ALTERATIONS OF RESTING-STATE REGIONAL AND NETWORK-LEVEL NEURAL FUNCTION AFTER ACUTE SPINAL CORD INJURY

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Abstract—*Object:* The purpose of this study was to investigate functional alterations of the brain in the early stage of spinal cord injury (SCI) and further investigate how these functional alterations relate to SCI patients' sensorimotor functions.

Methods: Twenty-five patients with SCI and 25 matched healthy controls underwent imaging by using resting-state functional magnetic resonance imaging (fMRI). The amplitude of low-frequency fluctuations (ALFF) were used to characterize regional neural function, and the seed-based functional connectivity (FC) was used to evaluate the functional integration of the brain network.

Results: Compared to healthy controls, patients with SCI showed decreased ALFF in the bilateral primary sensorimotor cortex, and increased ALFF in the bilateral cerebellum and right orbitofrontal cortex (OFC). The ALFF value in the left cerebellum was negatively correlated with the clinical total motor score in patients with SCI. Furthermore, SCI patients mainly showed decreased inter-hemispheric FC between the bilateral primary sensorimotor cortex, as well as increased intra-hemispheric FC within the motor network, including the primary sensorimotor cortex, premotor cortex, supplementary motor area (SMA), thalamus and cerebellum. Subsequent correlation analyses revealed that increased FC within the primary sensorimotor cortex, SMA, and cerebellum negatively correlated with the total American Spinal Cord Injury Association (ASIA) motor score.

Conclusions: Our findings provide evidence that SCI can induce significant regional and network-level functional alterations in the early stage of the disease. We hypothesized these alterations may be an adaptive phenomenon following SCI, reflecting a compensatory mechanism during the early stage of SCI. © 2014 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: spinal cord injury, functional MRI, resting state, functional organization.

INTRODUCTION

Spinal cord injury (SCI) is a common neurological condition characterized by loss of sensory and motor below the spinal lesion (Dietz and Curt, 2006). Although various therapies have been developed for restoring motor function in SCI patients, current treatments for SCI have limited effectiveness and are far from satisfactory (Bradbury and McMahon, 2006; Dietz and Curt, 2006). The lack of insight into the neuropathology of SCI is holding back improvements in SCI therapies. In recent years, more and more studies in humans have shown that the adult brain is capable of extensive reorganization following the peripheral and central nervous system injury (Chen et al., 2002; Fridman et al., 2004; Agosta et al., 2011). Similarly, loss of sensory and motor function results in functional brain reorganization in patients with SCI, and these reorganizations may play a vital role during the recovery of motor function (Jurkiewicz et al., 2007; Kokotilo et al., 2009; Nardone et al., 2013). However, specific functional changes in the human brain following SCI remain poorly understood.

To our knowledge, only few functional neuroimaging have, to date, investigated the pattern of functional brain reorganization in SCI patients (Curt et al., 2002; Cramer et al., 2005; Cermik et al., 2006; Freund et al., 2011; Lundell et al., 2011). However, findings of these studies have been inconsistent, partly because of potential confounders associated with different rehabilitative strategies, extensive disease duration, and diverse sensorimotor tasks of functional magnetic resonance imaging (fMRI). Notably, most of these studies explored functional reorganization in chronic SCI patients with an extensive disease duration (1–30 years), relatively few attempts have been made to investigate SCI-related functional changes in the early course of diseases. Given the important role of early functional reorganization in the

recovery process, studies of early stage of SCI appear more meaningful than studies of chronic patients.

Resting-state fMRI is a recently developed fMRI method which has been shown to be a promising approach to assess the functional alterations. Low-frequency (0.01–0.08 Hz) fluctuations of the blood oxygenation level-dependent (BOLD) signal in resting-state fMRI are thought to be physiologically meaningful and reflect spontaneous neural activity (Shmuel and Leopold, 2008). This technique has been widely used in a range of neuropsychiatric diseases, such as Alzheimer's disease (Sorg et al., 2007), multiple sclerosis (Filippi et al., 2013), and depression (Lui et al., 2011). All of these studies suggested that resting-state fMRI is a promising approach to study neuropsychiatric disease. However, to our knowledge, no studies have reported SCI-related functional changes using resting-state fMRI.

In this study, we used resting-state fMRI to explore the regional and network level brain functional changes in the early stage of SCI. For regional brain changes, we calculated the amplitude of low-frequency fluctuations (ALFF) of the resting-state fMRI data. By calculating the square root of the power spectrum of BOLD signals in a low-frequency range (usually 0.01–0.08 Hz), ALFF are believed to reflect regional spontaneous cerebral neural activity (Zang et al., 2007). For network level brain changes, we calculated the resting-state functional connectivity (FC) among brain regions using a seed-based approach. The FC has emerged as a promising approach to investigate the functional integration of the brain. Based on the previous studies, we hypothesized (1) that patients with SCI would show regional and network level neural functional alterations during the resting-state mainly in the sensorimotor system, and (2) that these alterations of intrinsic neural activity would correlate with the clinical sensorimotor scores of SCI patients.

EXPERIMENTAL PROCEDURES

Participants

A total of 50 right-handed participants were recruited in this study from the Department of Rehabilitation of the Southwest Hospital, including 25 SCI patients and 25 healthy controls. The medical ethics committee of the Third Military Medical University (Chongqing, China) approved the current study and all participants gave written informed consent to the participation according to the Declaration of Helsinki. The extent of motor and sensory impairment was assessed by a qualified clinician (Dr. H. Liu) using the classification scale of the American Spinal Cord Injury Association (ASIA), including the ASIA-Impairment-Scale and the ASIA Motor Score plus ASIA Sensory Scores (Marino et al., 2003). A full neurological examination was performed in order to exclude accompanying neurological disorders of the peripheral and central nervous systems. No patient suffered from a psychiatric disorder or had a history of traumatic brain injury. The healthy controls were free of neurological or psychiatric diseases as assessed by a clinician (Dr. R. Yan). None of them received psychotropic medication. Clinical and demographic data from all participants are shown in Table 1.

MRI data acquisition

Images were obtained using a 3.0-T MRI system (TIM Trio, Siemens, Erlangen, Germany) with an eight-channel phased-array head coil. Resting-state functional images were acquired using an echo-planar-imaging (EPI) sequence with the following parameters: 36 axial slices with a slice thickness = 4 mm and no slice gap, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, field of view (FOV) = 256×256 mm^2, data matrix = 64×64, resulting in a voxel size of $4 \times 4 \times 4$ mm^3, total volumes = 240. Participants were instructed simply to remain relaxed with their eyes closed. For each participant, another high-resolution structural T1-weighted anatomical sequence was scanned in a sagittal orientation using a Three-dimensional magnetization-prepared rapid gradient-echo (3D MP-RAGE) with the following parameters: TR = 1900 ms, TE = 2.52 ms, FA = 15°, slice thickness = 1 mm, data matrix = 256×256, isotropic voxel $1 \times 1 \times 1$ mm^3.

Functional image processing

Resting-state fMRI data preprocessing and statistical analyses were performed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 2010 (Math Works, Natick, MA, USA). To avoid manipulation error confounds and standardize the process, we used the batch-processing tool data processing assistant for resting-state fMRI (DPARSF (data processing assistant for resting-state); http://www.rfmri.org/DPARSF) (Chao-Gan and Yu-Feng, 2010). For the resting-state fMRI data of each subject, the first 10 volumes of functional images were discarded to allow for steady-state magnetization and stabilization of participant status. EPI images were slice-timing corrected to the middle slice acquired in time, and realigned to correct for head motion with a mean volume created. Next, all functional data were normalized to the MNI space by applying transformation parameters that were

Table 1. Demographic and clinical characters of the study sample

Characteristics	SCI patients	Controls	p Value
Participants	25	25	–
Gender (male: female)	13:12	13:12	1
Handedness (right: left)	25:0	25:0	1
Mean age (years)	36.9 ± 5.8	36.2 ± 8.3	0.87
Educational level (years)	12.1 ± 3.5	13.5 ± 3.8	0.58
Mean disease duration (weeks)	9.3 ± 2.9	–	–
ASIA total motor score, mean	48.9 ± 26.3	100 ± 0	< 0.001
ASIA light touch sensory score, mean	46.9 ± 32.1	112 ± 0	< 0.001
ASIA pinprick sensory score, mean	45.3 ± 29.9	112 ± 0	< 0.001

SCI: spinal cord injury; ASIA: American Spinal Cord Injury Association.