Longitudinal Cortical Volume Changes Correlate With Motor Recovery in Patients After Acute Local Subcortical Infarction

Chao Dang, MD, PhD*; Gang Liu, MD, PhD*; Shihui Xing, MD, PhD; Chuanmiao Xie, MD, PhD; Kangqiang Peng, MD; Chuo Li, MD, PhD; Jingjing Li, MD, PhD; Jian Zhang, MD, PhD; Li Chen, MD, PhD; Zhong Pei, MD, PhD; Jinsheng Zeng, MD, PhD

Background and Purpose—Secondary changes in the volume of motor-related cortical regions and the relationship with functional recovery during the acute stage after cerebral infarction have not been determined. In the present study, we quantified changes in gray matter (GM) volume in motor-related cortical regions and analyzed their correlations to clinical scores in patients with focal cerebral infarct.

Methods—Fifteen patients with acute subcortical infarct underwent longitudinal high-resolution structural MRI and clinical assessment 3 times during a 12-week period (weeks 1, 4, and 12). Fourteen age- and sex-matched controls underwent MRI examination. Voxel-based morphometry was used to quantify changes in global GM volume; in addition, relationships between GM volume changes in volumes of interest and clinical scores were analyzed.

Results—In patients with cerebral infarction, GM volumes detected by voxel-based morphometry both decreased and increased significantly in diffuse cortical regions during the observation period (P<0.001). GM volumes within volumes of interest decreased significantly in the ipsilateral supplementary motor area and contralateral insula, but they increased in the contralateral supplementary motor area over time (all P<0.017). The changes of GM volumes in the ipsilesional and contralesional supplementary motor area correlated with the changes in the Fugl–Meyer scale scores (ipsilesional, r=0.52; P=0.048; contralesional, r=0.74; P=0.002) and Barthel Index (ipsilesional, r=0.56; P=0.030; contralesional, r=0.65; P=0.009).

Conclusions—These results suggest that secondary GM changes occur in diffuse areas and structural changes in some specific motor-related cortex may inhibit or promote functional recovery after an acute subcortical cerebral infarct. (Stroke. 2013;44:2795-2801.)

Key Words: cerebral infarction ■ gray matter ■ magnetic resonance imaging ■ neuronal plasticity

Although delayed degeneration of fiber tracts both proximal and distal to a primary infarct lesion can potentially hamper functional recovery, neurological deficits improve spontaneously to a certain extent after an acute subcortical or pontine infarct.1–3 Recently, it was reported that increased gray matter (GM) volumes in cognition-relevant brain areas (hippocampus and precuneus) were positively correlated with spontaneous motor recovery, whereas decreased GM volumes in the motor-related brain areas were not associated with improvement in motor function during a 1-year period after acute subcortical infarct.4 In contrast, other studies of patients with chronic stroke have reported that increased GM volumes in the hippocampus and sensorimotor areas were bilaterally and significantly correlated with motor improvement, whereas reduced GM volumes in multiple brain areas predicted lesser motor improvement after constraint-induced movement therapy; moreover, no increase in GM volume was detected in patients receiving conventional rehabilitation therapy.5,6 Notable, constraint-induced movement therapy was found to be superior to conventional rehabilitation therapy only during the chronic stage of recovery. This may be because the overtraining effects of constraint-induced movement therapy can lead to significantly less upper limb motor improvement at 90 days after infarct.7 Importantly, changes in volume in motor-related cortical regions and the relationship of these changes to functional recovery after a cerebral infarct have yet to be determined.

In the present study, we hypothesized that a unilateral subcortical infarct could lead to remote cortical GM changes, and...
that the changes might be, to some degree, correlated with clinical assessments of recovery. We used optimized voxel-based morphometry (VBM) and assessed volumes of interest (VOIs) to longitudinally quantify and monitor changes in GM volume subsequent to an acute subcortical focal infarct during a 12-week period. Correlations between GM volume changes and clinical scores were analyzed.

Materials and Methods

Participants
A total of 15 patients were consecutively recruited from our hospital. Inclusion criteria were as follows: (1) first episode of unilateral subcortical cerebral infarct within 7 days of onset involving the anterior circulation without cortical lesions as confirmed by T1, T2, and diffusion-weighted MRI; (2) no occlusion of major intracranial arteries assessed by MR angiography or transcranial Doppler ultrasound; (3) baseline scores on the National Institutes of Health Stroke Scale were <4 and accompanying motor deficits in both the upper and the lower extremities; (4) age 18 to 75 years; and (5) all patients received routine rehabilitation therapies. Exclusion criteria were as follows: (1) unstable vital signs; (2) a history of neurological disorders; (3) aphasia or severe cognitive impairments that might prevent completion of the study; and (4) the presence of pacemakers, defibrillators, aneurysm clips, and prohibited medical implants that are contraindicated for the MRI procedure. This research was approved by the First Affiliated Hospital of Sun Yat-Sen University Clinical Research Review Board. Oral and written informed consent were obtained from each subject personally or by proxy.

Experimental Design
The study protocols were planned as 12-week longitudinal investigations, during which patients with stroke underwent neurological assessment and acquisition of MRI data 3 times after infarction occurred, during the first week after symptom onset (<7 days), at the end of the fourth week (28±4 days), and at the end of the 12th week (84±4 days). A cross-sectional enrollment design also included a group of healthy controls (n=14; 4 women and 10 men, age-matched) younger than 75 years, with a median age of 45 years (range, 31–68), and 14 of whom were men, with a median age of 45 years (range, 31–68), and 14 of whom were men, with a median age of 45 years (range, 31–68).

Behavioral Assessment
Detailed neurological examinations included a neurological deficit evaluation using the National Institutes of Health Stroke Scale, a motor deficit evaluation using the Fugl–Meyer scale,4–10 and a life independence assessment using the Barthel index. All of the behavioral assessments were scored on the same day as the MR examination.

Image Acquisition
Imaging data were acquired using a 3.0-T MR system (Siemens Trio System, Erlangen, Germany). The structure scanning parameters were as follows: T1-weighted sagittal magnetization-prepared rapid gradient echo, repetition time=2530 ms, echo time=3.45 ms, inversion time=1.0 ms, flip angle=7°, field of view=256×256 mm, voxel dimension=1×1×1 mm voxels, and slice thickness=1.0 mm, 192 slices.

MRI Analysis
The structural T1-weighted images data were processed with VBM toolbox (VBM8.0; http://dbm.neuro.uni-jena.de/vbm/) for the Statistical Parametric Mapping 8 software package (http://www.fil.ion.ucl.ac.uk/spm/) running on Matlab R2010 (MathWorks). An optimized VBM technique was applied that included 2 steps. In the first step, to minimize errors while maximizing the sensitivity of the segmentation results, a customized template was constructed from the healthy control group data.11,12 The GM template was normalized to the Montreal Neurological Institute GM template. Finally, the customized GM template was smoothed using an isotropic Gaussian kernel with a full-width at half-maximum of 8 mm. The customized GM template was used for the VBM study in patients.

In the second step, the process longitudinal data module was applied. Details of the preprocessing are described in the VBM8 manual (dbm. neuro.uni-jena.de/vbm8/VBM8-Manual.pdf). Briefly, the 3 scans for each patient were inrasubject-realigned and averaged to a reference mean image, bias-corrected, segmented, and normalized to the customized GM template. The normalized GM data were finally realigned. Images were smoothed using a Gaussian filter with full-width at half-maximum of 8 mm. To prevent focal infarct tissue from affecting the algorithm, focal infarct lesions were masked manually using MRicro (version 1.40; www.mricro.com); in addition, images were refined during the segmentation and normalization processes and were equated for deficit side by flipping from right to left of patients with left limb hemiparesis.13,14 The stroke lesion volumes were manually outlined on the initial T2-weighted images slice by slice using MRicro software.15

To further investigate the clinical associations of specific brain regions related to motor function, VOI analyses were performed on the basis of previous studies of brain regions that mediate voluntary motor function after stroke. Accordingly, the following VOIs were chosen: bilateral precentral gyrus, supplementary motor area (SMA), cerebellum anterior lobe, insula, and putamen.15,17–24 These VOIs were defined by the Automated Anatomical Labeling templates implemented in Wake Forest University PickAtlas (http://fmri.wfubmc.edu/cms/software). We subsequently calculated the number of voxels in standard Montreal Neurological Institute space of each VOI and converted into milliliters by importing each patient’s GM data to the VOI templates.

Statistical Analysis
To examine differences in regional GM volumes between different time points, a flexible factorial model in Statistical Parametric Mapping for statistical analysis was used to test for longitudinal effects in the patient group. The statistical threshold was set at P<0.001 (uncorrected; cluster threshold=100 voxels) to detect volume changes. Statistical analyses of clinical data and VOI data were conducted with SPSS 11.0 (SPSS, Chicago, IL). The data were determined to be not normally distributed (Shapiro–Wilks test) and were accordingly presented as medians and interquartile ranges. Because the infarct in patients was located either in the left or in the right hemisphere, a Mann–Whitney test was used to compare median GM volumes within the defined VOIs between the left and the right sides of the brain in control subjects to test for asymmetries. If no asymmetries were observed, then median VOI values from bilateral sides of the control subjects’ brains were compared with the VOI values for the patients’ brain to avoid any possible bias.14,25 Friedman test was used to compare the clinical scores and GM volumes within the defined VOIs that were measured repeatedly over time. Wilcoxon signed-rank test with Bonferroni correction was used for post hoc comparisons. Spearman rank correlation analysis was used to determine associations between changes in clinical scores and the GM volume changes within the defined VOIs. The changes in clinical scores over time and the GM volume changes within the VOIs were defined as follows:

Aclinical scores or VOI values=measure measured in the 12th week−value measured in the first week.

We chose to use changes in clinical scores and volume changes within the defined VOIs rather than the final values achieved because we believe that this approach better reflects biological processes.26,27

Results

Demographic and Clinical Findings
Demographic information and clinical findings for 15 patients with first episode of subcortical cerebral infarction are detailed in Table 1 and lesion locations are shown on axial slices of the diffusion-weighted image in the Materials and Methods in the online-only Data Supplement (Figure 1 in the online-only Data Supplement). Among the patients, 4 were women and 11 were men, with a median age of 45 years (range, 31–68), and 14 of...
the patients had experienced ≥1 vascular factor. Eight of the 15 patients had right hemisphere subcortical cerebral infarction. The median National Institutes of Health Stroke Scale score on admission was 8 (range, 5–16). Fugl–Meyer scores showed that all patients experienced improvement of motor function during the 12 weeks of the study, and 13 patients achieved a favorable functional outcome, with Barthel index ≥95 at the end of follow-up. Fourteen age-matched healthy controls (median age, 47.5 years; range, 30–75; 10 men and 4 women) were recruited. All of the control subjects claimed that they had no history of abnormal vascular condition, including stroke history.

Whole-Brain GM Volume After Stroke
Whole-brain VBM analysis revealed GM volume changes after first episode of cerebral infarction. Reduced GM volumes (mostly located in the ipsilesional hemisphere) and increased GM volumes (mostly located in the contralateral hemisphere) were detected as illustrated in Figure 1.

As shown in Figure 1A, reduced GM volumes were found on both sides of the brain from the time of onset to the fourth week, with significant GM volume changes noted in the cerebellum, ipsilesional frontal-temporal lobes, and in other GM regions. Small clusters of increased GM volumes were found in the ipsilesional caudate from the time of onset to the fourth week.

At the end of the 12th week after stroke onset, GM volumes progressively decreased, particularly on the ipsilesional side of the brain (Figure 1B). Diffuse GM volumes changed after the 12th week of onset, and more regions of GM volume increased, especially in the contralateral basal ganglia (putamen, 2343 voxels; *P*<0.001, uncorrected), with small clusters in the ipsilesional pallidum (299 voxels; *P*<0.001, uncorrected) and anterior cingulate (458 voxels; *P*<0.001, uncorrected).

Superimposing voxels with significant changes in GM volume during weeks 4 and 12 both decreased and increased GM volumes and were more significant during week 12 than during week 4 (Figure II in the online-only Data Supplement).

VOIs After Stroke
Compared with healthy controls, GM volume changes in specific VOIs are presented in Table 2. GM volumes within the VOIs in patients decreased in the ipsilateral precentral gyrus during week 12, decreased in the ipsilateral insula and ipsilateral putamen at all time points, and increased in the contralateral SMA and putamen during weeks 4 and 12 after onset.

As shown in Table 2, GM volumes within the VOIs had statistically significant differences over time, as detected by the Friedman test in ipsilateral SMA, contralesional SMA, and insula (all *P*<0.05). A comparison of VOIs between different time points is shown in Table 2. Compared with the first week, GM volumes within the defined VOIs were decreased significantly in the ipsilateral SMA and contralesional insula during the 12th week (all *P*<0.017). In contrast, GM volumes within the defined VOIs were increased in contralateral SMA during weeks 4 and 12 (all *P*<0.017).

Correlational Analyses Between Clinical Assessments and VOIs
By the 12th week, all patients exhibited some degree of functional recovery. All the clinical scores showed statistically significant changes over time (Friedman test, *P*<0.01). The

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Side of Lesion</th>
<th>Volume of Lesion, mL</th>
<th>Sex</th>
<th>Risk Factors</th>
<th>Fugl–Meyer Scale</th>
<th>National Institutes of Health Stroke Scale</th>
<th>Barthel Index</th>
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<td>Week 12</td>
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<td>5</td>
<td>M</td>
<td>HT and dyslipidemia</td>
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<td>55</td>
<td>57</td>
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<td>2</td>
<td>45</td>
<td>L</td>
<td>8</td>
<td>M</td>
<td>HT and habitual smoking</td>
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<td>89</td>
<td>90</td>
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<td>68</td>
<td>R</td>
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<td>87</td>
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<td>7</td>
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<td>11</td>
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<td>M</td>
<td>ET</td>
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<tr>
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<td>L</td>
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<td>M</td>
<td>Habitual smoking and HT</td>
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</table>

DM indicates diabetes mellitus; ET, essential thrombocythemia; F, female; HT, hypertension; L, left; M, male; R, right; and SLE, systemic lupus erythematosus.
Wilcoxon signed-rank test showed that significant neurological improvements had been achieved by the week 12 compared with weeks 1 and 4 ($P<0.017$).

As illustrated in Figure 2, the Spearman rank correlational analyses showed that the GM volume changes in the ipsilesional and contralesional SMA correlated with the changes in the Fugl–Meyer scale across all patients (ipsilesional, $r_s=0.52$; $P=0.048$ and contralesional, $r_s=0.74$; $P=0.002$). Moreover, the changes in ipsilateral and contralateral SMA were also correlated with changes in the Barthel index (ipsilesional, $r_s=0.56$; $P=0.03$ and contralesional, $r_s=0.65$; $P=0.009$).

**Discussion**

In the current study, all 15 patients with focal subcortical infarction showed decreased and increased GM volumes in areas distant from the primary lesion site, and these changes

<table>
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<th>Table 2. Volume of Interest Gray Matter Values</th>
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<td>SMA</td>
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<td>Patient</td>
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</table>

Data represent median (QL–QU) in mL ($n=15$). CL indicates contralateral; GM, gray matter; IL, ipsilateral; NC, normal controls; SMA, supplementary motor area; and VOI, volumes of interest.

*Because the infarct in patients was located either in the left or in the right hemisphere, median VOI values from bilateral sides in the control subjects were used to compare with the VOIs of the patients to avoid any possible bias. The GM volumes within the defined VOIs were measured in milliliters.

† Compared with controls ($P<0.05$, Mann–Whitney test).

‡ Compared with first week ($P<0.017$, Wilcoxon signed-rank test with Bonferroni correction).
al22 demonstrated that surgical revascularization can improve flow and areas of cortical thinning. Furthermore, Fierstra et al.

...spondence exists between decreased regional cerebral blood flow and associated cortical thinning. Alternatively, it can be speculated that decreased use of hemiplegic limbs would induce atrophy in motor regions of the cortex. Consistent with this hypothesis, Chu and Jones17 have reported significant decreased volumes of sensorimotor cortex in the damaged hemisphere in animal studies. Regarding the decreased GM volumes in similar brain regions as in the present study, the reduced improvements in motor function that were correlated with greater reductions in GM volumes in the ipsilateral SMA may be because of the reduced usage of hemiplegic limbs contralateral to cerebral infarction.

Another interesting finding of the current study was that the increasing GM volumes of several regions were specifically and positively correlated with improvements of clinical scores, and this was particularly true for regions on the contralateral side of the brain. Although the mechanisms responsible for increasing GM volumes are not clearly understood, we can speculate that structural brain plasticity contributed to the recovery of neurological function in our subjects. This finding is consistent with that of a study demonstrating that rats with focal cerebral ischemia showed significant motor skill learning along with significantly increased cortical volumes in layer II/III neopil; moreover, dendritic volume per neuron was increased in the sensorimotor cortex contralateral to the side of the lesion.17 Similar studies have shown that plastic changes, such as synaptogenesis and dendritic growth, appear in the contralesional hemisphere.32,33 The results of our study suggest that the recovery of motor function was positively correlated with the increase of GM volumes in the motor-related cortex (contralateral SMA), and this might be viewed as selective neuroplastic recruitment.

Driemeyer et al.34 performed an experimental VBM study with humans who learned juggling and verified that activation-dependent structural brain plasticity was associated with a highly selective increase in brain GM. Functional MRI research often focuses on functional forms of neuroplasticity; interestingly, a functional MRI study showed that during periods of increased functional demands on the human motor cortical system, certain regions, such as the primary sensorimotor areas and SMA, showed highly localized activation.35 Grefkes et al.35 demonstrated that motor deficits of patients with stroke...
were associated with key motor areas that seemed to show a functional imbalance as measured by functional MRI. These findings indicate neuroplasticity and compensatory regional changes that may influence the pathway toward recovery from stroke.26–28

The brain can be viewed as a set of widely distributed networks. In the present study, several cortical brain regions showed significant changes in volume during the longitudinal scans in the absence of a statistical correlation with motor recovery. The changes in the motor-related cortical regions may be viewed as the selective neuroplastic recruitment of the unaffected motor network in compensation for damage induced by the lesion.21,39–41 Although structural damage from stroke is focal, remote dysfunction can occur in many distant regions connected to the area of lesion. It should be considered that improvement or decline of nonmotor functions, such as memory, speech, executive function, and other cognitive functions, may be because of neuroplastic changes in specific brain regions not addressed in the present study. Recovery from stroke involves not only motor regions of the brain but also many other functional regions.

The present study has limitations. The data were from a small number of patients having experienced a specific acute subcortical infarct; furthermore, the age range of the patients (31–68 years) may limit the applicability of our results to significantly older patients. In addition, the control subjects in our study did not have risk factors for stroke, potentially limiting their comparability with our patient population, and data were only collected from controls during 1 time point. Finally, patients were followed-up for only 12 weeks, and it is conceivable that a longer period of observation might enrich and improve our understanding of the impact of remote changes in GM volume on motor recovery over time.

In conclusion, our study shows that secondary changes in GM volumes occur distal to the primary subcortical cerebellar infarct during a 12-week period after the stroke event. Secondary changes in GM volume can be quantified by the VBM approach and specific motor-relevant brain regions may either inhibit or contribute to functional recovery after a subcortical cerebral infarct.

Acknowledgments

The authors thank Professor Jiqian Fang and Dr Shengxue Wei, Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-Sen University, for statistical assistance.

Source of Funding

This study was supported by the National Basic Research Program of China (2011CB707804), grants from the Natural Science Foundation of China (39940012, 81100050, and 81200903), the Joint Funds of the Natural Science Foundation of China (U1032005), the Project of Science and Technology New Star of Pearl River (2012J2200089), grants from the Department of Education of Guangdong Province, the Bureau for Science and Information Technology of Guangzhou, the National Key Clinical Department, National Key Discipline, and Guangdong Key Laboratory for diagnosis and treatment of major neurological diseases.

Disclosures

None.

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*Stroke*. 2013;44:2795-2801; originally published online August 8, 2013;
doi: 10.1161/STROKEAHA.113.000971

*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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Longitudinal cortical volume changes correlate with motor recovery in patients after acute local subcortical infarction - online supplement

- Number of supplementary figures: 2

- Supplement Figure I. Lesion locations

Figure I: Lesion locations (white arrows) are shown on axial slices of the diffusion-weighted magnetic resonance images obtained from patients with subcortical cerebral infarction during the first week after stroke onset. R, Right; L, Left.
Supplement Figure II.

Figure II: Gray matter volume demonstrating significant changes at the 4th (green color) and 12th weeks (red color) vs. onset were superimposed. Voxel-based morphometry analysis revealed that significant changes in common regions (white arrows) between the 2 measurements; however, greater overall changes in gray matter volume were seen in the 12th week. CL, contralesional hemisphere; IL, ipsilesional hemisphere.