P<0.001$ ) of arm and leg force (▨) and dexterity (■) on the affected side. b, Reduced dexterity and finger movement rate of the recovered hand compared with the nonaffected ipsilesional hand. Error bars indicate SDs.

each of these realigned image slices, the stroke lesion was outlined. The number of voxels in the affected slices multiplied by the slice distance was used to calculate the infarct volume.

## Results

The patients had recovered remarkably well from their first severely disabling hemiparetic stroke. In the acute stage, the patients suffered from a dense hemiparesis, including absolute inability to move the affected hand or fingers. This resulted in severely depressed limb force and dexterity scores (Figure 1a). MRI showed that the infarctions involved the parietal cortex, most parts of the sensorimotor cortex, the parietal and frontal operculum, and the striatum. However, the lesions spared the dorsolateral precentral gyrus inclusive of the motor hand area, the knee and posterior limb of the internal capsule, and the thalamus even in the patient with the largest stroke lesion (Figure 2). After recovery, all patients were ambulatory again and had regained the ability to perform individual finger movements with the recovered hand, as reflected by improved motor impairment scores (Figure 1a). However, compared with the nonaffected ipsilesional hand, the recovered hand still remained somewhat impaired, as evident from a slightly reduced dexterity score and slowed movement rate during performance of finger movement sequences (Figure 1b).

The rCBF images showed that 2 functional networks were differentially expressed in the patients and controls (Table 1). The first network (PC1) accounted for 30% of the variance of the data and was expressed during the resting state. It was related to the volume of the stroke lesion and therefore reflected the lesion effect on rCBF at rest. A second differentiating network (PC3) was expressed during sequential finger movements and explained 12% of the variance. This PC demonstrated differences between the patients and controls during finger movements. Since this PC correlated with lower motor scores initially after stroke, it was termed recovery related. However, there was no correlation of PC3 and the finger movement rate. In addition, age was not significantly related to PC3 or to the clinical or behavioral measures. A third network (PC8) differentiated the finger movement from the resting conditions in patients and controls. It accounted for 2% of the variance. Since PC8 did not differentiate the patients from controls but the movement from the resting scans, it was not disease related but was



**Figure 2.** Anatomic locations of the functional connectivity patterns (PC loading  $>0.63$ ). The lesion-affected network (PC1) coded in blue involves the stroke lesion, a mirror focus in the contralesional hemisphere, and bilateral basal ganglia and thalamus. The recovery-related network (PC3) coded in green involves bilateral visual association areas, cingulate cortex, hippocampal formation, and bilateral cerebellum. The movement-control pattern (PC8) coded in yellow involves contralesional dorsolateral premotor cortex and ipsilesional supplementary motor area. Spatial overlap of PC1 and PC3 (red) is present in the contralesional extrastriate cortex and the contralesional thalamus. In this display the stroke lesion that was the largest in this study is visible because of masking in the connectivity patterns.

related to movement activity. Again, there was no correlation with the finger movement rate.

Figure 2 illustrates the spatial topography of the different functional networks. The lesion-affected network (PC1) involved the core and perilesional stroke area; the contralesional motor, medial parietal, and lateral occipital cortex; and the bilateral basal ganglia and thalamus. The recovery-related network (PC3) was characterized by interactions among bilateral occipital and prefrontal cortical areas; contralesional cingulate, hippocampal formation, and dorsal thalamus; and the bilateral cerebellum. Notably, the recovery-related network did not involve cortical and subcortical structures of the motor circuitry, which will be discussed below. The third network (PC8) involved the contralesional dorsolateral premotor cortex and the ipsilesional supplementary motor area in the frontomesial cortex known to be related to control of movement activity (see below). Figure 2 also shows that the core areas of PC1 and PC3 spatially overlapped in the contralesional extrastriate cortex and the lateral part of the contralesional thalamus (Table 2). These data demonstrate that the chronic, recovery-related changes took place in brain



**TABLE 1. Group-Differentiating Principal Components**

PC	Functional Networks	Group Characteristics
PC1	Lesion-affected	Resting controls vs resting stroke patients Relation to lesion volume: $r=0.78$ ; $P<0.02$
PC3	Recovery-related	Hand movements in controls vs recovered hand movements in stroke patients Relation to initial deficit: $r=0.77$ ; $P<0.03$
PC8	Movement-control	Resting controls vs hand movements in controls Resting controls vs nonaffected ipsilesional hand movements in stroke patients Resting controls vs recovered hand movements in stroke patients Resting stroke patients vs nonaffected ipsilesional hand movements in stroke patients

Group separation was significant at  $P<0.05$  (2-tailed  $t$  test).

areas that were also affected by the infarction but were in a remote location. Note that the expression of PC1 was independent of the expression of PC3, suggesting that neither the lesion extent nor the motor impairment itself affected the PC overlap between the participating functional networks. In contrast, there was no anatomic overlap of the core areas of PC1 and PC8 or of PC3 and PC8.

### Discussion

Functional recovery is a major goal in stroke treatment. As was observed recently, passive recovery mechanisms dependent on the regression of ischemia must be differentiated from active reorganization effected over a longer time course.<sup>24</sup> In the early postischemic phase, spontaneous reperfusion with subsequent regression of oxygen depletion as well as regression of corticospinal tract damage has been shown to play an important role in recovery from hemiparesis.<sup>25–28</sup> Additionally, perilesional dysfunctional changes influence recovery in the early phase after cortical stroke.<sup>29–31</sup> In the chronic phase after infarction, reorganization of functional circuits, leading to local expansion of cerebral activation areas and recruitment of parallel projecting cortical areas in the ipsilesional and contralesional hemispheres, has been shown to be operative.<sup>32–39</sup> These long-term reorganizational changes result in active learning processes and are associated with complete or profound neurological restitution with respect to gait and hand use. However, subtle deficits may remain, which are clearly apparent from laboratory testing.<sup>40–42</sup> It is therefore not surprising that our patients suffered slightly impaired dexterity and a reduced capacity to perform sequential finger movements, despite a remarkable recovery of their clinical states and maximal grip force (Figure 1). It is possible that the widespread and lesion-

specific metabolic changes after cerebral ischemia as observed in our patients were responsible for a residual deficit, as has been reported for patients with hemiparesis, neglect, and aphasia.<sup>2–4,43,44</sup> However, a consequential relationship between the observed widespread and remote changes in cerebral activity and functional recovery has not been demonstrated.

In this study we show by means of a PCA that brain areas participating in a network related to recovery from brain infarction in the middle cerebral artery territory were also shared by another network that was affected by the stroke lesion. Specifically, the lesion-affected PC1 shared the same core areas as PC3 (Table 1). Since PC3 differentiated movement activity of the recovered hand in the patients from that of controls and greater expression of this pattern in the patients correlated with lower motor scores initially after stroke, PC3 reflected an activity fundamentally related to stroke recovery. Note that PC3 did not differentiate the movement condition from rest and therefore exhibited no relation to motor activity as such. Since initially after stroke no individual finger movements could be performed by the patients and the finger movement rate after recovery did not correlate with the expression of PC3, no quantitative relation of motor recovery and PC3 could be demonstrated. Nevertheless, recovery of function was subserved by areas remote to the lesion site, which were simultaneously affected by the lesion itself. Interestingly, the third differentiating pattern (PC8) discriminated the movement from the rest scans in both patients and controls, indicating that it was related to motor activity but not to motor recovery. The core areas involved in PC8 were the dorsolateral premotor cortex and the supplementary motor area, which have been shown to play an important role during the acquisition of new movement trajectories and during complicated finger movement sequences in healthy volunteers.<sup>13,45–47</sup> Thus, PC8 appeared to be related to higher-order aspects of movement control. However, these areas have prominent corticospinal projections<sup>48,49</sup> that make them suited for assistance and substitution of the damaged motor cortex. Since PC8 was not recovery related, it is not surprising that it was spatially incongruent with the lesion-affected and the recovery-related patterns.

PCA has been proposed as a way to isolate independent brain systems or networks in functional imaging data.<sup>50</sup> We supplemented the PCA with statistical testing of the paramet-

**TABLE 2. Spatial Overlap of the Core Areas of the Lesion-Affected and Recovery-Related Networks**

Anatomic Structures	Coordinates		
	x	y	z
Lateral thalamus contralesional	22	–23	6
Cuneus contralesional	25	–71	22
Lingual gyrus ipsilesional	–22	–85	–6
Lingual gyrus contralesional	19	–90	–6

Coordinates in stereotaxic space (mm).<sup>23</sup>

ric PC values to identify group-differentiating networks. By this approach, we have identified in motor cortical hemiparetic stroke a lesion-affected network of widespread abnormalities that involved not only the affected cerebral hemisphere with decreased blood flow but also the unaffected contralesional hemisphere, as well as subcortical structures such as the basal ganglia and the thalamus (Table 1 and Figure 2). Our findings are consistent with recent descriptions of contralateral abnormalities in electroencephalographic and magnetoencephalographic recordings of spontaneous and movement-related brain activity after hemiparetic stroke.<sup>51,52</sup> Additionally, in accordance with earlier observations in patients with supratthalamic infarctions in the middle cerebral territory,<sup>3</sup> no lesion-related abnormalities were observed in the contralesional cerebellum. We also report here that in our patients a recovery-related corticosubcortical network was engaged during movements of the recovered hand. By spatial overlay, it was shown that the lesion-affected and the recovery-related networks shared the same core areas in the thalamus and in visual association areas (Figure 2 and Table 2). Thus, these sharing areas accommodated simultaneously passive metabolic lesion effects and active recovery-related changes in locations remote to the site of the brain infarction. This observation corresponds to the original conception of diaschisis as a restorative mechanism in stroke recovery.<sup>1</sup>

It was not possible to demonstrate the exact involvement of single nuclei in the thalamus by diaschisis in this study because of the limited spatial resolution of the PET images. However, the lateral part of the contralesional thalamus was predominantly involved. In the lateral thalamus, a number of nuclei are closely adjacent to each other; these nuclei process motor, somatosensory, and visual information.<sup>53–57</sup> Since there are bilateral connections of the thalamus,<sup>58,59</sup> lesion-related effects, even on the contralesional side, may not be unexpected. The involvement of extrastriate areas in the occipital cortex may suggest that the sensorimotor cortex exerted an effect on the visual cortex, as has been reported for motor activity in healthy subjects.<sup>60</sup> On the other hand, it may be that motor activity after recovery from hemiparetic stroke engaged processing of higher-order visual information in extrastriate occipital cortex. These cortical areas involved in the recovery-related pattern have been shown to be activated in normal subjects during the perception of illusionary contours, visual imagery, and visual attention to motion.<sup>61–65</sup> Recently, we identified a corticosubcortical network in the thalamus and extrastriate cortex that afforded cross-modal visuomotor plasticity after stroke.<sup>66</sup> Indeed, it is well known that visual guidance assists recovery from sensorimotor deficits after brain lesions.<sup>67,68</sup> This may be relevant for relatively complex motor tasks such as those used in this study but not for simple motor tasks and also may be critically affected by the side of the stroke lesion.

The diaschisis observed in this study was almost exclusively located in the contralesional hemisphere, supporting recent rCBF data regarding subacute motor and language recovery after stroke.<sup>69,70</sup> In contrast, early in stroke, diaschisis in the contralesional hemisphere does not assist in recovery.<sup>70,71</sup> Rather, enhanced metabolic interactions in motor circuitry in the ipsilesional thalamus, contralesional cerebel-

lum, and frontomesial cortex were found to be predictive of motor recovery early after stroke.<sup>72</sup> These remote structures, which also represent loci of diaschisis, seem to subserve active relearning. Since in our patients restitution of function was mediated by intact networks of mainly the contralesional hemisphere, it is conceivable that additional or preexisting lesions (particularly in subcortical locations) would attenuate the patients' capacity for functional restitution. It is well known that repetitive lesions induce progressive disability in vascular types of dementia.<sup>73–75</sup> Further work using network-analytic approaches to functional imaging data appears useful to reveal the specificity and dynamics of brain dysfunction and recovery patterns after stroke.

## Acknowledgments

This study was supported by Sonderforschungsbereich 194 of the Deutsche Forschungsgemeinschaft. Dr Azari was the recipient of an Alexander von Humboldt fellowship. The authors thank W. Hamkens, Institute of Biochemistry, Research Center Jülich, for skillful tracer production and L. Theelen and L. Tellmann for expert assistance with PET scanning and PET data preprocessing.

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