COULD EXPERIENCE MODULATE IMAGERY OF LIMB MOVEMENTS? A CASE IN INDIVIDUALS WITH SPINAL CORD INJURY

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Could Experience Modulate Imagery of Limb Movements? A Case in Individuals with Spinal Cord Injury

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CETIFICATE OF ORIGINALITY

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Abstract of dissertation entitled:

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Abstract

The mechanisms underlying reorganization of the neural system due to paralysis of the lower limbs after spinal cord injury (SCI) remains unclear. This study aims to use functional imaging to investigate the neural changes brought by the loss of physical movements and sensory feedback in the lower limbs among a group of chronic SCI participants.

The participants were 11 adult patients who suffered from SCI at the T7-T11 level, resulting in complete paralysis of the lower limbs. The control group was composed of 13 healthy participants with matched demographic characteristics. The experimental task used was visuomotor imagery tasks requiring participants to engage in visualization of repetitive tapping movements of the upper or lower limbs. The task processes involved retrieval of visuomotor images of the limbs, visualization of tapping of upper or lower limbs in working memory, and inspection of the direction of movements of the designated limb. The tapping movements had three rhythmic patterns

of 0.8, 1.0, and 1.33 Hz, respectively. A typical trial began with three auditory cues presented at one of the three rhythmic patterns. The participant was to follow the rhythm of the tones and begin visualizing the tapping movement of upper or lower limbs, one after the other, for 2.1 to 4.4 s. After hearing a high-pitched tone, the participant was to pause the visualized movements and indicate which side of the limb was toward the platform at that instance by pressing a button on a keyboard. The duration of capturing blood oxygen-level dependent (BOLD) responses by the scanner was 2.0 s, beginning from the presentation of the third auditory cue. There were two conditions: upper and lower limb. Accuracy rate and mean response time were the behavioral parameters of the task. The participant received training on the tapping movements and gained an accuracy rate reaching at least 70% before proceeding to the scanning session. Clinical measures on cognitive functions and post-SCI impairments were administered to the participants.

Behavioral data, including the visuomotor task and clinical measures, were compared between the SCI and healthy control group. Between-group effects on the BOLD responses elicited from the task conditions were tested. The relationships between the BOLD responses and the behavioral and clinical variables were explored. It was hypothesized that, in the lower limb condition, the SCI participants

would display stronger BOLD responses than the healthy control participants in the motor-related subcortical structure such as the basal ganglion and other regions outside of the sensorimotor areas. This would reflect possible neural changes among the SCI participants due to the post-injury loss of sensorimotor experience from the lower limbs. It was also hypothesized that, when compared with the healthy control group, the SCI participants would have stronger BOLD responses elicited in the sensorimotor areas for imagery under the upper limb condition. This would reflect the post-SCI reorganization of the neural system as a result of the experience-dependent plastic changes of the motor system.

No significant between-group differences were revealed in the accuracy rates and response times on the upper and lower limb task conditions. The SCI participants had significantly lower performances on the tests concerning working memory (Rey Verbal Auditory Learning Test) and executive functions (Trail Making Test).

The main findings of this study were in the significantly stronger BOLD responses elicited in the left lingual gyrus among the SCI participants compared to the healthy control participants when engaging in imagining lower limb movements. The right external globus pallidus (GPe) also showed significantly stronger activations among the SCI participants. No between-group differences, however,

were revealed in the BOLD responses in the sensorimotor areas. The stronger activations in the GPe suggested plausible increases in relaying input to and output from the basal ganglion during the visuomotor imagery processes. Stronger activations of the GPe suggested possible sub-cortical excitability among the SCI participants under the lower limb condition. The stronger activations in the left lingual gyrus indicated increases in the involvement of visual function during the visuomotor imagery for the SCI participants. This was supported by the stronger activations in the middle occipital gyrus in the lower limb versus the upper limb condition contrast among the SCI participants compared to the healthy control participants. These findings suggested possible compensatory strategies adopted by the SCI participants for the post-injury loss of sensorimotor inputs from the lower limbs. A similar strategy would have been used when the SCI participants visualized the repetitive movements of the lower limbs. The lack of increase in BOLD responses within the sensorimotor areas in the lower limb condition was likely to be attributable to the diminished movement feedbacks experienced by the SCI participants.

For the upper limb condition, the results indicate that the SCI participants showed significantly stronger BOLD responses than the healthy control participants in extensive areas over the brain including the bilateral right precentral gyrus, the left postcentral gyrus, the right

middle frontal gyrus, the bilateral superior temporal gyrus, the right superior and inferior parietal gyrus, the right external GPe, and the thalamus. The stronger BOLD responses in the widely distributed bilateral sensorimotor areas for the SCI participants in the upper limb condition suggested possible systematic post-injury changes of the motor control system. The stronger activations found in the GPe in the upper limb condition were comparable to those in the lower limb condition. This suggested that the post-injury neural changes were likely to be at a systemic level, influencing both upper and lower limbs.

In contrast, the healthy control participants displayed significantly stronger BOLD responses than the SCI participants in the frontal areas including the middle frontal gyrus, the medial frontal gyrus, the inferior frontal gyrus, and the left anterior cingulate gyrus for both the upper and lower limb conditions. These neural substrates were by and large mediating visuomotor imagery processes such as working memory, motor inhibition, and set shifting. These corresponded to the declined working memory and executive functions among the SCI participants as reflected from the significantly lower performances on the clinical measures when compared with the healthy control participants.

The present study supported the notion that the SCI participants probably underwent post-spinal-cord-injury plasticity in neural

substrates, mediating visuomotor imagery of upper and lower limbs. The results highlighted the significant post-injury changes in the responses of the GPe within the basal ganglion and its involvement in the visuomotor imagery. Without sensorimotor inputs, as the lower limbs had been paralyzed, the SCI participants were found to rely more on the visual system to undergo the visuomotor imagery. These plastic changes may have other impacts on neural processes among the SCI participants. Future studies should investigate how the post-injury plastic changes among SCI individuals would impact the preparation and execution of upper and lower limb functions by comparing complete and incomplete lesions.

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This thesis comes to an end, but also a new beginning.

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LIST OF ABBREVIATIONS

Abbreviation	
AC	Anterior Commissure
ACC	Accuracy Rate
ACC/RT	Composite Quotients of Accuracy Rate to Response Time
AD	Automatic Dysreflexia
AIS	American Spinal Cord Association Impairment Scale
ALFF	Amplitude of Low-frequency Fluctuation
ASIA	American Spinal Cord Association
BA	Brodmann Area
BG	Basal Ganglia
BOLD	Blood Oxygen-level Dependent
CMA	Cingulate Motor Area
CNS	Central Nervous System
CRRC	China Rehabilitation Research Center
CST	Cerebral-spinal Tract
DLPFC	Dorsolateral Prefrontal Cortex
DTI	Diffusion Tensor Imaging
EPI	Echo Planar Imaging
fMRI	Functional Magnetic Resonance Imaging
FWHM	Full Width at Half Maximum

GCS	Glasgow Coma Scale
GP	Globus Pallidus
GPe	External Globus Pallidus/
	Globus Pallidus External Segment
LOC	Loss of Consciousness
M1	Primary Motor Cortex
MA	Motor Attempt
MAS	Modified Ashworth Scale
MFG	Middle Frontal Gyrus
MI	Motor Imagery
MMSE	Mini Mental Status Examination
MNI	Montreal Neurological Institute
MP-RAGE	Magnetisation-prepared Rapid Gradient-echo
MRI	Magnetic Resonance Imaging
PC	Posterior Commissure
PFC	Prefrontal Cortex
PM	Premotor Area
PMC	Premotor Cortex
PMv	Ventral Premotor Area
Post-MTG	Posterior Middle Temporal Gyrus
Pre-SMA	Pre-Supplementary Motor Area
PTA	Post-traumatic Amnesia

RAVLT	Rey Auditory Verbal Learning Test
RF	Reticular Formation
ROI	Region of Interest
RT	Response Time
S1	Primary Sensory Area
SCA	Spinal Cord Area
SCI	Spinal Cord Injury
SDMT	Symbol Digit Modalities Test
SFG	Superior Frontal Gyrus
SMA	Supplementary Motor Area
STG	Superior Temporal Gyrus
TBI	Traumatic Brain Injury
TMS	Transcranial Magnetic Stimulation
TMT	Trial Making Test
TMT-A	Trial Making Test-A
TMT-B	Trial Making Test-B
VAS	Visual Analog Scale
VBM	Voxel-based Morphometry
VFQ-25	Visual Functioning Questionnaire
VMIQ	Vividness of Motor Imagery Questionnaire
VN	Vestibular Nuclei

Chapter Ⅰ

INTRODUCTION

This chapter gives an overview of the present research study on possible plastic changes of the brain and their modulation of neural mechanisms in individuals who suffered from spinal cord injuries (SCI). This chapter begins by outlining the statement of purpose, followed by the background and rationale for conducting this study, and ends with a description of the organization of the thesis.

Statement of Purpose

The subjects were individuals with spinal cord injury that resulted in the paralysis of the body parts below the injury level. The physical deficits were revealed to influence their brain functions because of plastic changes in the brain. This study aimed to explore a selected area of these plastic changes and investigate how these changes would associate with specific functional reorganizations among a group of SCI patients with complete paralysis below the thoracic level. Due to the paralysis of the lower limb, a custom-designed motor imagery task tapped the neural processes, which mimicked motor preparation and motor planning function of the lower limbs of the SCI individuals. Functional magnetic resonance imaging (fMRI) technique with a high spatial resolution captured the

neural activities in terms of changes of the BOLD signals associated with the motor imagery processes. The motor imagery task had both lower- and upper-limb conditions, with the latter as the control task. There were two groups of participants: one group was SCI patients and the other group was healthy individuals serving as the control group.

There were three objectives in this study:

1. To identify the plastic changes in the brain related to deficits of the lower limb functions among the SCI participants
2. To explore the underlying mechanisms of the functional changes related to the plastic changes in the brain
3. To investigate the relationships between cognitive functions and plastic changes in the brain among the SCI participants

Background and Justification of Study

Spinal cord injury (SCI) leads to partial or full disconnections in the spinal cord within the central nervous system. These disconnections result in physical and sensory impairments that are largely irreversible. The impairments are the consequence of ruptures in the nerve fiber tracts that pass on ascending sensory and descending motor information. They result in profound and permanent sensory and motor dysfunctions of the body below the injury site. Recent studies report noticeable reorganizations of the brain after SCI (Hotz-Boendermaker et al., 2008;

Nardone et al., 2013; Sabbah et al., 2002), which impacted the brain functions of patients with SCI. Researchers began to investigate how the disruptions at the spinal cord level would affect the cortical and subcortical functions mediated by the brain.

Studies on animals indicated a notable decrease in the number of neurons in the primary motor cortex after SCI (Wrigley et al., 2009). They further explained that the effects were attributable to the disrupted neural pathways in the damaged spinal cord. Voxel-based Morphometry (VBM) study in humans showed structural reorganization after SCI—a reduction in gray matter volume within the primary motor cortex, the medial prefrontal cortex, and the adjacent anterior cingulate cortex (Tandon et al., 2013). These studies provide evidence of possible plastic changes in the brain subsequent to SCI. It opens up a window for exploring the mechanisms underlying functional changes due to post-SCI neuroplasticity.

The post-SCI structural changes in the brain would result in the modulation of functions originally mediated by the affected neural substrates. The main reason is that the motor cortex and its related neural substrates previously receiving afferent input via the spinal cord have been deprived of stimulation (Schwab, 2002; Tandon et al., 2013). A few studies suggested that the intact sensorimotor cortices with the preserved neural connections ended up receiving afferent inputs from

their adjacent cortex (Tandon et al., 2013; Nardone et al., 2013). The same applies to the efferent outputs from the sensorimotor cortices to other associative areas. The deprivation of afferent and efferent signals has been shown to result in the reorganization of the sensory and motor cortex topography. In the rat model, the cortical representation of the forelimb was found to be magnified and invaded the adjacent deafferent hind limb area (Wrigley et al., 2009). Among paraplegic individuals, it was reported that the post-SCI experience resulted in an increase in the volume of the primary motor cortex (M1) for representing the hand and other non-primary cortical and subcortical regions; and for representing the forearm (Curt et al., 2002a). Among the individuals with tetraplegia, the cortical areas representing the forearm were found to extend into those representing the hand and fingers. These plastic changes were postulated as due to the overriding dominance of the activities of the forearms over those of the hands and fingers. The extent of the plastic changes is related to the levels of the injury and the function preserved.

These post-SCI structural and functional changes were found to occur within a very short time period after the injury. The changes would continue to evolve insidiously over months or years and possibly last a lifetime. Electrophysiological studies proved that deafferentation credited to SCI exerted changes in the cortical networks within the first

hour (Wrigley et al., 2009). The changes in the topography, such as within the primary somatosensory cortex, occurred as early as three days after the injury (Endo et al., 2008). The time-dependent changes were revealed to vary across different regions of the brain. For example, during the first month post-injury, activities of the bilateral M1 (synaptic sprouting) were found to heavily contribute to the plastic changes, whereas it was the contralateral M1 and bilateral ventral premotor area (PMv) that contributed to the plastic changes during the three to four months post-injury (Nishimura et al., 2011). However, no definite contributions to these plastic changes were declared.

Besides the deficits in memory, attention and processing speed have been evidenced with low blood pressure in SCI (Jegede et al., 2010). A pilot study carried out by our research team revealed that impairments of attention, working memory, switch shifting, and response inhibition occur in chronic SCI patients compared to the healthy control. It was assumed that the cognitive function was impaired in chronic SCI patients due to a number of factors, such as brain blood flow, hypotension, as well as less physical activities.

Motor imagery tasks were used widely in previous studies to explore the neural mechanism of motor control, especially in the stage of motor preparation, motor planning, or motor programming, with the overlapped neural networks during motor execution and motor imagery.

The neural process of motor imagery consists of image generation, image maintenance, image inspection and image transformation, in which a top-down and experience-driven process was mediated (Holmes & Calmels, 2008). Successful retrieval of motor representations and competent working memory are essential for performing the motor imagery task appropriately. The most frequently used motor imagery tasks include repetitive finger tapping, wrist and elbow flexion and extension, and ankle dorsiflexion and plantarflexion (Kokotilo et al., 2009). The repetitive motor imagery task used in this study was performed under both upper- and lower-limb conditions, with the aim to explore plastic changes of the brain and underlying mechanisms.

Organization of Chapters

This thesis is composed of six chapters, including the Introduction as Chapter 1. Chapter 2 reviews the literature on the theory of motor control; in particular, the neural processing of motor preparation, motor programming and motor planning, the mechanism of the formation and storage of motor memory, as well as the neurological deficits and the plastic changes in the brain of SCI patients. Chapter 3 describes the methods in this study, including the subject recruitment, the motor imagery paradigm, the clinical measures on

higher cognition, fMRI data acquisition, as well as the preprocessing of imaging data and the statistical analysis. Chapter 4 reports the results of this study, including the demographics of the subjects, behavioral results during the experimental task, cognitive test results, imaging contrasts, and correlations among these variables. Interpretation of the findings of this study will be presented in Chapter 5. Chapter 6 completes this thesis with the conclusion, limitations, and clinical relevance.

Chapter Ⅱ

LITERATURE REVIEW

This chapter includes the neural processing of motor control, particularly, motor preparation. Then the characteristics of the motor memory and the contributions of physical experience are articulated. The plastic changes after SCI are reviewed systematically. Lastly, the rationale, research question, and hypothesis are described.

Motor control

Motor Preparation

Voluntary movements consist of two neural processes, motor preparation (motor planning and motor programming) and motor execution (Cui et al., 2000). The motor preparatory activity is also referred to as “set activity,” which includes motor planning and motor programming, as well as the possible suppression of unintentionally triggered movements, while the motor execution is the application of this motor planning and programming, including the influences on the environment (Krams et al., 1998). These two basic processes of voluntary movement could be defined as motor control, which is interacted with the body and the surrounding environment, how the central nervous system (CNS) generates purposeful and coordinated movements (Latash et al., 2010). The main goal of motor control is to

achieve voluntary movements through the neural processes of motor programming in operating with precisely defined variables, such as selection, sequence, force, trajectory, speed, direction, and so on (Prodoehl et al., 2009; Schluter et al., 2001; Turner et al., 2003).

Motor programs or plans are defined as the central representation of the schemes of behavior, which are stored in the brain (Summers & Anson, 2009). Motor programs were thought to control behavior without the involvement of sensory input. For instance, if one wants to catch a ball, one will need to mentally predict where the ball is going to land and at the same time move the body and the hand to the appropriate position for intercepting the ball. This involves complicated feed forward calculation, which forms an essential element in the production of motor output without online use of sensory feedback (Ebner & Pasalar, 2008; Seidler et al., 2004).

To the same situation, throwing a ball to hit a target is also an internally generated movement of which the actions will not be affected by somatosensory feedback (Imamizu et al., 2000; Mehta & Schaal, 2002). In other words, throwing a ball involves execution of a series of preplanned movements that does not require much feedback from the body. The preplanned movements are voluntary in nature, which probably is dependent on individuals' previous experiences on the same task as this informs the posture to be assumed and integration of the

balance and musculoskeletal systems. It was assumed that the execution of preplanned and voluntary movements was driven by existing motor programs that store in the brain in Shadmehr & Krakauer's computational motor control model, and these existing motor programs were retrieved from a neural network in which motor representations were stored (Fuster, 1995; Millers, 2010; Shadmehr & Krakauer, 2008). As commented by Millers (2010), this can only be attributable to the existence of a memory that is specific to motor functions. A successful motor preparation is necessary to complete the motor execution, and it depends on the integrative and coordinated efforts of the whole motor control system to generate appropriate motor outputs.

Motor Control Output Hierarchy

In view of the command delivering of the motor control system, it is typical that the spinal cord acted as a pathway to send signals, and the last station in which the motor commands was transmitted into the peripheral nerves. In fact, not only the spinal cord, but also various levels of the motor control system played an important role in the adjustment and integration of the motor outputs.

According to Millers (2010), the motor output system can be divided into four levels: spinal cord, brain stem, subcortical and

cerebral cortex (See Figure 1). These levels are speculated to be organized in a hierarchy. Each successive level builds upon the capabilities of the layer below it. Each level has its particular role in the whole process of motor control, especially in the motor preparation section (Fuster, 1995).

The first level of motor control involves spinal neurons, in which the descending commands from higher centers and the sensory feedback from the peripheral receptors were integrated. The interneurons in the spinal cord received and integrated the sensory feedback from the proprioceptive secondary neurons, then interacted with the motor neurons, which directly received the motor commands from the upper levels (Hultborn & Nielsen, 2007; Millers, 2010; Scott et al., 2004).

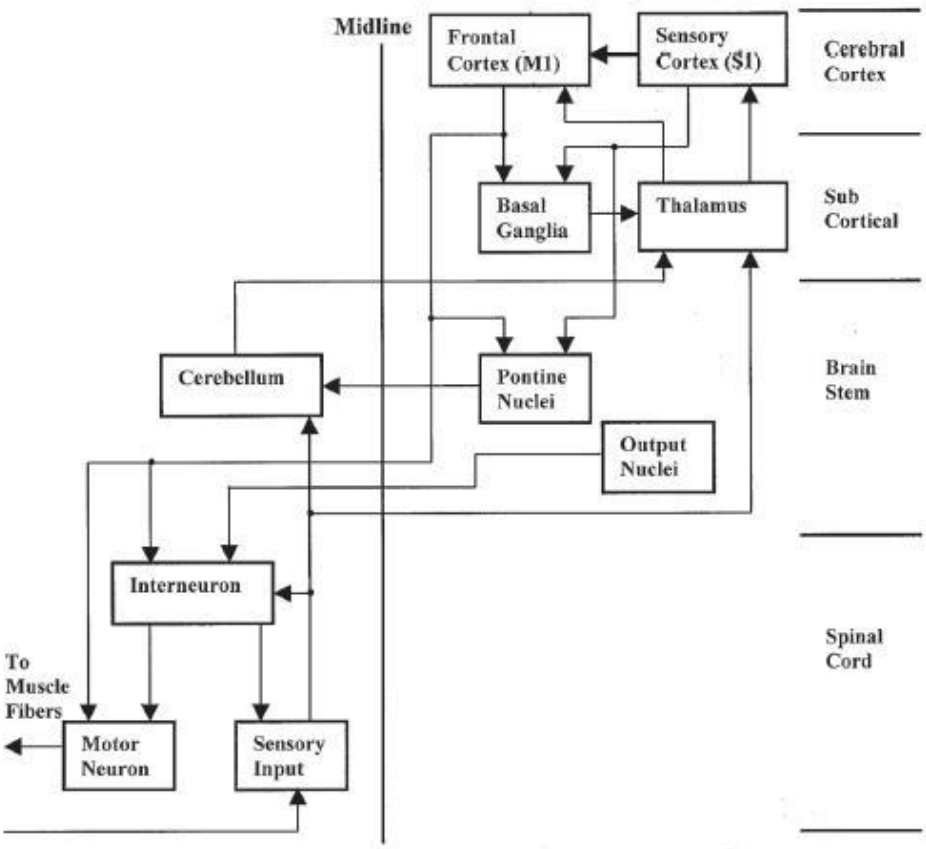


Figure 2.1 Neural motor control system (from Millers, P85, Figure 2-18 Neural Output System, 2010)

The second level relies on the brain stem nuclei and cerebellum, which constitute the output control loop together with cerebral motor cortex and thalamus. Typically, the reticular formation (RF) and vestibular nuclei (VN) in the brain stem regions, played important role in postural control and locomotion (Corfield et al., 1999; Scott et al., 2004). The cerebellum plays an integral role in the control of voluntary skeletal movement, such as the feedback processing, the timing of

voluntary movement, force control, and the storage of acquired skills (Cui et al., 2000; Flament et al., 1996; Halsband & Lange, 2006; Jueptner & Weiller, 1998; Kawato & Gomi, 1992; Keisker et al., 2009; Schmitt et al., 2009; Van Mier et al., 1999). Recently, more and more studies evidenced the role of cerebellum in the motor control (Kawato, 1999; Stoodley & Schmahmann, 2010). The typical neural mechanism is internal model, which will be elaborated later. Cui et al. (2000) reported that the lateral part of the cerebellum contributed to the motor preparation, while the intermediate part participated into the motor execution.

The third level, which influences the selection and sequence of voluntary movement and acts as the relay station, is the subcortical area, including the basal ganglia (BG) and thalamus (Haber & Calzavara, 2009; Herrero et al., 2002; Romanelli et al., 2005). BG plays a vital role in motor planning and sequences of movements, while the thalamus is the relay station of the neuroanatomical projection between the BG and dorsolateral prefrontal cortex (DLPFC) and also the relay station of the cerebellum and cerebral cortex (Haber et al., 2009). Based on these two neural structures, which are parts of the frontal cortex motor control loop (the main controller of voluntary movement), the role of the frontal cortex in driving voluntary movement is possible (Miyachi, 2009).

The cerebral cortex is the fourth and final level. The role of this level is critically involved in the initiation, planning, and execution of voluntary action (Passingham, 1998; Scott, 2004). It contains the M1, the premotor cortex, and the prefrontal cortex (PFC) (Battaglia-Mayer et al., 2003; Bengtsson et al., 2009). Numerous axons of pyramidal neurons of M1 send their projections directly to the motor neurons in the spinal cord (Keisker et al., 2009). The frontal cortex serves to control the skeletal muscle and exerts overall control of voluntary movement as the newest neural component.

As a summary, although the above four levels functionally interact with each other in the motor control system, each level of the whole motor output system respectively relies on particular neural substrates with the corresponding functions, subserving to neurophysiological processing of motor control. The consequences on motor control are unclear, especially regarding the motor preparation that results in motor outputs. It is not if any level of part of this motor output system is impaired. Explorations on the neural substrates involved in motor preparation will help us to make it clear.

Neural Substrates Involved in Motor Preparation

Prefrontal Cortex

The PFC is the frontal association cortex that stores the patterns

of motor memory, and is responsible for motor planning. Neuropsychological studies showed that the prefrontal networks representing the memory of the task are those that mediate it (Alivisatos, 1992; Krieghoff et al., 2009; Olivier et al., 2007; Quintana & Fuster, 1993). Neuroimaging studies showed the evidence of the prefrontal cortex got involved in the representation of movement (Corbetta et al., 2002; Hallett, 2007; Mars et al., 2008). Roland and Friberg's (1985) study found that prefrontal activation is especially marked when the subject is mentally planning motor sequences. Furthermore, from the prefrontal lesion studies, it presented that in humans the prefrontal cortex is essential for planning and initiation of action and consequently for all manner of creative behaviors. In addition, prefrontal lobe lesions seem to disturb the short-term representation of specific movements as required for integration of temporally extended behavior (Doya, 2000). Frontal patients have problems remembering the order and execution of externally or internally generated motor responses (McAndrews & Milner, 1991; Petrides, 1992).

It is probably also in the prefrontal cortex where motor actions are temporarily represented as needed in the context of behavioral sequences (Cunnington et al., 2006). The deficits of prefrontal lesions result in the difficulty in forming and using internal representations in

studies on monkeys and humans.

Evidence also showed that the prefrontal cortex played an overarching role in the temporal organization of behavior, which is manifest in a wide range of behavioral activities (Fleming, 2009; Fuster, 2004). A retrospective function of short-term sensory memory and a prospective function of short-term motor set (for the forthcoming response) further the superordinate role of temporal integration, in forming of new, complex, and temporally extended structures of behavior. This capacity relied on the prospective set and the related capacity to form internal representations of prospective action (planning) (Buneo et al., 2002). Neurochemical studies demonstrated that dopamine seems to mediate prefrontal neuronal transactions in motor memory and the temporal organization of motor behavior (Sawaguchi et al., 1990).

Although a wealth of evidence showed the participation of the prefrontal lobe in the motor planning, there is no evidence of somatotopic or kinematic organization in the prefrontal cortex, except the frontal eye field. Movement representation in the more anterior prefrontal cortex is most probably idiosyncratic to the individual, context-dependent, and poorly defined topographically. In general, motor representation appears better organized in the premotor cortex.

Premotor Cortex

As the secondary somatosensory cortex in the parietal lobe, the premotor cortex (PMC) contains multiple body maps, which are utilized to pattern detect the current active procedural memory and also drive the M1. The PMC is involved in the preparation of actual movement (Cisek, 2006 a & b; Cisek & Kalaska, 2005; Gerloff et al., 2006; Johnson et al., 2002). The learned patterns contained in the PMC connect movements together into actions over time, by which many small movements are coordinated into a large complex movement (Amiez et al., 2006; Toni et al., 2002). Also the force and velocity of movement are modulated by the PMC (Davare et al., 2007; Keisker et al., 2009; Grol et al., 2006).

The premotor cortex is conventionally divided into two portions: a lateral area (6b), called the premotor area (PM) and a medial area (6a), called the supplementary motor area (SMA) (Song, 2009). Unit and stimulation studies show that to some extent, both are somatotopically organized and contain separate kinetic maps (Fried et al., 1991; Kurata, 1992). In addition, both premotor areas seem to get involved in the motor preparation or the set of movement because of the anticipatory discharge of neurons before movement (Di Pellegrino & Wise, 1991). However, it is important to note that the anticipatory discharge of premotor neurons generally begins after that of prefrontal neurons and

before that of primary motor neurons, which strongly suggests that the processing of the motor set begins first in the prefrontal cortex, then involves the premotor cortex, and finally moves to the motor cortex (Fuster, 1995; Rushworth et al., 2004). At each cortical stage, the motor set engages the connective loop of that cortical stage with subcortical structures (basal ganglia and lateral thalamus) (Purzner et al., 2007).

Based on the neuropsychological and neuroimaging results, it has been demonstrated that the SMA involves in the initiation of voluntary movement, while the PM contributes to the control of externally referenced and automatic movements (Cisek, 2006; Gerloff et al., 2006; Mushiake et al., 1991; Passingham, 1985). Also a few of studies demonstrated that the planning and real-time control of the vision-guided movements required the involvement of the parietal cortex and the premotor regions (Ogawa et al., 2006; Vaillancourt et al., 2007).

In general, single-unit studies show that motor representation in the premotor cortex is not defined in terms of particular effectors, muscles, or muscle groups, but in terms of global movement, trajectory, or target (Millers, 2010; Nowak et al., 2005; Schluter et al., 2001). So it is said that premotor areas encode motor acts rather than individual movements. Here, what the motor acts encoded is not the mere physical parameters of the movement with regard to the body but the

coordinates of external space, the motor sequence, and the goal. The motor acts anticipated in PM and SMA were defined by their goal, their temporal gestalt, or their trajectory (Millers et al., 2010; Strens et al., 2003).

Mushiake et al. (1991) reported that the majority of task-related SMA elements were especially activated if the movement was initiated automatically other than by a visual stimulus, in verse, it was true for PM. Other studies showed M1 unit activations are closely linked in time to movement execution and are invariant regardless of trigger or other conditions (Grol et al., 2006; Nowak et al., 2004). In general, it presents that the signals activating PM representation and motor set come mostly from external receptors, possibly through the posterior association cortex, whereas the signals activating SMA representation and set come mostly from internal sources, possibly from the prefrontal cortex just above.

Judging from this, it seems that the SMA is hierarchically somewhat higher than the PM cortex. Units in the SMA seem to represent more general, voluntary, complex, and goal-oriented actions than PM units. Moreover, SMA units show a degree of plasticity in their commitment to a task (Lotze et al., 2006).

Primary Sensorimotor Cortex

It is M1 that directly controls individual groups of muscle fibers via the motor neuron in the spinal cord. The motor cortex decomposes complex behaviors into ever more granular patterns driving individual muscle fiber groups, rather than building up complex patterns as output (Johnson-Frey et al., 2005; Millers et al., 2010; Umilta et al., 2007). M1 receives motor control input from the premotor areas and from the cerebellum mediated by the ventral lateral nucleus of the thalamus (Penhune et al., 1998). The inputs from the cerebellum represent learned motor control patterns (Cui et al., 2000; Keisker et al., 2009).

The M1 demonstrated a picture of extensive functional overlap and distribution, where somatotopy is defined mainly by neuronal innervations of synergic muscles (Fuster, 1995; Millers et al., 2010). And this organization is carried down through the brain stem and spinal cord to individual muscles in a consistent, organized fashion. Thus, M1 could represent a wide selection of patterns of movement that are only loosely organized in topographical fashion. And the movements result from the joint action of all the cells in the cluster, and thus from a population code (Georgopoulos et al., 1993). After training or experience, new patterns of connectivity can be formed in M1. Rearrangements in that connectivity may result from synchronous synaptic convergence of inputs from higher up in the motor hierarchy (e.g., from the premotor cortex) and inputs of somatosensory and

proprioceptive origin (Grol et al., 2007; Pavlides et al., 1993). Again, M1 is a plastic structure showed by the imaging studies (Cui et al., 2000; Grafton et al., 1998). The properties of the motor actions, such as the space and time, become more automatic and concrete, less voluntary and abstract with the top-down networks formed from the prefrontal lobe to M1 (Millers et al., 2010).

The representations of normal behavior of any degree of complexity contain elements of representation at several levels and, therefore, are widely distributed throughout the hierarchy. And the interaction between different levels may involve subcortical loops, through the basal ganglia, lateral thalamus and cerebellum (Cunnington et al., 2003; Purzner et al., 2007). By those interactions high-level programs can control subordinate and nested routines and thus support the continual interplay of voluntary and automatic action that makes up normal sequential behavior.

Parietal Cortex

Experiments in monkeys indicated that the parietal areas also contribute to the preparation process (Toni et al., 2001). In 2006, de Lange et al. illustrated that in the role of the parietal and frontal cortex, the motor variables were transformed from the external into the internal coordinate systems. For example, when it made the somatosensory

information about the body position into a motor plan, the posterior parietal cortex might get involved primarily. In view of this neural process, the posterior parietal cortex integrates the information about modalities and the efferent copy of motor sets, so as to reveal the estimated end-points of the movements. Then it might be transformed to the dorsal premotor cortex, in order to select an appropriate motor plan.

Basal Ganglia

As we all known that motor control and higher cognitive functions, including the reinforcement learning and procedural memory the, were the typical functions of basal ganglia (BG) . The role of BG in motor control is mainly involved in regulating voluntary movement, motor planning and procedural learning. As early as 1985, the BG was assumed to preferentially play a role in memory-contingent motor control and ongoing relevance (Goldberg, 1985). Hikosaka and Wurtz (1985) also reported that the BG contributed to the motor control with the memory of “where” to move when the direct sensory feedback control was absent. Further, the classical view was that the cerebral regions were involved in the initiation of goal-directed actions. Nevertheless, the updated concept described that the BG could make decision on the time in which a presumed motor program should be

elected and initiated, acting as the role of motor program release, by relieving the pallidal inhibition (Grillner et al., 2005). In addition, Cunnington et al. (2002) also found that the BG was involved in the self-initiated movement with the memory of "when" to move.

Besides the role in motor programming, action selection is emphasized as another important role of BG, subserving to the prediction of future reward and reward delivery. The BG was dealt as a vital key in selecting various motor programs, especially the inputs from the cortex and thalamus were received by the striatum, with a high threshold for the transmitting of dopamine. The consensus of many studies was that the discharge rate of most pallidal neurons increases in response to behavioral events, such as action selection or motor initiation (Goldberg & Bergman, 2011). Other studies showed that different conditions of movement triggers lead to various patterns of discharge rates of pallidal neurons, by the evidence that the increment of pallidal neurons was associated with the memory-contingent condition, such as self-initiated or self-guided movements, while, decreased firing of the pallidal neurons occurred in response to the sensory-triggered movements. In addition, psychophysical and electrophysiological studies demonstrated that movement parameters, such as velocity, direction, and speed, can be modulated after the earliest stages of movement initiation with the

parallel neural activities in BG.

As many aspects concerning the properties of motor control of BG, the effects of the memory context were explored as though they were in line with those of movement kinematics. It is confirmed that memory context plays a vital role in the BG circuits for voluntary movement. A study carried out by Kimura et al. (1996) showed that the motor related memory was stored in the BG with the neurons in BG activated during the memory-guided saccade. As shown in previous studies, the motor memory accompanying motor skills learning was stored long-term in BG (Doyon & Benali, 2005; Graybiel, 2008). As reported by Menon et al. (2000), under the memory-guided condition, increased motor sequencing demands lead to activation in BG, in particular in the posterior putamen and globus pallidus (GP), which involves in the maintenance and representations in working memory, then the planning and timing of motor sequencing. In fact, it is proposed that the storage of temporal sequencing in the posterior putamen and GP contributed to this working memory for motor planning. By virtue of the inputs and outputs of the BG structure, it was able to serve for the function of motor-related storage.

In contrast, findings of some studies were not suggestive of this view. In the opinion of Turner and Desmurget (2010) supported by a single-cell recording study, the BG served as a vigorous tutor for the

goal-directed movement performance, which is important for motor learning rather than storage or recall of learned skills, while, the motor cortices may contribute to this role of long-term storage. Turner et al. (2003) also stated that the increment of neural activities in the BG area was ascribed to the increasing movement extent and speed.

Complex neural connections among BG and other neural substrates are substantial for this vital function. The striatum received information from the associative, motor, and limbic areas, then transmitted to the substantia nigra/globus pallidus and the thalamus, finally projected back to the corresponding cortical areas. Similarly, the subregions involved in the different body parts of the motor cortex transmitted to specific domains of the putamen, afterwards, they were transformed back to the original cortical areas. These parallel loops contributed to the basic role of BG functions. It is well known that the BG-thalamocortical circuit contributes preferentially to the control of self-initiated movements (Taniwaki et al., 2003), in which the successful retrieval of motor memory is important.

In sum, the prefrontal lobe, the premotor area, the primary sensorimotor cortex, the parietal cortex, and the basal ganglia contribute to the neural process of motor preparation. A set of neural activities are also involved in this process, including the initiation of action, selection of the action, inhibition of involuntary movement, and

parameters programming, such as the speed, direction, velocity, and timing. In practice, it's difficult for us to differentiate with certainty the role of each one in various neural substrates and to segment the neural process into different substrates. One possibility is that these neural substrates work synergistically within a special neural network and were associated with each other by specific mediators. It is noteworthy that one element extensively articulated and emphasized by each substrate is the motor memory, by which the successful restorage and retrieval is vital to perform the motor preparation appropriately. We need more research to identify it and address how these neural substrates functionally work together to assist in the control of motor preparation.

Motor Memory

Motor Representation

Memory is the capacity to store and retrieve information about what you have experienced and what you have learned (Millers, 2010). There are four distinct classifications of memory including short-term memory, long-term memory, declarative memory and procedural memory (Cowan, 2008; Fuster, 1995; Millers, 2010). Control of movements involves perceptual-cognitive representations, which are proposed to be depot in the long-term memory (Mechsner, 2004;

Mechsner et al., 2001). During motor programming, the characteristics of invariants may be stored in long-term memory. The generalization of motor programs showed that the motor-related durations, forces, and patterns of the muscle activity are stored in long-term memory in the way of the invariants of motor programs (Schmidt & Lee, 1998). Other studies proved that movements are arranged and depot in memory as perceptible events in the way of the automatic and flexible motor activity (Schack & Mechsner, 2006).

Motor representations in motor memory are the image-perception of motor acts and behavioral sequences, including motor learning, motor skills and classical conditioning (Fuster, 1995). As with any other memory, it could be divided into four processes. They are encoding, consolidation, retrieval, and reconsolidation (Alberini, 2005; Misanin et al., 1968; Nader, 2003; Walker, 2005; Walker et al., 2003). During the encoding, skills or evens are primarily attained. Then, those memories are dealt with during consolidation before retrieval. After retrieval, the memory was further processed as reconsolidation. In concert with these processes, motor memory made progress functionally from a short-lasted fragile style to long-lived style (DeZazzo & Tully, 1995). Running through this process, neural motor representations involved vitally in these motor-cognitive processes, by the contributions of distinct neural substrates.

Cerebric Regions of the Motor-related Memory

Neuroimaging studies on motor behavior have showed that activation in the left PMv and posterior middle temporal gyrus (post-MTG) (Johnson-Frey, 2004; Kellenbach et al., 2003). This area will be activated when the action observations were carried out. The left posterior parietal cortex were recruited when subjects retrieve given movements, such as grasping or tool-utilized movements (Chao & Martin, 2000; Johnson & Grafton, 2003; Johnson-Frey, 2004; Kellenbach et al., 2003). And the prefrontal lobe contributed to the working memory and related processes, i.e., planning during the consolidation stage of the motor memory (Deco & Rolls, 2005). Moreover, some research also indicates that patients with damage to the left posterior parietal cortex have difficulty retrieving appropriate action representations. In the subcortical level, studies showed that the BG contributed to the learning of repetitive motor sequences, with the attributions to the striatal-thalamic-cortical loop. Therefore, we can draw a conclusion that the regions shown above have close relationships with the motor-related memory.

Interaction between Working Memory and Long-term Memory in Motor Preparation

Some studies of neural substrate indicated that both of the

prefrontal cortex and posterior cortical cortices involved in the initial perception and comprehension on the basis of short-term working memory's storage. These studies also show the relationship of the short-term memory with the long-term memory. More exactly, they describe that the underlying mechanisms of short-term storage relied in an augment in neural synchrony between the prefrontal lobe and posterior lobe, which can strength the long-term memory in the way of material-related representations of short-term memory. A possible explanation of these findings is that the long-term memory systems involve in the posterior cortical cortex make the basis for working memory, with the fact that the posterior system might be responsible for the short-term memory deterioration. Crowder (1993) suggested that the rules in which the short-term memory and long-term memory worked were similar and it was impossible to separate the storage system of the long-term and short-term memory definitely. As depicted by Crowder, memory storage comes up in the same brain areas in which the information was initially and primarily dealt with. Although we cannot find any research on the relationship between the motor-related long-term memory and the motor-related short-term memory, we can assume that it may have some relationship to the motor-related long-term memory and the motor-related short-term memory based on the studies shown above.

Importance of Physical Experience

A study conducted by Schack (2004) reflected that compared with novices, motor representations in experts were much better structured and be varied to the functional and biomechanical demands, in terms of the different levels of physical experience. When somebody is subjected to improved motor skills, the time is necessary to better understand the consolidation of motor-memory. A study demonstrated that the motor system activities decreased with the enhanced experiences during the sequence-specific learning, indicating that the sequence-specific motor representations were strengthened 6 weeks later using skill experiences (Wymbs & Grafton, 2014). Even the implicit memory system of a specific action were formed by years of practice, the explicit memory system could interfere it when the movement was performed, even take away all the traces of implicit memory.

A few of studies showed that continued explicit involvement is sufficient to disturb the performances of implicit sequence learnt for a long period (Song, 2008 & 2009). And the role of the specific areas in holding motor memory was time-limited in the brain. On account of the fragility to the interference and the capacity to master a second movement depending on time although acquired before, it provides the neuronal basis and opportunities of motor memory changes even

behind the acquisition.

What the physical experiences directly bring in is the consequent sensory feedback, which is important to the system of motor control, from the initiation, planning, and monitoring to adjusting in the motor preparation and execution. Previous studies show that the brain will build the connection between motor commands and sensory feedback when it learns a motor performance task so that the consequences of this self-automatic movement. Correct and precise predictions of the consequence is critical to select the optimal motor plan in order to achieve the aims of this action, in particular, in the self-generated motor commands (Izawa et al., 2008; Shadmehr & Krakauer, 2008; Synofzik et al., 2008); therefore, this process is necessary to develop skilled movements related to a broad range of human behavior (Rizzolatti et al., 2002). Although this ability is vital for implementing skilled movements and it is realistic to produce the ability to predict the aims and consequences of the movements that (Miall, 2003; Rizzolatti & Luppino, 2001) often known as “theory of mind.” In other words, the ability to implement skilled movements is associated with the ability to correctly recognize these actions when carried out by others (Ochipa et al., 1997). Thus, sensory feedback from the practice plays a critical role in motor learning.

It is summarized that, in accordance with specific goals and

restraints, the patterns of action representations in long-term memory might provide the neural basis for motor control in skilled voluntary movements, with the well built-up and integrated perceptual-cognitive related brain structures. Generalization patterns of skill learning that the neural system will be engaged in represent the new information during learning which is viewed as a signature of the neural system (Poggio & Bizzi, 2004; Shadmehr, 2004). Even though the long-term motor representations were evidenced to last at least 5 months in Shadmehr and Brashers-Krug's (1997) study, there was no time scale for its persistence. It comes to the conclusion that the motor representations are physically experience-dependent (Olsson et al., 2008). Physical experiences are not only to enhance motor representations in motor memory but are also the way to alter the current motor representations in order to adapt for a new skill. A new question was posed about what will happen to the motor representations when the physical experiences disappear forever, and further research would be needed to answer it. This assumption is significantly meaningful to the maintenance of motor memory in sports skills and rehabilitation strategies.

Spinal Cord Injury

Introduction

SCI, a catastrophic injury that partially or completely disrupts the connection between the spinal cord and the brain, is a common and serious neurological injury with a variety of system dysfunctions, usually throughout life (Kokotilo et al., 2009). The disconnection of nerve fiber and tracts that transform ascending sensory and descending motor information leads to impressive and permanent sensorimotor and autonomous dysfunctions for the body below the injury site.

On a global scale, nowadays every year the incidence of SCI announced locates between 10.4 and 83 per million population (Wyndaele & Wyndaele, 2006), that is, one lesion less than every one minute to seven minutes on the earth. The injury occurs mostly between the ages of 16 to 30 according to the European and North American statistics. And the reasons of injuries are multiple, i.e., in the United States, the motor vehicle accidents occupy about 40%, violence 25%, falls and sports accidents 20% and 5–10% respectively. According to the report by the Canadian Paraplegic Association in 2008, about 50% of the SCI are diagnosed as quadriplegia/tetraplegia and suffer from paralysis of both upper limbs and lower limbs, as well as the trunk, while the rest SCI are diagnosed with paraplegia experiencing the paralysis below the injury level. In view of the extent

of the injury, SCI is functionally sorted as complete or incomplete based on the quantities of motor activity retained or sensation presented below the injury level (Maynard et al., 1997). In the SCI with incomplete injury, the residual spinal cord allows some information pass on. However, this kind of transmission is often fragmentary or distorted, resulting in some kinds of neurological complications, such as neuropathic pain and spasticity (Raineteau & Schwab, 2001). The disorders of motor, sensory, and autonomic function in SCI can have an profound influences on function (Yu, 1998). Several therapeutic approaches are under investigation for reducing disability after SCI. And enormous efforts are taken out to explore the clinically underlying mechanisms referred to the functional recovery after SCI.

A number of interventions have been adopted to try to restore motor functions in the individuals with spinal cord injury. Some focus on repairing the damaged spinal cord (Dobkin & Havton, 2004), some focus on driving muscles or devices with electro-physiological signals originated from cortical neural activities (Carmena et al., 2003; Friehs et al., 2004). Both interventions are based upon the assumption that the brain worked well as before the injury to the spinal cord, and were capable of generating signals needed to drive limb movement in the neural process of motor control. However, recent functional and neurological studies showed the reorganization of the brain function

though some features are preserved (Corbetta et al., 2002; Hotz-Boendermaker et al., 2008; Sabbah et al., 2002).

Reorganization of Brain after SCI

Recently the concept of “New Anatomy” has been described as the brain altered in structure and function, and often highly personalized changes in the neural process of sensory perception and motor output based on the studies on human SCI (Dimitrijevic et al., 1997; McKay, 2012). Many properties of brain motor system function retained after the chronic and complete SCI. A study conducted by Corbetta et al. (2002) revealed that the cortical representations of the motor and sensory function might be retained in the absence of voluntary movements or intentional sensations in the subject 8 years after high cervical injury with some recovery. Sabbah et al. (2002) also showed that even several years after injury, the attempt to move, the mental evocation of the action, or the visual feedback of passive proprio-somesthesic stimulation could elicited the activation of lower limb cortical networks to some extent, it indicated that some kinds of local cortical reorganization happed to SCI. There were some common areas, such as the prefrontal area, the parietal area, premotor area, thalamus, putamen and cerebellum, activated among the motor programs of the implementation of foot movements and their internal

recognition in chronic paraplegic patients (Hotz-Boendermaker et al., 2008). Kokotilo et al. (2009) concluded that many studies found a significant increase in activation magnitude in activation of motor areas. The common areas with increased activation included the bilateral M1, primary sensory area (S1), SMA, PM, cingulate motor area (CMA), parietal cortex, cerebellum, thalamus, and BG. It is mostly proposed that these plastic changes were attributed to the unmaking of the silent horizontal connections, and the improvements of the synaptic efficiency.

Apparently, various derangements of brain excitation, poor modulation of function in view of the change in task demands, and emergence of interesting brain events were reported more frequently. Turner et al. (2001) showed evidence that there were unusual cortical patterns of activity when attempting to move limbs below injury in chronic SCI patients.

Some studies reported the temporal and spatial shift of the brain activation in SCI. With the passage of time, there was a gradual increment in M1 activation and reduction in secondary motor area activation in SCI, as the functional recovery moved into the chronic phase, until the activation was similar to the controls. Nevertheless, in the subacute phase after SCI, the inverse activation was observed. These changes might reflect the immediate role of secondary motor

areas in increasing motor planning and developing new motor strategies. The spatial shift related to the completeness of injury and the level of injury. The incomplete SCI (who could shift their toes) inclined to the posterior shift (Green et al., 1999), whereas the activation shifted in the medial, superior and posterior direction, be accompanied by the higher levels of injury (Mikulis et al., 2002). It is suggested that the increased activity in S1 and a posterior shift of activation relied on the damaged corticospinal tract, which might related to the increased loss of axons in M1 and surviving axons from S1 after SCI (Green et al., 1999). However, another possible explanation indicated that the shift in S1 acts as the motor commands formation or somatosensory processing.

A comparison was made during foot movement between the chronic, complete SCI patients and the healthy controls by Cramer et al. (2005), with the following interesting results. Firstly, the activation volume reduced with highly abnormal variance of signal change, especially in primary sensorimotor cortex, which was consistent to the fact that the corresponding areas related to motor cortex are extended for practiced movements, however, for the non-practiced movements, it is stable or contracted (Martin et al., 2005). Based on the theories that smaller activation is usually related to weaker force output (Ward & Frackowiak, 2003) and to slower frequency of movement (Schlaug et

al., 1996), the possible explanation of this decrement of activation is due to the decrease of sensory input after complete SCI. Secondly, there activation patterns observed were abnormal, e.g., during attempted movement the activity of pallido-thalamocortical loop increased, while during imagined movement the primary sensorimotor cortex showed unusual processing. This increased recruitment relied on the disorganized basal ganglia influences upon thalamus and cortex (Freund et al., 2011; Henderson et al., 2011; Middleton & Strick, 2000). Lastly, the modulation leading by the change in task or force level was absent in patients with SCI. These findings indicate that neuronal activities in brain regions are associated with motor control, i.e., the brain representation of a plegic limb is retained but disordered, manipulating with twice normal variability. Furthermore, Humphrey et al. (2000) found that increasing lasting-period of SCI was related to the activation reduced in the area of motor cortex during attempted foot movement in the subjects with paraplegia. It has been postulated that the motor imagery ability were affected by the motor state and motor experience (Guillot & Collet, 2005; Olsson & Nyberg, 2010).

The activation volume varied from different studies. A comparison between nine SCI subjects and twelve healthy controls was conducted by Curt et al. (2002a), and the results demonstrated that in paraplegia, though without any unique topographical reorganization in

M1, the representation of upper limb muscles without impairements is altered,. The increased volume in M1 and additional activation in non-primary motor areas and in subcortical regions show that the activation of the whole sensorimotor system was affected by even distant spinal damage. A new generalized body and related functional disorders could induce the brain reorganization, and it was speculated that the potential changes in excitability of the cortex may occur after SCI (Nardone et al., 2013).

They might be many factors contributing to the variances of activation. Bruehlmeier et al. (1998) found that in both paraplegia and tetraplegia, the intensity of activation was related to the injury level disrupted by the SCI, and abnormal additional activation were observed in the whole brain. In other words, the injury level of SCI varied the plastic changes, with the hints that the injury level of SCI participants recruited in further studies should locate in a certain range. In view of the body functions remained, it seems that injury in thoracic level was a better choice. However, the thoracic spinal cord innervates the whole trunk, and the injury at the upper level and the lower level of the thoracic spinal cord also leads to a big difference in the function. In addition, the SCI patients in upper thoracic level suffer from the dysfunction of breathing for the paralysis of intercostal muscles (Aarabi et al., 2012). As a result, the best sample to conduct study on

the brain plastic changes after SCI should focus on the lower thoracic level in order to achieve the best homogeneity.

It has been noted that the observed activation of the thalamus and cerebellum was very strong, which implied that these supraspinal sensorimotor centers were reorganized with abnormal neuronal activities, as a result from consequence of a reduced and altered afferent input from the spinal cord. It is known that the afferent inputs from the spinal cord were processed by the thalamus and cerebellum. Moreover, the thalamus matched the corticospinal output with the spino-cerebellar afferent input with internal loops from the basal ganglia and the cerebellum, serving as a relay nucleus to the motor cortex (Alexander et al., 1986; Haber & Calzavara, 2009). From this perspective, it has been presumed that a stronger activation was associated with the relatively complex processing of remaining input, originating from reducing afferent input from the spinal cord, or facilitated the neural centers referred to, such as the thalamus and cerebellum.

Nevertheless, it has been noted that the adaptive reorganization relied on various levels in the adult neuro-motor system. They were in the cortical and subcortical motor centers, in the spinal cord regardless of the level of the injury, and also relied in the residual motor fiber tracts that connect various levels (Raineteau & Schwab, 2001). There

are two possible underlying mechanisms of the functional reorganization: one is in the pre-existing circuits served as synaptic plasticity, and the other is the sprouting and anatomical reorganization that may result in the formation of new circuits. Also Courtine et al. (2008) pointed out that the reorganization between descending inputs and intrinsic spinal cord circuits that relays information from lesion sites is the substantial basis for the preservation and adaptive changes of the supraspinal control. In addition, the corticospinal tract (CST) and the extrapyramidal system, such as the reticulospinal system also contribute to the reorganization. Freund et al. (2012) evidenced that CST integrity is directly correlated with lower spinal cord area (SCA) and cortical reorganization, based on the anatomical changes that loss of CST axons and/or myelin in humans with chronic complete thoracic SCI has been evidenced by diffusion tensor imaging (DTI) analysis. While, with the lesion model of macaque monkeys, Zaaimi et al. (2012) evidenced that medial brainstem pathways, mainly the reticulospinal systems, undergo functional changes after corticospinal lesions, rather than the spared ipsilateral corticospinal fibers. It is assumed that these plastic changes in the extrapyramidal system also have influences on the functional recovery of SCI (Hurd et al., 2013).

It is widely considered controversial whether the preservation of motor representations exists after SCI. In some earlier studies, they

found that motor representations are not disappeared after SCI, and that motor imagery (MI) is preserved by the current ability to implement the motor task (Hotz-Boendermaker et al., 2008). Oppositely, with Jurkiewicz et al. (2007)'s longitudinal observation on the progressive changes of brain activation with the restoration of wrist extension, it showed that the cortical reorganization following spinal cord injury depended on the current ability to execute the movement for the lasting physical experience and sensory feedback. Another updated study found some interesting results (Freund et al., 2011). Firstly, there was a fronto-parietal transformation representing that the motor representation of the complex task was processed as a novel and cognitively demanding task, and this has been evidenced by another study with the activation on pre-frontal cortex rather than motor cortex during physically engaged task (Olsson & Nyberg, 2011). In addition, the inferior frontal gyrus have been activated as the demand on working memory and episodic memory within the context of working memory and long-term memory tasks (Ranganath et al., 2003). Secondly, although the SMA was activated regardless of the ability to execute the movement or not, a different part of SMA relevant to the motor control and already stored motor representations was activated, rather than the motor learning area—which was activated in the normal control group. As a result, this shift of neural networks suggested that

original motor representations were altered after a complete spinal cord injury, and the cortical motor representations will be reorganized. In general, it was speculated with these findings that even if the SCI performed a high load of general physical training, reorganization of the motor representations of motor tasks would take place after SCI.

The Underlying Mechanism of Brain Reorganization after SCI

To match the internal representations of the actual and possible condiitons of the limbs is the neural basis for planning, preparing and executing action (Frith et al., 2000). In view of the theories articulated before, with comparison between the predicted sensory consequences of the action and the actual sensory feedback, it is practical and available to match the final position of the limbs with a voluntary movement (Desmurget & Grafton, 2000; Wolpert & Ghahramani, 2000).

Since peripheral cutaneous and proprioceptive afferents of the lower limbs are unavailable in complete SCI patients, this process can be accomplished solely by means of stored motor programs and the resulting stream of motor commands with their sensory signals generated through corollary discharge (Blakemore & Sirigu, 2003). The additional fact that the SCI patients have continuous daily visual control of their body may also play a role in maintaining an internal

representation of their limbs through a continuous updating by simply looking at them (Schiffer & Schubotz, 2011; Wolpert et al., 1998). These speculations are supported by the retained integrity of the internal action representation.

Spatial and biomechanical properties related to the moved body part, such as the proprioceptive, kinaesthetic and visual information, were detected and matched to the motor schemas, in which stored in the premotor and motor regions, in order to perform the movement preparation and execution (Gerardin et al., 2000).

Once the movement command produced, the parietal lobe, in particular, the superior parietal lobe, also receives the copy of this command, which was matched onto the internal template to estimate and produce expected outcomes (McGonigle et al., 2002; Wolpert et al., 1998). Other brain areas, such as the premotor cortex, also receive the efference copy, and prepare for the errors adjustments once detected by the comparison and estimation of the sensory outcomes (Lewis, 2006). In the individuals with SCI, the sensory feedback is modified or absent, the internal mechanisms expected the sensory consequences of an action and produced the location of a limb, instead of the actual sensation of the limbs in the environment.

It has been articulated that the visual and kinaesthetic information of the limbs were stored in the parietal areas, in accordance

with the motor regions (Sirigu et al., 1996; Stecklow et al., 2010). A few of studies reported that the inability on maintaining an internal representation of the body and internal movement simulation results from the damage to the parietal lobe (Macuga & Frey, 2014; Sirigu et al., 1996; Wolpert et al., 1998). These findings imply that incorporating into the cerebellum in sensorimotor integration, the parietal cortex plays an important role in learning skills and retrieving of skilled movements (Andersen & Buneo, 2003; Blakemore & Sirigu, 2003; Shadmehr & Holcomb, 1997). The plastic and adaptive changes were observed as the enhanced parietal and cerebellar activations in chronic SCI patients when performing motor attempt (MA) and MI. The reorganization of the cerebral cortex is not obvious in the short term following SCI, and that partially preserved sensory cortex function may contribute to maintaining neural function. And in individuals with SCI, involvement of stronger cognitive component during MA and MI, such as the polar frontal cortex and parietal lobe, which related to the motor memory retrieval (Smith et al., 2010). In short, the functionality of these areas might be reorganized by the absence of sensory input to maintain a body representation, so as to make motor plans functionally.

In essence, whenever the time, deafferentation means that there is no sensory feedback to adjust the command to move the limb and so the limb is perceived to have moved intentionally.

Moreover, these plastic changes could be induced by special interventions. For example, the robotic BWSTT, one kind of the intensive task-specific rehabilitative trainings, can facilitate supraspinal plasticity of motor centers, which involved in locomotion in motor-incomplete SCI. And the improvements in over-ground locomotion were followed by the increased activation in cerebellum (Winchester et al., 2005). Despite lack of voluntary motor control and peripheral feedback for the individuals with complete SCI, the motor performance were improved by the motor imagery training as altering brain function, especially the activation changes in the putamen, globus pallidus, and primary motor cortex (Cramer et al., 2007). Also the routine intervention and the restoration after injury contribute to the brain reorganization after SCI (Kokotilo et al., 2009). Therefore, attention should be paid to the clinical interventions and rehabilitation training of SCI for its role in the plastic changes in further research.

Summary

In general, voluntary movements consist of two basic processes, motor preparation (motor planning and programming) and motor execution (Cui et al., 2000). The motor preparatory activity is also referred to as “set activity,” which reflected motor planning, and motor programming and possibly the suppression of automatically intended

movements. Based on the knowledge of motor learning, motor skills could be stored in the special brain structures as the long-term motor memory, in the form of the movement-related invariants encoding in the conceptual representational frameworks in long-term memory as elements, units or nodes, such as the duration and force of the muscle activation. After attaining the motor skill being encoded, with the retrieval and later performance, this initial training could be consolidated and reconsolidated as long-term motor memory in seconds and years. Then a recall and recognition memory could be retrieved according to the movement demands. Combining the retrieval of these motor invariants/representations and the encoding of the actual feedback from the peripheral and environment, more adjustments and adaption were edited into the instant movement commands to execute the actual movement, resulting in behavior. In other words, the long-term motor memory picked up is necessary for the motor planning and motor preparation as a template to perform the movements acquired before. If the patient is lacking in the later performance after acquiring the motor skill, what will happen in the reconsolidation of this motor memory? Up to now, there was no report about this issue. The doubt we should further explore is the loss of long-term motor memory or the disability of the retrieving of the long-term motor memory.

In the analogy with the visual projection system, the most important neural substrates, the frontal cortex, thalamus, basal ganglia and cerebellum, within the motor control output system, play their own respective roles. The frontal cortex is the projection screen, and the thalamus is the lens-controlling projector. The basal ganglia, as the projectionist, selects one motor memory from the frontal cortex to assure only one motor memory to be executed. The cerebellum, performing as motor movie components through the functions of record and playback machine, stores the segments of learned motor movie containing skeletal output. There are three main areas related to the motor control output, which are the prefrontal cortex, premotor cortex and M1. The prefrontal cortex, which houses the patterns of procedural memory, plays the role of motor planning. The premotor cortex contains learned patterns to coordinate many small movements into a large complex movement, as well as the force and velocity. M1 directly controls the motor neurons in the spinal cord with receiving the motor input from the premotor cortex and cerebellum via the ventral lateral nucleus of the thalamus. In additional, the declarative memory system and the motor memory system interact and interplay efficiently with each other within the pattern detection to perform accurate voluntary movements.

Both the attempting move and mental evocation of the lower

limbs could activate the sensorimotor cortex. There are not necessary to processing the sensitivity and motion about the lower limbs in order to activate the cortical networks of motor control without ascending and descending spinal tracts. It is now important to know how much this kind of neural processing is maintained after the accident to spinal cord (Sabbah et al., 2000).

The brain function is central to voluntary movement, and it was deranged substantially after complete SCI. Histological, electrophysiological and neuroimaging studies have revealed that both structural and functional changes would take place after SCI. In spite of a number studies having been carried out in this field, the findings are not thoroughly consistent, such as the neural substrates and volumes activated, the spatial shift, the reservation of the motor representations, as well as the underlying mechanisms, because of the existence of many confounding factors, for example, the homogeneity of the SCI participants, the injury level, the time post injury, complications and the rehabilitation training. Thus, all of these should be considered and clarified in future studies.

Although we don’t know if these plastic changes will help or hinder for the restorative treatments, essentially, it is the abnormalities of neural events comparing to the normal subjects. These abnormalities are potential factors, which is important to the movement restoration

after SCI. Therefore, it is vital for us to make clear what the exact changes after SCI are, how they occur, and what are the influences on the brain and functional recovery. Further, clinical interventions that aim to improve motor function after chronic SCI likely also need to attend to these abnormalities of brain function.

Rationale and Hypothesis

Rationale

Reorganization of brain function in people with CNS damage was common, and has been identified as one of the preliminary mechanisms involved in the recovery and rehabilitation of sensorimotor function. Changes in both cortical and subcortical areas activated were found of individuals with SCI. These patterns appeared to be dynamic and influenced by the level, completeness, and time after injury, as well as extent of clinical recovery. In addition, several aspects of reorganization of brain function following SCI resembled those reported in stroke. These studies demonstrated that brain networks involved in different demands of motor control remain responsive even in chronic paralysis. In the individuals with spinal cord injury, the ascending and descending fibers in spinal cord are disrupted, resulting in the abruption of the motor commands to the muscles as well as the sensory and proprioception feedback to the brain structures. So the

movements (and possibly sensory function) of the body parts below the level of the lesions in the spinal cord are not intact. So, whether SCI can generate such conditions in the brain (top-down) is the key question to answer, as disconnected sensorimotor areas are typically preserved while their efferent motor commands do not reach the effectors, and, consequently, no longer receive appropriate afferent feedback. It is currently unclear how the disruption of motor efferents and sensory afferents influences brain motor control function.

Motor planning, motor program and motor preparation are mediated by long-term motor memory. It is henceforth important for us to gain an understanding of how motor-related long-term memory could be modulated by lack of motor performance and feedback. We used chronic spinal cord injury as a model for studying this phenomenon. As kinesthetic imagery has been found to share an overlap neural network with that of motor execution, a mental imagery paradigm can tap on intended motor execution of individuals with spinal cord injury as the actual execution of movement is impossible in this group. MI involves in internal activation of the representation of a specific motor action without any overt motor output and is governed by the principles of central motor control (Sharma et al., 2006). The neural network of MI overlapped partially with the motor control loop.

As elaborated above, the brain motor system function is known

to be deficient after SCI. Motor output is dynamic and adjustable, it requires modulation and adaption during the performance of most tasks. The effect of chronic SCI on modulation of brain motor function, and the ability of motor intention and motor preparation are to be explored by this study. Patients suffering from complete lower thoracic SCI provide a unique model for an accurate comparison with healthy control in brain activation respectively under upper-limb condition (normal) and lower-limb condition (affected) during motor imagery, without any effects from systematic bias of motor function. In addition, it may be clinically and scientifically meaningful to investigate the differences between the sub-acute and chronic SCI individuals. This study is important as it would help understand the mechanisms of the reconsolidation and maintenance of motor-related long-term memory and the role of afferent feedback from the peripheral to maintain the motor-related long-term memory.

Research Question

1. Which neural substrates would undergo changes in individuals currently suffering from SCI, due to deprivation of experience in motor execution in the lower limbs?

2. How would the plastic changes modulate the neural processes associated with imagery of motor execution in the lower limbs?

3. How does the lack of experience in motor execution modulate the processes related to motor preparation and motor-related long-term memory?

Hypothesis

There were two motor imagery tasks employed in this study. They were imagery of repetitive movements in the lower limb and the upper limb conditions.

Under the lower-limb condition, it was hypothesized that participants in the SCI group would have lower performances in terms of accuracy rates and response times than the participants in the healthy control group. The reason would be that the SCI participants did not have experience in lower limb movements after injuries in the spinal cord, which compared less favorably with the healthy control participants. The lack of experience would result in the SCI participants less readily recalling visuomotor images during the imagery processes. It was also hypothesized that the SCI participants would have weaker BOLD responses than the healthy control participants associated with the imagery processes of movements in the lower limb condition. The neural substrates eliciting the BOLD responses would include the primary sensorimotor cortex, the SMA, the parietal cortex, the prefrontal cortex, and the cingulate gyrus. The SCI participants would have lower performances than the healthy control participants on the

cognitive tests. It was hypothesized that the results of the cognitive tests among the SCI participants would have significant relationships with their performances on the lower limb condition of the motor imagery task, and the BOLD responses related to the post-SCI plastic changes.

Under the upper-limb condition, there would be no between-group differences in the task performances. This is because the experiences in movements in the upper limbs would be similar in both groups. It was hypothesized that the BOLD responses of the SCI participants would be different from those of the healthy control participants, which reflect systemic neural changes after injuries to the spinal cord. The differences in the BOLD responses would be found in the primary sensorimotor cortex (suggesting over-excitability) and in the basal ganglia (suggesting inhibition of excitability), and in the parietal and frontal cortices associated with the modulated processes in visualizing movements of the upper limbs.

Chapter 3

Method

This chapter provides an overview of the study design, describes the fMRI task and scanning protocol, and introduces the approach to the statistical analysis.

Subjects

Nineteen healthy participants and eighteen participants with chronic spinal cord injury (Table 3.1) were recruited from China Rehabilitation Research Center (CRRC) in Beijing. The two groups of participants were matched on age, gender, education and time point of scanning. All the participants were recruited through posting recruitment notices on the notice boards in CRRC. Participants with SCI who satisfied the inclusion and exclusion criteria (see below) were asked to attend a clinical interview and physical examination to determine the level and completeness of injury. They were conducted by a medical specialist on spinal cord injury at CRRC.

The procedures of this study were vetted and approved by the Ethics Committee on Human Studies of CRRC and Departmental Ethics Committee of Department of Rehabilitation Sciences, The Hong Kong Polytechnic University. Each participant was asked to sign a written informed consent form with a description of the study, risk of fMRI scanning, study procedures, as well as the transportation tool

prior to participation in the study. Each participant was assigned a code which was utilized throughout the whole study, including the training, scanning, data processing and analysis.

Table 3.1 Clinical data and neurological grades using the American Spinal Injury Association Impairment scale (ASIA) of SCI patients

No.	Age	Sex	Aetiology	Injury level	ASIA	Time post injury (months)
301	37	M	Fall	T11	A	9
302	38	M	Fall	T10	A	12
303	41	F	Traffic accident	T11	A	13
304	23	F	Fall	T10	A	41
305	28	F	Traffic accident	T10	A	44
306	16	F	Traffic accident	T7	A	67
307	55	M	Fall	T10	A	79
308	52	M	Heavy pound	T10	A	52
309	40	F	Heavy pound	T8		97
310	46	M	Traffic accident	T6	A	107

311	33	M	Traffic accident	T8		98
312	57	M	Traffic accident	T6	A	172
313	32	M	Fall	T10	A	63
314	28	M	Sports	T10	A	35
315	49	M	Fall	T10	A	110
316	36	M	Fall	T8	A	76
317	33	F	Heavy pound	T10	A	85
318	31	M	Traffic accident	T6	A	56

Inclusion criteria

- All are between 18 and 55 years old (to decrease the confounding effect of aging on cognition).
- Right hand and foot dominance assessed with Edinburgh Inventory (Lacourse et al., 2005; McFarland & Anderson, 1980); foot dominance assessed with the Waterloo Footedness Questionnaire – Revised (Elias et al., 1998; Mulder et al., 2004).
- Good general cognitive function assured by the Mini Mental Status Examination (MMSE) (Gupta et al., 2008; Hannesdottir et al., 2009). The scores should be at or more than the following for different education levels: illiteracy ≥ 17, primary school level ≥ 20, middle school level or higher level ≥ 24.
- Good auditory function evaluated by the Pure Tone Audiometry (Kim et al., 2009).
- Good visual function evaluated by the Visual Functioning Questionnaire (VFQ-25).
- For the SCI group, traumatic injury to the spine resulting in complete lesions in the spinal cord classified as grade A with AIS (American Spinal Injury Association Impairment Scales), which means there is not any motor or sensory residual below the injury level (Kraus et al., 1975; Hagen et al., 2010). Further,

complete lesion levels to the spinal cord are between T7 (7th thoracic) and T12 (12th thoracic) according to AIS evaluation (see Appendix Ⅳ). And, the time of injury for the chronic SCI is at least six months of history of paraplegia (Yoon et al., 2007; Syklova et al., 2006).

Exclusion criteria:

- Documented traumatic brain injury (TBI). Any case in the following retrospectively reviewed from the medical document or history will be excluded (Stein & Spettell, 1995; Hagen et al., 2010; Tolonen et al., 2007).
- The score of Glasgow Coma Scale (GCS) is less than 15.
- Loss of consciousness (LOC).
- Post- traumatic amnesia (PTA).
- Seizure.
- Palpable depressed skull fracture.
- Brain surgical intervention.
- Any intracranial lesion on neuroimaging examination.
- Any finding in the neurological examination by the neurologist.
- Diagnosed in the medical document.
- Documented autonomic dysreflexia (AD). The criteria for diagnosing AD are based on those defined by the medical team at China Rehabilitation Research Centre using the literature

evidence (Krassioukov et al. 2009). The minimum increase in blood pressure in an AD episode is 20mmHg, i.e., mild/partial and presenting with symptoms such as piloerection and stuffy nose (Krassioukov et al. 2007).

- Diseases of the nervous system
- Previous history of systemic illness, such as cardiovascular diseases (hypertension and cardiac infarction), cerebrovascular accident, diabetes, chronic headache, depression, psychiatric disorders, seizure disorders and convulsions
- Pregnancy
- Acute co-morbidities
- Treatment involving use of transcranial magnetic stimulation (TMS)
- Special occupations that demand skilled lower extremity movements: i.e., professional athletes, pianist.
- Contradictions to MRI study, such as cardiac pacemakers, therapeutic or accidental presence of magnetizable metals or prosthesis in the body, claustrophobia, and so on.
- Additional exclusionary criteria differed by group, with chronic SCI group excluded from serious complications, such as ulcer pressure, respiratory infection, urinary tract infection, deep vein thrombus, as well as other physical discomfort.

- History of alcohol and drug abuse.

The following clinical information was collected only when SCI participants were recruited. It included the occupation before injury, daily activities before injury, cause of injury, unconsciousness during injury, medical history, medication list, complications (such as spasticity, pain, etc.), alcohol use before and after injury, recovery from SCI, SCI residual impairments and disabilities, social history, daily activities after SCI, and the rehabilitation training.

Study design

The Repetitive Movement Imagery task

The experimental paradigm used within functional brain imaging was repetitive movement imagery task, herein called motor imagery task. The motor imagery task required the participant to mentally rehearse alternate and repetitive tapping of the lower limbs (involving both left and right ankles) or the upper limbs (involving both left and right wrists).

There were two conditions in the motor imagery task, upper versus lower limbs. All the movements were rhythmic and alternating involving the right and left limbs. The participant was to keep pace with the internally generated rhythm and imagine the right and left limbs tap alternatively on a table (whereby the upper limb was the hands) or on the floor (whereby the lower limb was the feet), and

henceforth the movements of the limbs according to the rhythm. The participant was asked to attend and visualize the movements (start with the right side) and by the end of the task respond by identifying which side of the limb would be towards the platform. Before the experiment, the participants practiced on each of the conditions under different rhythmic patterns (0.8, 1, and 1.33 Hz) and debriefing was conducted on the imagery process and the skills mastered.

Experimental task design

A trial began with displaying a cross (500~2000 ms), which denoted the beginning of a new trial (See Figure 3.1). A train of three 500 ms low pitch (300 Hz) and rhythmical tones was presented. The tone indicated the frequency of the rhythm of which the repetition or tapping movements would be imagined. The frequencies of the tone varied across trials ranging from 0.8, 1, to 1.33 Hz. The participant was to follow the rhythm of the tones and began visualizing the movements one after the other. The participant continued to visualize the movements according to the rhythm until the presentation of a 500 ms high pitch tone (1700 Hz). The scanning began after the presentation of the 3rd low pitch tone.

The movement always began with the right limb in a starting position—placed on the platform, whereas the left limb is on the top of uprising position. After hearing the high pitched tone, the participant

would pause the visualized movements and indicate which side of the limb at that instance was towards the platform by pressing on the button (using right index finger for right-side limb, and right middle finger for left-side limb) on a keyboard. The time between the beginning of the presentation of the 3rd low pitch tone (denoting the frequency of the visualized movements) and the presentation of the high pitch tone (denoting a response) ranged from 2.1 to 4.4 s. The duration of capturing BOLD responses by the scanner was 2.0 s beginning from the presentation of the 3rd low pitch tone. The interval for making responses made by the participant varied from 2.0 to 3.9 s, followed by the beginning of the next trial. The response made by the participant on the keyboard for each trial was registered, while the responses of all valid trials were turned into accuracy rate and mean response time of the participant.

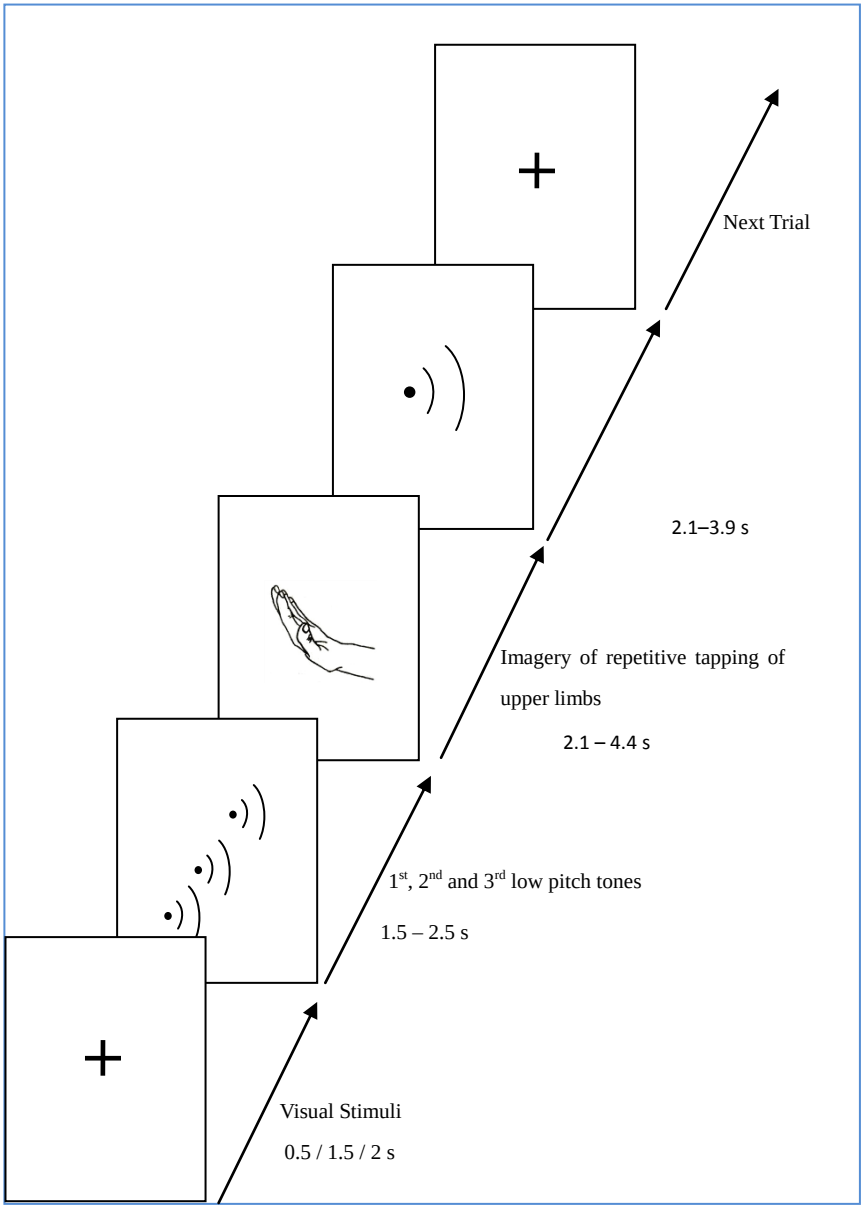
There were two conditions in the motor imagery task: upper limb tapping and lower limb tapping. Under each condition, there were three frequencies set for the repetition of the movements to be visualized. Each frequency had four variations with each referring to a specific moving direction to the platform of the right or left limb at equal probabilities. They were 12 trials from each frequency with a total of 36 trials for each condition. These 36 trials were divided into two blocks, with equal probabilities moving towards the platform and equal

block time, lasting 170 s. Each trial in one block occurred randomly. After completion of one block, there was a rest period that lasted for 30 s. There were two task blocks and two rest periods in one session, and the session for upper limb condition began first with the following session for lower limb condition. The duration of one session was 6 minutes 40 seconds. Relatively fewer trials were employed in each task condition. This was meant to strike a balance between the power of the analysis and the time required for completing the functional scans. As a consequence, interleaved task and rest trial design was not adopted as this would further weaken the power of the analysis (Mastrovito, 2013; Northoff et al., 2010 a & b). Each participant completed two sessions. The total duration of completing the motor imagery task and functional scanning was 13 minutes and 20 seconds.

During the imagery of the repetitive tapping movements, the participants were instructed to visualize the left and right ankles (in the lower limb condition) or the left and right wrists (in the upper limb condition) engaging in rhythmic and alternative tapping movements. The movements began with the right limb posing on the platform as the starting position, whereas the left limb was on the other side of the extreme point as wrist or ankle extension. Once the first low pitch tone was given, the right and left limb began tapping in opposite directions. For the lower limb, no matter the frequency of the imagined tapping

movement, the right foot would complete the movement cycle by settling on the floor (plantarflexion at the right ankle) when the left foot lifting up from the floor would achieve the extreme point of extension (dorsiflexion at the left ankle). For the upper limb, no matter the frequency of the imagined tapping movement, the right hand would complete the movement cycle by placing the palm on the table (flexion at the right wrist) when the left hand lifting up from the table would achieve the extreme point of extension (extension at the left wrist). The frequency of the taps should follow that indicated by the three low pitch tones. The visualization of the alternating "left-right-left …" tapping towards the platform was to continue until the presentation of the high pitch tone. When the high pitched tone sounded, the participant was to freeze the imaginary movements and recall the direction of the limb movement. The response indicating the direction of the imaginary movement was made by pressing on a respective button on the keyboard.

Figure 3.1 Summary of the paradigm of the motor imagery task (take the upper limb as example)



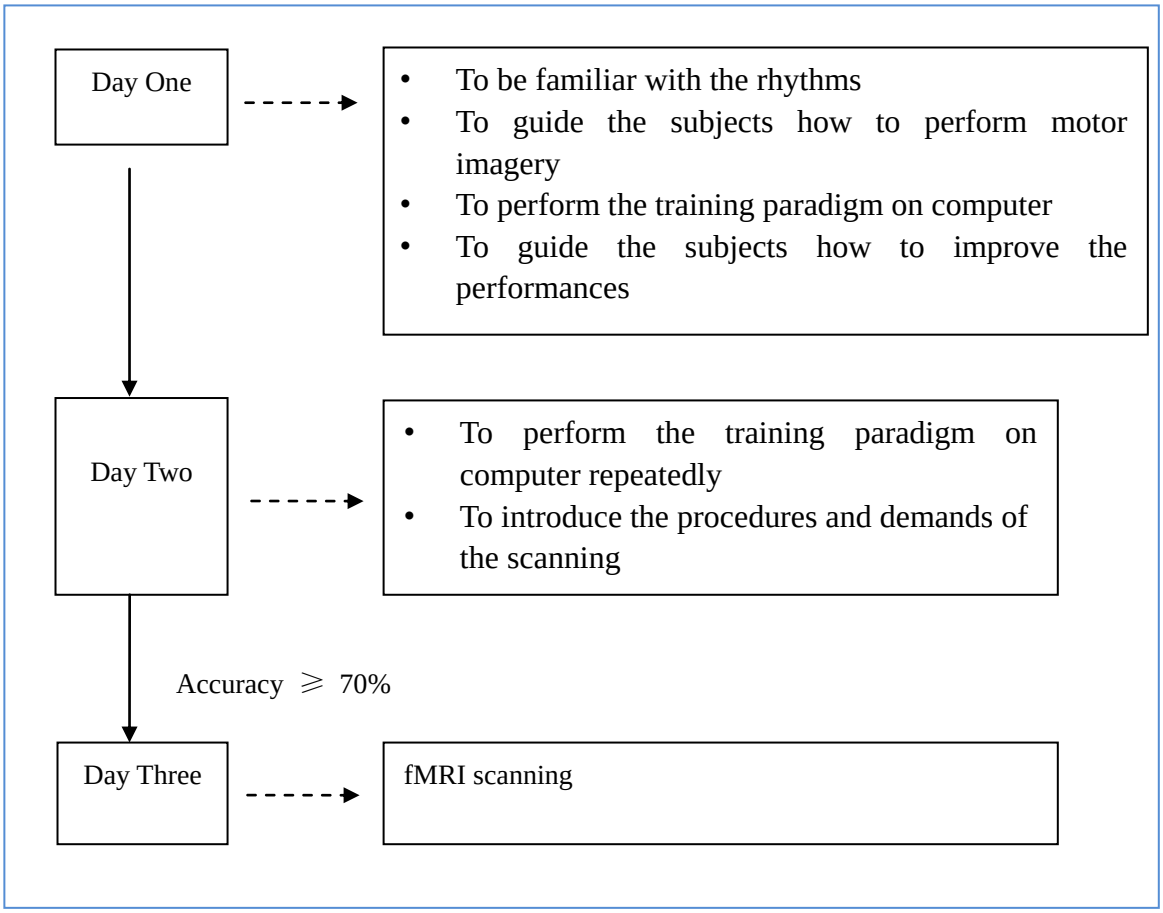
Training session

To ensure optimal task performance, participants were trained on the task processes before entering into the scanner and perform on the motor imagery tasks. There were two consecutive training sessions with each conducted on one day. The scanning session was conducted

on the following day after completing the two-day training (Figure 3.2). In the first training session, the participant was to be familiar with low pitch tones, which were differentiated according to three different rhythms (0.8 Hz, 1 Hz, and 1.33 Hz). Two video clips were prepared for the participant to view, which captured the movement requirements respectively for the upper limb and lower limb conditions. The clip for the upper limb condition showed the rhythmic and alternating movements of the left and right hands (movements at the wrists). The clip for the lower limb condition showed the movements of the left and right foot (movements at the ankles). The participant was reminded to view the actual movements of the limbs carefully. The participant was instructed to mentally mimic the movements as shown in the video clips. Thus, the subjects carried out the training paradigm with the computer, and the feedback of the accuracy was given to the subjects and they were taught how to improve the accuracy. The first training session lasted for about 30 minutes. The second training session focused on familiarizing the participant with the motor imagery tasks to be conducted when he/she was in the scanner. The procedure and task requirements were explained to the participant. The participant was to complete the four blocks of task conditions. The responses made by the participant were collated and checked. The participant would continue on the second round of the task until the accuracy rate reached 70%.

The time for the participant to complete the second training session ranged from 25 to 30 minutes.

Figure 3.2 Summary of the training protocol



Procedures

The potential subjects firstly were screened by a telephone interview after each registered on the notice board, and then evaluated by a senior clinical doctor, Dr. Yang, through a set of physical examinations and measurements, including general physical examination, visual and auditory testing, general cognitive measures,

handedness and dominant foot, the ability of motor imagery, as well as the specialized neurological examination for the SCI subjects. The valid subjects were confirmed with the inclusion and exclusion criteria described above.

When the subjects decided to participate in this study, a tentative date for the fMRI scanning would be scheduled. Two days before the scanning, the training session began, and the subjects received the standardized training described as the "Training session" above so as to assure the accuracy of completing at least 70% of the task.

With the aim of training obtained, the subjects were transported to Beijing Xuanwu Hospital to carry out the fMRI scanning. On the same day of the scanning, the subjects were asked to finish the neuropsychological tests with a certified psychologist, including the Digit Span Forward Test, the Digit Span Backward Test, the Rey Verbal Auditory Learning Test – Chinese Version, the Symbol Digit Modalities Test, the Trial Making Test A & B – Chinese Version, and the Stroop Test – Chinese Version (Jegede et al., 2010). (See Appendix Ⅴ-Ⅸ)

All subjects were asked to avoid caffeine or alcohol for at least twelve hours prior to behavioral testing or fMRI scanning.

After the end of the imaging experiment, subjects were questioned whether they use any mental strategy to perform the

experimental task and whether they had recognized any difference in the rhythm of the sequences presented during the entire scanning session.

Instruments

Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT consists of the short-delay recall, long-delay recall, and the recognition subtests, which contributes to evaluate the memory function. The words recalled correctly in each subtest (the immediate recall, short-delay recall, and the recognition test) was calculated and recorded as the scoring (Richards et al., 1988). With this test different domains of memory were evaluated, including the short-term auditory-verbal memory, learning strategies, retroactive and proactive inhibition, presence of confabulation of confusion in memory processes, retention of information, and differences between learning and retrieval (Ricci et al., 2012; Schoenberg et al., 2006). In this study, the attention was paid to screen the ability of immediate recall, short-term memory, retrieval, and recognition by the direct results of these three subtests.

Digit Span Forward and Backward Test

In the Digit Span Forward and Backward Test, a list of numbers is read out at the rate of one per second, and the test begins with three numbers increasing until the subjects commit errors during the repeating stage within the requirements in the exact order or in the

reverse order (Gupta et al., 2008). One trial recalled correctly was scored as 1, and the total scores were calculated respectively for the forward and backward test. The attention and short-term memory (or working memory) was assessed with this test.

Symbol Digit Modalities Test (SDMT)

The SDMT detects cognitive impairments on visuoperceptual processing, working memory, psychomotor speed and integration (Sheridan et al., 2005). Using a reference key, the examinee has 90 seconds to pair specific numbers orally with given geometric figures (Dowler et al., 1997). The numbers of the paired numbers with correct response and with uncorrected response were calculated as the scoring.

Trail Making Test (TMT)

The TMT requires the subjects to ‘connect the circles’ of 25 consecutive targets on a sheet of paper as quickly as possible. Both Part A and B were adopted. In Part A, the targets are all numbers, whereas the numbers and letters alternate in Part B. The time cost respectively was calculated as the scoring. For the variance of the tasks, different domains of cognition were evaluated. Part A is to evaluate the processing speed mainly, whereas Part B is responsible for the assessment of set shifting dominantly (Waldstein et al., 2005; Jegede et al., 2010).

Stroop Test

The Stroop Test consists of three parts: the Stroop Word, Stroop Color and Stroop Word-Color. In Stroop Word and Stroop Color subtests the participants were required to read the word themselves and the color of the symbols respectively as quickly as possible. In the Stroop Word-Color subtest, the participants were required to say the print-color of the letters independently of the written word. The reaction time in each part was scored to evaluate the attention processing speed with part one and part two, and to evaluate the interference or response inhibition with part three (Dowler et al., 1997; Jegede et al., 2010).

fMRI acquisition

Equipment

All fMRI scans were conducted at Beijing Xuanwu Hospital on a 3 Tesla scanner (Siemens Medical Solutions, Germany). Earplugs and headphones were given to the subjects to get the order and auditory stimuli, avoid the noise of the MRI machine, and to enable communication. The subjects' heads were placed in the foam cushions surrounded to restrict movement throughout the scanning. Visual Basic (Visual Studio 2005 version) installed in a standard RRI computer was used to present the visual stimuli. The visual stimuli were projected on a screen in front of the scanner, and seen by the subject in the way of a mirror attached to the head coil. The exact spot, the angle, and the

height of the screen was adjusted and marked in the floor, so as to ensure the same conditions of the visual stimuli for all participants.

Parameters

BOLD functional images were acquired using T2* weighted gradient echo planar imaging (EPI) sequences covering 32 slices (3 mm thick, zero gap), aligned oblique axially, and encompassing the entire cerebral cortex. The parameters for functional images are the following: TR=2000 ms, TE=30 ms, FOV=220 X 220, flip angle=90 °, voxel size=3.4 X 3.4 X 3.0mm, interleaved acquisition.

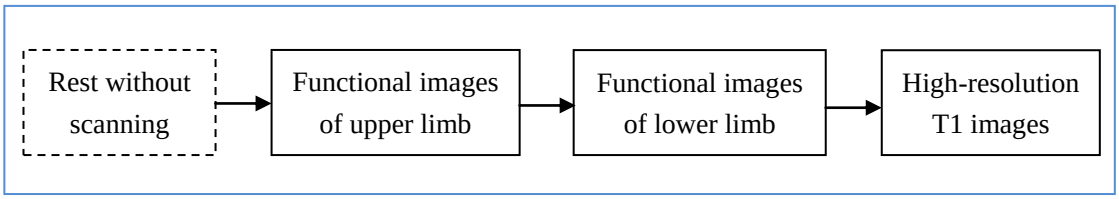
The parameters for structural images are the following: TR=1600ms, TE=2.13ms, FOV= 256 X 256, flip angle=90 °, slice thickness=1mm (no gap), voxel size= 1.0 X 1.0 X 1.0mm, interleaved acquisition.

Scanning protocol

With the visual stimuli and auditory stimuli equipment placed down appropriately, the subject lay down for a break of about two minutes (See Figure 3.3). Firstly, the task-related functional imaging was collected with the same EPI sequence when the subject performing the motor imagery task. The last step was to acquire the high-resolution T1-weighted structural images by using a MP-RAGE sequence. The structural images were used for normalizing individual brain structure to standardized space and localizing anatomical structure in order to

facilitate the precise determination of the structures in relation to the functional activation sites.

Figure 3.3 Protocol of the brain scan



Data analysis

Behavioral data

Both the accuracy rate and response time of the repetitive and daily tasks were recorded. The comparison within two factors, i.e., Group (chronic SCI versus healthy control), and limbs (upper limb versus lower limb) will be performed using repeated ANOVA in SPSS 17.0.

Functional imaging data

Image preprocessing

All fMRI images were analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm). Firstly, the first 10 images were discarded to allow for T1 equilibration effects. Then, the scanning quality was checked by artifacts in the images, and whole data of subject number 311 and the lower limb related data of subjects 114 and 310 were excluded. Manual correction was the primary step to make all the

images match with the MNI template, and the midpoint of anterior commissure (AC) was fixed up as the coordinate X=0, Y=0, Z=0, and the AC-PC (posterior commissure) line was corrected horizontally to make sure the coordinate of PC was X=0, Z=0.

The preprocessing of all the functional images was carried out by the following sequence: Slice Timing; Realign:Estimate & Reslice; Coregister:Estimate; Segment; Normalize:Write; and Smooth (www.bic.Mni.mcgill.ca/brainweb).

Slice Timing was used to correct differences in image acquisition time between slices. In my study, the slice order was "2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31," and slice 31 was selected as the reference slice. The lower limb data of subjects 115 and 318 were excluded for some unclear mistakes during the processing.

Realign:Estimate and Reslice was to remove movement artifact in the scanning by a 6 rigid body spatial transformation. The subjects were excluded with head motion of more than 1.5mm maximum displacement in any of the x, y, or z directions, or 1.5 º of any angular motion throughout the course of scan. The whole data of subjects 107, 305, and 314 were excluded.

Coregister:Estimate was to make the structural images match the Mean Image produced in the last step. What I had to mention here was

that in this step, the East Asian Brains template was chosen as the template to conduct Affine Regularization, considering that all the subjects were of the Chinese race. The images were checked with the completion of this process. The entire data of subjects 110, 114, and 310 were removed for the distortion and loss of neural substrates.

Segment was to segment the coregistered images into white matter, gray matter and cerebral spinal fluid, in order to better correct the bias. All the data remaining has a good result in this step (Ashburner & Friston, 2005).

Normalize:Write was to make the realigned images match the Montreal Neurological Institute (MNI) template with the segmented parameter and re-sampled to 3 mm isotropic voxels using the normalization parameters estimated during unified segmentation. Here the bounding box was changed to “-90 -126 -72; 90 90 108” in order to match the brain size. The registration of the functional data to the template was checked for each individual subject.

Subsequently, the functional images were spatially smoothed with a Gaussian kernel of $4 \times 4 \times 4$ mm^3 full width at half maximum (FWHM) to decrease spatial noise.

To further reduce the effects of confounding factors, linear regression was used to further remove the effects of head motion and other possible sources of artifacts (Fox et al., 2005): (1) six motion

parameters, (2) whole-brain signal averaged over the entire brain, (3) linear drift. Following this, temporal filtering (0.01 Hz < f < 0.08 Hz) was applied to the time series of each voxel to reduce the effect of low-frequency drifts and high-frequency noise (Biswal et al., 1995; Lowe et al., 1998; Greicius et al., 2003) by using Resting-State fMRI Data Analysis Toolkit (http://resting-fmri.sourceforge.net).

ALFF analysis

ALFF analysis was performed using REST software (www.restfmri.net). After the linear trend was removed, the fMRI data were temporally band-pass filtered (0.01 < f < 0.08 Hz) to reduce the very low-frequency drift and high-frequency respiratory and cardiac noise (Biswal et al., 1995; Lowe et al., 1998). The time series for each voxel was transformed to the frequency domain and then the power spectrum was obtained. The square root was calculated at each frequency of the power spectrum. This averaged square root was taken as ALFF (Zang et al., 2007). For standardization, the ALFF of each voxel was further divided by the global mean of ALFF values within a brain mask, which was obtained from the intersection of the brain of all subjects' T1 images.

Statistical analysis

A two-sample t-test was performed to investigate the ALFF difference between the patients and normal controls. An uncorrected

voxel-level intensity threshold of $p < 0.05$ with a minimum cluster size of 35 contiguous voxels was used to correct for multiple comparisons using the AlphaSim method (http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf). This yielded a corrected threshold of $P < 0.01$.

Regional time course analysis

A secondary analysis of the regional BOLD time series signal within general linear model was conducted to estimate the effects of task presentation in the regions of interest (ROI). The ROIs were defined as the activated clusters in each anatomical neural substrate based on the previous results of whole brain analysis. Each valid event of imagery task with correct responses was assumed to produce a response lasting 10 time points (~18s response epoch) after the performance of the imagery task, in which the time course of BOLD responses per ROI were computed as the expected hemodynamic response function (HRF), reflecting the real neural activities of as the most reliable index (Boynton et al., 1996; Chung et al., 2006; Hoffman et al., 2011). No assumptions were made about the shape of the response at this stage of analysis.

Correlation analysis

For both the SCI and healthy control groups, Spearman correlation coefficients were carried out between the magnitudes of

MR signal of the ROIs, the clinical measure, the behavioral results during the experimental task, and the specific clinical data for the SCI group. The accuracy rate (ACC), the response time (RT), and the composite quotients (ACC/RT) were computed as the behavioral results from the experimental task. And the clinical measures included the cognitive tests, such as the short delay, long-term delay, and the recognition of the RAVLT, the Digit Span Forward and Backward Test, the TMT A & B, the SDMT, and the Stroop Word, Stroop Color, and Stroop Word-Color test (Jegede et al., 2010). To further explore the relationships among these variables, step-wise regression analysis was carried out when they interacted complicatedly.

Further, clinic data collected were analyzed only for the SCI group, including the time post injury (measured by months), the intensity of rehabilitation training (measured by the numbers of rehabilitation training carried out), the use of wheelchair (measured by the distance everyday), the neuropathic pain (measured by Visual Analog Scale), and the spasticity (measured by the Modified Ashworth Scale, MAS) of the SCI subjects.

Chapter IV

RESULTS

This chapter presents the results of this study. It will begin by comparing the demographic characteristics of subjects in the SCI and healthy control groups, their behavioral results in the experimental tasks, and the clinical measures on the executive function. This will then be followed by a comparison of the BOLD responses captured during the experimental tasks and their associated analyses, including the ROIs and correlational analyses.

Demographic Characteristics of the Participants

After reviewing the responses of the subjects in the experimental tasks, there were thirteen subjects whose results were not valid. Invalid results included low accuracy rates of the behavioral responses made by the subjects in the experimental tasks inside the scanner and low quality of the functional imaging signals captured in the scanning. The thirteen subjects included two SCI and one healthy participants removed due to excessive head motions, one SCI and two healthy participants removed due to low-quality images, and four SCI and three healthy participants removed due to low accuracy rates on the experimental tasks, with values less than 30% for both the upper-limb and lower-limb conditions.

There were 11 SCI patients and 13 healthy subjects entered into the analysis. The demographic characteristics of these subjects are presented in Table 4.1. The time post injury in the SCI group varied from 9 to 172 months. Comparisons of the characteristics suggested no significant differences in age [$t(22) = -1.156$, $p = 0.26$], the mean year of education [$t(22) = 1.386$, $p = 0.18$], and the proportions of gender between the healthy control and SCI groups [Chi-square ($df = 1$) = 0.001, $p = 0.973$]. These indicated that the demographic characteristics of the subjects entering into the analysis were comparable across the SCI and healthy control groups.

Table 4.1 Demographic characteristics of SCI patients and healthy

control subjects entered into the analyses

	SCI (n=11)	Healthy Control (n=13)
Male (%)	6 (54.5)	7 (53.8)
Age (SD[#]) (years)	37.1 (12.0)	31.9 (10.0)
Education (SD) (years)	11.1 (3.6)	13.2 (3.7)
Time post injury (months)	64.9 (47.4)	-
Neuropathic pain[##]	5.1 (2.2)	-
Rehab training [###]	3.9 (1.6)	-
Spasticity[####]		
MAS 0	2	
MAS 1	2	
MAS 1+	4	
MAS 2	2	
MAS 3	1	
MAS 4	0	

Key: [#]SD=standard deviation;

[##] Measured by the Visual Analog Scale (VAS)

[###] Measured by the numbers of training programs carried out

[####]Measured by the Modified Ashworth Scale (MAS)

Behavioral Results in the Experimental Tasks

The participants performed the motor imagery tasks inside the scanner. The performances were expressed in terms of accuracy rate and response time. A 2 x 2 repeated measure ANOVA, Condition (Lower Limb vs Upper Limb) and Group (SCI vs Normal Control), was conducted to test the differences in task performances, including ACC, RT, and their composite quotients (Table 3.2). The composite quotients were computed by dividing the ACC by the RT, named as ACC/RT. The results showed that Condition had no significant effect on subjects' ACC [$F(1,22) = 0.458$, $p = 0.51$], RT [$F(1,22) = 3.86$, $p = 0.06$], and ACC/RT [$F(1,22) = 1.372$, $p = 0.25$]. Likewise, Group showed no significant effect on subjects' ACC [$F(1,22) = 0.119$, $p = 0.73$], RT [$F(1,22) = 0.235$, $p = 0.63$], and ACC/RT [$F(1,22) = 0.248$, $p = 0.62$]. The Condition x Group interaction also showed no statistically significant effect on the ACC [$F(1,22) = 1.353$, $p = 0.26$], RT [$F(1,22) = 0.027$, $p = 0.87$], and ACC/RT [$F(1,22) = 0.484$, $p = 0.49$].

For the upper-limb condition, the mean accuracy rates were 45.7% and 46.8% for the SCI and healthy control groups, respectively (Table 4.2). There were no significant between-group differences in the ACC [$t(22) = 0.218$, $p = 0.83$]. The mean RT were 1069.6 ms and 1135.2 ms for the SCI and healthy control groups, respectively. Similarly, no significant differences were revealed between these two groups [$t(22) = 0.452$, $p = 0.66$]. For the lower-limb condition, the

ACC of the two groups were slightly lower than those for the upper-limb condition. The ACC were 49.7% and 45.7% for the SCI and healthy control groups, respectively, and it seemed that the ACC were higher for the SCI than the healthy control group. No significant between-group differences were found [$t(22) = 0.218$, $p = 0.18$]. The RT were 993.6 ms and 1045.3 ms for the SCI and healthy control groups, respectively, which were not significantly different [$t(22) = 0.476$, $p = 0.64$]. In addition, the RT for the lower-limb condition were slightly faster than those of the upper-limb condition in both groups. And in the SCI group, the result of the ACC for the lower-limb condition was higher than that for the upper-limb condition. Although significant differences were observed under both conditions, the ACC/RT seemed only slightly better under the upper-limb condition [$t(22)=-1.051$, $p=0.31$] than the lower- limb condition [$t(22)=0.06$, $p=0.95$].

Table 4.2 ACC and RT of subjects in the SCI and healthy control groups on the motor imagery tasks

	Upper-limb Condition			Lower-limb Condition		
	ACC (%)	RT (ms)	ACC/RT	ACC (%)	RT (ms)	ACC/RT
SCI (n=11)	45.7 (14.2)	1069.6 (358.7)	0.052 (0.012)	49.7 (12.8)	993.6 (295.3)	0.055 (0.022)
Healthy Control (n=13)	46.8 (10.2)	1135.2 (350.9)	0.046 (0.017)	45.7 (9.7)	1045.3 (236.2)	0.055 (0.023)

Behavioral Results on Cognitive Tests

The following tests were administered to subjects one day before the brain scan: Digit Span Forward and Backward Tests; RAVLT; Trial Making Tests A and B (TMT-A & B); SDMT; and Stroop Word, Color, and Word-Color Test. Among them, between-group differences were revealed in two tests (Table 4.3). For RAVLT, the subjects in the SCI group (Mean = 29.5, SD = 3.1) scored significantly lower on Short Delay than those in the healthy control group (Mean = 33.3, SD = 5.2). Those in the SCI group (Mean = 25.3, SD = 3.4) also scored significantly lower on Recognition than their healthy control counterparts (Mean = 28.0, SD = 1.9). Subjects in the SCI group (Mean = 50.3, SD = 36.2) performed significantly lower than those in the healthy control group (Mean = 22.1, SD = 20.3), as reflected from the difference scores (i.e., B minus A) on TMT.

Table 4.3 Performances on cognitive tests of participants in the SCI and healthy control groups

	SCI Group Mean (SD)	Healthy Control Mean (SD)	t-value (22)	p-value
Digit Span Test				
Forward	10.6 (2.1)	11.2 (2.9)	0.562	0.58
Backward	5.1 (3.4)	6.8 (4.0)	1.103	0.28
RAVLT				
Short Delay	29.5 (3.1)	33.3 (5.2)	2.108	0.04*
Long Delay	12.3 (1.8)	12.8 (2.0)	0.735	0.47
Recognition	25.3 (3.4)	28.0 (1.9)	2.302	0.03*
SDMT	46.0 (11.1)	54.3 (12.4)	1.718	0.10
TMT				
A (s)	41.5 (15.6)	32.7 (17.1)	-1.296	0.21
B (s)	91.8 (50.8)	54.9 (31.6)	-2.091	0.05
B-A (s)	50.3 (36.2)	22.1 (20.3)	-2.292	0.04*
Stroop Test #				
Word	0.547 (0.130)	0.454 (0.166)	-1.493	0.15
Color	0.715 (0.119)	0.675 (0.237)	-0.526	0.61
Word-Color	1.118 (0.169)	1.03 (0.245)	-1.015	0.32

Note: # In the Stroop Test, the scores were computed as composite quotients by dividing the time required for completing the test by the number of correct responses.

* $p \leq 0.05$.

Brain Imaging – Whole Brain Analyses

This section presents the results of BOLD responses captured when participants were performing on the upper-limb and lower-limb conditions of the motor imagery tasks. An uncorrected voxel-level intensity threshold of $p \leq 0.05$ with a minimum cluster size of 35 contiguous voxels was used to correct for multiple comparisons using the AlphaSim method (http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf). This yielded a corrected threshold of $p \leq 0.01$.

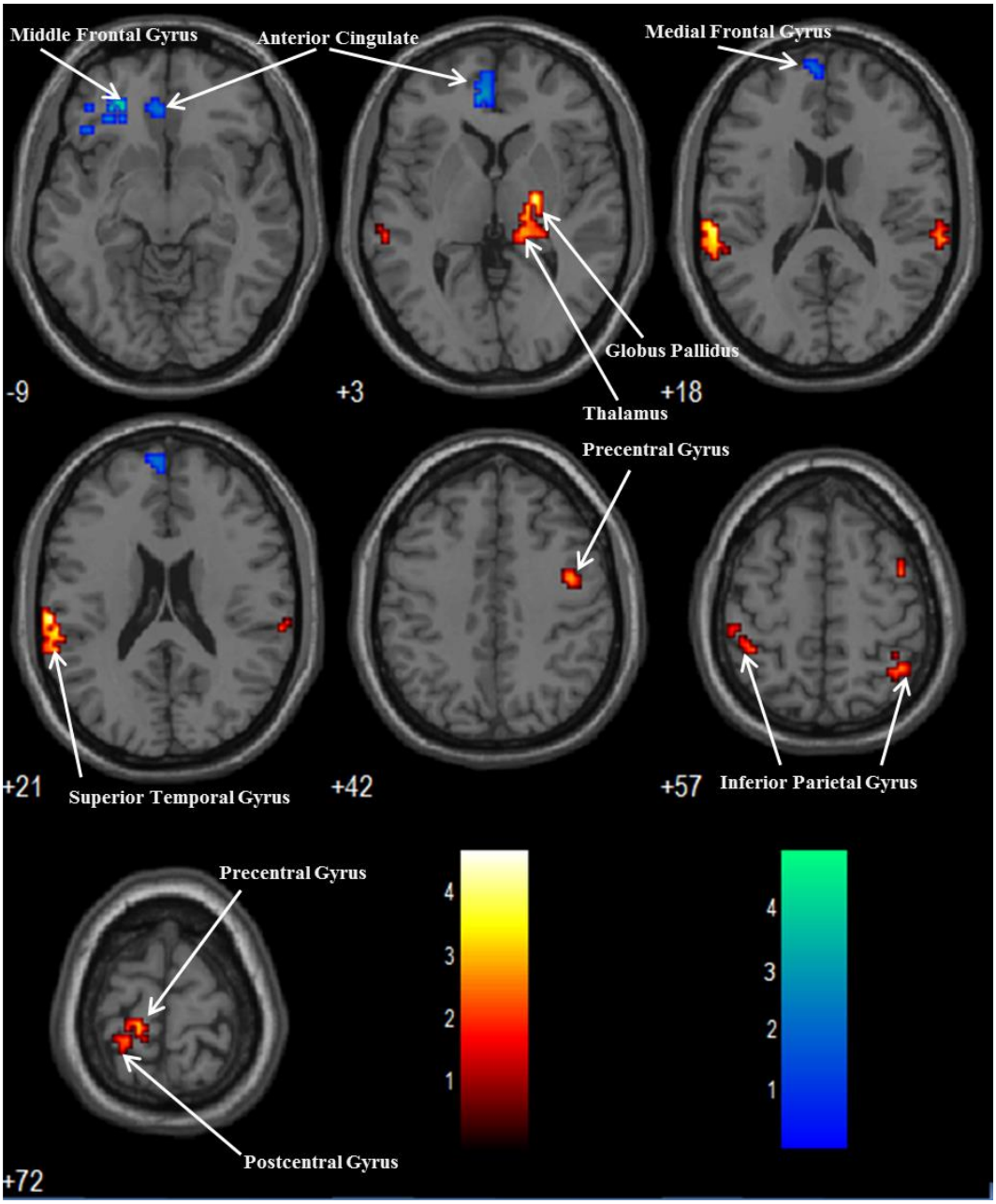
There were two group contrasts conducted for the BOLD responses elicited during the upper-limb condition. For the healthy versus SCI group contrast, the healthy control group showed significantly stronger BOLD responses than the SCI group in the left middle frontal gyrus (BA 11, BA 47), left anterior cingulate (BA 32), and left medial frontal gyrus (BA 10) (Table 4.4; Figure 4.1). For the SCI versus healthy control contrast, the results revealed significantly stronger BOLD responses in the SCI than the healthy group in the left inferior parietal gyrus (BA 40), left precentral gyrus (BA 4), and left postcentral gyrus (BA 2). Stronger BOLD responses in the SCI group were also revealed in the right globus pallidus, right thalamus, right superior temporal gyrus (BA 42), right inferior parietal gyrus (BA 40), and right precentral gyrus (BA 6). Activations in the right globus

pallidus were further located in the lateral aspect of the neural substrate, which is called the external globus pallidus or globus pallidus external segment (GPe), and those in the right thalamus were located in the right pulvinar.

Table 4.4 BOLD responses elicited in the upper-limb condition of the motor imagery tasks between participants in the SCI and healthy control groups (cluster size ≥35, $p < 0.01$with multiple corrections)

Cluster	**Label**	**L/R**	**BA**	**Coordinates(MNI)**			**T-scores**
				x	*Y*	*z*	
	Healthy *vs* SCI						
49	Middle Frontal Gyrus	L	11	-27	42	-9	4.88
108	Anterior Cingulate	L	32	-9	45	3	3.06
	Medial Frontal Gyrus	L	10	-6	63	21	2.32
	SCI *vs* Healthy						
74	Inferior Parietal Gyrus	L	40	-63	-24	21	4.70
90	Globus Pallidus	R		21	-12	3	4.18
	Thalamus	R		15	-30	0	3.98
93	Precentral Gyrus	L	4	-15	-30	72	2.97
	Postcentral Gyrus	L	2	-42	-39	63	2.84
37	Superior Temporal Gyrus	R	42	66	-33	18	2.77
42	Inferior Parietal Gyrus	R	40	42	-51	57	2.65
39	Precentral Gyrus	R	6	42	-3	42	2.54

Figure 4.1 Group contrasts of BOLD responses between the SCI and healthy control groups when performing the upper-limb condition of the motor imagery task



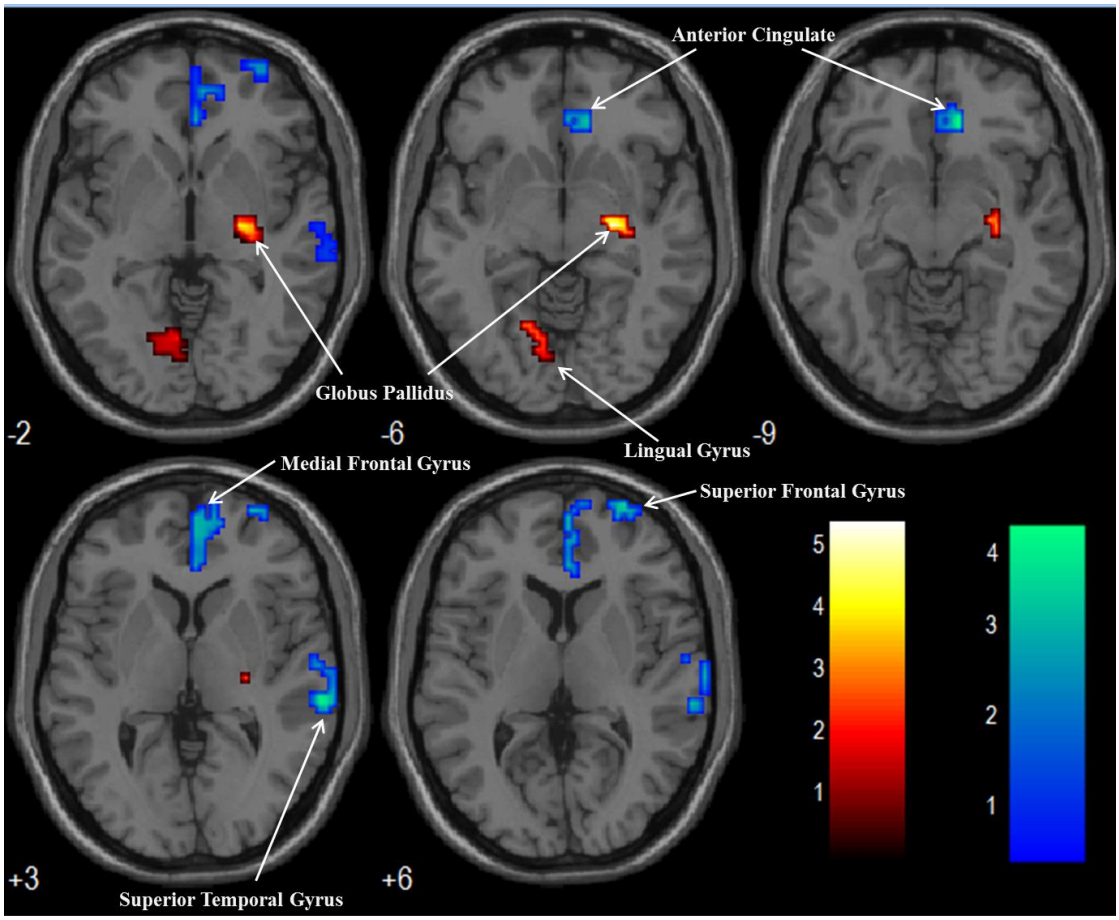
Note: Warm color: SCI versus Healthy Control; Cool color: Healthy Control versus SCI

Similarly, two group contrasts were conducted for the BOLD responses elicited during the lower-limb condition. For the healthy versus SCI group contrast, the healthy control group showed significantly stronger BOLD responses than the SCI group in the right anterior cingulate (BA 24), right medial frontal gyrus (BA 10), right superior temporal gyrus (BA 22), and right superior frontal gyrus (BA 10) (Table 4.5; Figure 4.2). For the SCI versus healthy group contrast, the SCI group showed significantly stronger BOLD responses than the healthy control group in the right globus pallidus and left lingual gyrus (BA 18). According to MNI coordinates, the BOLD responses clustered in the GPe.

Table 4.5 BOLD responses elicited in the lower-limb condition of the motor imagery task between participants in the SCI and healthy control groups (cluster size ≥35, $p < 0.01$with multiple corrections)

Cluster	**Label**	**L/R**	**BA**	**Coordinates(MNI)**			**T-scores**
				x	*y*	*z*	
	Healthy *vs* SCI						
114	Anterior Cingulate	R	24	3	36	0	3.72
	Medial Frontal Gyrus	R	10	3	54	3	2.71
43	Superior Temporal Gyrus	R	22	63	-27	3	3.45
34	Superior Frontal Gyrus	R	10	30	66	6	3.18
	SCI *vs* Healthy						
34	Globus Pallidus	R		24	-15	-6	5.42
30	Lingual Gyrus	L	18	-12	-67	-2	2.74

Figure 4.2 Group contrasts of BOLD responses between the SCI and healthy control groups when performing the lower-limb condition of the motor imagery task



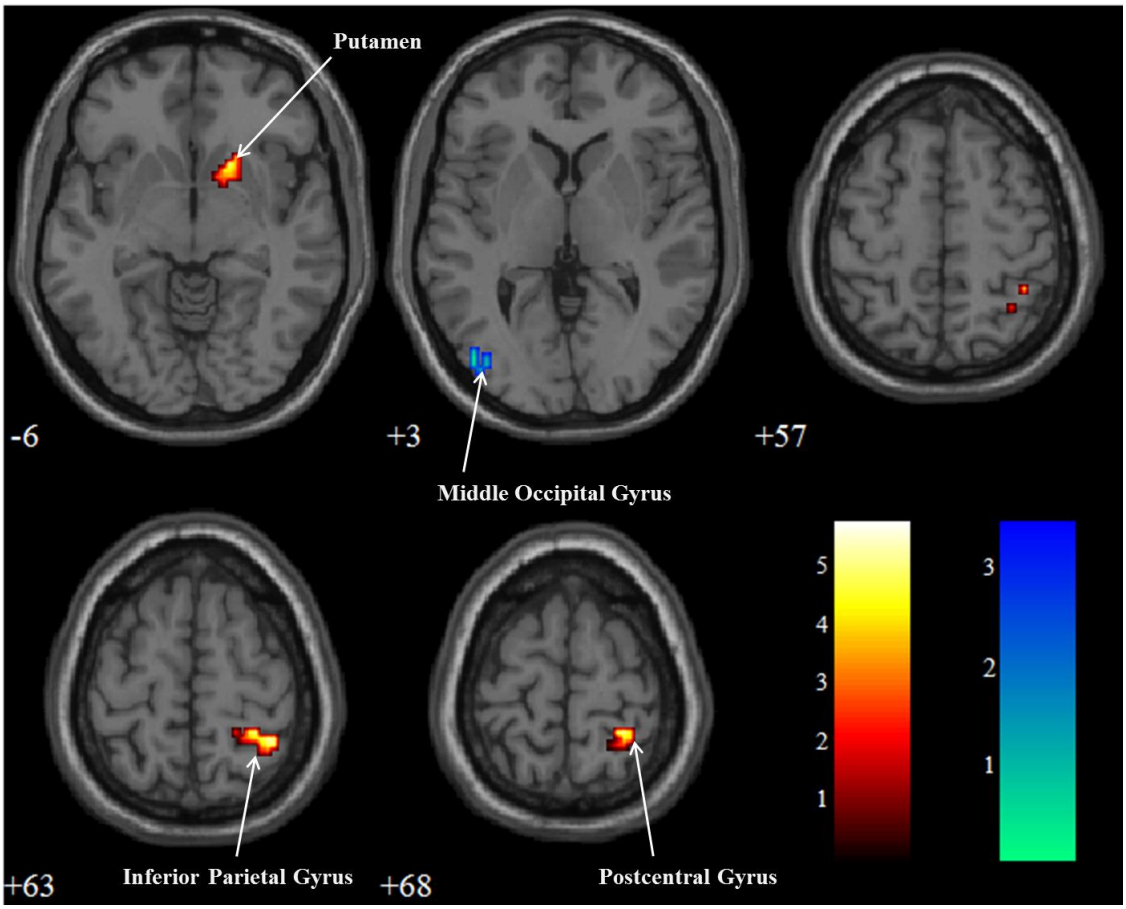
Note: Warm color: SCI versus Healthy Control; Cool color: Healthy Control versus SCI

Meanwhile, two limb-condition contrasts were conducted for the BOLD responses elicited during the experimental task in the SCI group. For the lower-limb condition versus the upper-limb condition contrast, the lower-limb condition showed significantly stronger BOLD responses than the upper-limb condition in the left Middle Occipital Gyrus (BA 19) (Table 4.6; Figure 4.3). For the upper-limb condition versus the lower-limb condition contrast, the upper-limb condition showed significantly stronger BOLD responses than the lower-limb condition in the right Postcentral Gyrus (BA5), the right Inferior Parietal Gyrus (BA 40), and right Putamen.

Table 4.6 BOLD responses elicited during the motor imagery tasks between the upper- and lower-limb conditions in the SCI group (cluster size ≥20, $p < 0.05$ with multiple corrections)

Cluster	**Label**	**L/R**	**BA**	**Coordinates(MNI)**			**T-scores**
				x	*y*	*z*	
	lower *vs* upper						
24	Middle occipital gyrus	L	19	-45	-78	3	3.43
	upper *vs* lower						
51	Postcentral gyrus	R	5	27	-38	63	5.80
	Inferior parietal gyrus	R	40	39	-41	57	5.37
23	Putamen	R		18	14	-6	5.13

Figure 4.3 Contrasts of BOLD responses between the upper- and lower-limb conditions of the motor imagery task in the SCI group



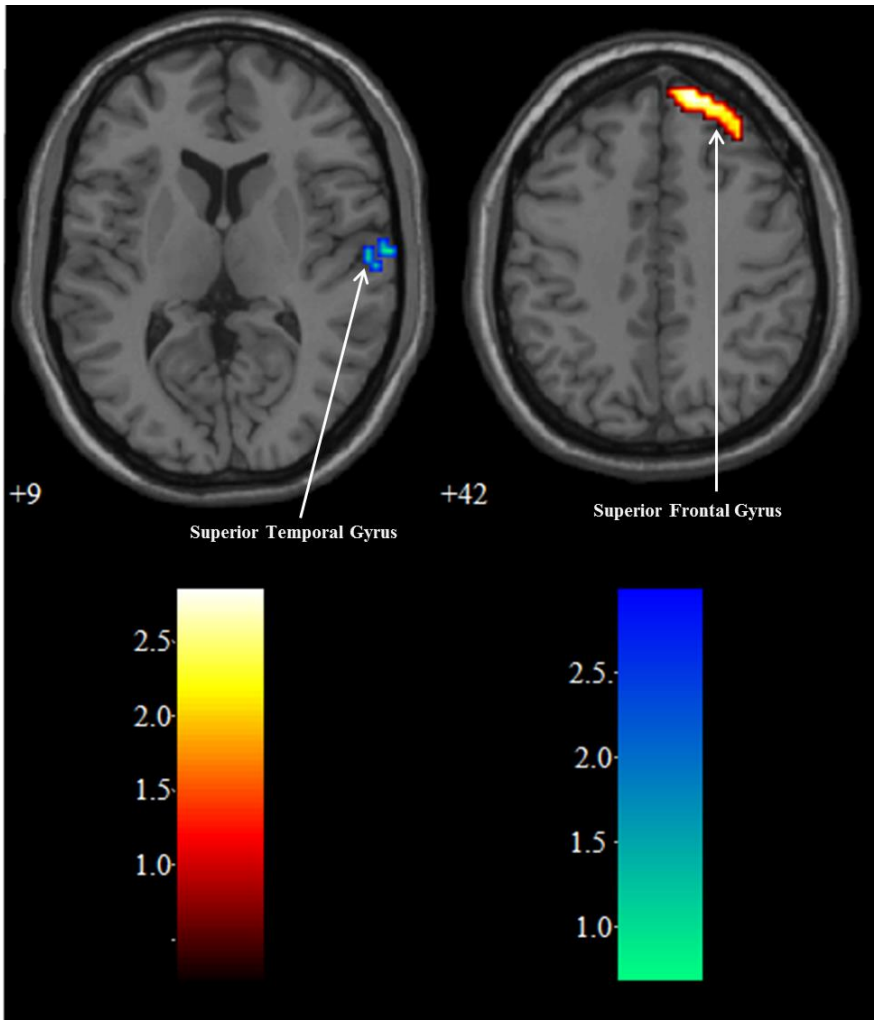
Note: Warm color: Upper Limb versus Lower Limb; Cool color: Lower Limb versus Upper Limb

Also, two limb-condition contrasts for the BOLD responses elicited during the experimental task were conducted in the healthy control group. For the lower-limb condition versus the upper-limb condition contrast, the lower-limb condition showed significantly stronger BOLD responses than the upper-limb condition in the left Superior Temporal Gyrus (BA 42) (Table 4.7; Figure 4.4). For the upper-limb condition versus the lower-limb condition contrast, the upper-limb condition showed significantly stronger BOLD responses than the lower-limb condition in the right Superior Frontal Gyrus (BA 8).

Table 4.7 Contrasts of BOLD responses elicited between the upper- and lower-limb conditions of the motor imagery task in the healthy control group (cluster size ≥20, $p < 0.05$ with multiple corrections)

Cluster	**Label**	**L/R**	**BA**	**Coordinates(MNI)**			**T-scores**
				x	*y*	*z*	
	lower *vs* upper						
20	Superior Temporal Gyrus	L	42	69	-12	9	2.31
	upper *vs* lower						
60	Superior Frontal Gyrus	R	8	15	51	42	2.63

Figure 4.4 Contrasts of BOLD responses between the upper- and lower-limb conditions of the motor imagery task in the healthy control group



Note: Warm color: Upper Limb versus Lower Limb; Cool color: Lower Limb versus Upper Limb

Brain Imaging – Regional Time Course Analysis of the BOLD Responses

This section presents the results of the regional time course analysis based on the regions activated in the whole brain analysis. The regions contained the neural substrates that showed significant between-group contrasts on BOLD responses for both the upper-limb and lower-limb conditions as well as the neural substrates obtained from the significant between-condition contrasts for the SCI and healthy control groups. The percentage changes of the MR signals across seven time points (2 s for each time point) were tested for between-group differences for each identified region. Repeated measures ANOVAs of Group (SCI versus healthy control) x Time (one-seven time points) were conducted. The same procedure was repeated for the upper-limb and lower-limb conditions. In this study, ROIs were defined with reference to the neural substrates, which showed a significant interaction effect between Group x Time on the MR signal changes across the first 12 s in the between-group contrasts on BOLD responses for the upper-limb and lower-limb conditions. Further analyses of the comparisons of the MR signal changes in the time points with maximum differences were carried out by independent t-tests for the ROIs.

Upper-limb Condition

Healthy Control Group versus SCI Group

For the upper-limb condition, in the healthy control group versus the SCI group, the neural substrates entering into the contrast were the left middle frontal gyrus, left anterior cingulate, and left medial frontal gyrus. The Group x Time effects were statistically significant [$F(2.574, 54.062) = 3.500$, $p = 0.027$] on the % MR signal change in the left middle frontal gyrus but not on that for the left anterior cingulate [$F(2.992, 65.818) = 1.367$, $p = 0.261$] or the left medial frontal gyrus [$F(2.571, 56.572) = 0.735$, $p = 0.516$]. The left medial frontal gyrus was defined as ROI #1. Post-hoc comparisons for ROI #1 revealed that the Time effect on the % MR signal changes across the first 12 s was statistically significant for the healthy control group [$F(2.374, 28.487) = 4.244$, $p = 0.019$], and significant differences of the % MR signal changes were found among the 0 s and 4 s ($p = 0.007$), the 0 s and 6 s ($p = 0.003$), the 4 s and 6 s ($p = 0.009$), the 4 s and 8 s ($p = 0.020$), the 4 s and 10 s ($p = 0.041$), and the 6 s and 8 s ($p = 0.001$) time points. However, the effect of Time on the % MR signal changes was not significant for the SCI group for ROI #1 [$F(6, 60) = 1.285$, $p = 0.280$]. Independent t-tests between the two groups for each time point showed significant differences at the time point 2 s [$t(22) = 2.154$, $p = 0.043$], the time point 4 s [$t(22) = 2.163$, $p = 0.042$], and the time point 6 s [$t(22) = 2.109$, $p = 0.047$] (see Figure 4.5). The details of the significant

time points with maximum differences between conditions were depicted in Table 4.8.

SCI Group versus Healthy Control Group

Significant Group x Time effects were revealed on the % MR signal change in the left precentral gyrus [F(3.373, 74.198) = 2.858, p = 0.037]. Other Group x Time effects were not significant on the left inferior parietal gyrus [F(2.586, 56.902) = 0.515, p = 0.647], right globus pallidus [F(3.566, 78.458) = 1.184, p = 0.323], right thalamus [F(2.408, 52.968) = 1.212, p = 0.311], left postcentral gyrus [F(3.542, 77.922) = 1.202, p = 0.316], right superior temporal gyrus [F(2.434, 53.554) = 1.971, p = 0.140], right inferior parietal gyrus [F(3.135, 68.960) = 0.782, p = 0.513], and right middle frontal gyrus [F(2.164, 47.616) = 0.398, p = 0.690]. The left precentral gyrus was defined as ROI #2. Post-hoc comparisons revealed that the Time effect on the MR signal changes of ROI #2 across the first 12 s was significant for the SCI group [F(6, 60) = 3.317, p = 0.007], and significant differences of the % MR signal changes were found among the 0 s and 4 s (p = 0.024), the 0 s and 6 s (p = 0.011), the 2 s and 4 s (p = 0.023), and the 2 s and 6 s (p = 0.038) time points. In contrast, the Time effect was not statistically significant for the healthy control group [F(2.315, 27.778) = 0.963, p = 0.405]. Independent t-tests between the two groups for each time point showed significant differences of the % MR signal

changes at the 6 s [t(22) = -2.708, p = 0.013] and 8 s [t(22) = -2.254, p = 0.034] time points (see Figure 4.6 and Table 4.8).

Lower-limb Condition

Healthy Control Group versus SCI Group

For the lower-limb condition, the healthy control group, compared with the SCI group, showed significant Group x Time effects on the % MR signal change for the right medial frontal gyrus [F(3.826, 84.177) = 4.985, p = 0.001] but not for the right anterior cingulate [F(3.898, 85.763) = 1.341, p = 0.262], right superior temporal gyrus [F(4.366, 96.046) = 1.572, p = 0.183], or right superior frontal gyrus [F(3.125, 68.745) = 2.133, p = 0.101]. Thus, the right medial frontal gyrus was defined as ROI #3. Post-hoc comparisons for ROI #3 revealed that the Time effect on the % MR signal changes across the first 12 s was significant in the healthy control group [F(3.142, 37.706) = 21.152, p < 0.001]. Among the healthy control group, significant differences of the % MR signal changes were found among the 0 s and 4 s (p < 0.001), the 0 s and 6 s (p < 0.001), the 0 s and 8 s (p = 0.005), the 0 s and 12 s (p = 0.015), the 2 s and 4 s (p < 0.001), the 2 s and 6 s (p < 0.001), the 2 s and 10 s (p = 0.029), the 4 s and 6 s (p = 0.009), the 4 s and 8 s (p = 0.021), the 4 s and 10 s (p < 0.001), the 4 s and 12 s (p = 0.001), the 6 s and 8 s (p < 0.001), the 6 s and 10 s (p < 0.001), the 6 s and 12 s (p < 0.001), the 8 s and 10 s (p = 0.015), and the 10 s and 12 s (p = 0.004)

time points. However, the Time effect on the % MR signal changes across the first 12 s was found to be marginally significant for the SCI group for ROI #3 [F(6, 60) = 1.966, p = 0.085]. Independent t-tests between the two groups of each time point showed significant differences at the 4 s [t(22) = 2.921, p = 0.008] and the 6 s [t(22) = 2.928, p = 0.008] time points (see Figure 4.7 and Table 4.8).

SCI Group versus Healthy Control Group

In the SCI group versus the healthy control group, the Group x Time effects on the % MR signal changes were statistically significant for both the right globus pallidus [F(3.214, 70.699) = 2.792, p = 0.043] and the left lingual gyrus [F(3.287, 72.307) = 4.575, p = 0.004], which were defined as ROI #4 and ROI #5, respectively.

Post-hoc comparisons for ROI #4 (the right globus pallidus) revealed a significant Time effect on the % MR signal changes across the first 12 s in the healthy control group [F(2.831, 33.975) = 7.540, p = 0.001]. Significant differences in the % MR signal changes were found among the 0 s and 2 s (p = 0.004), the 0 s and 4 s (p = 0.004), the 0 s and 12 s (p = 0.009), the 2 s and 8 s (p = 0.021), the 2 s and 10 s (p = 0.013), the 4 s and 6 s (p = 0.001), the 4 s and 8 s (p = 0.003), the 4 s and 10 s (p = 0.002), the 6 s and 8 s (p = 0.018), the 6 s and 10 s (p = 0.041), the 8 s and 12 s (p = 0.007), and the 10 s and 12 s (p = 0.005) time points. However, the Time effect was not significant on the % MR

signal changes for the SCI group [F(2.834, 28.344) = 0.824, p = 0.486]. Significant differences in the % MR signal changes were found for ROI #4 between the two groups at the 4 s [t(22) = 2.166, p = 0.041], the 6 s [t(22) = 2.303, p = 0.031], and the 12 s [t(22) = 2.212, p = 0.038] time points (see Figure 4.8A and Table 4.8).

Post-hoc comparisons for ROI #5 (the left lingual gyrus) revealed a significant Time effect on the % MR signal changes across the first 12 s in the SCI group [F(3.128, 31.280) = 3.185, p = 0.036]. Significant differences in the % MR signal changes were found among the 0 s and 4 s (p = 0.024), the 4 s and 8 s (p = 0.043), and the 4 s and 10 s (p = 0.041) time points. However, the Time effect on the % MR signal changes across the first 12 s was found to be marginally significant for the healthy control group for ROI #5 [F(2.507, 30.080) = 2.673, p = 0.074]. Significant differences in the % MR signal changes were found for ROI #5 between the two groups at the 4 s [t(22) = -2.226, p = 0.037], the 8 s [t(22) = 2.093, p = 0.048], and the 10 s [t(22) = 2.131, p = 0.044] time points (see Figure 4.8B and Table 4.8).

SCI Group

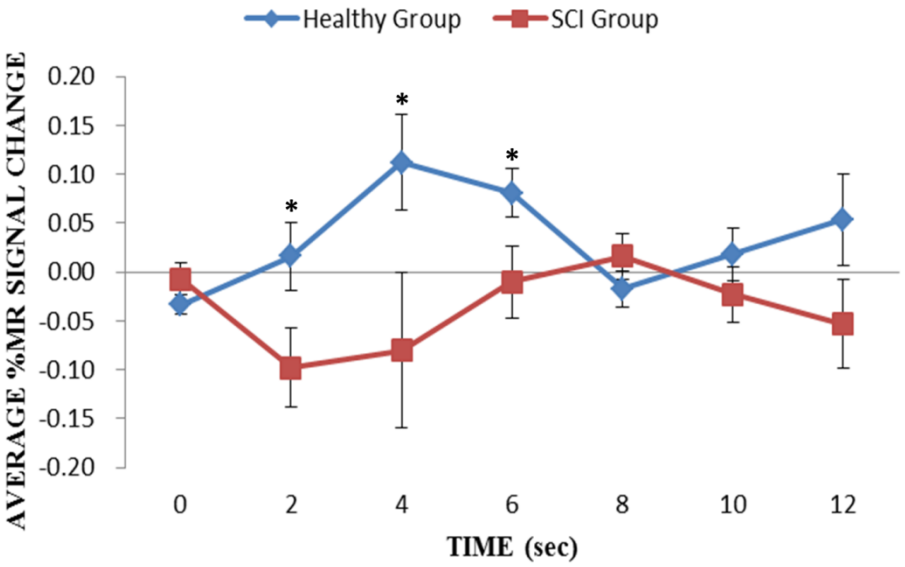
For the SCI group, regarding the lower- versus upper-limb condition contrast, no significant difference of the Group x Time effect on the % MR signal change in the left middle occipital gyrus was revealed [F(3.480, 69.591) = 0.168, p = 0.938]. For the upper- versus

lower-limb condition contrast, the Group x Time effects on the % MR signal changes were not significant in the right postcentral gyrus [F(2.273, 45.460) = 0.493, p = 0.638], right inferior parietal gyrus [F(2.732, 54.636) = 0.417, p = 0.723], or right putamen [F(2.794, 55.885) = 0.774, p = 0.505], which was highlighted in the whole brain analysis. Thus, there were no ROIs defined for the SCI group, neither for the lower- versus upper-limb condition contrast nor for the upper- versus lower-limb condition contrast.

Healthy Control Group

For the healthy control group, regarding the lower- versus upper-limb condition contrast, there was no significant difference of the Group x Time effect on the % MR signal change in the left superior temporal gyrus [F(3.782, 90.774) = 0.906, p = 0.460]. For the lower- versus upper-limb condition contrast, there was no significant interaction of the Group x Time effect on the % MR signal changes revealed in the right superior frontal gyrus [F(3.609, 86.610) = 0.263, p = 0.885]. Also, no ROIs were defined under this condition.

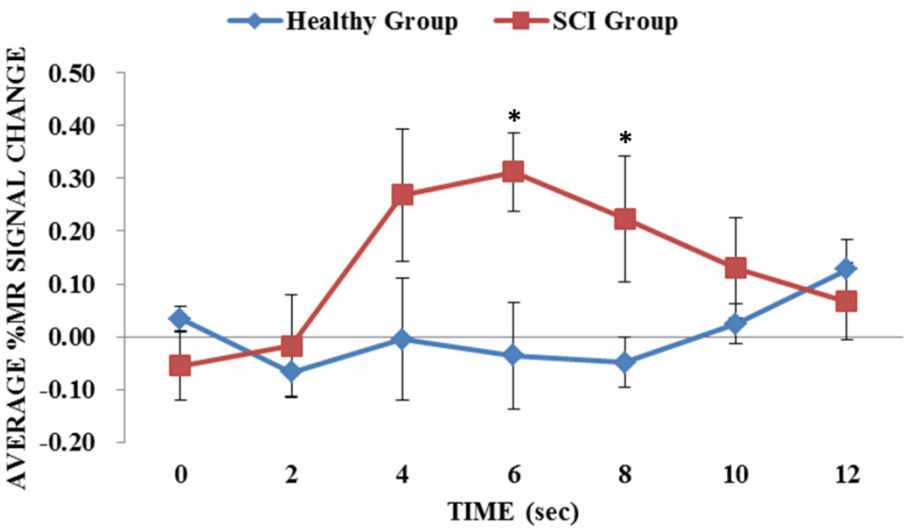
Figure 4.5 Results of regional time course analyses for ROI #1 (the left Middle Frontal Gyrus)



Note: The regional time course analyses for ROI #1 revealed the significant interaction effect between Group x Time on the average % MR signal changes elicited in the upper-limb condition of the motor imagery task across time points 0 s to 12 s in the contrast of the healthy control group versus the SCI group [$F(2.574, 54.062) = 3.500$, $p = 0.027$].

* $p<0.05$

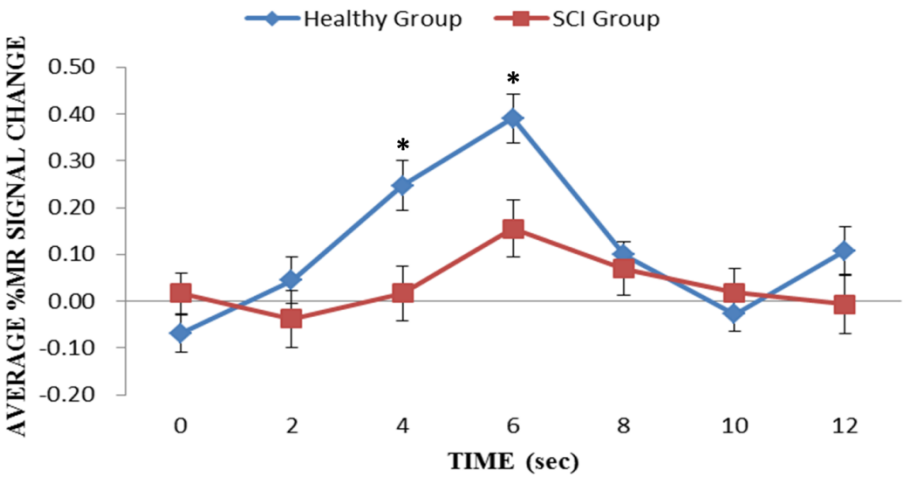
Figure 4.6 Results of regional time course analyses for ROI #2 (the left Precentral Gyrus)



Note: The regional time course analyses for ROI #2 revealed the significant interaction effect between Group x Time on the average % MR signal changes elicited in the upper-limb condition of the motor imagery task across time points 0 s to 12 s in the contrast of the SCI group versus the healthy control group [$F(3.373, 74.198) = 2.858$, $p = 0.037$].

* $p<0.05$

Figure 4.7 Results of regional time course analyses for ROI #3 (the right Medial Frontal Gyrus)

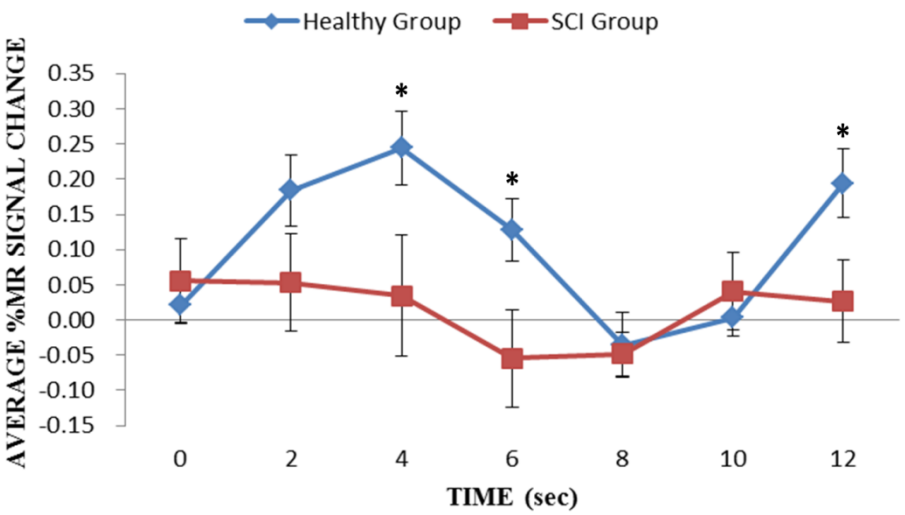


Note: The regional time course analyses for ROI #3 revealed the significant interaction effect between Group x Time on the average % MR signal changes elicited in the lower-limb condition of the motor imagery task across time points 0 s to 12 s in the contrast of the healthy control group versus the SCI group [$F(3.826, 84.177) = 4.985$, $p = 0.001$].

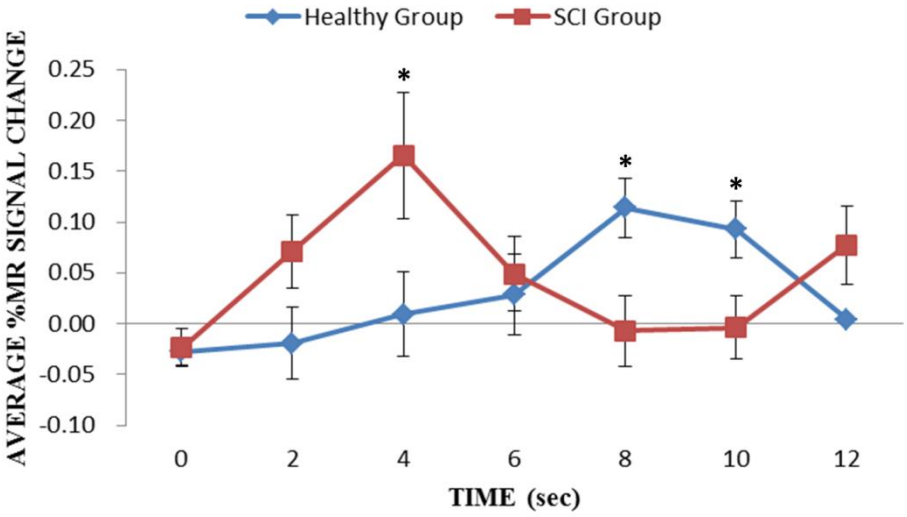
* $p<0.05$

Figure 4.8 Results of regional time course analyses for ROI #4 (the right Globus Pallidus) and ROI #5 (the left Lingual Gyrus)

(A)



(B)



Note: The regional time course analyses for ROI #4 and ROI #5 revealed significant interaction effects between Group x Time on the average % MR signal changes elicited in the lower-limb condition of the motor imagery task across time points 0 s to 12 s in the contrast of

the SCI group versus the healthy control group: (A) ROI #4, right globus pallidus [F(3.214, 70.699) = 2.792, p = 0.043]; (B) ROI #5, left lingual gyrus [F(3.287, 72.307) = 4.575, p = 0.004].

* $p<0.05$

Table 4.8 Comparisons of the maximum difference value of the average % MR signal change of the ROIs

ROI	L/R	Label	Time points with significant maximum difference	Average % MR signal change (SEE)				*t*-Values	*p*-Values
				SCI group		Healthy Control			
				Upper Limb	Lower Limb	Upper Limb	Lower Limb		
1	L	Middle Frontal Gyrus	2s	-0.098 (0.041)	_	0.016 (0.034)	_	2.154	0.043
			4s	-0.080 (0.079)	_	0.112 (0.049)	_	2.163	0.042
			6s	-0.010 (0.037)	_	0.081 (0.025)	_	2.109	0.047
2	L	Precentral Gyrus	6s	0.313 (0.074)		-0.036 (0.100)		-2.708	0.013
			8s	0.224 (0.119)		-0.049 (0.048)		-2.254	0.034
3	R	Medial Frontal Gyrus	4s	_	0.017 (0.059)	_	0.247 (0.053)	2.921	0.008
			6s	_	0.156 (0.062)	_	0.391 (0.052)	2.928	0.008
4	R	Globus Pallidus	4s	_	0.035 (0.086)	_	0.244 (0.052)	2.166	0.041
			6s	_	-0.055 (0.069)	_	0.129 (0.044)	2.303	0.031
			12s	_	0.026 (0.059)	_	0.194 (0.049)	2.212	0.038
5	L	Lingual Gyrus	4s	_	0.166 (0.062)	_	0.009 (0.038)	-2.226	0.037
			8s	_	-0.007 (0.034)	_	0.114 (0.044)	2.093	0.048

	10s	-0.004 (0.031)	_	0.093 (0.033)	2.131	0.044

Correlation Analysis

This section presents the further analysis on the relationships among BOLD responses of these special neural substrates or ROIs, behavioral measures, and clinical measures. As described in the last section, it yielded a total of 5 ROIs (#1-5) (See Figures 4.5-4.8 and Table 4.8).

The BOLD responses elicited from specific neural substrates were expressed in the form of amplitudes of the responses within ROIs. The behavioral measures evaluated the ACC, RT, and ACC/RT during participants' performances in the upper- or lower-limb conditions of the motor imagery tasks. The following were manipulated as the clinical measures: the scores of the Digit Span Forward and Backward Tests; the scores of the Short Delay, Long-term Delay, and Recognition Tests of the RAVLT; the results of the Trial Making Tests A and B (TMT-A and TMT-B) and the difference values of TMT (B minus A); the scores of the Symbol Digit Modalities Test (SDMT); and the scores of the Word, Color, and Word-Color Test. Analyses were conducted based on the task conditions for each of the healthy control and SCI groups.

Upper-limb Condition: Healthy Control Group

For the healthy control group, the left middle frontal gyrus (BA 11) was defined as ROI #1. The scores of the TMT-B were

significantly and positively related to the amplitudes of BOLD responses of ROI #1 (r = 0.573, p = 0.040). No other significant correlations were found under this condition.

Upper-limb Condition: SCI Group

For the SCI group, the left precentral gyrus (BA 4) was defined as ROI #2. No significant correlations were found between the amplitudes of BOLD responses of ROI #2 and the SCI group's performances during the experimental task as well as the clinical measures. Importantly, moderate and negative correlations were revealed between the time post injury and the magnitudes of MR signal of ROI #2 (r = -0.723, p = 0.012).

The ACC of the performances during the experimental task was moderately and negatively related to the results of Long-term Delay of RAVLT (r = -0.703, p = 0.016). And the RT of the performances during the experimental task was moderately and negatively related to the difference values of TMT (B minus A) (r = -0.604, p = 0.049), while the SCI group's ACC/RT of the task had significant and positive correlations with the results of TMT-A, TMT-B, and the difference values of TMT (B minus A) (r = 0.806, p = 0.003; r = 0.706, p = 0.015; and r = 0.643, p = 0.033, respectively) and negative correlations with the results of Recognition of RAVLT (r = -0.696, p = 0.017) and the SDMT (r = -0.790, p = 0.004).

The scores of the Modified Ashworth Scale were moderately and negatively correlated with ACC/RT of the task ($r = -0.609$, $p = 0.047$), and the Color scores of the Stroop Test were found ($r = -0.706$, $p = 0.015$). We also found that the intensities of the rehabilitation training program were negatively related to the ACC during the experimental task ($r = -0.723$, $p = 0.012$) and positively related to the results of the Long-term Delay of RAVLT ($r = 0.621$, $p = 0.041$). And a negative correlation was found between the intensities of walking training with lower-limb braces and the Color scores of the Stroop Test ($r = -0.639$, $p = 0.034$).

Lower-limb Condition: Healthy Control Group

For the healthy control group, the right medial frontal gyrus (BA 10) was defined as ROI #3. No significant relationships were exhibited among these variables under this condition (all $p > 0.05$).

Lower-limb Condition: SCI Group

For the SCI group, the activated clusters in the right globus pallidus and left lingual gyrus (BA 18) were defined as ROI #4 and #5, respectively. The amplitudes of BOLD responses of ROI #5 were significantly and negatively related to the results of the Digit Span Forward Test ($r = -0.632$, $p = 0.037$) and the results of the Short Delay of RAVLT ($r = -0.728$, $p = 0.011$). A moderate and negative correlation was revealed between the Recognition of RAVLT and the

ACC/RT of the task ($r = -0.647$, $p = 0.031$).

Marginal significance was shown between ROI #4 and the intensity of neuropathic pain in the SCI participants ($r = 0.546$, $p = 0.082$). No obvious correlations were found between other variables under this condition (all $p > 0.05$).

Chapter Ⅴ

DISCUSSION

This chapter begins with the neural process associated with the repetitive motor imagery task performed in this study. Thus, the different findings of the upper limb condition and lower limb condition will be discussed under the specific model of spinal cord injury, especially based on the changes of BOLD signal changes over time compared to the healthy control participants. Importantly, the underlying mechanisms are emphasized to understand the plastic changes of the experience-dependent motor representations and the clinical significance suggested by these findings.

Summary of findings

This study aimed to use functional imaging to investigate the underlying mechanisms of the neural changes brought by the losses of physical movements and sensory feedback in the lower limbs among a group of chronic SCI participants. For the upper limb condition, the results indicate that the SCI participants showed significantly stronger BOLD responses than the healthy control participants in extensive areas of the brain, including the bilateral precentral gyrus, the left postcentral gyrus, the right middle frontal gyrus, the bilateral superior temporal gyrus, the right superior and inferior parietal gyrus, the right

external globus pallidus (GPe) and the thalamus. For the lower limb condition, there were more activations in the right GPe and left lingual gyrus in the SCI participants than the healthy control participants. The results suggest the plastic changes in the brain were systematic after SCI, and participants used the visual cortex in motor programming and planning processes. These are likely to compensate for the loss of physical experience by the participants due to paralysis after SCI.

Behavioral and Clinical Measure Results

The functional task employed in generating the BOLD signals was adopted from previous motor imagery studies on SCI. For the lower limb condition, a common task used is imagery of repetitive flexion and extension movements of the foot (ankle) with a rate of 0.5Hz (Alkadhi et al., 2005; Cramer et al., 2005; Hotze-Boendermaker et al., 2008). The upper limb task involves imagery of wrist flexion/extension movements at a similar rate (Curt et al., 2002 a & b; Jurkiewicz et al., 2007). The behavioral results were accuracy rate and response time, indicating participants' abilities in performing the imagery of the upper and lower limb movements. In this study, the accuracy rates for the healthy control group were 46.8% and 45.7% for the upper and lower limb conditions,

respectively, whereas they were 45.7% and 49.7%, respectively, for the SCI group. For the response time, in general, the SCI group performed faster on both the upper (1069.6 ms versus 1135.2 ms) and lower limb tasks (993.6 ms versus 1045.3 ms) than the healthy control group. However, these differences did not reach statistical significance. The behavioral results therefore were not different between the SCI and healthy control group.

The accuracy rate of the SCI participants on the upper limb repetitive imagery task was negatively correlated with their scores on the Long-term Delay of the RAVLT ($r=-0.703$, $p=0.016$). Their response times were negatively correlated with the scores on the TMT (B minus A) ($r=-0.604$, $p=0.049$). The ACC/RT of the SCI participants on the upper limb repetitive imagery task were positively correlated with the scores on the TMT-A, TMT-B, and the difference values of TMT (B minus A), respectively ($r=0.806$, $p=0.003$; $r=0.706$, $p=0.015$; $r=0.643$, $p=0.033$), and correlated negatively with the scores on the Recognition of RAVLT ($r=-0.696$, $p=0.017$) and the SDMT ($r=-0.790$, $p=0.004$). These results suggested that the extent of cognitive decline among the SCI participants, including processing speed, memory recall, inhibition, and set shifting, contributed to higher performance on the imagery of the upper limb movements. In other words, the SCI participants who had lower cognitive abilities

performed better on the upper limb imagery task among the SCI participants.

For the lower limb repetitive imagery task, only the ACC/RT of the SCI participants were negatively correlated with their scores on the Recognition of the RAVLT ($r=-0.647$, $p=0.031$). Similar to the condition of upper limbs, it indicated that the patients with worse cognitive functions, in particular, the memory recall, had higher task performance. These inverse relationships between the cognitive function and behavioral performances during the imagery task under both the upper limb and lower limb conditions for the SCI participants suggested that some plastic changes occurred as compensation in order to implement the imagery task, and these plastic changes were systematic and influenced both the intact and paralyzed limbs, although the loss of physical experience happened only to the paralyzed limbs.

The Neural Process Associated with the Repetitive Motor Imagery Tasks

The Neural Process of Motor Imagery

The motor imagery task of this study required the participants to visualize upper and lower limb movements. Whole brain analyses revealed extensive activations of participants' brains, including the

premotor cortex (PMC), the supplementary motor area (SMA), superior parietal lobe, prefrontal cortex (PFC), the anterior cingulate gyrus, the superior temporal gyrus (STG), the globus pallidus (GP) and the lingual gyrus (see Tables 4.4 and 4.5). These results concur with those revealed in previous studies involving motor imagery of SCI participants (Alkadhi et al., 2005; Cramer et al., 2005; Hotze-Boendermaker et al., 2008; Sabbah et al., 2002). Motor imagery involves a series of mental processes. These include image generation, image maintenance, image inspection, image transformation, and motor preparation and programming (Holmes & Calmels, 2008; Jackson et al., 2006; Mulder et al., 2007). Activations in the frontal regions were associated with image generation, whereas activations in the central, temporal and occipital regions were found to mediate image maintenance and transformation (De Beni et al., 2007).

Previous studies indicated that imagery of the upper and lower limb movements resulted in activations of similar brain areas (Aono et al., 2013). These findings suggested that despite the differences in the topography over the somatosensory areas, imagery of movements of the upper and lower limbs seems to share similar neural networks. It is noteworthy that the results of this study revealed significant differences in the contrasts between the upper and lower limb

conditions among the SCI participants. These findings suggested possible plastic changes in the brains of the SCI participants resulting from the paralysis of the lower limbs. More importantly, the changes appear to be systematic involving both the lower and upper limbs (see below).

The Neural Process of Rhythm

The frequencies of the rhythm of the movements in the imagery task were 0.8Hz, 1Hz and 1.33Hz. These frequencies were meant to produce slow to fast repetitive movements (Toma, 2002). The presentations of the rhythms were in random order. This was to minimize the potential learning and anticipation effects that would have confounded the neural processes and hence the BOLD signals associated with performance on the imagery task. The auditory cues presented in one of these three frequencies enabled the participant to recall the movement rhythm previously learnt in the training, which tapped into retrieval from the long-term memory process (Ivry & Spencer, 2004; Jantzen et al., 2004; Molinari et al., 2003; Thaut, 2003). Teki et al. (2011) described this process as retrieval of cognitive timing sequence in favor of motor planning, but without motor execution. Our results revealed significant activations in the GP, which is located in the basal ganglia. Previous studies reported that

basal ganglia subserved the perception of rhythmic sequences among patients with Parkinson's disease (Grahn & Brett, 2009; Teki et al., 2011). Furthermore, other studies on animal and humans reported that the striatum among the striato-thalamo-cortical network was the "core-time" (Meck et al., 2008; Spencer et al., 2003). This study did not reveal significant activations in the striatum, which perhaps is due to the relatively small sample size and the use of different functional tasks among the human studies.

Upper Limb Task Condition between Healthy and SCI Groups

Healthy Control versus SCI

Participants in the healthy control group had stronger BOLD responses in the left middle frontal gyrus (MFG) (BA 11), left anterior cingulate (BA 32) and left medial frontal gyrus (BA 10) than those in the SCI group (see Table 4.4 and Figure 4.1). In other words, these activations in the SCI group were weaker than those in the healthy control group. The BA 10 and BA 11 are part of the orbitofrontal cortex (Kringelbach, 2005). The stronger activations in the prefrontal cortex during imagery of the upper limb movements suggested that healthy control participants were more likely to rely on the working memory, response inhibition, and executive function than the SCI participants (Grezes & Decety, 2001; Hanakawa et al., 2008 & 2003;

Mulder et al., 2007; Sauvage et al., 2013 & 2014). Another significant finding is the stronger activations in the anterior cingulate cortex among the healthy control participants. Our results concur with those of other studies that reported that SCI participants showed weaker activations in the anterior cingulate cortex than their healthy controls on upper limb related tasks (Adleman et al., 2002; Botvinick et al., 2004; Crottaz-Herbette & Menon, 2006; Munzert et al., 2008). The anterior cingulate cortex mediates human executive functions such as inhibitory control, response selection, selective attention and conflict monitoring (Barch et al., 2000; Botvinick et al., 2004; Lorist et al., 2005; Munzert et al., 2008). Sauvage et al. (2011) reported that the cingulate cortex, together with the frontopolar, prefrontal and insular, were recruited for mediating the executive control function during motor imagery. The anterior cingulate gyrus was found to mediate self-regulatory processes (Margulies et al., 2007). Its connections with the pre-SMA, prefrontal cortex further suggested that the anterior cingulate gyrus formed a cognitive network of motor preparation (Devinsky et al., 1995; Paus, 2001; Pandya et al., 1996). The weaker activations in the prefrontal-cingulate network among the SCI participants in this study suggested that their upper limb motor preparatory processes were modulated. Such modulation effects, called the post-SCI systematic neural reorganization phenomenon,

were likely to be the consequence of the injuries to the spinal cord or paralysis of the lower limbs due to the injuries.

To gain further understanding of the modulation effects on the prefrontal-cingulate network, clinical results of the SCI participants were correlated with the brain imagery results. The intensity of the BOLD signals in ROI #1 (left middle frontal gyrus) were positively and moderately correlated with the results of the Trial Making Test-B ($r=0.573$, $p=0.040$). There are two observations here. First, the imagery of the upper limb movements involved set shifting and response inhibition as reflected by the TMT-B. This is consistent with another study that reported that TMT-B involved shifting and response inhibition processes (Tombaugh, 2004). Second, the significantly weaker BOLD signals detected at 2s, 4s and 6s in the left MFG (ROI #1) suggested that the modulation of the upper limb motor preparation process among SCI participants happened at the beginning half of the motor imagery processes (see Figure 4.5 and Table 4.8). De Beni et al. (2007) suggested that the earlier time course corresponded to the image-generation process. In other word, paralysis of the lower limb impacted the image-generation process of the upper limb among the SCI participants.

The brain imaging results were supported by the differences in the clinical measures between the SCI and healthy control groups.

The SCI group showed lower performance in the short-term delay and recognition task of RAVLT and in the TMT than the healthy control group (see Table 4.3). It appeared that the ability of working memory and switch shifting was affected in the SCI group. Nevertheless, this did not seem to affect participants' performances on the upper limb repetitive imagery task. The results point to the direction of development of compensatory processes among the SCI participants during motor-related activities. This proposition will be further deliberated in the next section on the contrast between SCI and healthy control groups.

SCI versus Healthy Control

The results indicated more extensive between-group differences in the BOLD signals when the SCI group was contrasted with the healthy control group (see Table 4.4 and Figure 4.1). They included the left precentral gyrus (BA4), right precentral gyrus (BA6), left postcentral gyrus (BA2), right superior temporal gyrus (BA42), left inferior parietal gyrus (BA40), right inferior parietal gyrus (BA40), right thalamus and right GPe. The neural substrates identified were similar to those reported in previous studies on SCI using upper limb-related imagery tasks (Curt et al., 2002 a & b; Jurkiewicz et al., 2007; Kokotilo et al., 2009; Sabbah et al., 2002). In all these neural substrates, the SCI participants showed stronger BOLD responses

than the healthy control participants during imagery of upper limb movements. These differences would have been the consequence of the injuries to the spinal cord suffered by the SCI participants (Crawley et al., 2004; Freund et al., 2011; Henderson et al., 2011; Jurkiewicz et al., 2006; Wrigley et al., 2009).

The extensive activations in the sensorimotor areas among the SCI participants during imagery of upper limb movements can be explained by the post-injury plastic changes in the brain. Previous studies on SCI patients revealed spatial shift and expansions of the intact sensorimotor cortices (mediating the upper limbs) to the de-afferented and de-efferented sensorimotor cortex (mediating the lower limbs) (Corbetta et al., 2002; Lotze et al., 2006; Mikulis et al., 2002; Wrigley et al., 2009). By using the motor imagery paradigm, the activations of the sensorimotor cortices such as the bilateral precentral gyri and left postcentral gyrus were not specific to the topographic representation of the lower limbs. This is a limitation of employing an imagery paradigm in brain imaging.

The inferior parietal gyrus was reported to play an important role in generation and transformation of visuo-spatial images particularly during visuomotor imagery (de Lange et al., 2006; Sirigu et al., 1996; Suchan et al., 2002; Toni et al., 2001). In our study, stronger activations of the right inferior parietal gyrus among the SCI than

healthy control participants suggested that paralysis of the lower limbs modulated the generation and transformation of upper limb images during the repetitive movement imagery processes.

The fronto-temporo-parietal network was found to mediate the image transformation process (Sack et al., 2005; Sasaoka et al., 2014). The concurrent activations of the frontal and temporoparietal regions were especially noteworthy when timing (or rhythm) was involved in the imagery task (Schwabe et al., 2009). We regarded the image transformation process as an essential component of motor preparation (Gerardin et al., 2000; Lafleur et al., 2002; Lotze & Halsband, 2006; Svoboda et al., 2006). In this study, the stronger activations in the right superior temporal gyrus (STG, BA42) among the SCI as compared to those of the healthy control participants were noteworthy. Cramer et al. (2005) reported similar findings: the STG were activated when SCI participants imagined the foot crushing an object. Other researchers noted that the activations of the right STG were associated with visuomotor processing (Hotze-Boendermaker et al., 2008). Nevertheless, Cramer et al. (2005) and other researchers postulated that activations of the STG were attributed to imagery associated with auditory processes such as use of auditory cues (Nishitani et al., 2004; Yoo et al., 2001). The notion of STG mediating auditory-related processes was further reported in studies

involving participants who perceived rhythmic sounds or mentally rehearsed a piece of music (Lotze et al., 2003; Meister et al., 2004). In this study, every trial began with two consecutive auditory cues to indicate the tempo of the repetitive movements of the upper limb to be imagined by the participant. Avanzino (2013) employed a similar method for eliciting different rhythmic motor sequences, whereas Olsson (2008) reported activations in the left STG during auditory imagery. The findings of the STG were partly specific to the task design of this study.

The activations in the sub-cortical areas, including the right GPe and right thalamus, were important findings. Cramer et al. (2005) reported activations in the GP among the SCI participants during imagery of lower limb actions. These researchers further postulated that the neural activities were pathological—that is, they originated from the SCI. The GPe is a gray matter nucleus within the GP. In the primate, the GPe was found to structurally connect through input and output to other nuclei within the GP (Benhamou et al., 2012). As a result, the role of the GPe within the GP was postulated to serve as a relay center within the larger structure. The BG was structurally connected with the cerebral cortex, thalamus, cerebellum and the spinal cord and played an important role in voluntary motor control, associative and limbic functions (Herrero et al., 2002; Turner et al.,

2003). This formed the BG-thalamo-cortical circuit, which mediates motor control processes (Ward et al., 2013). It is inferred that the reorganization in the voluntary motor control system was systematic in multiple levels. Similarly, the thalamus is a relay center between sub-cortical structures and the cortical brain areas. The stronger activations in the right GPe and thalamus suggested that the SCI participants, after paralysis of the lower limbs, endured systematic changes in the sub-cortical structures, particularly those associated with relaying sensorimotor information between the spinal cord and the cortex. Such systematic changes appeared to not be restricted to the affected body parts—the lower limbs—but to the upper limbs as well.

The results from regional time course analysis provide additional information on the processes mediated by the left precentral gyrus (BA4), identified as ROI #2 in this study (see Figure 4.6). Significant Group x Time BOLD signal changes were revealed at 6 s and 8 s in the course of imagery of movements of the upper limbs (see Table 4.8). At these two time points, the percentages of the changes among the SCI participants were significantly larger than those among the healthy participants. Our findings were supported by other studies that reported increases in activations in the precentral gyrus and other sensorimotor areas for the SCI group (Alkadhi et al., 2005; Curt et al.,

2002; Hotze-Boendermaker et al., 2008). The activations of the left precentral gyrus were found to be significantly and negatively correlated with the participants' time of occurrence of the SCI ($r=-0.723$, $p=0.012$). Our findings were consistent with those reported by Sabbah et al. (2002) that activations of the sensorimotor cortex declined with post-injury time. Olsson (2012) further explained that the decrease in the neural activities in the sensorimotor cortex among chronic SCI patients were related to the diminished motor representation of the lower limbs in the brain. It is, however, important to note that our findings were obtained from the imagery of upper limb movements. These further support the notion that the post-SCI plastic changes were systematic in nature, influencing the upper limbs, which were not affected by the injury.

Lower Limb Task Condition between Healthy and SCI Groups

Healthy Control versus SCI

Similar findings with the upper limb condition were revealed for the lower limb condition in the healthy control and SCI groups. Significant between-group differences in activations were revealed in the right anterior cingulate gyrus (BA24), the right superior frontal gyrus (BA10), the right medial frontal gyrus (BA10) and the right superior temporal gyrus (BA22) (see Table 4.2 and Figure 4.2).

Likewise, these neural substrates were previously found to relate to motor imagery processes (Grezes & Decety, 2001; Hanakawa et al., 2008 & 2003; Mulder et al., 2007; Sauvage et al., 2013 & 2014). Here, they referred to imagery of repetitive movements of the lower limbs. As opposed to the upper limb condition, the significant neural substrates were all in the right hemisphere. Hétu et al. (2013) revealed that brain activations during the lower limb-related motor imagery task, when compared with the upper limb counterpart, were largely located in the right hemisphere such as the sensorimotor association areas. Other researchers related activations of the right hemisphere to the motor programming for locomotion (la Fougere et al., 2010). This offers an explanation on the right dominance for imagery of the lower limb movements.

Regional time course analyses only showed significant Group x Time effects at 4 s and 6 s in the right medial frontal gyrus (ROI #3) (see Figure 4.7). The results were comparable to those revealed for the upper limb condition (significant at 2 s to 6 s). This means that there were significantly stronger activations in the right medial frontal gyrus for the healthy control participants than for the SCI participants, which were consistent with those reported by Kokotilo et al. (2009). The right anterior cingulate gyrus, the right superior frontal gyrus, and right superior temporal gyrus were also found activated in the

whole brain analysis, which concur with Hétu's (2013) and la Fougere's study (2010) on the motor programming for locomotion. This frontal-cingulate-temporal network was found to mediate the working memory related to motor imagery process (Sauvage et al., 2013 & 2014). These further supported that motor-related working memory was affected by the experience deprivation among the SCI participants.

SCI versus Healthy Control

There were two neural substrates that showed significantly stronger activations in the SCI than in the healthy control group. They were the right GPe and left lingual gyrus (BA18) (see Table 4.2 and Figure 4.2). Regional time course analysis indicated significant Group x Time effects for the right GPe (ROI #4) at 4 s, 6 s and 12 s [see Figure 4.8(A) and Table 4.8]. The SCI group had a significantly smaller percentage BOLD signal change than that of the healthy control group mainly during the first half of the response and by the end of the response. The results indicated that the SCI participants had smaller BOLD signal changes in the right GPe than the healthy control participants when imagining lower limb movements. Our findings were consistent with those reported in Hotze-Boendermaker's study (2008), which used a lower limb motor

imagery task among the SCI patients.

For the left lingual gyrus (ROI #5), significant between-group differences in the regional time course analysis were revealed at 4 s, 8 s and 10 s [see Figure 4.8(B) and Table 4.8]. The percentage changes were different between the first and second halves of the responses. The first half of the responses was dominated by the larger percentage BOLD signal change among the SCI participants in the left lingual gyrus. In contrast, the latter half of the responses were dominated by the larger percentage change among the healthy control participants. The initiation of the responses in the left lingual gyrus among the SCI participants appeared to be earlier than that of the healthy control group. The involvement of the left lingual gyrus in imagery of lower limb movements among SCI participants is a new finding. It was known that lingual gyrus mediated visual perception, and visual-motor imagery process (Jackson, 2006; Olsson et al., 2008). Stronger activations in the left lingual gyrus, which is located in the occipital lobe, suggested that SCI participants relied more on the visual system to mediate motor imagery of the lower limbs. Previous studies concluded that the occipital lobe played an important role in visuomotor imagery, by mediating image retrieval and generation in the working memory during visual-motor imagery process (Jackson, 2006; Schoenberg et al., 2006; Svoboda et al., 2006). Zapparolo et al

(2013) also reported visual compensation during motor imagery due to the declined memory function and less effective sensory feedback to complete the motor imagery task. Our findings indicated that SCI participants, when compared with the healthy control participants, used the visual system more to generate, maintain and transform lower limb images during visualization of the related movements. This could be attributed to the long-term lack of motor input from the paralyzed lower limbs among the SCI participants. The SCI participants developed visual compensation for lost motor input. This proposition was supported by the significant relationships between activations of the left lingual gyrus and cognitive abilities of the SCI participants. The BOLD responses of the left lingual gyrus (ROI #5) were negatively correlated with the scores on the Digit Span Forward Test ($r=-0.632$, $p=0.037$) and Short delay of RAVLT ($r=-0.728$, $p=0.011$). These two tests tapped into working memory of individuals (Halpern & Zatorre, 1999; Schoenberg et al., 2006; Svoboda et al., 2006).

The abovementioned findings on the GPe and lingual gyrus were inconsistent with those reported by Cramer et al. (2005) and Hotz-Boendermaker et al. (2008). These studies revealed activations of extensive neural regions among the SCI participants. They included the left precentral gyrus, left thalamus, bilateral SMA, right

anterior cingulate gyrus and right cerebellum. These results, however, were contrary to those reported in the study of Sabbah (2002), in which no activations were observed when a T6 complete lesion SCI patient (19 years post injury) performed a lower limb imagery task. The lack of brain activation observation was shared by Olsson (2012), who found diminished motor representations during imagery of stair walking by a T2 complete lesion SCI patient (2 years post injury). The discrepancies between the results of this study and those of other studies could be due to the differences in the characteristics of the patients recruited for the study and the difficulty level of the tasks used for engaging in the motor imagery processes. Further studies should explore how these factors may confound the results among the SCI participants.

It is important to note that stronger activations in the GPe and lingual gyrus among the SCI participants might have compensated for the lower cognitive abilities in performing the lower limb imagery task. For the SCI group, greater percentage of signal change in the BOLD responses were observed during the first half of the lower-limb imagery task [see Figure 4.8(A)], suggested possible involvement of right GPe in the image generation (De Beni et al., 2007). Anatomically, GPe serves as a relay station connecting cerebral cortex, thalamus, cerebellum and the spinal cord (Benhamou et al.,

2012; Herrero et al., 2002; Turner et al., 2003). Compared to the internal part of globus pallidus (GPi), GPe was more a control station for the excitability of the cortical-BG-thalamus network in movements (Aron, 2011; Ridderinkhof et al., 2011) and the cortical-BG-cerebellar network for motor memory storage (Doya, 2000). In Albin's (1989) study, GPe responded to motor-related memory while GPi did not. With the support that SCI participants had significantly lower scores on the working memory (RAVLT) and executive functions (TMT), these suggested that the increases in activation of GPe would mediate retrieval of motor images for the image generation.

It is noteworthy that the stronger activations in the GPe were also revealed in the upper limb imagery task. In other words, the speculated compensatory processes of the GPe did not seem to be task-specific. Instead, they were systematic to motor imagery for both lower and upper limbs with the involvement in early processes in imaging. With Cramer's study (2005), the activations of the laterality might be related to the task. The validity of the speculation of the enhanced involvement of GPe in motor imagery and perhaps motor executive needs further studies.

Injury to the spinal cord resulted in loss of experience of movements of the lower limbs. This is the consequence of lesions of

the lumbar spine, leading to paralysis of the lower limb for the rest of one's life. The lack of experience of lower limb movements hinders imagery of these movements. Despite the lack of between-group differences in the behavioral results, the brain imaging results for imagery of lower limb movements indicated substantially weaker activations in the primary sensorimotor cortex, prefrontal cortex and the parietal cortex for the SCI than for the healthy control participants. On the contrary, stronger activations in these areas were observed among the SCI participants under the upper limb condition. These results suggested that the motor-related processes during imagery of lower limb movements were modulated by the post-injury lack of physical experiences of the paralyzed lower limbs among the SCI participants.

SCI Group Activations between Upper and Lower Limb Conditions

For the SCI group, stronger activations in the right postcentral gyrus (BA5), the right inferior parietal gyrus (BA40) and the right putamen were revealed in the contrast between upper and lower limb conditions (See Table 4.6 and Figure 4.3). These neural substrates were related to the process of motor imagery (Jurkiewicz et al., 2006; Wrigley et al., 2009). The right putamen played a similar role with the

GPe—i.e., as a relay center within the basal ganglion (Alkadhi et al., 2005; Hotze-Boendermaker et al., 2008). Significantly stronger activations in the middle occipital gyrus (BA19) were revealed in the contrast between lower and upper limb conditions. This finding was consistent with the contrast between the SCI and healthy groups in the left lingual gyrus. Similarly, the results suggested possible visual compensation for the loss of physical experience due to the paralyzed lower limbs among the SCI participants (Zapparoli et al., 2013).

Healthy Control Group Activations between Upper and Lower Limb Conditions

For the healthy control group, stronger activations were observed in the right superior frontal gyrus (BA8) in the contrast between lower and upper limb conditions (see Table 4.7 and Figure 4.4). Stronger activations in the left superior temporal gyrus (BA42) were detected in the contrast between the upper and lower limb conditions. These findings reflected the specificity of the motor imagery processes involved in the upper and lower limb conditions.

Chapter Ⅵ

Conclusion

This chapter includes the conclusion of this study, the limitations and the significance for clinical practice.

Conclusion

This study investigated the functional reorganization of the brains of individuals suffering from SCI with brain imaging. In particular, we are interested in exploring the plasticity of parts of the brain associated with sensorimotor functions of the upper and lower limbs. We employed a custom-designed task by engaging the SCI participants in imagining repetitive movements of the hands at the wrist or the feet at the ankle. The questions asked are: 1) Do SCI participants, when compared with the healthy control participants, use different strategies when engaging in the motor imagery task? 2) Are the roles of working memory and response inhibition during the motor imagery task different between the SCI and healthy control participants? and 3) Are the neural changes among the SCI participants systematic—i.e., involving the areas subserving both the lower and upper limbs?

Behavioral results indicated that participants' task performance on imagining repetitive movements of the upper and lower limbs was

comparable between the SCI and healthy control groups. It is, however, counter-intuitive that the significantly lower cognitive abilities in working memory and executive functions among the SCI participants did not seem to affect their performance on the motor imagery tasks. It was plausible that specific post-injury compensatory processes at the sub-cortical level occurred (see GPe below), which would have augmented the motor imagery processes among the SCI participants.

The most significant findings were that the SCI participants showed stronger activations than the healthy control participants in the right GPe and the left lingual gyrus during imagery of repetitive movements of the lower limbs. The GPe is a relay center within the globus pallidus and therefore for the basal ganglia. Stronger activation of the GPe resulted in enhanced excitatory outputs to the basal ganglia. It is speculated that the enhanced GPe was one of the areas of post-injury compensation among the SCI participants for motor-related activities. And GPe plays an important role in retrieval of the motor-related long-term memory for image generation. While in SCI, the modulated motor-related long-term memory is likely to be due to the loss of movement execution and practice. Another observation is the stronger activations in the lingual gyrus during the imagery of the lower limb movements. This suggested the possibility

that SCI participants adopted a different strategy that relies more on visual images when engaging in motor imagery. It was postulated that the lack of sensorimotor experience from the paralyzed lower limbs enhanced the development of visual-based compensation among the SCI participants. These modulated motor-related long-term memory is likely to be due loss of movement execution and practice in SCI.

When the SCI participants imagined upper limb movements, stronger activations than the healthy control participants were revealed in the bilateral primary sensorimotor cortex, right superior frontal gyrus, right superior and inferior parietal gyrus, right GPe and right thalamus. These findings suggested that when compared with healthy controls, the SCI participants showed neural changes at the system level. These changes were likely to be influenced by the consequence of paralysis of the lower limbs due to the spinal cord injury. Interestingly, the GPe was found to elicit stronger activations in the imagery of both lower and upper limb movements. It was plausible that the GPe played an important role in response to the post-injury deprivation of input from the lower limbs and subsequently modulated other motor-related processes such as those for imagining movements of the upper limbs. The mechanism underlying the speculated system-wide compensation is beyond the scope of this study. Future studies should design experimental

methods that can separate the various processes related to motor control and execution so as to better understand the compensation mechanism. It is also recommended that future studies include SCI participants with different levels and types of lesions to test the generalizability of the results.

Limitations

The findings of this study were likely to be confounded by the design of the functional task employed, which was imagery of upper and lower limb movements. Auditory cues were used to assist participants to recall the learnt movement rhythms. Motor planning and control were manifested without the actual execution of the movements. It is noteworthy that motor imagery elicited more extensive but weaker BOLD responses from the target neural substrates than motor execution. This weakened the power of the analyses conducted on the brain imaging results. Also, the motor imagery task used in this study was complicated of which the participants found difficulties in achieving high accuracy, which might reduce the power of analyses.

Another limitation of this study was the use of functional brain imaging, which biased the BOLD signal responses against the SCI participants, particularly for the lower limb movements. This is

because the SCI participants did not experience lower limb movements after the spinal cord injury. Engaging in imagery of lower limb movements posed additional challenges to the SCI participants. Future studies should employ other brain imaging methods such as structural, diffuse tensor imaging and resting state to minimize potential bias between the SCI and healthy control groups.

The sample sizes of the SCI and healthy control groups were relatively small. This also weakened the analyses. Due to the difficulty of recruiting potential SCI participants to join the study, the post-injury time was not controlled well. This posed threats to the homogeneity of the SCI participants, which may have affected the results. The same applied to the increased variability of cognitive functions, which also could have impacted on the results. Future studies should tackle each of these limitations to improve the quality of the results and power of the analyses.

Lastly, there was no control task were utilized, which resulted that they were not allowed construction of ROIs from the whole-brain analyses.

Clinical Relevance

Obviously, the brain function, in particular the function of motor control, was affected after SCI. Nevertheless, either the neural repair

and regeneration, or the compensation by bioengineering techniques such as brain-computer interface, was adopted as the strategy for functional recovery after SCI; a normal brain function as the central controller was the common assumption. This indicated to us that researchers should pay more attention to brain function in individuals with SCI.

If the abnormal pattern of the GPe activation is fixed by further studies, it may contribute to the mechanism of spasticity and neuropathic pain in SCI patients. Referring to other motor disorders attributed to the dysfunction of BG, appropriate interventions may be carried out in clinical practice, such as the application of DBS and neurotransmitter drugs in Parkinson's disease (Papuc & Rejdak, 2013; Giugni & Okun, 2014). Moreover, further understanding of the abnormal pattern of GPe activation may help to explore the role of the extrapyramidal system in the rehabilitation strategy for SCI patients.

Despite the fact that voluntary motor actions and peripheral feedback were lacking, we found that motor imagery training improved motor performances and altered brain function in subjects with complete paralysis. In healthy subjects, it was observed that motor system activation can be modified by a 1-week course of motor imagery practice (Lacourse et al., 2004). Increased activation was observed in left putamen after a week of foot motor imagery training

in SCI, which might reflect the process of motor learning despite the completely lack of voluntary motor output (Cramer et al., 2007). In virtue of advantages of the motor imagery itself, even though either the magnitude activated or the behavioral gains by MI were smaller than physical exercise, MI was accessible for the subjects who suffered from weak or paralyzed limbs in the way of mental practice and experiences. Meaningfully, it is suggested that MI training would be an effective and potential approach that can be valuable for the restorative interventions targeting SCI. However, the time window for interventions is important and needs further research.

Finally, our results supported the notion that motor imagery is an effective approach for exploring the brain motor function. Furthermore, it is a unique tool to study the motor-related brain function for subjects who suffered from paralysis. Thus, it suggests that clinicians should test the ability of motor imagery and cognitive functions after SCI as a screen for brain function.

Appendix Ⅰ Letter of Ethics Approval of Department Committee, Department of Rehabilitation Sciences

THE HONG KONG
POLYTECHNIC UNIVERSITY
香港理工大學

MEMO

To : CHAN Che Hin, Department of Rehabilitation Sciences
From : NG Yin Fat, Chairman, Departmental Research Committee, Department of Rehabilitation Sciences

Ethical Review of Research Project Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following research project for a period from 20/06/2011 to 31/08/2013:

Project Title : Could experience modulate motor control function? A case in individuals with spinal cord injury

Department : Department of Rehabilitation Sciences

Principal Investigator : CHAN Che Hin

Please note that you will be held responsible for the ethical approval granted for the project and the ethical conduct of the research personnel involved in the project. In the case the Co-PI has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Departmental Research Committee Department of Rehabilitation Sciences in advance of any changes in the research proposal or procedures which may affect the validity of this ethical approval.

You will receive separate notification should you be required to obtain fresh approval.

NG Yin Fat
Chairman
Departmental Research Committee
Department of Rehabilitation Sciences

Appendix Ⅱ Letter of Ethics Approval of the Ethics Committee on Human Studies, China Rehabilitation Research Center

中国康复研究中心北京博爱医院医学伦理委员会对

《脊髓损伤后大脑运动相关长期记忆功能与运动调控功能研究》

项目审批件

批件号	医学伦理委员会 2011-017
审查会议日期	2011 年 4 月 20 日
审查会议地点	北京博爱医院 F4 会议室
临床研究项目名称	脊髓损伤后大脑运动相关长期记忆功能与运动调控功能研究
审查文件	临床研究文件（课题任务书等) 向受试者提供的知情同意书 伦理审查申请报告
临床研究单位	北京博爱医院 脊柱脊髓神经功能重建科
主要研究者	李建军
伦理审查方式	会议审查
会议审查到会	时海峰、孔德明、宓忠祥、王贵明、王连禹、孙进、高钧、付光、何静杰、杨祖福、赵超男
审查意见	研究方案符合伦理原则
审查结论	同意
主任委员签字	

盖章

日期 2011 年 4 月 20 日

AppendixⅢ Informed Consent

中国康复研究中心

科研知情同意书

科研题目： 脊髓损伤后大脑运动相关长期记忆功能与运动调控功能研究

科研人员： 李建军教授，Chetwyn Chan 教授，高峰医师

研究资料：

本研究主要是为了了解亚急性期、慢性期脊髓损伤者与健康人的运动相关长期记忆和运动控制的不同。您将接受持续三天的实验任务训练，以了解实验流程和内容，每天一小时。您还将参与神经心理学测试（Rey 氏听力语言学习测验，前向和后向数字广度测试，史楚普实验，符号数字模式转换测验，划线试验）和大脑功能磁共振扫描。本研究结果有助于加深对脊髓损伤后大脑运动控制功能的变化及其潜在机制的理解，有助于为脊髓损伤后康复策略和康复治疗方案的制订提供新的方向和指导。

同意书：

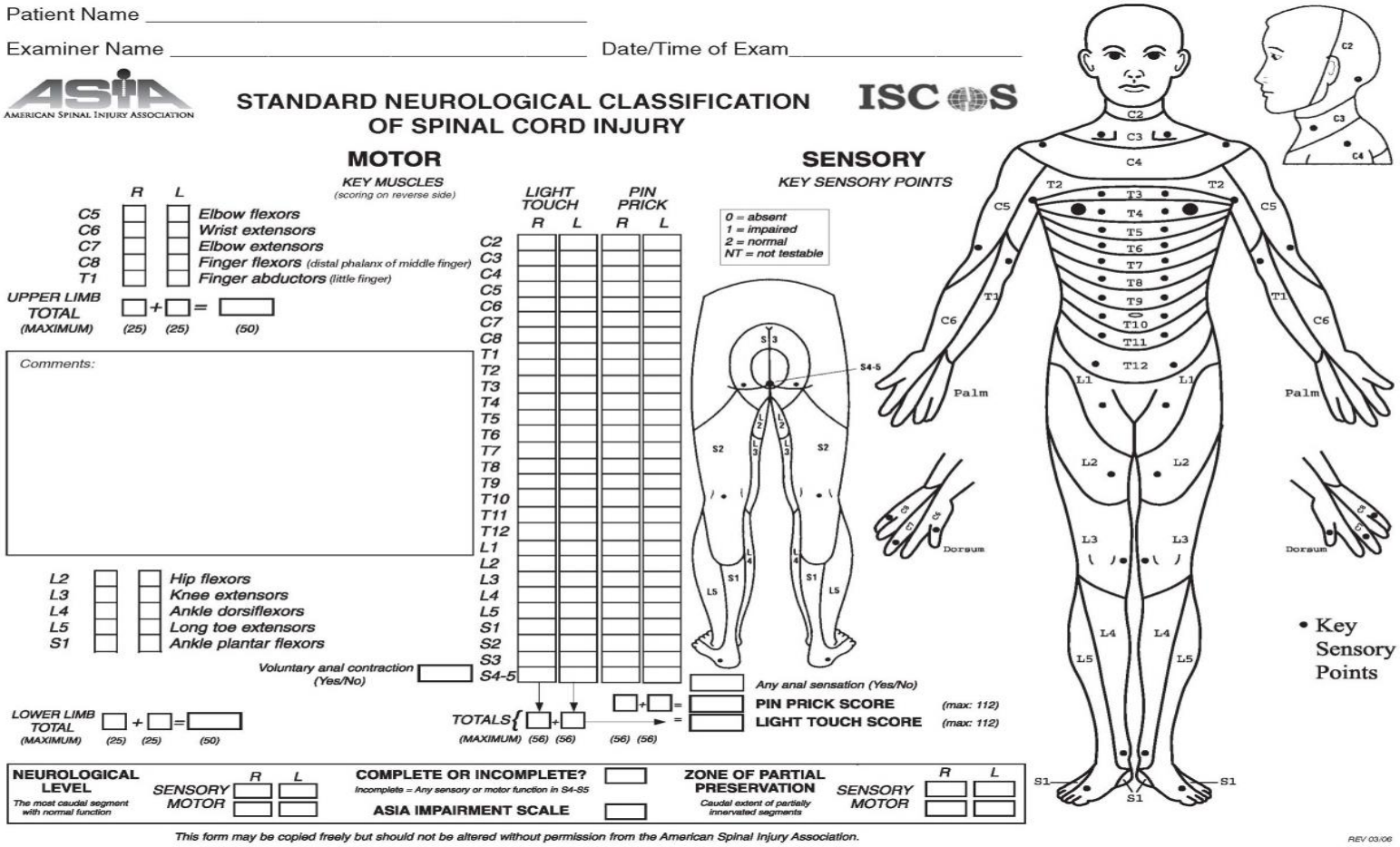
本人_____通过听取口头解释已了解此次研究的具体情况。本人愿意参加此次研究，本人有权在任何时候、无任何原因放弃参与此次研究，而此举不会导致您受到任何惩罚或不公平对待。您的资料将不会泄露给参与此研究无关的人员，您的名字或相片不会出现在任何出版物上。

本人可以用电话 8756 来联系此次研究课题执行人，高峰住院医师。本人亦明白，参与此研究课题需要本人签署一份同意书。

签名（参与者）： 日期：

签名（证人）： 日期：

Appendix Ⅳ Standard Neurological Classification of Spinal Cord Injury, American Spinal Injury Association



Appendix Ⅴ Rey Auditory Verbal Learning Test

编号：_____ 研究者：_____ 日期：_____

T1. 记忆

T1.1 记忆——即刻记忆

指导语：下面我给您念一些物体的词，我念完以后，请您把记住的词告诉我。不用按顺序说，记得什么就说什么。然后我会再给您念几遍，请您把每次记住的词都告诉我，**包括前一次已经说过的词，**看您最后能记住多少。好吗（检查者以每个词一秒的速度清楚的读出，用 1、2、3 等阿拉伯数字进行记录。每次 2 分钟回忆时间）。

项目	第一遍	第二遍	第三遍
胳膊			
猫			
斧子			
床			
飞机			
耳朵			
狗			
锤子			
椅子			
轿车			
眼睛			
马			
刀子			
钟			
自行车			
正确的个数			

T1.1 总分	3 遍正确回忆总数	□□

休息 3 分钟。

编号：_____ 研究者：_____ 日期：_____

T1.2 记忆——延迟回忆

指导语：“还记得我刚才给您念了好几遍的那些词吗？请您尽可能多的回忆出来（2 分钟回忆时间。用 1、2、3 等阿拉伯数字进行记录）”。

胳膊		椅子	
猫		轿车	
斧子		眼睛	
床		马	
飞机		刀子	
耳朵		钟	
狗		自行车	
锤子			

T1.2	正确回忆的个数	□□

T1.3. 记忆——长时延迟再认

指导语：下面我念 30 个词，其中有我刚才让您记过的，有些是新加进去的，请您告诉我哪些是我让您记的，哪些是新加进去的[暗影者为干扰项目，对虚报词——“错把干扰词当作让其记忆的词”打×，击中的词打√，击中数－虚报数(√的个数-×的个数)为再认得分]。

镜子		嘴唇	
锤子		树	
刀子		胳膊	
蜡烛		鼻子	
摩托车		太阳	
斧子		卡车	
钟		眼睛	
椅子		鱼	
飞机		耳朵	
乌龟		自行车	
马		蛇	
大腿		板凳	
狗		公共汽车	
桌子		床	
猫		轿车	

T1.3	击中数－虚报数	□□

Appendix Ⅵ Digit Span Test – Forward and Backward

Subject Code _____ Date _____

T2. 数字广度测试

顺背		通过 或不通过	得分 2, 1, 或 0
3.	3 – 6 – 5		
	2 – 4 – 9		
4.	3 – 1 – 7 – 4		
	4 – 6 – 2 – 9		
5.	1 – 8 – 5 – 2 – 4		
	8 – 7 – 1 – 9 – 5		
6.	2– 4 – 7 – 3 – 9 – 1		
	1 – 9 – 5 – 7 – 4 – 3		
7.	5 – 6 – 3 – 9 – 2 – 1 – 8		
	6 – 4 – 3 – 2 – 8 – 5 – 1		
8.	2 – 7 – 5 – 8 – 6 – 4 – 9 – 3		
	9 – 4 – 3 – 7 – 6 – 2 – 5 – 8		
9.	7 – 5 – 8 – 3 – 6 – 1 – 9 – 2 – 4		
	5 – 9 – 2 – 7 – 4 – 1 – 6 – 3 – 8		

总分: _____

倒背		通过 或不通过	得分 2, 1, 或 0
3.	8 – 7 – 2		
	5 – 8 – 1		
4.	7 – 8 – 6 – 4		
	8 – 4 – 1 – 7		
5.	8 – 2 – 5 – 9 – 4		
	5 – 8 – 6 – 3 – 9		
6.	9 – 2 – 4 – 8 – 7 – 1		
	3 – 7 – 4 – 9 – 1 – 6		
7.	8 – 7 – 5 – 2 – 6 – 3 – 9		
	4 – 8 – 1 – 2 – 5 – 9 – 7		
8.	1 – 6 – 2 – 9 – 3 – 5 – 7 – 4		
	6 – 2 – 5 – 8 – 9 – 4 – 1 – 3		
9.	9 – 2 – 5 – 8 – 1 – 4 – 7 – 3 – 5		
	2 – 7 – 4 – 8 – 5 – 3 – 9 – 1 – 6		

总分: _____

Examiner _____

Appendix Ⅶ Trial Making Test A & B

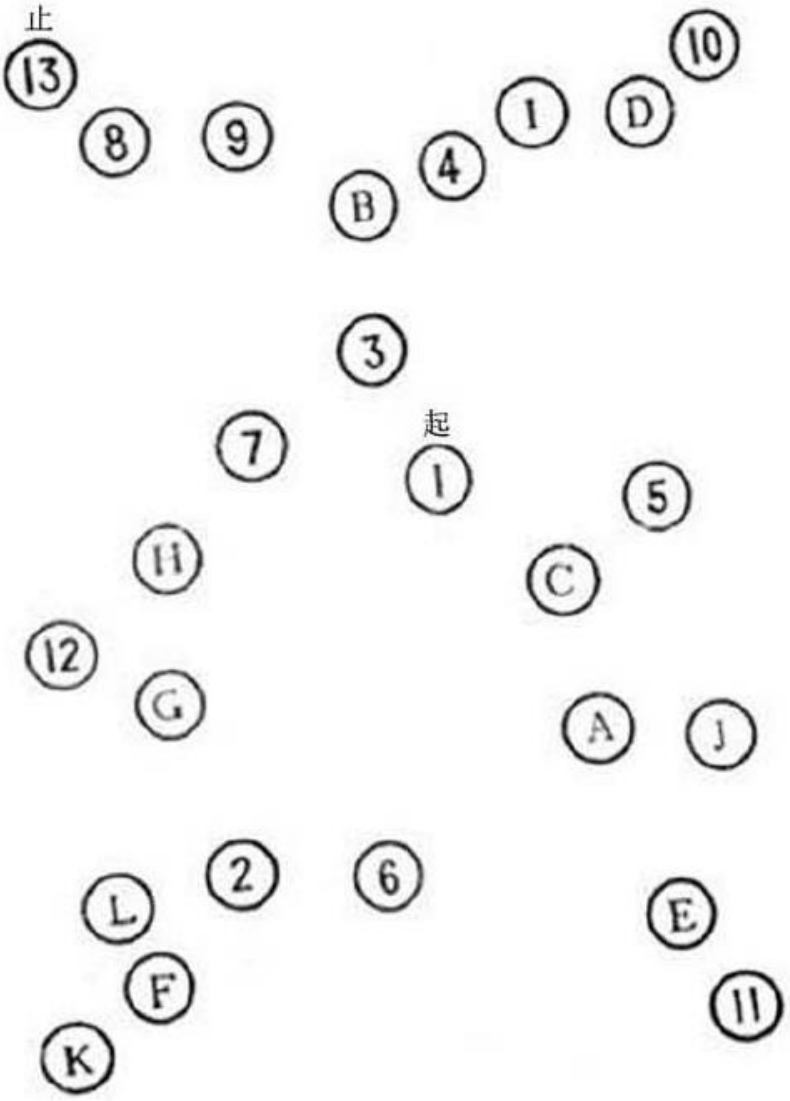
编号：_____ 研究者：_____ 日期：_____

T3.1 连线测验 A

时间：_____

编号：_____ 研究者：_____ 日期：_____

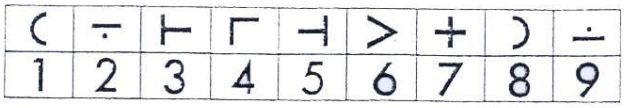
T3.1 连线测验 B

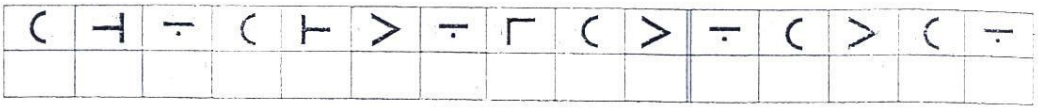


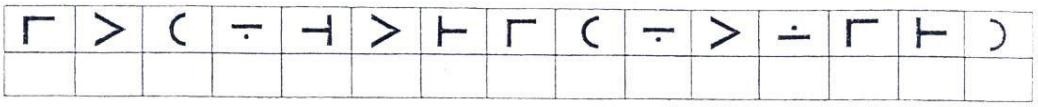
时间：_____

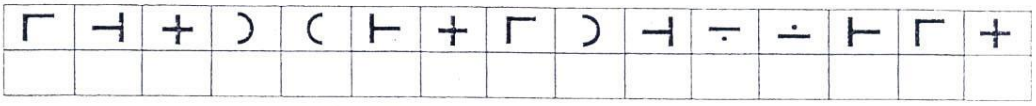
Appendix Ⅷ Symbol Digit Modality Test

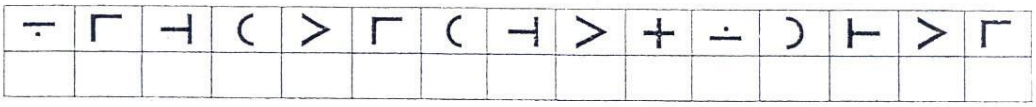
KEY

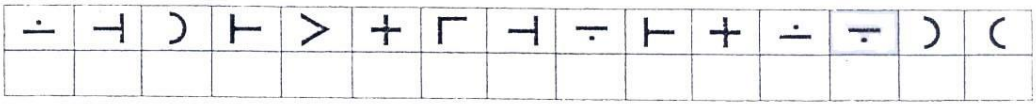


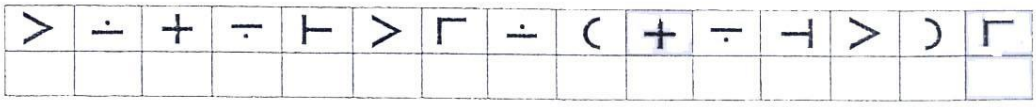


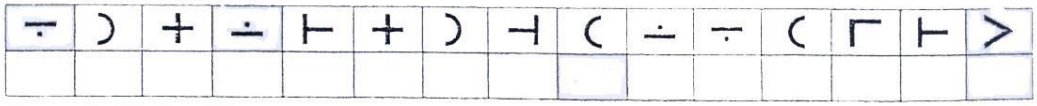


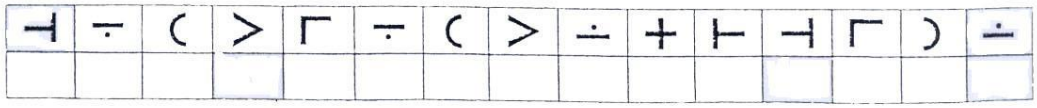












Subject Code:

Date:

Examiner

Corrected:

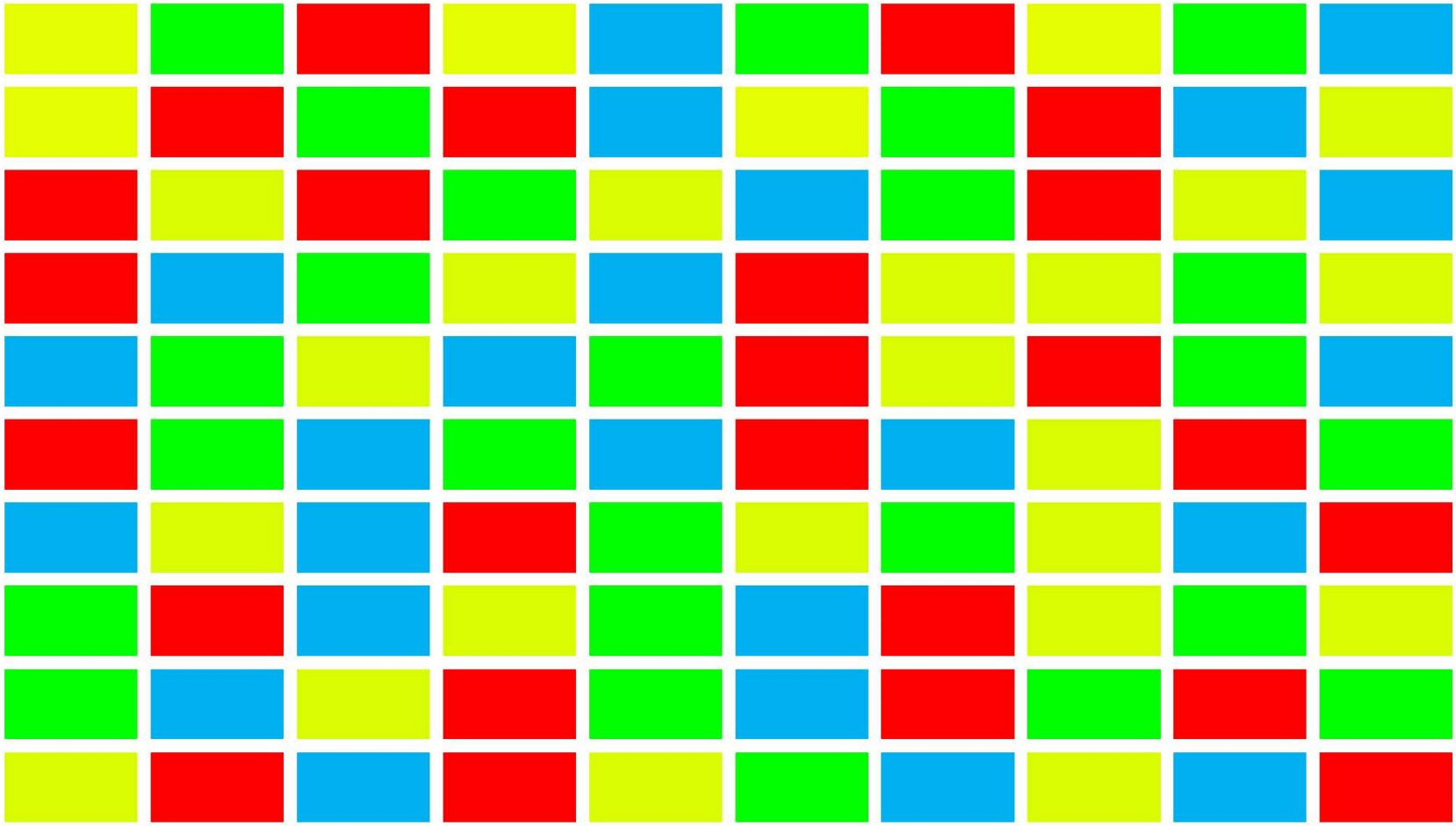
Uncorrected:

Appendix Ⅸ Stroop Test (Word, Color, Word-Color)

Word Test

绿	红	黄	蓝	黄	红	蓝	绿	红	黄
绿	蓝	红	黄	红	绿	黄	绿	红	绿
黄	红	蓝	黄	红	黄	蓝	绿	蓝	绿
蓝	红	黄	蓝	红	绿	蓝	红	蓝	红
绿	蓝	红	绿	蓝	黄	蓝	绿	黄	绿
黄	蓝	红	黄	绿	蓝	黄	蓝	绿	红
绿	蓝	黄	绿	红	蓝	黄	绿	黄	蓝
红	黄	红	绿	蓝	红	黄	绿	蓝	红
黄	绿	红	黄	红	黄	绿	黄	绿	蓝
绿	蓝	黄	蓝	红	蓝	绿	蓝	黄	蓝

Color Test



Word-Color Test

绿	红	黄	蓝	黄	红	蓝	绿	红	黄
绿	蓝	红	黄	红	绿	黄	绿	红	绿
黄	红	蓝	黄	红	黄	蓝	绿	蓝	绿
蓝	红	黄	蓝	红	绿	蓝	红	蓝	红
绿	蓝	红	绿	蓝	黄	蓝	绿	黄	绿
黄	蓝	红	黄	绿	蓝	黄	蓝	绿	红
绿	蓝	黄	绿	红	蓝	黄	绿	黄	蓝
红	黄	红	绿	蓝	红	黄	绿	蓝	红
黄	绿	红	黄	红	黄	绿	黄	绿	蓝
绿	蓝	黄	蓝	红	蓝	绿	蓝	黄	蓝

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