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Motor Recovery at 6 Months After Admission Is Related to Structural and Functional Reorganization of the Spine and Brain in Patients With Spinal Cord Injury

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Abstract: This study aimed to explore structural and functional reorganization of the brain in the early stages of spinal cord injury (SCI) and identify brain areas that contribute to motor recovery. We studied 25 patients with SCI, including 10 with good motor recovery and 15 with poor motor recovery, along with 25 matched healthy controls. The mean period post-SCI was 9.2 ± 3.5 weeks in good recoverers and 8.8 ± 2.6 weeks in poor recoverers. All participants underwent structural and functional MRI on a 3-T magnetic resonance system. We evaluated differences in cross-sectional spinal cord area at the C2/C3 level, brain cortical thickness, white matter microstructure, and functional connectivity during the resting state among the three groups. We also evaluated associations between structural and functional reorganization and the rate of motor recovery. After SCI, compared with good recoverers, poor recoverers had a significantly decreased cross-sectional spinal cord area, cortical thickness in the right supplementary motor area and premotor cortex, and fractional anisotropy (FA) in the right primary motor cortex and posterior limb of the internal capsule. Meanwhile, poor recoverers showed decreased functional connectivity between the primary motor cortex and higher order motor areas (supplementary motor area and premotor cortex), while good recoverers showed increased functional connectivity among these regions. The structural and functional reorganization of the spine and brain was associated with motor recovery rate in all SCI patients. In conclusion, structural and functional reorganization of the spine and brain directly affected the motor recovery of SCI. Less structural atro-

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phy and enhanced functional connectivity are associated with good motor recovery in patients with SCI. Multimodal imaging has the potential to predict motor recovery in the early stage of SCI. *Hum Brain Mapp 37:2195–2209, 2016.*

Key words: spinal cord injury; atrophy; cortical reorganization; magnetic resonance imaging; motor recovery

INTRODUCTION

Spinal cord injury (SCI) is a common cause of disability, which significantly decreases quality of life [Ma et al., 2014]. During the past 20 years, although various therapies have been developed for restoring motor function in SCI, to date, there are no efficient and reliable clinical treatments available for SCI patients [Dietz and Curt, 2006]. One potential reason holding back improvements in SCI therapy is that current strategies, such as physical therapy, drug therapy, tissue engineering, and cell-based therapy generally assume intact brain motor system function for driving limb movements. Most of these studies have focused on local changes in the spinal injury site and neglect the intimate interconnection with the brain [Cramer et al., 2005].

In recent years, there has been increasing evidence that loss of sensory and motor function following SCI results in extensive functional reorganization of the sensorimotor cortex in humans and animals [Moxon et al., 2014; Nardone et al., 2013a]. Several studies have shown that SCI contributes to structural reorganization of the spine and brain [Freund et al., 2011; Jurkiewicz et al., 2006; Lundell et al., 2011]. Henderson et al. [2011] showed that brain functional reorganization following long-standing SCI is associated with a significant change in brain structure. To date, spinal cord atrophy [Freund et al., 2011; Lundell et al., 2011], brain white matter and grey matter atrophy [Freund et al., 2012; Jurkiewicz et al., 2006; Wrigley et al., 2009], and cortical functional reorganization [Henderson et al., 2011; Jurkiewicz et al., 2007] in the sensorimotor areas have been demonstrated in the later stages of SCI. Although it is well established that brain reorganization occurs in chronic SCI, the onset and role of these changes are still unknown in the acute phase of injury. Given that motor recovery of SCI occurs mainly in the early stages of disease (within 1 year after injury), studies of structural and functional reorganization in acute patients appear more meaningful than studies of chronic patients [Steeves et al., 2011].

Aguilar et al. [2010] investigated the acute neurophysiological changes occurring in the primary somatosensory cortex of anesthetized rats after spinal cord transection. They demonstrated that the complete thoracic transection of the spinal cord could immediately (within 1 h) change the state of large cortical networks, and that these changes play a critical role in the early brain functional reorganization after SCI. Similarly, our studies have also shown that SCI causes significant functional and structural changes of the sensorimotor system in the early stage of disease (within 8–10 weeks) [Hou et al., 2014a,b]. However, it remains unclear whether this structural and functional reorganization contributes to the motor recovery of SCI. To the best of our knowledge, only one prospective longitudinal study has been performed in patients with acute traumatic SCI. That study showed extensive corticospinal tract and sensorimotor cortex atrophy at 40 days after SCI, with faster degenerative changes relating to poorer recovery [Freund et al., 2013]. These early studies of SCI are important but are not sufficient to draw conclusions on the role of brain reorganization in motor recovery, especially whether the functional reorganization translates into functional gain or further impairment. This question is important because it could further our understanding of the mechanism of spontaneous functional recovery following SCI. It also has the potential to provide additional information for predicting clinical outcomes, as well as leading to new therapeutic approaches to enhance beneficial or reduce maladaptive reorganization.

To address this question in the present study, we used multimodal MRI to perform a systemic investigation of the cross-sectional cord area proximal to the site of injury (C2/C3 level) and cortical structural/functional changes after SCI and define their effects on motor recovery. We hypothesized that patients with different outcomes of motor function would show different structural and functional reorganization patterns following SCI. Furthermore, we hypothesized that reorganization of the spine and brain would directly affect the motor recovery of SCI.

Abbreviations

ANCOVA	Analysis of co-variance
ASIA	American Spinal Injury Association
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional MRI
MP-RAGE	Magnetization-prepared rapid gradient-echo sequence
SCI	Spinal cord injury
SMA	Supplementary motor area

MATERIAL AND METHODS

Study Participants

This study was approved by the Medical Ethics Committee of the Third Military Medical University

(Chongqing, China), and written informed consent was obtained from all participants before enrollment. Patients with acute SCI were recruited consecutively from the Department of Rehabilitation at the Southwest Hospital (Chongqing, China) from September 2012 to December 2013.

SCI was confirmed by routine clinical X ray computed tomography images, electromyography, and neurological assessment. No patient had a psychiatric disorder or a history of traumatic brain injury. Neurological assessment was performed using the American Spinal Injury Association (ASIA) Standard Neurologic Classification of SCI (Committee et al., 2012). The ASIA impairment scale (AIS) and ASIA motor score were assessed at admission (baseline) and 6 months later. The evaluators who conducted the ASIA assessments were blinded to the study hypothesis. MRI was conducted on the day of the patient's arrival and took place prior to any treatment.

Disease duration was calculated from the time of injury to MRI scan. The interval between injury and MRI scanning ranged from 2 to 12 weeks (mean 9 weeks). Secondary injury including ischemic/apoptotic cascade, edema, and inflammation usually occur within the first 2 weeks after SCI [Park et al., 2004], therefore, these potentially confounding factors may have had little influence on brain structural and functional reorganization. All the patients with SCI received 3 h of therapy per day, 6 or 7 days per week. The length of stay in the acute rehabilitation unit depended on the patient's condition and progress and varied from one to several weeks (average length of stay was 40 days).

After discharge, all of the patients continued to receive care at the rehabilitation clinic and/or as outpatients. Patients with SCI were split into two groups (good recoverers and poor recoverers) according to the clinical outcome of motor recovery at 6 months follow-up. Good recoverers achieved an increase of at least one AIS grade from baseline to 6 months follow-up. Poor recoverers had no significant upward conversion of AIS grade at 6 months follow-up. We also calculated the recovery rate of motor function in all patients with SCI, which was defined as follows: (motor score at 6 months follow-up − motor score on admission) ÷ (100 − motor score on admission) ×100% [Waters et al., 1996].

Twenty-five right-handed healthy volunteers with no history of neurological or psychiatric diseases were recruited as controls, and were well matched for age and gender with the patients.

MRI Acquisition

Images were obtained using a 3.0 T MRI system (TIM Trio, Siemens, Erlangen, Germany) with an eight-channel phased-array head coil. For each participant, conventional brain T1-weighted, T2-weighted and fluid-attenuated inversion recovery (FLAIR) images were obtained to exclude organic disease and white matter hyperintensity lesions. All MR images were assessed by two experienced radiologists. Resting-state functional MRI (fMRI), structural imaging and diffusion tensor imaging (DTI) were all performed on the same day. During MRI, all participants were instructed to relax with their eyes closed and lie still without moving. Resting-state functional images were acquired using an echo-planar-imaging (EPI) sequence in contiguous axial planes with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, number of slices = 36, slice thickness = 4 mm, field of view (FOV) = 256 × 256 mm^2, and matrix = 64 × 64, isotropic size = 4 × 4 × 4 mm^3. For each participant, fMRI lasted for 480 seconds, and 240 volumes were obtained. In addition, high-resolution structural T1-weighted anatomical images were acquired in a sagittal orientation using a 3D magnetization-prepared rapid gradient-echo sequence (MP-RAGE) with the following parameters: TR = 1,900 ms, TE = 2.52 ms, flip angle = 15°, slice thickness = 1 mm, FOV = 256 × 256 mm^2, matrix = 256 × 256, and isotropic voxel = 1 × 1 × 1 mm^3. For each participant, MP-RAGE scanning lasted for 272 seconds. DTI images were acquired using a single-shot twice refocused spin-EPI sequence in contiguous axial planes with the following parameters: TR = 10,000 ms, TE = 92 ms, flip angle = 90°, number of slices = 75, slice thickness = 2 mm, FOV = 256 × 248 mm^2, matrix = 128 × 124, and isotropic size = 2 × 2 × 2 mm^3. The diffusion-sensitizing gradients were applied along 64 non-collinear gradient directions with $b = 1{,}000$ s/mm^2 and an acquisition without diffusion weighing with $b = 0$ s/mm^2. For each participant, the DTI scanning lasted for 384 seconds.

Cross-Sectional Spinal Cord Area Analysis

The methodology developed to measure cross-sectional spinal cord area at cervical level C2/C3 was first used to quantify the clinical symptom severity of multiple sclerosis [Horsfield et al., 2010; Losseff et al., 1996], and was applied to SCI by Freund et al. [2010, 2011]. A transversal spinal cord mask was created on the 3D MP-RAGE images with the C2 disc as a caudal landmark. The spinal cord area from the mask was automatically estimated in each slice and averaged using a semi-automated segmentation method [Losseff et al., 1996]. To confirm the reliability of morphometric measurement of cross-sectional spinal cord area, we repeated the measurement in all participants by two different investigators, and did not find any significant difference using a paired t test.

CORTICAL THICKNESS ANALYSIS

Cortical thickness measurements were performed using CIVET software (version 1.1.9; Montreal Neurological Institute at McGill University, Montreal, Quebec, Canada). The T1-weighted MR structural images of each participant

were corrected for non-uniformity using the N3 algorithm [Sled et al., 1998] and linearly registered into an MNI152 standard space [Collins et al., 1994]. The corrected and registered images were automatically segmented into gray matter, white matter, cerebrospinal fluid, and background using the INSECT algorithm [Zijdenbos et al., 2002]. The Constrained Laplacian-based Anatomic Segmentation with Proximity algorithm was applied to generate the inner and outer gray matter surfaces comprising 40,962 vertices for each hemisphere [Kim et al., 2005]. Finally, the cortical thickness was measured by taking the absolute distance between corresponding vertices on the extracted inner and outer surfaces [Lerch and Evans, 2005].

DTI Analysis

White matter image preprocessing and statistical analysis were performed using the DTI Studio software (version 2.4, Johns Hopkins Medical Institute, Laboratory of Brain Anatomical MRI; http://cmrm.med.jhmi.edu). After image acquisition, the echo planar distortions induced by eddy currents were corrected using an algorithm that determined the optimum affine transformation to be applied to each diffusion-weighted image. Individual maps of FA were calculated from the DTI data on a pixel by pixel basis. Voxel-based analysis was performed using SPM8 software (SPM8, Welcome Department of Imaging Neuroscience, Institute of Neurology, University of College London, UK; http://www.fil.ion.ucl.ac.uk/spm). After normalizing all b0 images to standard MNI space using the EPI template supplied by SPM8, the original voxel size was resampled to $3 \times 3 \times 3$ mm. These derived parameters were applied to the FA maps to normalize them to the MNI space. Finally, the normalized FA maps were spatially smoothed using an isotropic Gaussian filter (8-mm full width at half maximum) to improve the signal-to-noise ratio.

Functional Connectivity Analysis

Functional connectivity preprocessing and statistical analysis were also done with SPM8 software. To avoid manipulation error confounds and standardize the process, we used the batch-processing tool data processing assistant for resting state fMRI (DPARSF; http://www.restfmri.net) [Chao-Gan and Yu-Feng, 2010]. For the resting state fMRI data of each participant, the first 10 volumes of functional images were discarded to allow for steady-state magnetization and stabilization of participant status. EP images were slice-timing corrected to the middle slice acquired in time, and realigned and resliced to correct for head motion with a mean volume created. Structural images were co-registered with the mean volume of functional images and subsequently segmented by an inbuilt unified segmentation routine in SPM8. The parameter created by segmentation was applied to functional images, non-linear normalization to the MNI template brain, and each voxel was resampled to isotropic $3 \times 3 \times 3$ mm. As a final step, the resting state fMR images were smoothed using an 8-8-8 mm FWHM Gaussian kernel. The head motion of all participants during resting-state fMRI acquisition was observed, and data were discarded if the translation exceeded 2 mm or if rotation exceeded 2°.

Functional connectivity was analyzed using the REST software package (http://www.restfmri.net) using a seed voxel correlation approach [Fox et al., 2005]. The right supplementary motor area (SMA) and right premotor cortex were selected as regions of interest (ROIs) for functional connectivity analysis on resting-state fMRI data. Several possible spurious sources of variance, including the estimated head motion parameters, global brain average signals, and average signals from the cerebrospinal fluid and white matter, were removed from the data through linear regression. After band-pass filtering (0.01–0.08 Hz) and linear trend removal, a reference time series for each seed was extracted by averaging the time series of voxels within each ROI. A correlation analysis was conducted between the seed ROI and the remaining voxels in the whole brain. The resulting r values were converted using Fisher's r-to-z transformation to improve the Gaussianity of their distribution.

To evaluate the reliability of the resting-state fMRI findings, we conducted the following procedures. First, we randomly divided the healthy controls into two subgroups. Group I had 13 participants and Group II had 12. We then compared the functional connectivity differences between the groups using two-sample t tests. The two control subgroups showed no significant differences in functional connectivity ($P > 0.05$, corrected for multiple comparisons), which suggested that resting state fMRI is a reliable method to assess brain functional abnormalities.

Statistical Analysis

Differences in age, sex, years of education, and cross-sectional spinal cord area among the three groups were compared by conducting one-way analysis of analysis of variance and the χ^2 test using SPSS version 18.0. Statistical tests on the cortical thickness, white matter, and functional connectivity maps were performed using a voxel-based, one-way analysis of co-variance (ANCOVA) with *post hoc t* tests controlling for age, sex and years of education. Statistical inferences were made with a voxel-level threshold of $P < 0.05$, after family-wise error correction for multiple comparisons. For clusters identified in the ANCOVA, we performed follow-up between-group, voxel-wise t tests to characterize group differences using the same thresholds within a mask showing group differences from the ANCOVA. Finally, to determine the relationship between the structural and functional reorganization of the spine and brain and clinical characteristics, the mean values of

TABLE I. Demographic and clinical characteristics of healthy controls and patients with SCI

Characteristics	Healthy controls ($n = 25$)	Good recoverers ($n = 10$)	Poor recoverers ($n = 15$)	P value
Mean age ± SD (years)	36.5 ± 9.3	37.9 ± 13.9	35.8 ± 11.5	0.63[a]
Age range (years)	20–45	19–56	19–52	–
Gender (male/female)	15/10	6/4	8/7	0.91[c]
Mean years of education (years)	12.8 ± 3.9	12.1 ± 2.9	12.5 ± 3.3	0.71[a]
Disease duration (weeks)		9.2 ± 3.5	8.8 ± 2.6	0.57[b]
No. with cause of SCI		Fall (4), motor vehicle accident (6)	Fall (5), motor vehicle accident (10)	0.73[c]
Initial site of impairment (based on motor loss)		C6 (1), C8 (1), T5 (1), T6 (1), T7 (1), T8 (1), T9(1), T10 (2), T12 (1)	C5 (2), C6 (1), C8 (1), T5 (1), T6 (2), T7 (1), T8 (3), T9 (2), T11 (1), T12 (1)	0.55[c]
No. with AIS grades (baseline)		A(1), B(4), C(3), D(2)	A(7), B(3), C(3), D(2)	0.35[c]
No. with AIS grades conversion (6 months)		A to B (1), B to C (3), B to D (1), C to D (2), C to E (1), D to E (2)	No conversion	–
Mean ASIA motor score (baseline)		71.9 ± 16.3	58.5 ± 26.5	0.17[b]
Mean ASIA motor score (6 months)		85.5 ± 11.5	61.3 ± 26.4	0.01[b]
Mean motor recovery rate (%)		50.6 ± 14.4	12.1 ± 10.6	<0.001[b]

Abbreviation: ASIA, American Spinal Injury Association; AIS, ASIA impairment scale; SCI, spinal cord injury.
[a]Indicated P value in one-way analysis of variance among the three groups.
[b]P value with independent samples t test.
[c]P value with χ^2 test.

all voxels in the abnormal areas revealed by ANCOVA were extracted separately using the volume of interest in SPM8. The mean values at the spinal level (cross-sectional spinal cord area) and brain level (cortical thickness, fractional anisotropy value, and functional connectivity strength) were input into SPSS 18.0 to conduct Pearson correlation analysis with clinical motor recovery rate of all SCI patients.

RESULTS

Demographic and Clinical Characteristics

We recruited 25 patients with SCI and 25 healthy controls. Ten patients showed an upward conversion of AIS grade at 6 months follow-up (good recoverers) and 15 showed no significant upward conversion (poor recoverers). The demographic and clinical characteristics of all participants are given in Table I. The three groups were well-matched for age, sex and years of education. No significant differences were observed in disease duration between the two SCI subgroups ($P > 0.05$). However, the clinical baseline of injury severity between the two subgroups differed markedly: the good recovery group contained only one patient (AIS grade A), while the poor recovery group had seven patients. Significant differences were also observed in total ASIA motor score at baseline and at 6 months follow-up ($P < 0.05$) between the two subgroups. As with motor functional recovery rate, good recoverers showed significantly greater motor recovery rates than poor recoverers showed (50.6% *vs.* 12.1%). The motor recovery rate was significantly negatively correlated with baseline neurological impairment ($r = -0.33$; $P < 0.05$) and disease duration since injury ($r = -0.31$; $P = 0.005$), while it did not correlate with the length of stay in acute unit, sex or age in the patients with SCI.

Cross-Sectional Spinal Cord Area Analysis

We measured cross-sectional cord area at the C2/C3 level, which was above the site of injury. The C2/C3 cross-sectional spinal cord area in healthy controls, good recoverers and poor recoverers was 83.2 ± 3.9, 80.5 ± 4.8 and 73.5 ± 5.2 mm^2, respectively. Poor recoverers exhibited lower spinal cord area compared with healthy controls ($P < 0.001$) and good recoverers ($P = 0.002$). Although the spinal cord area was 2.7 mm^2 lower in good recoverers than it was in healthy controls, this difference was not significant ($P = 0.091$) (Fig. 1).

Cortical Thickness Analysis

One-way ANCOVA showed four brain regions that had significant differences in cortical thickness, namely the bilateral primary motor cortex, right SMA, and right premotor cortex. Compared to healthy controls, poor and good recoverers had significantly decreased cortical thickness in the bilateral primary motor cortex. In addition to reduced cortical thickness in the primary motor cortex, poor recoverers also showed decreased cortical thickness in the right SMA and premotor cortex when compared to healthy controls. A direct comparison between the two patient groups revealed significantly decreased cortical

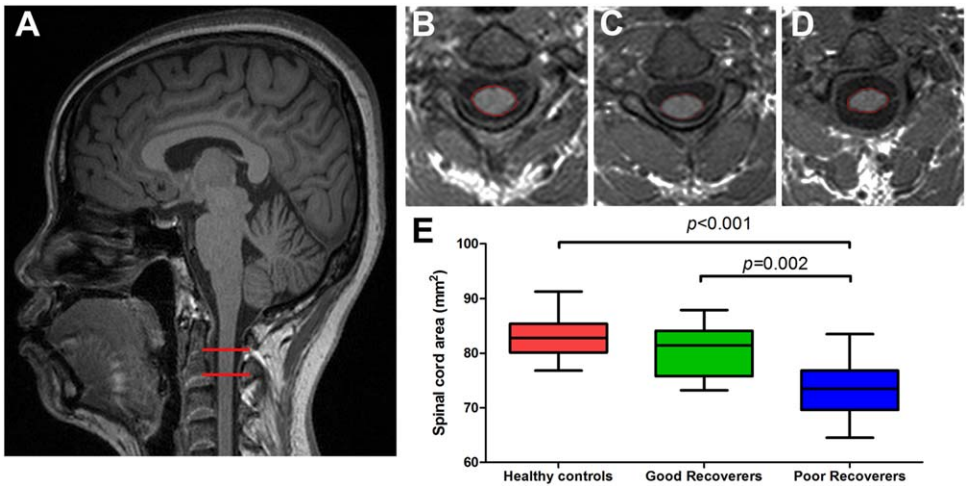

Figure 1.

Cross-sectional spinal cord area differences among three groups of participants. (**A**) T1-weighted image showing the region of cross-sectional cord area measurement (within red horizontal bars). Spinal cord area in a healthy control (**B**), good recoverer (**C**), and poor recoverer (**D**). (**E**) Box plots showing the atrophy of cord area in poor recoverers relative to both healthy controls and good recoverers. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

thickness in the right SMA and premotor cortex in the poor recoverers compared to the good recoverers (Fig. 2, Table II).

White Matter Microstructural Analysis

The three groups differed in white matter fractional anisotropy (FA) mainly in the right internal capsule and bilateral primary motor cortex. Compared to the healthy controls, poor recoverers showed reduced FA in the right primary motor cortex and posterior limb of the internal capsule; good recoverers showed no significant difference in white matter microstructure. When comparing the two patients groups directly, the poor recoverers showed reduced FA in the bilateral primary motor cortex and right posterior limb of the internal capsule (Fig. 3, Table III).

Resting-State Functional Connectivity Analysis

Cortical thickness analysis showed significant anatomical differences between the two SCI subgroups, mainly in the right SMA and premotor cortex, therefore, we speculated that these two areas may play a vital role in the motor recovery following SCI. Previous studies have also shown that SMA and premotor cortex contribute to motor recovery of patients with stroke [Riecker et al., 2010; Wang et al., 2012]. Thus, we performed seed-based resting-state functional connectivity analysis to explore whether functional reorganization of these two areas plays an important role in motor functional recovery of SCI. We found that the two SCI groups showed distinct functional reorganization patterns in these two seed areas. Specifically, when the seed was located in the right SMA, poor recoverers showed decreased functional connectivity mainly in the right primary motor cortex and left SMA. On the contrary, the good recoverers showed increased functional connectivity in the bilateral primary motor cortex and left SMA. Similar results also were found in the seed of the right premotor cortex. Poor recoverers showed decreased functional connectivity in the right primary motor cortex; conversely, good recoverers showed increased functional connectivity. A direct comparison between the two patient groups showed significantly increased functional connectivity between the right SMA and right primary motor cortex and left SMA, as well as increased functional connectivity between the right premotor cortex and right primary motor cortex and right SMA in the good recoverers (Fig. 4, Table IV).

Correlations Between Structural/Functional Reorganization and Extent of Motor Recovery

At the spinal level, the cross-sectional spinal cord area was positively correlated with the motor recovery rate in all patients with SCI ($r = 0.59$, $P = 0.002$). At the brain level, the FA values in the right primary motor cortex and the cortical thickness in the right SMA were positively correlated with the motor recovery rate in all the patients with SCI ($r = 0.76$, $P < 0.001$; $r = 0.75$, $P < 0.001$; respectively) (Fig. 5A). The functional connectivity strength between the right SMA and right primary motor cortex and left SMA were positively correlated with the motor recovery rate in all the patients with SCI ($r = 0.78$, $P < 0.001$; $r = 0.75$, $P < 0.001$; respectively). In addition, the

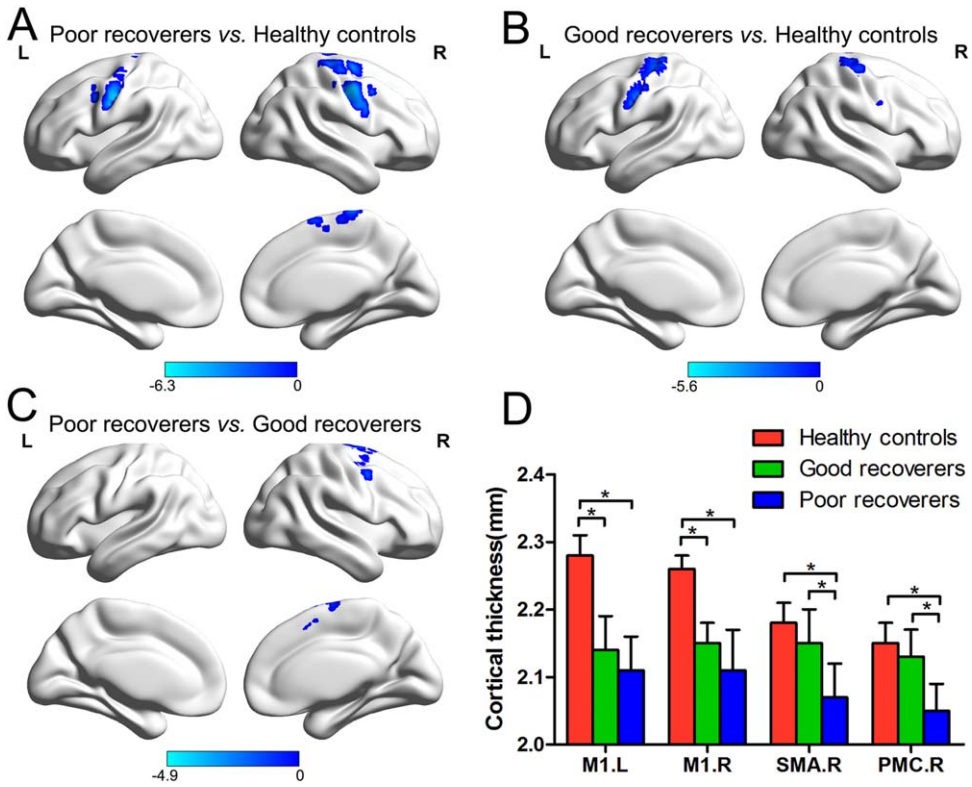

Figure 2.

Cortical thickness atrophy in poor recoverers and good recoverers. (**A**) Smaller cortical thickness in the bilateral primary motor cortex (M1), right SMA and premotor cortex (PMC) in poor recoverers relative to healthy controls. (**B**) Smaller cortical thickness in the bilateral M1 in poor recoverers relative to healthy controls. (**C**) Smaller cortical thickness in the right SMA and PMC in poor recoverers relative to good recoverers. (**D**) Bar graph showing the cortical thickness values of the three groups at the peak of the abnormal regions. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

functional connectivity strength between the right premotor cortex and right primary motor cortex was also positively correlated with the motor recovery rate in all the patients with SCI ($r = 0.79$, $P < 0.001$) (Fig. 5B).

Additional stepwise multiple regression analysis was conducted to test which spinal and supraspinal data were the superior predictors. The best set of parameters predicting the extent of motor recovery at 6 months included cortical thickness in the right SMA, functional connectivity strength between the right SMA and right primary motor cortex, and functional connectivity strength between the right premotor cortex and right primary motor cortex. The regression coefficient, standard error and t values are given in Table V.

DISCUSSION

It is often seen in clinical settings that patients with acute SCI with similar AIS grades may have different outcomes in motor function; some patients show some recovery on motor function, whereas others show no obvious recovery. The present investigation addressed the question of whether different outcomes of motor function can be attributed to differences in structural and functional reorganization of the spine and brain. Our findings demonstrated that structural and functional reorganization patterns directly affect motor function recovery at 6 months after admission. Specifically, at the structural reorganization level, poor recoverers showed more serious and widespread structural damage of the spine and brain than the good recoverers showed. The extent of the structural damage was associated with the motor recovery rate in all the patients with SCI. At the functional reorganization level, poor recoverers had decreased functional connectivity between the primary motor cortex and higher order secondary motor areas (SMA and premotor cortex). Good recoverers mainly showed significantly increased functional connectivity among these regions, and functional reorganization in the brain was positively correlated with motor recovery rate in all patients with SCI. Our findings may shed some lights on the role of structural and functional reorganization in the early stage of SCI recovery,

TABLE II. Difference in cortical thickness among patients with SCI with good motor recovery, poor motor recovery and healthy controls

Anatomical region	MNI coordinate x	y	z	Voxel size	Peak *t* value
Poor recoverers < healthy controls					
Left M1 (BA4)	−49	−10	39	85	−6.28
Right M1 (BA 4)	49	−7	45	125	−5.89
Right SMA (BA 6)	3	6	72	50	−4.76
Right premotor cortex (BA 6)	23	−6	64	43	−5.38
Good recoverers < healthy controls					
Left M1 (BA 4)	−53	−5	32	107	−5.59
Right M1 (BA 4)	38	−18	60	73	−5.35
Poor recoverers < good recoverers					
Right SMA	5	−27	70	29	−4.17
Right premotor cortex	21	−10	67	46	−4.85

Abbreviation: SCI, spinal cord injury; BA, Broadmann area; M1, primary motor cortex; SMA, supplementary motor area; MNI, Montreal Neurological Institute. $P < 0.05$, corrected for multiple comparisons with family-wise error correction.

and further our understanding of the mechanisms underlying motor functional recovery after SCI.

Clinical Features

One of the main strengths of the present study was the early stage of SCI. Most previous structural and functional studies of SCI were in patients with chronic disease (range 1–30 years). Our present findings provide evidence that SCI causes significant structural and functional changes during the early stage of the disease, and may even be related to the extent of motor recovery at 6 months. Our structural findings are partly consistent with another recent study [Freund et al., 2013], which showed that extensive atrophic and microstructural changes of corticospinal axons and sensorimotor cortical areas occur as early as 40 days after SCI. These structural findings in the early stage of the disease may change the traditional view that degenerative changes in the brain motor systems occur slowly following SCI [Freund et al., 2007; Hains et al., 2003]. Meanwhile, our findings may provide a forceful imaging basis for the early clinical intervention.

In the study of the functional recovery in patients with SCI, one important question that remains largely unanswered is when one selects time points to study recovery and how long post-injury is likely to optimize the ability to understand recovery curves. Previous animal studies have shown that complete thoracic transection of the spinal cord can immediately (within 1 h) change the functional state of large cortical networks [Aguilar et al., 2010]. Therefore, in theory at least, it is better to study reorganization of the brain as early as possible because it could lead to a better understanding of the pathophysiological mechanisms of long-term cortical reorganization. However, the first few days of the acute stage following SCI are usually accompanied by spinal shock, in which the person's reflexes do not work [Boland et al., 2011]. During this stage (within 1 week), it is difficult to determine an exact illness evaluation and prognosis, because some function beyond what is currently being seen may occur later. At this acute stage, doctors may need to operate to remove the fractured fragments that are compressing the spine and stabilize the spine [Dvorak et al., 2015]. Once the acute phase is over and the person has been stabilized (~2 weeks after injury), patients enters the rehabilitation stage of treatment. Treatment during this phase has the goal of returning as much function as possible to the person. Although neurological improvement following SCI may

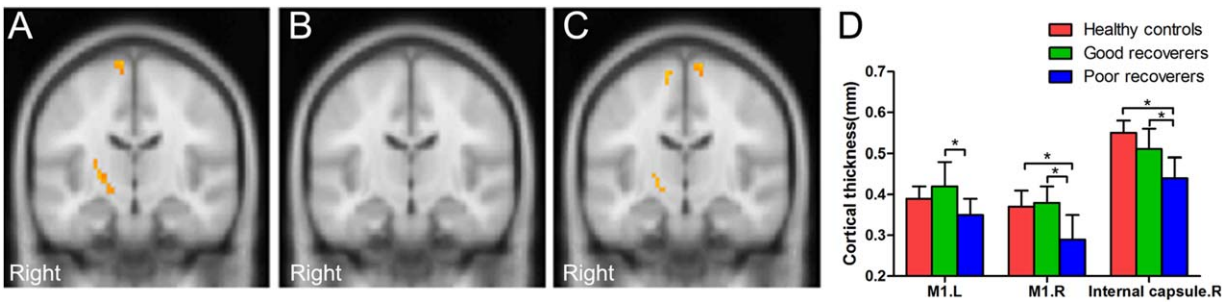

Figure 3.

White matter fractional anisotropy differences among the three groups of participants. (**A**) Smaller fractional anisotropy in the right primary motor cortex (M1) and posterior limb of the internal capsule in poor recoverers relative to healthy controls. (**B**) No significant difference of fractional anisotropy in good recoverers relative to healthy controls. (**C**) Smaller fractional anisotropy in the bilateral M1 and posterior limb of the internal capsule in poor recoverers relative to good recoverers. (**D**) Bar graph showing the fractional anisotropy values of the three groups at the peak of the abnormal regions. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE III. Difference in white matter fractional anisotropy among patients with SCI with good motor recovery, poor motor recovery and healthy controls

Anatomical region	MNI coordinate x	y	z	Voxel size	Peak *t* value
Poor recoverers < healthy controls					
Right M1	−11	−19	65	21	−4.26
Right internal capsule	−21	−19	1	30	−4.33
Poor recoverers < good recoverers					
Right M1	5	−27	70	29	−4.37
Left M1	28	−19	61	25	−4.28
Right internal capsule	−21	−18	−3	19	−4.15

Abbreviation: SCI, spinal cord injury; M1, primary motor cortex; MNI, Montreal Neurological Institute. $P < 0.05$, corrected for multiple comparisons with family-wise error correction.

continue to occur beyond 1 year after injury [Kirshblum et al., 2004], most neurological recovery is thought to occur within the first 3 months after injury [Fawcett et al., 2007; Steeves et al., 2011]. Pollard and Apple [2003] have noted that >70% of neurological recovery occurs before discharge from rehabilitation. Therefore, the time points selected by the current study (range: 2–12 weeks, median: 4 weeks) seem to be a good choice to study the motor recovery in patients with SCI. Future longitudinal studies that enroll patients from 2 weeks after SCI might be appropriate, and provide further insights into the mechanisms of brain structural and functional reorganization and its effect on the extent of motor recovery.

Our study suggests that in patients with SCI, the extent of motor recovery in the 6 months following study enrolment is significantly negatively correlated with the time elapsed since injury. This finding is in line with a recent clinical study [Dvorak et al., 2015] and further supports the need to start rehabilitation in patients with SCI as soon as possible. In the current study, the clinical baseline of injury severity between the two subgroups differed markedly. Most patients in the good recovery group showed incomplete SCI, while most patients in the poor recovery group showed complete SCI. This finding is consistent with the subsequent finding that the extent of motor recovery is significantly negatively correlated with baseline neurological impairment. Previous clinical studies also showed that the baseline neurological impairment could be considered as a good prognostic indicator in the acute stage of SCI [Coleman and Geisler, 2004]. The age of the patient, considered to be a good prognostic indicator in the acute stage of SCI [Gwak et al., 2004; Wilson et al., 2014], was not associated with improvement of the motor deficit in our patients, which is in agreement with other studies [Furlan et al., 2010; New and Epi, 2007]. The previous studies suggested that medication and depression have an influence on motor recovery after central nervous system injury [Flaster et al., 2013]. However, in this study, we did not observe these potential confounding factors, given that there was no conclusive evidence in clinical studies to show the exact relationship between these potential confounding factors and outcome of SCI. Future clinical studies using large samples should demonstrate the potential relationship of medication and depression with functional recovery.

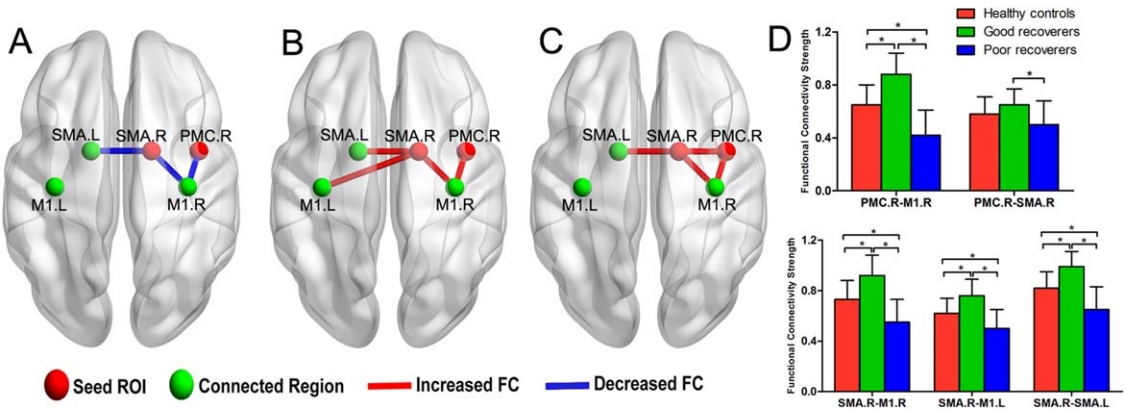

Figure 4.

Resting state functional connectivity differences among the three groups of participants. (**A**) Decreased functional connectivity in poor recoverers relative to healthy controls. (**B**) Increased functional connectivity in good recoverers relative to healthy controls. (**C**) Increased functional connectivity in good recoverers relative to poor recoverers. (**D**) Bar graph showing the fractional strength of the three groups at the peak of the abnormal regions. Abbreviation: SMA, supplementary motor area; M1, primary motor cortex; PMC, premotor cortex; FC, functional connectivity. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE IV. Difference in functional connectivity among patients with SCI with good motor recovery, poor motor recovery and healthy controls

Seed ROI	Connected region	MNI coordinate x	y	z	Voxel Size	Peak *t* value
Poor recoverers < healthy controls						
Right SMA	Right M1	27	−24	63	35	−3.91
	Left SMA	−3	0	63	29	−3.16
Right premotor cortex	Right M1	39	−18	59	41	−4.06
Good recoverers > healthy controls						
Right SMA	Right M1	36	−12	57	32	4.12
	Left M1	−21	−13	62	23	3.25
	Left SMA	−8	−12	63	30	3.86
Right premotor cortex	Right M1	52	−11	48	43	4.76
Good recoverers > poor recoverers						
Right SMA	Right M1	36	−12	55	46	4.53
	Left SMA	−8	−9	63	41	4.57
Right premotor cortex	Right M1	52	−12	48	55	5.29
	Right SMA	7	−11	63	23	3.25

Abbreviation: SCI, spinal cord injury; BA, Broadmann area; M1, primary motor cortex; SMA, supplementary motor area; MNI, Montreal Neurological Institute. $P < 0.05$, corrected for multiple comparisons with family-wise error correction.

Morphological Findings

There is evidence in patients with chronic SCI that cortical gray matter and white matter undergo atrophic changes in the sensorimotor system [Freund et al., 2011; Freund et al., 2012; Wrigley et al., 2009]. One recent study reported that significant structural atrophy of the spine and brain occurs in the first few months after SCI, and structural reorganization progresses with a specific spatial and temporal pattern [Freund et al., 2013]. In line with this early stage study, we also showed that patients with SCI had spinal cord atrophy, cortical atrophy and white matter microstructural abnormalities in the early stage of the disease. Furthermore, our study showed that poor recoverers had more serious and widespread structural damage of the spine and brain than good recoverers had. Thus, it seems that structural integrity of the spine and brain directly affects motor recovery in the early stage of SCI. Although the exact mechanisms for structural impairment of the brain motor systems following SCI remain unclear, it is possible that retrograde degeneration accounts for this finding [Guleria et al., 2008].

One of the most interesting outcomes of our study was that significantly decreased cortical thickness was found in the right SMA and premotor cortex in the poor recoverers more than that in the good recoverers. In particular, the cortical thickness in the right SMA was positively

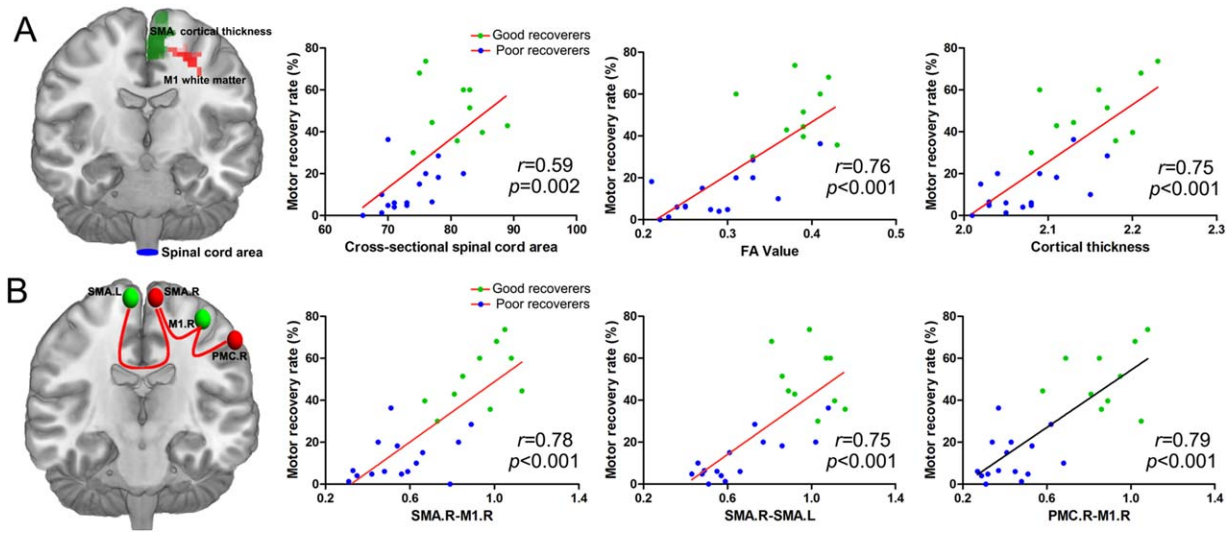

Figure 5.

Correlations between structural and functional reorganization and the recovery rate of motor function in all patients with SCI. (**A**) Cross-sectional spinal cord areas, fractional anisotropy (FA) values in the right primary motor cortex (M1) and the cortical thickness in the right SMA were positively correlated with the motor recovery rate. (**B**) The functional connectivity strength between the right SMA and the left SMA and right M1, and between the right premotor cortex (PMC) and the right M1 were positively correlated with the motor recovery rate in all patients with SCI. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE V. Multivariate multiple regression analysis showing prognostic predictors of the extent of motor recovery at 6 months in patients with SCI

Variables	Regression coefficient	SE	*t*	*P*
Cortical thickness in the right SMA	2.63	1.32	1.92	0.001
FC strength between the right SMA and right M1	1.08	0.75	1.24	0.03
FC strength between the right premotor cortex and right M1	1.96	0.63	1.78	0.01
Constant	−0.85			

Abbreviation: SCI, spinal cord injury; M1, primary motor cortex; SMA, supplementary motor area; FC, functional connectivity; SE, standard error.

correlated with the motor recovery rate in all patients. To the best of our knowledge, no previous structural MRI study has directly located the structural atrophy of these two regions during the early stage of SCI, however, it was captured in our study for the first time. These findings highlight the importance of the SMA and premotor cortex in the motor recovery of SCI. The importance of the SMA in motor recovery is supported by studies showing its role in the motor system, through efferent nerves to the primary motor cortex [Strick, 1988] and directly to the spinal cord [Biber et al., 1978]. The premotor cortex projects directly to the spinal cord and plays a role in planning movement, in the spatial and sensory guidance of movement, and in using abstract rules to perform specific tasks [Busan et al., 2009; Pastor-Bernier et al., 2012; Weinrich et al., 1984]. In other central nervous system injury, such as stroke, the SMA and premotor cortex also play an important role in the motor recovery of patients [Pantano et al., 1996; Riecker et al., 2010].

Functional Findings

There is increasing recent evidence in humans that the adult brain is capable of extensive functional reorganization following central nervous system injury [Agosta et al., 2011; Chen et al., 2002; Fridman et al., 2004]. One of the main functional reorganizations in patients with stroke and traumatic brain injury is recruitment of additional motor areas (SMA and premotor cortex) to compensate for reduced capacity of the primary sensorimotor cortex to generate sufficient motor output [Lotze et al., 2006; Wang et al., 2010]. These functional reorganizations are believed to play an important role in motor recovery and may be a hallmark of recovery from brain trauma (Grefkes and Fink, 2011. Our findings showed that patients with good and poor motor recovery had distinct functional reorganization patterns in these two areas. Increased functional connectivity of the primary motor cortex with the SMA and premotor cortex occurred in patients with good motor recovery, but not in those with poor motor recovery. Overall, it may reflect a compensatory role of the over-recruited neural resources for the recovery of SCI. These findings are consistent with a previous positron emission tomography study, which showed that the premotor cortex was the prominent contributor to motor recovery at 3–4 months post-SCI [Nishimura et al., 2007].

To explore further the compensatory role of brain functional reorganization, we investigated the relationships between motor recovery rate and functional connectivity measures. Positive correlations were found between the rate of motor recovery and functional connectivity between the primary motor cortex and SMA and premotor cortex. This finding emphasizes that increased functional connectivity between the primary motor cortex and higher order secondary motor areas (SMA and premotor cortex) plays a vital role in the motor recovery of SCI. It is, therefore, suggested that methods that enhance cortical functional connectivity with the higher order motor areas might be useful for further promoting recovery after SCI.

Clinical Implications

Our work provides useful information on brain reorganization associated with motor recovery in the early stage of SCI. The most striking finding of our study was that the extent of structural damage to the spine and brain was associated with the motor recovery rate in patients with SCI. Notably, this finding indicated that structural atrophy of the spinal cord and brain motor cortex was predictive of slow or poor recovery, whereas the better the structural integrity of the spinal cord and brain, the faster and better the motor recovery. Thus, preserved structural integrity of the brain motor system above the injury site appears to be critical for good functional outcome after SCI, and could therefore be a primary target for therapeutic repair strategies.

Our findings may also explain why current therapeutic approaches for SCI have limited effectiveness and are far from satisfactory. Over the past decade, a variety of experimental therapies has emerged to promote axon regeneration at the lesion site in the hope of promoting functional recovery [Thuret et al., 2006], including the application of neurotrophic factors [Kwon et al., 2002], drug therapy [Baptiste and Fehlings, 2006], and cell-based therapies [Guest et al., 2005]. These therapeutic approaches to reduce disability following SCI generally assume intact brain motor system function, that is, the cell bodies of damaged axons remain alive. However, the current findings showed that SCI could cause significant structural damage in the brain motor systems, which may indicate damage to the cell bodies in the brain motor system. If the cell body is damaged, the axon will die as well [Carlson et al., 2000] and therapeutic interventions to promote axon

regeneration would be futile. In general, loss of cortical projection neurons may contribute to the lack of functional recovery and limit the gains that can be achieved with exogenous treatment. That is the reason why current therapeutic approaches promoting regeneration of the injured spinal cord have limited effectiveness. Thus, future interventional studies should target both the injured spinal cord and brain [Nardone et al., 2013b]. It is also reasonable to speculate that therapeutic repair strategies aimed at modulating or reversing structural reorganization of the spine and brain may have therapeutic potential [Choe et al., 2013; Dobkin et al., 2007]. Given that structural changes occurred early, as revealed by the current study, these interventions should ideally be used in the early stages after SCI.

From a clinical point of view, establishing whether measurable early alterations in structural or functional reorganization affect final functional outcome would be of importance for early diagnosis, prediction and treatment selection. A previous study using positron emission tomography has shown that motor recovery is associated with metabolic improvement in the primary motor cortex and premotor cortex in macaque monkeys in the first 3 months of SCI [Nishimura et al., 2007]. Structural atrophy of the corticospinal axons and sensorimotor cortical areas remote from the site of SCI also could be considered as neuroimaging biomarkers for interventional studies [Freund et al., 2013]. Similarly, we observed a significant correlation between motor recovery at 6 months after admission and structural and functional reorganization of the spine and brain. The best predictors included the cortical thickness in the right SMA, and functional connectivity strength among the primary motor cortex, SMA and premotor cortex. Our findings could be meaningful for the prognostic evaluation of SCI. If regression of SMA atrophy or increased functional connectivity between the primary motor cortex and higher order secondary motor areas observed in the early stage of SCI, either spontaneous or therapy-induced, the motor recovery is potentially reversible as well. These findings might be valuable for optimizing the therapeutic strategies by stratification of patients for selection of drug or rehabilitation strategies and to assess treatment effects by monitoring the dynamic brain structural and functional changes during the course of treatment [Endo et al., 2009; Freund et al., 2013].

Limitations

The current study had some limitations. First, because this was a preliminary study, our results were limited to a small sample of patients with SCI with a heterogeneous level and degree of injury. Future studies that focus on different levels and degrees of SCI may help to further our understanding of SCI-related structural and functional reorganization. Second, imaging data at 6 months follow-up were not acquired because of budget limitations. We could not fully assess the dynamic changes in the patterns of structural and functional reorganization following SCI. Third, this study focused on motor function recovery in patients with SCI. Whether the cortical reorganization after SCI contributed to maladaptive changes such as neuropathic pain and mood disorders [Mole et al., 2014; Nicotra et al., 2006] remains to be determined. Theoretically, cortical reorganization following SCI is neither good nor bad [Moxon et al., 2014]. The good side of cortical reorganization can contribute to functional recovery, just as the current study found, but its bad side can be maladaptive and lead to phantom sensation and neuropathic pain [Gustin et al., 2010; Makin et al., 2013]. It is therefore critical for future studies to explore the phenomenology and mechanisms of cortical reorganization to develop and optimize cost-effective therapies to maximize functional recovery while minimizing neuropathic pain [Engineer et al., 2011]. Finally, given that this was a preliminary study to explore the role of brain structural and functional reorganization in motor recovery, we only used conventional voxel-based analysis to explore abnormalities in the brain. Future studies using the tract-based spatial statistics and tractographic approach will be necessary to gain further insight into the microstructural abnormalities in the white matter of patients with SCI.

CONCLUSIONS

To the best of our knowledge, this is the first study combining structural and functional imaging protocols to explore the relationship between recovery of motor function and reorganization of the spine and brain. Our study demonstrated that patients with good and poor motor recovery showed distinct functional reorganization patterns. Structural atrophy of the spinal cord and brain motor cortex was predictive of slow or poor recovery, whereas the better the structural integrity of the spinal cord and brain, the faster and better the motor recovery. Furthermore, increased functional connectivity between the primary motor cortex and higher order secondary motor areas play a vital role in the motor recovery of SCI. Consequently, our results indicate that structural and functional reorganization of the spine and brain directly affects motor recovery in the early stage of SCI, and future novel interventions should target both the injured spinal cord and brain. Meanwhile, the strong correlations between the structural and functional changes and the rate of motor recovery indicate that multimodal imaging of the spine and brain has the potential to predict motor recovery in the early stage of SCI. Future studies using a large study population to differentiate the level and degree of SCI, and performing MRI for a longer time (6 or 12 months) will be important to further our understanding of the patterns of SCI-related structural and functional reorganization.

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