NeuroImage: Clinical 14 (2017) 679–684

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

# Gray matter volume changes in chronic subcortical stroke: A cross-sectional study

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ARTICLE INFO

*Article history:*
Received 9 November 2016
Received in revised form 22 January 2017
Accepted 29 January 2017
Available online 02 February 2017

*Keywords:*
Gray matter volume
Lesion side
Motor recovery
Stroke

ABSTRACT

This study aimed to investigate the effects of lesion side and degree of motor recovery on gray matter volume (GMV) difference relative to healthy controls in right-handed subcortical stroke. Structural MRI data were collected in 97 patients with chronic subcortical ischemic stroke and 79 healthy controls. Voxel-wise GMV analysis was used to investigate the effects of lesion side and degree of motor recovery on GMV difference in right-handed chronic subcortical stroke patients. Compared with healthy controls, right-lesion patients demonstrated GMV increase ($P < 0.05$, voxel-wise false discovery rate correction) in the bilateral paracentral lobule (PCL) and supplementary motor area (SMA) and the right middle occipital gyrus (MOG); while left-lesion patients did not exhibit GMV difference under the same threshold. Patients with complete and partial motor recovery showed similar degree of GMV increase in right-lesion patients. However, the motor recovery was correlated with the GMV increase in the bilateral SMA in right-lesion patients. These findings suggest that there exists a lesion-side effect on GMV difference relative to healthy controls in right-handed patients with chronic subcortical stroke. The GMV increase in the SMA may facilitate motor recovery in subcortical stroke patients.


## 1. Introduction

Stroke is the major reason for disability, especially for motor deficit (Crichton et al., 2016). The motor function in most stroke patients can recover spontaneously, at least to some extent (Kwakkel et al., 2006). The neural mechanisms underlying spontaneous motor recovery after stroke have been linked to brain structural and functional reorganization. In terms of functional reorganization, the recovered or enhanced activation or functional connectivity of the motor-related regions has been associated with motor recovery in subcortical stroke (Golestani et al., 2013; Liu et al., 2015; Wang et al., 2010; Zhang et al., 2014). Similarly, structural reorganization has also been observed in subcortical stroke. For example, the increased gray matter volume (GMV) in motor- and cognitive-related cortical regions have been associated with motor recovery in subcortical stroke (Dang et al., 2013; Fan et al., 2013; Gauthier et al., 2008).

The cerebral hemispheric asymmetry (Chiu and Damasio, 1980; Corballis, 2014; Good et al., 2001; LeMay, 1986; Wada et al., 1975) may result in different structural and functional reorganization following stroke in the homologous region of the left and right hemispheres. However, most prior neuroimaging studies on stroke recovery have not taken the issue into consideration. They either only focus on one side of lesions (Fan et al., 2013; Xing et al., 2016) or flipped the imaging data from one side to another along the midline (Abela et al., 2015; Wang et al., 2014; Zhang et al., 2014). In other words, it is remains unclear whether brain structural and functional alterations are different in subcortical stroke patients with lesions in the left and right hemispheres, which may help to identify the common and specific changes following the left and right hemispheric subcortical damage.

There are great variations in the degree of motor recovery after stroke. It has been shown that subcortical stroke patient with partial recovery (PR) exhibits stronger and more extensive activation in the motor cortex than patients with complete recovery (CR) (Zhang et al., 2014). The latter shows a return to normal pattern of motor activation. This finding suggests that PR and CR patients may adopt different functional reorganization in response to stroke attacks. However, it remains

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http://dx.doi.org/10.1016/j.nicl.2017.01.031

unclear whether structural characteristics are also different between PR and CR patients with subcortical stroke.

In the present study, we recruited 97 subcortical stroke patients with varying degree motor recovery and 79 healthy controls. Based on the lesion location, patients were divided into subgroups with lesions in the left and right hemispheres. According to the degree of motor recovery, patients were divided into CR and PR subgroups. The left- and right-sided stroke patients were analyzed respectively. GMV differences among the three groups (CR, PR and healthy control groups) were compared using a general linear model (GLM), controlling for age, sex and scanners. Then, *post hoc* comparison and correlation analysis were performed to identify whether CR and PR patients exhibit similar GMV changes and whether these significant GMV changes were correlated with motor recovery in PR patients.

## 2. Materials and methods

### 2.1. Subjects

The subjects were recruited from three medical centers: Tianjin Medical University General Hospital, Tianjin Huanhu Hospital and the First Affiliated Hospital of Zhengzhou University. The study protocol was approved by the Medical Research Ethics Committees of the three hospitals, and all subjects provided written informed consent before examination. The inclusion criteria for patients were as follows: (1) first-onset ischemic stroke; (2) a single lesion located in the internal capsule and neighboring regions; (3) right-handed before the stroke; and (4) time after stroke onset > 6 months. The exclusion criteria for patients were the following: (1) recurrent stroke after first onset; (2) any other brain abnormalities; (3) severe white matter hyperintensity manifesting as a Fazekas et al. (1987) scale score of >1 based on T2-FLAIR; and (4) a history of drug dependency or psychiatric disorders. A total of 97 patients (72 men and 25 women; mean age, 56.1 ± 7.5 years) were included in this study according to above criteria. The degree of motor recovery was evaluated by the Fugl-Meyer Assessment (FMA) (Fugl-Meyer et al., 1975; Gladstone et al., 2002). According to the FMA of the whole extremities, stroke patients were further divided into CR (FMA = 100) and PR (FMA < 100) subgroups. Seventy-nine healthy subjects (50 men and 29 women; mean age, 55.3 ± 7.3 years) were also recruited as controls. These participants were respectively recruited from Tianjin Medical University General Hospital (33 patients and 25 controls), Tianjin Huanhu Hospital (29 patients and 25 controls) and the First Affiliated Hospital of Zhengzhou University (35 patients and 29 controls).

### 2.2. MR data acquisition

Three-dimensional sagittal T1-weighted images were acquired using three 3.0-Tesla MR scanners from the three hospitals, including two Discovery MR750 scanners (General Electric, Milwaukee, WI, USA) and a Magnetom Trio Tim MR scanner (Siemens, Erlangen, Germany). The repetition time (ms)/echo time (ms)/flip angle/matrix/slices were 8.2/3.2/11°/256 × 256/188 for MR750 scanner, and 2000/2.3/9°/256 × 232/192 for Trio Tim scanner, respectively. All scans used the same field of view (256 mm × 256 mm), slice thickness (1 mm and no gap) and spatial resolution (1 × 1 × 1 $mm^3$).

### 2.3. GMV calculation

The GMV maps were calculated using Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The structural MR images were segmented into gray matter (GM), white matter and cerebrospinal fluid using the standard unified segmentation model. After an initial affine registration, the GM concentration maps were nonlinearly warped using diffeomorphic anatomical registration through the exponentiated Lie algebra (DARTEL) technique (Ashburner, 2007). After that, we resliced the normalized GMV to a 1.5-mm cubic voxel. The GMV was obtained by multiplying GM concentration map by the non-linear determinants derived from the spatial normalization step (Liu et al., 2012). Finally, the GMV images were smoothed with a kernel of 8 × 8 × 8 $mm^3$ full width at half maximum. Then, the spatial pre-processing, normalized, modulated, and smoothed GMV maps were used for further analysis.

### 2.4. GMV analyses

Stroke patients with lesions in the left and right hemispheres were analyzed respectively. For each patient subgroup, the general linear model (GLM) was used to compare voxel-wise GMV differences in the cortical gray matter mask among the CR, PR and healthy groups with age, sex and scanners as covariates of no interest. Multiple comparisons were corrected using a voxel-level false discovery rate (FDR) method ($P < 0.05$). Finally, brain regions with significant GMV differences were extracted and entered into region of interest (ROI)-based analyses to observe whether structural changes were similar in CR and PR patients.

### 2.5. Correlation analyses

The ROI-based correlation analyses between mean GMV of these ROIs and FMA were performed in PR patients group using a partial correlation analysis with age, sex and scanners as covariates of no interest, and $P < 0.05$ was considered to be statistically significant. The reason for only including PR patients for correlation analysis is to avoid ceiling effect because the CR patients had the same FMA score.

## 3. Results

### 3.1. Demographic and clinical data

The demographic and clinical data of subjects are shown in Table 1. Forty-nine patients had stroke lesions in the left hemisphere and forty-eight in the right hemisphere. There were no significant differences in age ($P = 0.79$) and gender ($P = 0.15$) among the left-sided stroke patients, right-sided stroke patients and healthy controls. There were no significant differences in age ($P = 0.82$ for the left-lesion analysis; $P = 0.67$ for the right-lesion analysis) and gender ($P = 0.07$ for the left-lesion analysis; $P = 0.56$ for the right-lesion analysis) among the CR, PR and healthy groups. In addition, there were no significant differences in lesion volume ($P = 0.33$) and FMA of the upper ($P = 0.22$) and whole extremities ($P = 0.16$) between the left- and right-sided stroke patients. The lesion incidence map of stroke patients is depicted in Fig. 1.

### 3.2. GMV differences

When using a voxel-level FDR correction for multiple comparisons ($P < 0.05$), we did not find any significant GMV differences between stroke patients (CR and PR) with left-sided lesions and healthy controls. In patients with right-sided lesions, however, we found significant GMV differences among the CR, PR and healthy groups in the bilateral paracentral lobule (PCL) and supplementary motor area (SMA), the right middle occipital gyrus (MOG) and precentral gyrus (PreCG) (Table 2; Fig. 2). *Post hoc* analyses showed that both CR and PR patients had significantly increased GMV than healthy controls in the bilateral PCL (CR: $P < 0.001$; PR: $P < 0.001$) and SMA (CR: $P = 0.005$; PR: $P = 0.001$) and the right MOG (CR: $P = 0.004$; PR: $P = 0.002$). There were no significant GMV differences ($P > 0.05$) in these regions between CR and PR patients. PR patients had significant GMV decrease than CR patients ($P = 0.004$) and healthy controls ($P < 0.001$) in the right PreCG. However, there was no significant GMV difference between CR patients and healthy controls ($P > 0.05$) in the right PreCG.