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Original Research

Regulation of "Right Ankle Dorsiflexion" Motor Imagery on Brain Function of Spinal Cord Injury: A FOCA-Based Prospective Study

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Abstract

Background: Motor dysfunction is the main functional disability after spinal cord injury (SCI), seriously affecting the life and work of patients. In addition to spinal cord damage, the brain undergoes structural and functional plastic changes. This study explored brain function remodeling in patients with SCI and the effect of right ankle dorsiflexion motor imagery task on brain function. **Methods**: This prospective study enrolled 11 patients with SCI and dyskinesia of the right lower limb and 12 healthy subjects at the General Hospital of Western Theater Command PLA (January 2015 to December 2016). They underwent functional magnetic resonance imaging (fMRI) in the resting state and the "right ankle dorsiflexion" motor imagery task state. Four-dimensional (spatiotemporal) concordance (FOCA) of local neuronal activity was used for fMRI image analysis. The differences between SCI patients and healthy subjects were compared using the two-sample *t*-test. **Results**: In the resting state, compared with healthy subjects, patients with SCI showed decreased FOCA in the left putamen, right caudate nucleus, and right superior occipital gyrus and increased FOCA in the left precentral gyrus. In the right ankle dorsiflexion motor imagery task state, FOCAs in the right inferior temporal gyrus and left inferior parietal lobule were decreased in patients with SCI. **Conclusions**: After SCI, a series of changes in the structure and function of the brain occur. Research on brain plasticity after SCI might help explore the central mechanisms underlying functional recovery after treatments, providing more therapeutic strategies for SCI.

Keywords: spinal cord injury; functional magnetic resonance imaging; brain function regulation; motor imagery

1. Introduction

Traumatic spinal cord injury (SCI) results from damage to the spinal cord due to physical trauma, leading to transient or permanent loss of motor, sensory, and autonomic functions [1–3]. The common causes of SCI include motor vehicle accidents, falls, gunshot wounds, other forms of violence, and sports and recreational activities [1–3]. The annual incidence of SCI varies from 15 to 52.5 cases per million persons [3].

Spinal cord injury causes severe central nervous system lesions that can affect motor and sensory functions below the site of injury. In addition to the local injury to the spinal cord, SCI results in structural and functional plastic changes in the brain [4–7], such as atrophy and reduced volume of the brain sensorimotor cortex, sensorimotor-related white matter, corticospinal tracts [8–10], and sensorimotor-related cortexes [11–18].

Motor imagery is an active cognitive activity of the brain [19,20]. It is an active process in which an individual repeats an imaginary action according to the memory of the movement but without producing the actual physical movement. It is an active process in which an action is repeated internally without producing movement output. Motor imagery could improve the functions of non-paralyzed muscles in patients with complete SCI and the activities of daily living in patients with incomplete SCI [19,21,22]. Combined with other rehabilitation treatments, it can promote the recovery of motor function after SCI [23–25], but the mechanism remains unclear.

Therefore, the present study aimed to use functional magnetic resonance imaging (fMRI) and four-dimensional (spatiotemporal) consistency of local neural activities (FOCA) analysis to explore the mechanism of local brain function remodeling after SCI and the potential regulatory mechanisms of the motor-associated brain default network.

Table 1. Clinical data for patients with SCI.

Subject	Age (years)	Gender	Duration of education (years)	Duration of disease (months)	Injury level	AIS	Sensory scores	Motor scores
1	44	M	8	8	C3	D	116	43
2	29	M	9	7	C4	D	124	20
3	40	M	7	6	C5	B	60	20
4	18	F	12	10	T12	D	182	96
5	27	F	11	48	L2	C	178	69
6	42	M	9	150	L1	D	172	79
7	49	M	12	4	C3	D	116	79
8	32	M	12	29	T10	D	176	81
9	29	M	12	5	T10	A	144	50
10	30	M	6	5	T7	A	120	50
11	39	M	15	76	S1	D	220	86

SCI, spinal cord injury; AIS, American Spinal Injury Association Impairment Scale; M, male; F, female.

The results could provide a better understanding of the changes that occur in the brain after SCI and help guide the rehabilitation approaches.

2. Materials and Methods

2.1 Patient and Public Involvement

Patients and the public were not involved in the design, implementation, analysis, or dissemination of this research. The results will be disseminated to the public through publication in this journal.

2.2 Study Design and Participants

This prospective study enrolled patients with dyskinesia of the right lower limb after SCI and admitted to the Rehabilitation Department of The General Hospital of Western Theater Command PLA from January 2015 to December 2016. The study was approved by the Institutional Review Board of Western Theater Command PLA. All participants provided written informed consent prior to any study procedure.

11 patients with SCI were enrolled in this study. According to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) [26], 2 patients were labeled as grade A, 1 as grade B, 1 as grade C, and 7 as grade D. Muscle tests confirmed the presence of right ankle flexion dysfunction in all cases. The inclusion criteria of patients with spinal cord injury include: (1) age 18–50 years old, (2) years of total education $\geq$6 years, (3) right-handed, (4) Inpatient who can cooperate with the study. All patients received regular follow-up and rehabilitation therapy. Table 1 provides the details of SCI patients who participated in the study.

Healthy individuals were enrolled. The inclusion criteria were: (1) 18–55 years of age, (2) years of total education, (3) right-handed, (4) physical examination with health results, (5) normal sleep, (6) moderate body weight, (7) regular diet, (8) no addiction to tobacco, alcohol, tea, or coffee, or (9) no acute or chronic pain (including dysmenorrhea) in the past 3 months.

The following individuals were excluded from the study: (1) Based on medical history, routine head MRI and neurological examinations, individuals with craniocerebral injury and any neurological diseases were excluded, (2) individual with cognitive impairment, aphasia, inability to understand instructions, (3) individual with serious heart, liver, and kidney diseases.

2.3 Preparation before Scanning

The day before fMRI, the participants were trained on the precautions and scanning procedures before MRI. Foods that affects sleep were prohibited 24 h before scanning, such as drinks with alcohol, strong tea, and coffee. The participants were asked to sleep on time to ensure adequate sleep and a good mood. The MRI procedures were explained in detail. The participants were told to keep their heads still, close their eyes, breathe evenly, and maintain a stable state during the scan. Moreover, the participants had to try not to engage in thinking activities deliberately, avoid going to sleep, and not swallow frequently. The cooperation of the motor imagery task during MRI was detailed. After hearing the task instructions, the participants were asked to open their eyes and follow the task instructions on the screen of the visual presentation system to imagine the action of "right ankle dorsiflexion" in the form of kinesthetic motor imagery. The motor imagery was performed at a frequency the participants could adapt to. The participants were specifically told not to contract muscles and move the right ankle joint when performing the motor imagery tasks and keep their heads still. Moreover, the participants had to try this task repeatedly to ensure they could complete it as required. During the task state examination, the participants imagined the action of "right ankle dorsiflexion" according to the task instruction, and there was no muscle contraction or right ankle joint movement. Before starting the scan, the KVIQ-10, a simplified version of the Kinesthetic and Visual Imagery Questionnaire, was used to assess the participants' motor imagery ability [27]. The kinesthetic and visual imagery abilities were rated as five grades (0–5 points). The highest score was 5 points, indicating being as intense

Table 2. Characteristics of the participants.

Characteristic	SCI patients (n = 11)	Healthy control (n = 12)	*p*
Age, years, mean ± SD	34.5 ± 9.1	29.7 ± 5.6	0.073
Sex (male/female)	9/2	8/4	0.640
Duration of education, years, mean ± SD	10.3 ± 2.7	12.0 ± 3.0	0.161
KVIQ-10 score, mean ± SD	32.7 ± 10.6	31.6 ± 8.6	0.778

SCI, spinal cord injury; KVIQ-10, simplified version of Kinesthetic and Visual Imagery Questionnaire.

Table 3. Brain regions with changes in FOCA under the resting state between SCI patients and healthy individuals.

Brain region	BA partition	Number of voxels	Peak MNI coordinate (mm)			t (peak) [1]
			x	y	z	
Left putamen	48	109 [2]	–24	9	12	–3.118
Right caudate nucleus	NA	121	21	18	12	–3.353
Right superior occipital gyrus	NA	184	24	–102	9	–3.857
Left precentral gyrus	6	143 [2]	–33	–12	66	3.395

FOCA, Four-dimensional (spatiotemporal) concordance; MNI, Montreal Neurological Institute; BA, Brodmann area.

[1] t-value (peak) of the *t*-test. A negative value means that compared with healthy individuals, the FOCA of patients with SCI is lower. A positive value means that compared with healthy individuals, the FOCA of patients with SCI is higher. The higher absolute value of the t-value indicates that the difference in the mean value between the two samples is greater.

[2] represents this point on the MNI coordinate (–24, 9, 12). The difference is 3.118, located in the left putamen (BA is 48), and one cluster composed of 109 voxels; the threshold is set to $p < 0.01$ (uncorrected), cluster $>$10.

as executing the action, and the image as clear as seeing; the lowest score was 1 point: no image and no sensation. In the KVIQ-10, kinesthetic imagery and visual imagery, each had 25 points, and the total score was 50 points. The higher the score, the better the motor imagery ability of the patients.

2.4 fMRI Scan

The participants were supine on the examination bed with the head fixed in the head support and kept in a comfortable lying position. Scanning was performed using a Signa MR 750 3.0 T MRI system and a Discovery 750 3.0 T MR system (GE Healthcare, Waukesha, WI, USA). An 8-channel head standard coil was used for collection. First, the conventional three-dimensional planar location scan of the structure image was performed, and the 3D-spoiled gradient echo sequence was used to perform the transverse scan of the structure image. The location was performed according to the connection line of the anterior and posterior commissures. Then, 156 layers were scanned, including the whole brain from the calvarium to the basicranial region.

After the location scan, the participants closed their eyes, relaxed, breathed calmly, kept their minds clear, and avoided deliberately engaging in thinking activities and going to sleep; then, scanning under the resting state was started. The scan time of the resting state was 8 m and 30 s. Signal image acquisition adopted echo-planar imaging pulse (EPI) sequence, with a layer thickness of 4 mm, 35 layers in total, time of repetition (TR) = 2000 ms, time of echo (TE) = 30 ms, flip angle (FA) 90 °C, matrix 64 × 64, and field of view (FOV) 240 × 240 mm.

After the resting-state scan, the task-state scan was started. The task implementation adopted a block design, including task periods (T) and resting periods (R). There was a 10-s blank scan before the actual scan was started, and then the task block scan was entered. There were 12 blocks in the task period and 11 in the resting period. Each block lasted for 20 s; there was a 10-s blank scan before each scan, and the scan time for the entire task state was 470 s. The image acquisition still adopted the EPI sequence, with a layer thickness of 4 mm, and the overlap between the layers was 0.4 mm; there were a total of 35 layers, and the interlayer scanning was performed; TR = 2000 ms, TE = 30 ms, FA 90 °C, matrix 64 × 64, FOV 240 × 240 mm, and horizontal resolution 3.75 × 3.75 mm. During the task-state scan, the scanner asked the participants to open their eyes. The task instruction was displayed on the screen of the visual presentation system (fMRI Experiment System, Avotec, Inc., Stuart, FL, USA): "right ankle dorsiflexion"-"+"-"right ankle dorsiflexion"-"+"-"right ankle dorsiflexion"-"+"... until the end. According to the task instruction, the patient performed the imaginary "right ankle dorsiflexion" action through kinesthetic motor imagery and had to avoid muscle contraction and right ankle joint movement. The motor imagery "right ankle dorsiflexion" task alternated with resting (stop imagining). The motor imagery "right ankle dorsiflexion" lasted for 20 s, rested for 20 s, and then motor imagery was continued for 20 s, alternating for 12 motor imageries and 11 rests. Before starting the first motor imagery, there was a 10-s blank scan. A researcher supervised the motor imagery task to determine whether the participants had visible muscle contraction or ankle joint movement.

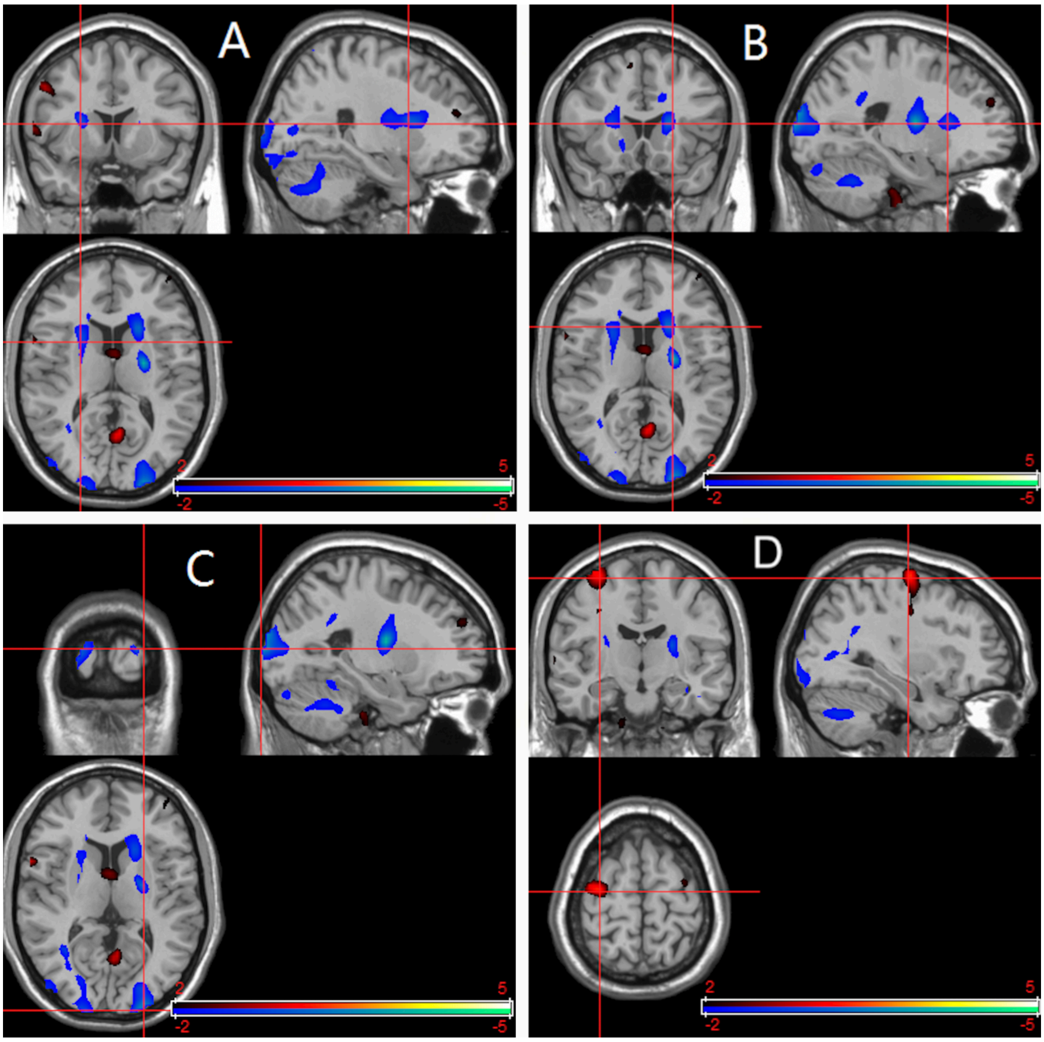

Fig. 1. Brain regions with changes in FOCA under the resting state between patients with SCI and healthy individuals. The intersections of the red lines in (A), (B), and (C) are the brain region with decreased FOCA value in SCI patients compared with healthy individuals. (A), (B), and (C) represent the left putamen, right caudate nucleus, and right superior occipital gyrus. Red represents increased spatiotemporal consistency of local brain regions, and blue represents decreased spatiotemporal consistency. The intersections of the red lines in (D) are the left precentral gyrus with increased FOCA value in SCI patients compared with healthy individuals. Red represents increased spatiotemporal consistency of local brain regions, and blue represents decreased spatiotemporal consistency. SCI, spinal cord injury; FOCA, Four-dimensional (spatiotemporal) concordance.

2.5 MRI Image Processing

MRI image processing and analysis were conducted using the NIT v1.1 software (Neuroscience Information Toolbox NIT.1.1, Key Laboratory for NeuroInformation of Ministry of Education, University of Electronic Science and Technology of China, Chengdu, China). The SPM8 (Statistical Parametric Map 8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) software was used to preprocess the data. The preprocessing process included image format conversion, removal of data in the first 10 s, time point correction, head movement correction, spatial standardization, removal of linear drift, removal of interference signals, removal of effects of linear trends (or low-frequency drift), and the head movement. Brain white matter and cerebrospinal fluid signals were removed. The time point correction used time phase difference caused by eliminating the interval scanning so that the acquisition time of each layer in the TR was consistent. Each scanned image frame was aligned with the first frame image in the entire scanning sequence according to a certain algorithm, and head movement correction was made.

2.6 Statistical Analysis

The data were analyzed using SPSS 17.0 (IBM Corp., Chicago, IL, USA). The continuous data were tested for normality and homogeneity of variance. If the continuous data met the normal distribution and homogeneity of variance, the data were presented as mean $\pm$ standard deviation,

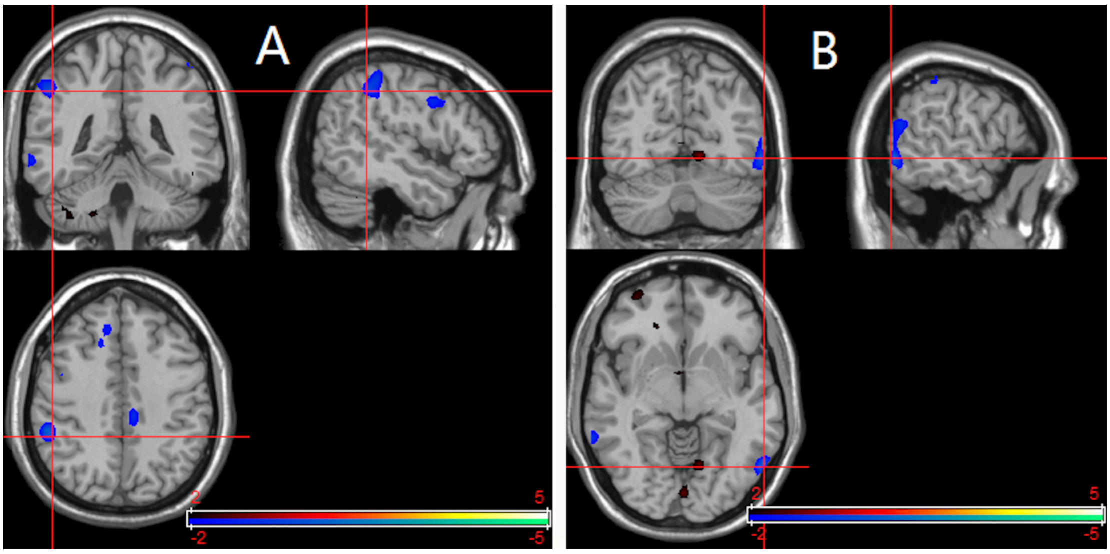

Fig. 2. Brain regions with decreased FOCA values under the task state between patients with SCI and healthy individuals. The intersections of the red lines are the brain region with decreased FOCA value under the right ankle dorsiflexion motor imagery task state in SCI patients compared with healthy individuals. (A) and (B) represent the left inferior parietal lobule and right inferior temporal gyrus, respectively. Red represents increased spatiotemporal consistency of local brain regions, and blue represents decreased spatiotemporal consistency.

and the t-test was used; otherwise, they were presented as median (range), and the non-parametric Mann-Whitney U-test was used. Categorical data were presented as n (%) and analyzed using the chi-square test. Two-sided p-values $<$ 0.05 were considered statistically significant. MRI image data analysis was performed by FOCA. Spatial smoothing was conducted on the images, and the Gaussian filter kernel parameter was set to 6 mm. A two-sample t-test was used to compare the differences between the SCI and healthy groups. The statistical threshold was set to $p < 0.01$, and cluster $>$10 was considered to indicate that the difference was statistically significant.

3. Results

3.1 Characteristics of the Participants

Twelve healthy individuals and 11 patients with SCI were enrolled. Among the healthy individuals, eight were males, and four were females. The mean age was 29.1 $\pm$ 5.6 years. The mean education was 12.0 $\pm$ 3.0 years. The KVIQ-10 scores were 31.6 $\pm$ 8.6 points. In the SCI group, there were nine males and two females. The mean age was 34.5 $\pm$ 9.1 years. The education was 10.3 $\pm$ 2.7 years. The time since SCI was from 4 months to 12 years. The KVIQ-10 scores were 32.7 $\pm$ 10.6 points. There were no significant differences between the two groups (all $p > 0.05$) (Table 2).

3.2 FOCA Differences in Local Brain Regions in the Resting State

In the resting state, compared with healthy individuals, SCI patients showed decreased FOCA in the left putamen, right caudate nucleus, and right superior occipital gyrus (Fig. 1A–C and Table 3), while FOCA was increased in the left precentral gyrus (Fig. 1D and Table 3).

3.3 FOCA Differences of Local Brain Regions in the Task State

In the "right ankle dorsiflexion" task state, compared with healthy individuals, SCI patients showed decreased FOCA in the right inferior temporal gyrus and left inferior parietal lobule (Fig. 2).

4. Discussion

Motor imagery can be used for rehabilitation after SCI [23–25] ,but the mechanisms are unclear. Therefore, this study explored the mechanism of local brain function remodeling changes after SCI. The results showed that in the resting state, compared with healthy individuals, SCI patients showed decreased FOCA in the left putamen, right caudate nucleus, and right superior occipital gyrus, while FOCA was increased in the left precentral gyrus. Furthermore, in the task state, compared with healthy individuals, SCI patients showed decreased FOCA in the right inferior temporal gyrus and left inferior parietal lobule.

SCI results in structural and functional changes in the brain [4–7]. Freund *et al.* [9] studied 10 patients with SCI and found that SCI can cause a decrease in the transverse area of the spinal cord, atrophy of the primary sensorimotor cortex, and a reduction in the volume of the white matter of the pyramids and cerebellar peduncle. Subsequently, a longitudinal study on the brain structure of 13 patients with acute traumatic SCI showed that the internal capsule, cerebral peduncle, and primary motor cortex gray matter displayed massive atrophy in the first month after injury, and correlation analysis was conducted regarding the degree of atrophy and the functional score. The results showed that the worse the functional recovery, the faster the atrophy [8]. Guleria *et al*. [10] observed the changes in the corticospinal tract after SCI using the DTI technique. In terms of brain function remodeling changes, according to previous studies, the brain regions involved in functional remodeling mainly included sensorimotor representative areas: primary motor cortex (M1), primary sensory cortex (S1), motor preparation, motor planning, and other motor cognition areas, premotor area (PMC), supplementary motor area (SMA), supplementary premotor area, inferior parietal lobule, and parietal lobe, as well as subcortical areas related to motor regulation and motor learning: thalamus, cerebellum, putamen, caudate nucleus, cingulate gyrus, etc. [11–14,16–18,25].

The present study showed that compared with healthy individuals, the local spontaneous activities of the left putamen, right caudate nucleus, and right superior occipital gyrus in patients with SCI under the resting state were more disordered in time, and the activity states of these brain regions were lower. The local spontaneous activities of the left precentral gyrus were more consistent in time and space, and the local stability of the activity state of this brain region was higher. It suggested that SCI can affect the changes in brain neuronal activities. The decrease in local spatiotemporal consistency of the left putamen, right caudate nucleus, and right superior occipital gyrus might reflect motor control disorders and visual information processing after SCI, and this change in brain function might impede functional recovery after SCI. On the other hand, the increase in the local spatiotemporal consistency of the left precentral gyrus might suggest a certain recovery of motor function after SCI, and this change in brain function might also be beneficial to the functional recovery after SCI.

Under the motor imagery task state, compared with healthy individuals, neural activities of the left inferior parietal lobule and right inferior temporal gyrus of patients with SCI were more disordered in time. In space, the local stability of the activity states of these brain regions was lower. The inferior parietal lobule is associated with motor attention, planning, and coding in motor processing [28–30]. The spatiotemporal consistency of the inferior parietal lobule was reduced, suggesting that SCI patients' abilities to process motor information at the stage of motor cognition, namely motor preparation and programming abilities, were reduced. The results were also similar to those of Cramer *et al*. [15] and Chen *et al*. [17]. They found that the activation of the inferior parietal lobule was decreased after SCI, and the volume of white matter fibers in the inferior parietal lobule cortex was decreased after SCI [15,17]. The inferior temporal gyrus receives the fibers emitted by the primary visual cortex and participates in visual information processing. The local spatiotemporal consistency of the inferior temporal gyrus related to visual information processing was poor, consistent with the results detected under the resting state in the present study, which might reflect the decrease in the visual information processing ability of SCI patients. The temporal lobe and the inferior parietal lobule belong to the brain default network [31]. A comprehensive analysis of multiple brain regions through the default network preliminarily found that motor imagery can inhibit the functions of some default network brain regions, such as the inferior parietal lobule and inferior temporal gyrus in patients with SCI, making it easier for the brain for processing external information. Hence, SCI patients are more likely to receive the stimulation of motor tasks to achieve motor relearning. It indicates that motor imagery might reflect the immediate effect of motor imagery on SCI by regulating the functions of some motor-associated default network brain regions.

Several studies have demonstrated the potential role of MI in motor recovery [24,25]. The combination of motor imagery and physical therapy can also be a new methodology for the rehabilitation of SCI Patients with spinal cord injury who are unable to access somatosensory input, since physiotherapy can improve sensorimotor strategies in body representation and promote the reliance on sensorimotor strategies by SCI patients [32]. This further suggests that, after SCI, motor cognition can be improved in association with the improvements of the physiotherapeutic interventions and SCI covary with motor cognition abilities. Another study using transcranial magnetic stimulation (TMS) to measure corticospinal excitability, demonstrates that motor cortex is differentially involved in different phases of mental rotation of hands. It also demonstrates the consistency between corticospinal excitability during mental rotation and the muscular activity during movement execution, as the correspondence between physical movements and mental constraints. This further suggests that motor imagery therapy requires a certain activation sequence, which starts from the activation of muscles and followed by the activation of the corticospinal pathway [33]. The above studies represent a general understanding of the correlations between motor imagery and cortico-spinal excitability, and inspire a new strategy for the remodeling of brain structure and function after spinal cord injury, as well as the rehabilitation strategy for spinal cord injury as motor imagination combined with physical therapy. It is helpful to analysis the mechanism of various therapeutic methods to promote functional recovery after spinal cord injury.

The present study has some limitations. First, it was a single-center study with a small sample size. There was no subgroup analysis of different injury times, degrees of injury, and injured segments of SCI patients, so the findings cannot fully reflect reality. It can also not elucidate the remodeling of brain function and the regulation of motor imagery on brain function after SCI. Second, the present study only selected FOCA as the data analysis method to observe the local brain functional changes after SCI. Therefore, only changes in local brain regions were examined, neglecting the functional interactions among brain regions. Thus, the present study cannot fully reflect the brain functional remodeling and the effect of motor imagery on brain functional interaction after SCI. Third, given that the present study only analyzed brain fMRI data and did not analyze the correlation with clinically relevant functional data, the results of the present study cannot yet be used for clinical assessment of the degree of injury and prognosis after SCI.

5. Conclusions

This study concludes that the remodeling of brain function after spinal cord injury may be realized as the changes of functional state of local brain regions, which is mainly manifested in the decrease of spatiotemporal consistency of the activity of local neurons in the motor related brain area in the resting state and the task state. The imagery right ankle dorsiflexion may increase the input of motor task stimulation by inhibiting the activity of the default network brain area of patients with spinal cord injury, thus, improving the motor relearning ability of the patients and promoting the recovery of motor functions after spinal cord injury.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

YJ, QW and ARZ designed the research study. YJ, QW, YC, RZP and SSZ performed the research. CL provided help and advice on the fMRI Scan. WCW analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The research is in accordance with the principles laid down in the Declaration of Helsinki. The present study was approved by the Institutional Review Board of The General Hospital of Western Theater Command PLA. All participants provided written informed consent prior to any study procedure. The protocol was approved by Institutional Review Board of The General Hospital of Western Theater Command PLA (Ethical approval number: 2014-08).

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Conflict of Interest

The authors declare no conflict of interest.

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