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 2 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 ($1 \times 1 \times 1$ 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 $8 \times 8 \times 8$ 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.

Table 1
Demographic and clinical information of stroke patients and healthy controls.

Variables	Left-sided stroke (n = 49)		Right-sided stroke (n = 48)		Controls (n = 79)	*P* value
	CR (n = 30)	PR (n = 19)	CR (n = 25)	PR (n = 23)		
Age, y	56.3 ± 7.5 (44–75)	55.4 ± 8.1 (43–68)	55.4 ± 6.6 (41–71)	57.0 ± 8.3 (40–71)	55.3 ± 7.3 (40–72)	0.79
Men, %	22 (73.3%)	17 (89.5%)	16 (64%)	17 (73.9%)	50(63.3%)	0.15
Duration, mo	18.6 ± 9.8 (6–52)	22.3 ± 15.9 (7–69)	17.6 ± 10.9 (6–53)	16 ± 6.3 (7–29)		
Lesion volume, ml	193.3 ± 223.5 (13–1008)		248.4 ± 322.7 (17–1680)			0.33
FMA						
Upper extremity	66 ± 0.0 (66)	51.5 ± 19.9 (10–66)	66 ± 0.0 (66)	45.8 ± 21.6 (3–66)		0.22
Whole extremity	100 ± 0.0 (100)	80.9 ± 25.2 (19–99)	100 ± 0.0 (100)	72.3 ± 26.9 (20–99)		0.16

Data are presented as the mean ± SD (range) for continuous data and n (%) for categorical data. CR, complete recovery; FMA, Fugl–Meyer Assessment; and PR, partial recovery.

3.3. Correlations between GMV changes and motor recovery

Correlations between GMVs of brain regions with significant structural changes and FMA scores in the PR patients are shown in Fig. 3. In PR patients with right-sided lesions, the FMA was correlated with GMVs in the bilateral SMA (upper extremity: pr = 0.485, $P = 0.035$; whole extremity: pr = 0.478, $P = 0.039$) (Fig. 3A) and the right PreCG (upper extremity: pr = 0.512, $P = 0.025$; whole extremity: pr = 0.497; $P = 0.030$) (Fig. 3B).

4. Discussion

In this study, we found that right-handed subcortical stroke patients with lesions in the right hemisphere showed more extensive GMV changes than those with lesions in the left hemisphere relative to healthy controls, suggesting a lesion side effect on GMV difference in chronic subcortical stroke. Although CR and PR patients showed similar GMV increase relative to healthy controls, GMV increase in the SMA was correlated with motor recovery in PR patients, suggesting a compensatory effect of the SMA on motor recovery in subcortical stroke.

The most important finding of this study is that right-handed subcortical stroke patients with lesions in the right hemisphere exhibited more extensive GMV increase than those with lesions in the left hemisphere relative to healthy controls, although these two groups of patients did not differ in age, sex, lesion size and motor recovery. Similarly, the intergroup differences in intra- and inter-network function connectivity are found to be evidently different between the left- and right-sided stroke patients (Wang et al., 2014). The exact neural mechanisms underlying the lesion-side effect on GMV following subcortical stroke are far from clear, however, several possibilities may be related to this effect. The right-sided stroke patients had GMV decrease than healthy controls in the motor cortex, but the left-sided patients did not show this change. These findings suggest that the right-sided stroke patients have greater secondary atrophy in the motor cortex than the left-sided patients, which is partly consistent with a previous study reporting a more severe damage of the affected corticospinal tract in the right-sided patients than in the left-sided patients (Liu et al., 2015). The more severe brain damage in the right-sided stroke patients might be related to the delayed treatment because the right-sided stroke patients have been reported to reach hospital later than the left-sided patients (Di Legge et al., 2005; Di Legge et al., 2006; Foerch et al., 2005). Generally, the more severe brain damage is associated with the more extensive brain reorganization. Thus, one possible neural mechanism underlying the lesion-side effect on GMV increase after subcortical stroke may be the difference in severity of brain damage. Another possibility may be related to the functional difference between the left and right hemispheres. The left hemisphere plays a more important role than the right hemisphere in the execution of movements in healthy subjects (Verstynen et al., 2005), which is confirmed in stroke patients (i.e. the right-sided patients show stronger interlimb coupling than the left-sided patients) (Lewis and Perreault, 2007). Thus, the right-sided patients with an intact left hemisphere may have greater potential to reorganize than the left-sided patients. Alternatively, a stroke in the left-dominant hemisphere may lead to more training or rehabilitation than a stroke in the right-non-dominant hemisphere in right-handed patients, which may result in non-significant impairment in left-sided patients. In addition, there was slight difference in lesion location between the left and right lesion groups (Fig. 1), which would also be related to the lesion-side effect on GMV. Of course, future studies are needed to clarify the neural mechanisms underlying the lesion-side effect after subcortical stroke.

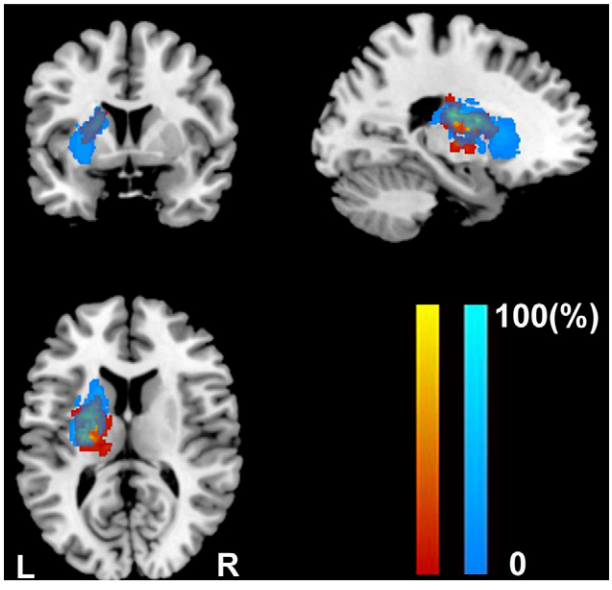

Fig. 1. Lesion maps of the left- and the flipped right-sided stroke patients. Warm color represents the left lesion map and cool color represents the flipped right lesion map.

Table 2
GMV differences between right-sided stroke patients and healthy controls ($P < 0.05$, FDR corrected).

Brain regions	BA	Peak MNI coordinate	Peak F	Cluster size (voxels)	GMV differences
B_PCL	4	−4.5, −24, 69	13.6	2482	Increase
B_SMA	6	1.5, 10.5, 66	11.1	237	Increase
R_MOG	39	49.5, −78, 28.5	15.3	494	Increase
R_PreCG	4	46.5, −9, 33	14.5	420	Decrease

Abbreviations: B, bilateral; BA, Brodmann Area; FDR, false discovery rate; GMV, gray matter volume; MOG, middle occipital gyrus; PCL, paracentral lobule; PreCG, precentral gyrus; R, right; SMA, supplementary motor area.

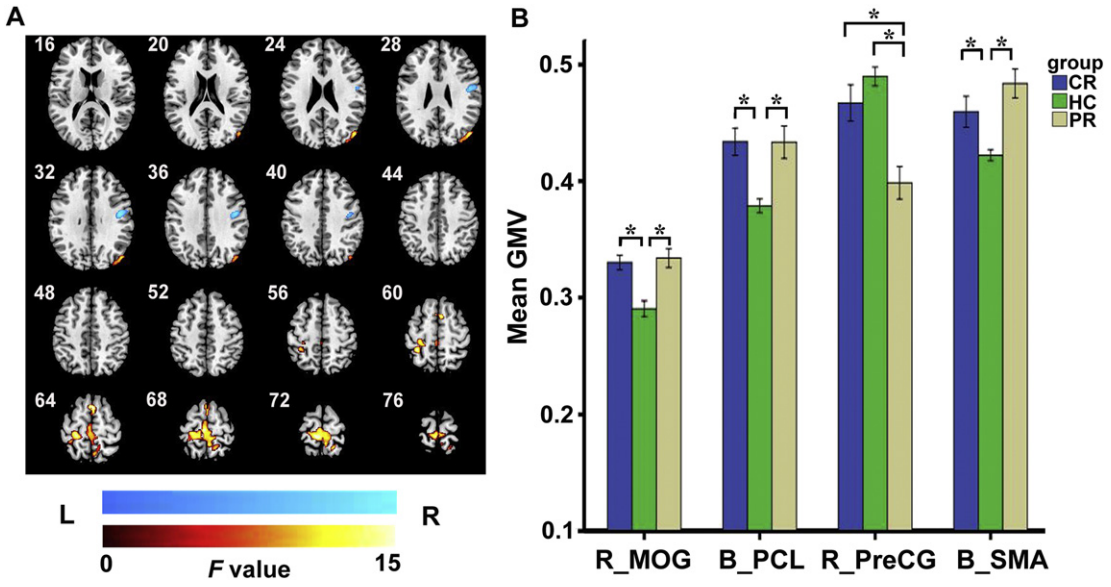

Fig. 2. Significant GMV differences in right-sided stroke patients compared with healthy controls ($P < 0.05$, FDR-corrected). Right-sided stroke patients exhibit increased GMV in the bilateral PCL and SMA and the right MOG, and decreased GMV in the right PreCG. Blue color represents GMV decrease and red-yellow color represents GMV increase. Abbreviations: CR, complete recovery; FDR, false discovery rate; GMV, gray matter volume; HC, healthy controls; L, left; MOG, middle occipital gyrus; PCL, paracentral lobule; PR, partial recovery; PreCG, precentral gyrus; R, right; SMA, supplementary motor area. $^{*}P < 0.05$.

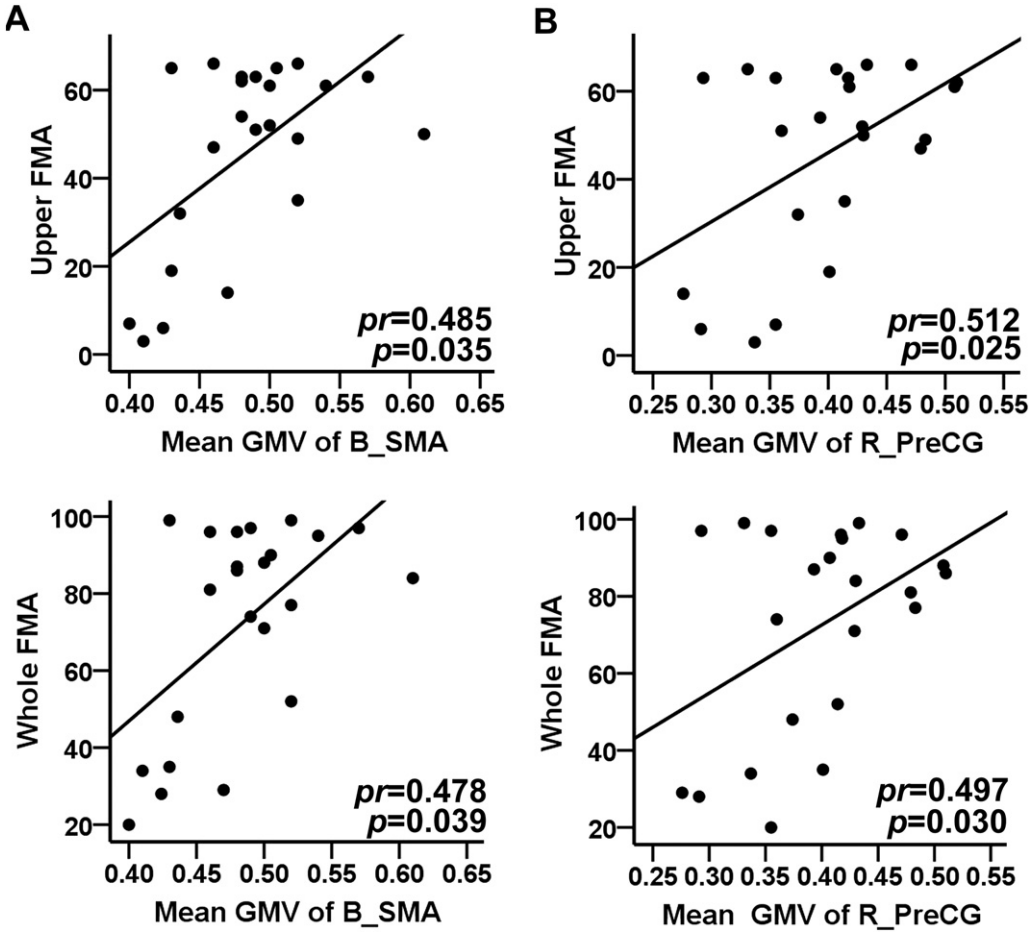

Fig. 3. Correlations between mean GMV with significant intergroup differences and FMA scores in PR stroke patients. A: the GMV in the bilateral SMA is correlated with the upper and whole extremity FMA scores in the right-sided PR stroke patients. C: the GMV in the right PreCG is correlated with the upper and whole extremity FMA scores in the right-sided PR stroke patients. Abbreviations: B, bilateral; FMA: Fugl-Meyer Assessment; GMV, gray matter volume; PR, partial recovery; PreCG, precentral gyrus; R, right; SMA, supplementary motor area.

In consistent with many previous studies (Chu and Jones, 2000; Dang et al., 2013; Fan et al., 2013; Kraemer et al., 2004), we also found GMV reduction in the primary motor cortex (M1) in the right-sided stroke patients relative to healthy controls, which has been explained by the retrograde axonal degeneration secondary the damage of motor pathway (Liang et al., 2007; Liang et al., 2008; Yu et al., 2009). In this study, we found GMV increase in several brain regions, but only GMV increase in motor-related region (SMA) was associated with motor recovery, which is well consistent with prior studies (Dang et al., 2013; Gauthier et al., 2008; Schaechter et al., 2006). GMV increases in spared cortices have been demonstrated in animal experiments, which may result from rehabilitation-induced increases in dendritic arborization and synaptic density (Chu and Jones, 2000; Gonzalez et al., 2004; Holtmaat and Svoboda, 2009).

It has been shown that the post-stroke structural and functional changes affect the degree of motor recovery. As for structural damage, we found that PR rather than CR patients showed significant GMV reduction in the M1. Moreover, GMV reduction in the M1 was associated with motor deficit in PR patients. These finding suggest that the secondary structural damage in the ipsilesional M1 may prevent patients from motor recovery. In contrast to difference in structural damage between PR and CR patients, both PR and CR patients showed similar degrees of GMV increase, suggesting that the GMV increase is independent on the degree of motor recovery in subcortical stroke. However, the positive correlation between the GMV of the SMA and motor score supports an association between GMV increase and motor recovery. The discrepancy may be explained by the fact that only a small portion of PR patients had a severe motor deficit, which leads to the lack of difference in GMV increase between PR and CR patients. Compared with healthy controls, motor-task-evoked activation has found to be increased in PR patients, but returns to a near normal level in CR patients (Marshall et al., 2000; Ward et al., 2003; Zhang et al., 2014). Moreover, the resting-state brain activity (amplitude of low-frequency fluctuation) is more significantly increased in CR patients than in PR patients (Zhang et al., 2014). These findings suggest that varied motor recovery may be related to the differences in structural and functional reorganization in subcortical stroke patients.

There are several limitations in the present study. First, the cross-sectional design may prevent us to investigate the longitudinal GMV changes and their associations with motor recovery following stroke. Second, the illness duration post-stroke is so wide (6–69 months), which may affect our GMV analysis. Third, we did not differ stroke lesions resulted from small and large vessel diseases, which have different clinical and pathological features. Finally, there was no data regarding the delayed treatment hypothesis for the current sample.

5. Conclusion

Compared with healthy controls, we found more extensive GMV differences in the right-sided subcortical stroke patients than in the left-sided ones, suggesting a lesion-side effect on GMV in right-handed subcortical stroke patients. The lesion-side effect should be considered in future studies on brain reorganization following stroke. GMV increase in the SMA was correlated with motor recovery in PR patients, suggesting a compensatory effect of the SMA on motor recovery in subcortical stroke.

Disclosures

The authors declare no conflict of interest.

Acknowledgments

This study was supported by the Natural Science Foundation of China (81271564, 81601472), the Natural Science Foundation of Tianjin (16JCZDJC36000), and TMUGH funding (ZYYFY2015006).

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