

# An fMRI Study on Supra-Spinal Contributions to Upper and Lower Limb Motor Control

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**AN FMRI STUDY ON SUPRA-SPINAL CONTRIBUTIONS  
TO UPPER AND LOWER LIMB  
MOTOR CONTROL**

by:

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A Thesis submitted to the Faculty of the Graduate School,  
Marquette University,  
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the Degree of Master of Science

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**ABSTRACT**  
AN FMRI STUDY ON SUPRA-SPINAL CONTRIBUTIONS  
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The differences in the neural mechanisms contributing to upper and lower extremity movement have not been fully elucidated, and this might be a factor that leads to the ineffectiveness of rehabilitation techniques for most stroke survivors. It is unclear whether therapies designed for upper extremities should also be used for the lower extremities, and vice versa. In this study, fMRI was used to examine the supraspinal control of UE and LE movement in both neurologically intact individuals and people with post-stroke hemiparesis. We compared the location, volume, and intensity of brain activity associated with upper and lower extremity pedaling and unilateral flexion/extension of the hand and ankle. We hypothesized that if the supraspinal control strategies were the same for upper and lower extremities, then the pattern of brain activity would be the same across upper and lower limb movement. Alternatively, if the strategies were not the same, then brain activation would differ for each task.

We found movement related brain activity in three cortical regions (S1, M1, and Brodmann Area 6) among healthy subjects. The location of activity complied with the somatotopic order in the sensorimotor cortex, but upper extremity produced greater activities during both pedaling and flexion/extension movement compared to the lower extremities. These observations suggested that the general brain activation strategies were similar between upper and lower extremities, while the involvement of cortical structures was more substantial for upper than lower limb movements. The four stroke subjects showed activity in the same regions as compared to the healthy group, yet the volume, intensity and symmetry of activation varied across the subjects and motor tasks. These observations suggested that there were multiple strategies for cortical reorganization after stroke and the controlling strategies for the effectors differed.

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## CHAPTER 1: GENERAL INTRODUCTION

### 1.1 Movement Control

Movement of the upper and lower extremities (UE and LE, respectively) is heavily controlled by the neural structures including the brain and the spinal cord, and each of these structures plays a specific role in smooth movement output. Previous studies have suggested that neural control of movement differed between UE and LE (Luft, et al. 2002; Kapreli, et al. 2006; Miyai, et al. 2001), yet the exact knowledge of UE and LE control remains unclear. Regarding differences between the UE and LE, two opposite points of view exist. First, the difference between UE and LE movement control could be due to different task demands for the UE and LE because the typical movements for them are different: Typical UE movements are discrete in nature and performed unilaterally or asynchronously, whereas typical LE movements are continuous and bilateral. For example, reaching to the door handle is a relatively brief and discrete task, which is performed with only one hand with a clear beginning and end; walking past the doorway involves continuous movement with both legs. Previous studies suggested that the motor control of bimanual and unimanual movement is different (Kermadi et al. 1998; Swinnen, 2002). Thus, the difference in movement control might result from differences in the typical movements for UE and LE.

Second, the differences between UE and LE could be due to differences in the fundamental neural control strategies. For example, previous imaging studies suggested that all the UE movements are volitionally controlled by the supraspinal system, including primary motor cortex (M1), supplementary motor cortex (SMA), and premotor cortex (Nirkko, et al. 2001; Sahyoun, et al. 2004), whereas LE movements might be

controlled automatically in the level of spinal cord (MacKay-Lyons 2002). These studies support the view that the control strategies are not related to the movement task, but rather to the end effectors. It has also been suggested that the UE movement is controlled by the motor cortex in the contralateral hemisphere, while the LE movement is controlled by the cortex in both of the hemispheres (Luft, et al. 2002; Kapreli, et al. 2006). To determine the exact difference between UE and LE control, matched tasks should be designed. If the LE performed bilateral and continuous movement, then similar movement should be performed by the UE, and vice versa. In current literature, UE and LE control are not examined or compared under matched task demands, because limb effects (i.e. UE verses LE) are not separated from task effects (bilateral versus unilateral, discrete versus continuous), thus, the exact differences are not well understood.

Knowledge of the way in which the brain and spinal cord control for UE and LE movements might influence the design of therapeutic interventions for people with post-stroke hemiparesis. Current interventions with some evidence of effectiveness include constraint induced movement therapy (CIMT) and bilateral extremity training (BET). For example, Wolf et al. (2007) reported that CIMT led to improvements of UE function; Johannsen et al. (2010) found short-term improvement of LE function after BET training; and Kim et al. (2012) reported that both bilateral and unilateral training strategies with a wearable robotic system improved limb function. Although these studies supported the effectiveness of CIMT and BET interventions, they were suboptimal because most patients failed to recover their UE and/or LE function to the normal level, which is a major goal and challenge for stroke individuals. One of the important factors that contribute to the limited effectiveness of rehabilitation is the incomplete understanding of

the neural control strategies underlying normal UE and LE movement. If we accept the assumption that the control patterns for UE and LE are not the same, then we should believe that the treatment designed for the UE might not be appropriate or effective for LE, and vice versa. It is rational to believe that a better understanding of limb movement control could influence the design of therapeutic interventions for stroke patients, leading to better motor function restoration in the future.

The purpose of this thesis was to examine the supraspinal control of UE and LE movement in both neurologically intact individuals and people with post-stroke hemiparesis under the same task demands. To make fair comparisons between UE and LE, subjects performed four tasks in the functional magnetic resonance imaging (fMRI) scanner: bilateral upper extremity pedaling ( $PED_{UE}$ ), bilateral lower extremity pedaling ( $PED_{LE}$ ), unilateral finger flexion/extension (FING), and unilateral ankle flexion/extension (FOOT). For the  $PED_{UE}$ , a custom-designed MR compatible pedaling device was fabricated for the present study, and the specifications are described in Chapter 2. For the  $PED_{LE}$ , FING and FOOT, the related devices have already been used in previous fMRI studies, and they are also mentioned in Chapter 2. Two separate comparisons have been made between UE and LE in the present study:  $PED_{UE}$  vs.  $PED_{LE}$ , both of which involved bilateral tasks, and FING vs. FOOT, both of which involved unilateral tasks.

## 1.2 Spinal control of locomotion

Spinal cord is the information pathway that connects the brain and the peripheral nervous system. Locomotion in mammals is to a large degree controlled directly by

intrinsic spinal networks called central pattern generators, or CPGs for short (Kiehn, et al. 2008).

In animal studies, it has been shown that the spinal cord controls the ongoing rhythmic flexion and extension during locomotion through CPGs located inside the spinal cord (Leon, et al. 1998; Kiehn, et al. 2008). Several studies have identified some locomotor-related neurons in the cat and the mouse spinal cord (Angel et al. 2005; Bonnot, et al. 2002; Quinlan, et al. 2007), and these neurons are supposed to provide rhythmic inputs to the related motor neurons (Kiehn, et al. 2008). If a high spinal transection is performed on a cat, the fore- and hind-limbs can each be made to generate alternating movements (Miller, et al. 1975; Pearson, et al. 1991); if a spinal transection is performed on lower thoracic level, the cat is still able to perform rhythmic ankle stepping on a treadmill without external weight support (Brown 1911; Grillner, et al. 1985).

In primate studies, there is only inclusive evidence for the function of CPGs. To demonstrate the existence of CPGs directly would require a complete spinal cord transection, yet most current studies only provide evidence from spinal cord injury individuals, and some studies even challenged the existence of independent CPGs in primates. Eidelberg (1981) failed to observe hindlimb stepping in his macaque monkey with a spinal transection. Other studies suggested that monkeys showed less hindlimb stepping than cats after partial transection of the spinal cord (Vilensky, et al. 1992).

Some indirect evidence for spinal CPGs in humans is observed from spinal cord injury (Dimitrijevic, et al. 1998). People with incomplete spinal cord injuries could perform involuntary rhythmic movements of the lower extremity (Brown and Kukulka

1993). In complete spinal cord injury, human spinal cord uses sensory information about ipsilateral limb loading to increase muscle activation (Ferris, et al. 2004).

The former studies also examined the neural coordination mechanisms in humans that regulate rhythmic activity between the UE and LE, and these studies added to the evidence that CPG activity contributes to rhythmic UE movement (Dragert, et al). For example, Wannier found that in walking, creeping and swimming, UE to LE coordination is well established and preserved even though the movement speed was controlled, and this finding demonstrated that UE to LE coordination observed in human walking is similar to the coordination of quadruped locomotion (Wannier, et al. 2001). Zehr examined the EMG signals and the cutaneous reflex to electric stimulus during both UE and LE rhythmic movement, finding that the amplitude of cutaneous reflex was modulated during both UE and LE movement (Zehr, et al. 2007, Zehr, et al. 2005, Dragert, et al. 2009). His work support the notion that UE and LE are regulated by the same mechanisms during rhythmic motion and this control might be ascribed to CPG-like activities (Zehr, et al. 2007).

### 1.3 Supraspinal control of movement

The supraspinal structures are essential in controlling extremity movement. In contrast to the simplicity of locomotion control, the cortical regions are related to dexterous movement such as signing, grasping and reaching. Neurons inside the primary motor cortex (M1) play a fundamental role in the control of voluntary movements. It has also been proved that the firing of motor neurons is positively correlated to the force, velocity and direction of the extremity movement (Guertin 2009; Lutz, et al. 2005; Mehta, et al. 2012; Kinoshita, et al. 2000). The role of the supplementary motor area (SMA) in

motor control is still under discussion. It is thought to be involved in the internal control of complex movements, and is a key structure for behavioral planning and execution.

Based on animal studies, some suggest that the supraspinal system is not essential for maintaining locomotion, but is important for adapting it to challenging environmental conditions. In human studies, CPGs are suspected to exist in spinal cord level and are under some supraspinal control, yet the evidence is indirect (M. MacKay-Lyons 2002). In fact, the locomotion tasks are strongly correlated to the activation of certain parts of the brain (Miyai, et al. 2001). Near-infrared studies have proved that constant treadmill walking demands increased oxygenated hemoglobin in SMA and paracentral cortex (Miyai, et al. 2001). Functional MRI (fMRI) studies found clear and consistent activity in the medial part of paracentral cortex during imagined locomotion, or locomotion-like movement. Petersen (1998) showed that stimulating the motor cortex with transcranial magnetic stimulation decreased the muscle activity during walking. These studies suggest that in humans, the cerebral cortex is required during locomotion.

#### 1.4 FMRI

We chose fMRI as an imaging method because it is a non-invasive tool for examining neural activity with high spatial and median temporal resolution. fMRI detects the blood oxygen level-dependent (BOLD) changes in the MRI signal that was related to the changes of blood flow nearby. An increase in neural activity will stimulate an increase in the local blood flow in order to meet the demand for oxygen (Gore, et al. 2003).

The contrast in MR images between two voxels is determined by the density (e.g., proton density), chemical concentration (e.g., lactate or acetylcholine), the content of a

particular molecular type (Huettel, et al.2008), and the relaxation (e.g.,  $T_1$ ,  $T_2$ ,  $T_2^*$ ). The term “relaxation” reflects the processes by which the spins tend to return to their equilibrium distribution in which there is no transverse magnetization and the longitudinal magnetization is at its maximum value (Huettel, et al. 2008; Matthews, et al. 2004).

The  $T_1$  and  $T_2$  relaxation time are both tissue-specific time constant, while the  $T_2^*$  relaxation time is comprised of  $T_2$  and the changes in spin precession frequencies due to the presence of inhomogeneities of the magnetic field (Huettel, et al. 2008). The changes in spin procession are strongly correlated to the concentration of deoxygenated hemoglobin: Oxygenated hemoglobin (Hb) is diamagnetic, and deoxygenated hemoglobin (dHb) is paramagnetic, so that only the later one has unpaired electrons and a significant magnetic moment (Huettel, et al. 2008). Paramagnetic substances distort the surrounding magnetic field, so that the nearby protons will precess at different frequencies, resulting in the more rapid decay of transverse magnetization. Therefore, the decreased relaxation time resulted of deoxygenated hemoglobin forms the basis for BOLD-contrast fMRI (Huettel, et al. 2008).

The changes in  $T_2^*$ -weighted images are supposed to be correlated to regional neural activities (Ogawa, et al. 1990). Ogawa and colleagues (1990) demonstrated that deoxygenated blood decreases the measured MR signal, while the change triggered by neuronal activity is known as hemodynamic response. Even though the increased metabolism during brain activity leads to larger amount of regional dHb, the demands of Hb will cause an increased inflow of oxygenated blood, and the whole procedure will result in a decrease in dHb concentration. Therefore, if the neuronal activity is extended

in time, the hemodynamic response will start with an “initial dip”, and increased to a “peak” value, then extended into a plateau as a result (Huettel, et al. 2008).

### 1.5 Specific aims

In this study, we compared the supraspinal control between UE and LE movement in both neurologically intact and stroke subjects under the same task demands. The bilateral tasks include  $PED_{UE}$  and  $PED_{LE}$ , and unilateral tasks include FING and FOOT. Comparison between  $PED_{UE}$  and  $PED_{LE}$  allows us to examine the supraspinal control between bilateral locomotor-like movements of the UE and LE. The comparison between FING and FOOT allowed us to examine the supraspinal control between unilateral finger and foot movement. The specific aims of this study include the following four points:

(1) Determine whether the pedaling device and the data collection system used in  $PED_{UE}$  task are MR compatible (Chapter 2);

(2) Determine whether the neurologically intact human brain uses different strategies for controlling UE as compared to LE in both bilateral and unilateral movements (Chapter 3);

(3) Determine whether the data collection system could be applied to the experiment on people with post-stroke hemiparesis (Chapter 4);

(4) Examine the supraspinal activity of people with post-stroke hemiparesis during UE and LE movement (Chapter 4).

We hypothesized that if the fundamental supraspinal controlling strategy for the UE and LE was the same, then the pattern of brain activity would be the same across the



UE and LE tasks. Alternatively, if the strategies were not the same, then activation pattern would differ for each task.

For specific aim 4, we recruited four stroke subjects in the study. Due to the limited subject size, however, we only present a case report for this part and use observation techniques to determine whether the stroke-affected brain uses novel supraspinal strategies to control limb movement; if so, whether these strategies are different for the paretic UE and LE.

## CHAPTER 2: MR DEVICES FOR ASSESSMENT OF UPPER AND LOWER EXTREMITY MOVEMENT

### 2.1 Introduction

Neural control of upper limb movement is often assessed by examining the BOLD activity as they complete a variety of active and passive hand and finger movements in the scanner. For example, subjects have performed finger and hand movements with specific devices such as piano-keyboard-like buttons (Hollinger, 2008), pneumatic manipulandum (Suminski, et al. 2007), and a device named Magnetic Resonance Compatible Smart Hand Interfaced Rehabilitation Device (Khanicheh, et al, 2006). Neural control of bilateral movements of the lower limbs, particularly locomotion, which is one of the most important functions of the lower limbs, had not been studied as frequently due to the difficulties of performing such movement including walking in the MR scanner (Mehta, et al. 2009).

Recently, researchers overcame limitations imposed by the MR scanning environment by performing walking-like movement, using alternative methods. For example, one method was to apply imagined walking instead of true walking in the movement tasks, so that walking was not exactly needed during the scanning (Jahn, et al. 2009). Another method was to choose other motor models with application of specific experimental devices: in one study, subjects performed gait-like stepping in an MR compatible robotic device during the scanning (Laura, et al. 2011); in another study, subjects performed bilateral pedaling movement with a lower extremity pedaling device (Mehta, et al. 2001).

In the present study, we compared the brain activity in four different tasks (PED<sub>UE</sub>, PED<sub>LE</sub>, left/right FING, and left/right FOOT). In FOOT and FING tasks, to monitor the subject's movement, we used an electric tapper to record the foot movement (Fig. 2-1), and used the rubber air-filled bladder and a pressure transducer to record the finger movement (Fig. 2-2 A, B), respectively. For PED<sub>LE</sub> task, the device, described and tested by Mehta in 2009 (Fig. 2-3; Mehta, et al. 2009), is a fMRI-safe pedaling device for the lower limb; and for PED<sub>UE</sub> we designed a MR compatible upper extremity pedaling device for this project (Fig. 2-4 A) in collaboration with Dr. Sheku Kamara from the Rapid Prototyping Center at the Milwaukee School of Engineering (MSOE). Unilateral tapping and the bilateral pedaling device for the lower limbs are described in detail in section 2.1.2. The unilateral tapping and the bilateral pedaling device for the upper limbs are described in detail in section 2.1.3.

In section 2.2, we report the MR compatibility experiment used to test our PED<sub>UE</sub> device only. All other devices were commercial or tested elsewhere. All the equipment applied in fMRI related experiment should be MR safe and MR compatible. The device is MR safe when it presents no additional risk to the subjects; and it is MR compatible when it neither significantly affect the quality of the functional signal nor have its operations affected by the MR scanner (Chizei, 1999; Schaefer, 2007). In general, ferrous objects should be excluded from the device material, because they might be lifted up or pulled away inside a strong magnetic field, leading to human injury or equipment damage; some other materials, including metal devices, and any conductive or dielectric materials are also not allowed in the device design, because those materials might lose function in the scanner, and could distort the magnetic field.

## 2.1 Devices Description

### 2.1.1 Lower Extremity Devices

The device used to produce and record FOOT movements have already been used in the scanner in previous studies (Figure 2-1; Cope, et al. 2010). On the top of the device, a circular plastic button (6.35 cm diameter) was connected to a switch (Jelly Bean Twist Top Switch, AbleNet, Inc., Roseville, MN) that was mounted on a base via a multi-articular arm such that the button could be oriented beneath the ball of the foot. When the switch was depressed, it created a change in voltage signaling the tap of the foot. The signal created by the switch was output to the parallel port of the desktop and recorded by the software Presentation (Neurobehavioral Systems, CA), which had been used successfully in previous studies (Mehta, et al. 2009; Mehta, et al 2012).

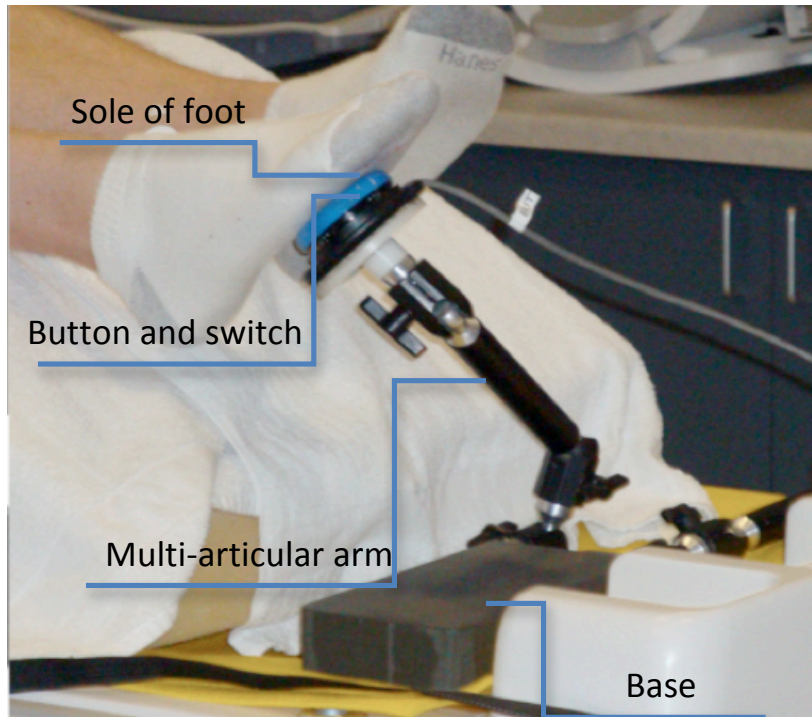


Figure 2-1. FOOT Task Equipment

The PED<sub>LE</sub> device was used to regulate the subjects' performance and provide support to the sole of the feet (Figure 2-2). It was designed by Mehta as a direct drive apparatus fabricated from non-metallic materials including polyvinyl chloride, Delrin, Phenolic, Nylon and wood (Mehta, et al. 2009). A flywheel was mounted on a pair of solid vertical supports, working as the crankshaft. The vertical supports were mounted on a base and secured with Nylon screw. Two pedals were coupled to the crankshaft via crank arms. A pair of sandals was mounted on the pedals in order to secure the feet. The crankshaft was made of Delrin, which was self-lubricated plastic material. The mechanical load on the pedaling device was produced by friction between the crankshaft and the vertical supports (Mehta and et al, 2008).

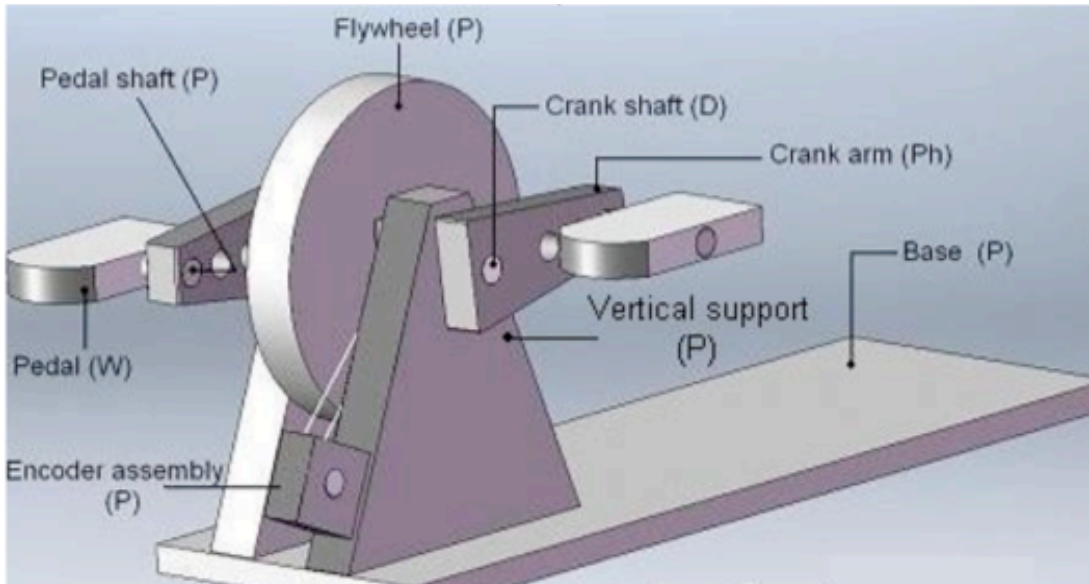


Figure 2-2. PED<sub>LE</sub> Task Equipment (Mehta, et al. 2009)

To monitor the subjects' leg movements, an MR compatible optical encoder (model TD 5207, Micronor Inc., CA) with resolution of 1.8° was used to measure crank position. The encoder was enclosed in housing, which was mounted on one of the vertical supports, and coupled to the crankshaft via a plastic chain and sprocket assembly arranged in a ratio 1:1.

The signal produced by the encoders was output to a controller unit (model MR310, Micronor Inc., CA) via a fiber optic cable. The controller converted the optical signals to electrical signals and produced analog outputs corresponding to crank position. Data were sampled at 2000 Hz using a 16-bit analog to digital converter, data acquisition software (micro 1401 mk II and Spike, Cambridge Electronic Designs, UK), and desktop computer. These data were used to compute mean pedaling rate across subjects and conditions.

The PED<sub>LE</sub> device has been proved to be MR compatible in Mehta's study (Mehta, et al. 2009). He found no visual detectable effect from the PED<sub>LE</sub> device, but observed brightness change to the scale less than 1%, signal-to-noise ratio change no larger than 1%. This result could be considered as MR compatible according to the conclusion of previous studies (Chinzei et al. 2000; Chinzei, et al. 1999; Gassert et al. 2006; Khanickeh et al., 2005; Suminski).

### 2.1.2 Upper Extremity Devices

In the unilateral FING task, a rubber air filled bladder (11.3cm X 5.7 cm) was inflated to approximately 1.0 psig (Figure 2-3 A), and was connected via plastic tubing to a pressure transducer and display unit (Figure 2-2 B, models LM/2345-02 and GM/ 060-3471-01, Sensotec, Columbus, OH). Signals from the air bladder were sampled at 2000 Hz using the same analog to digital converter and data acquisition software as described for PED<sub>LE</sub> task.

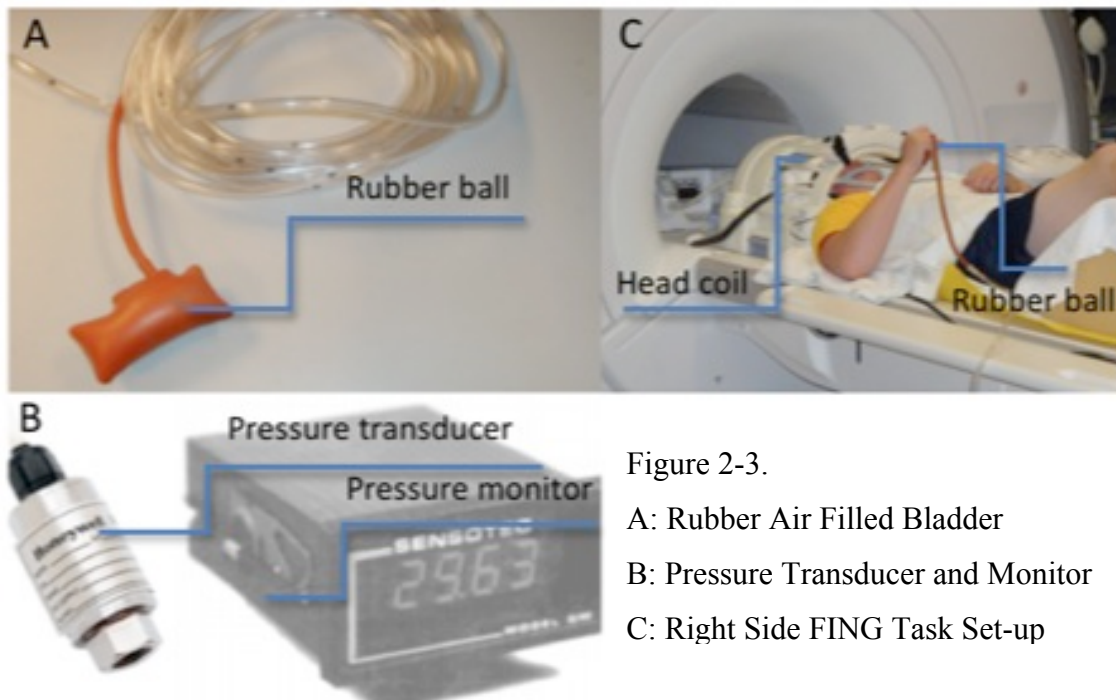


Figure 2-3.

A: Rubber Air Filled Bladder

B: Pressure Transducer and Monitor

C: Right Side FING Task Set-up

The upper extremity-pedaling device was fabricated as a direct drive, bearing free apparatus (Figure 2-4 A). It would be placed on the abdomen of the subject inside the scanner's entrance, so the size was limited to 7x15x7 in inch, fitting most human subjects, and was portable freely (Figure 2-4 C). The whole device was made of DuraForm Polyamide (PA), which is a kind of nylon based plastic material; so that its influence on the magnetic field should be negligible. A cylindrical crankshaft was fixed between two solid vertical supports that were mounted on a base. Two handles were coupled to the crankshaft by the way of crank arms. The diameter of the crankshaft was one-inch length to compensate for high shear forces due to uneven pedaling by the subject. DuraForm PA has an excellent surface resolution, so the friction of the bearings between the crank and support was negligible.



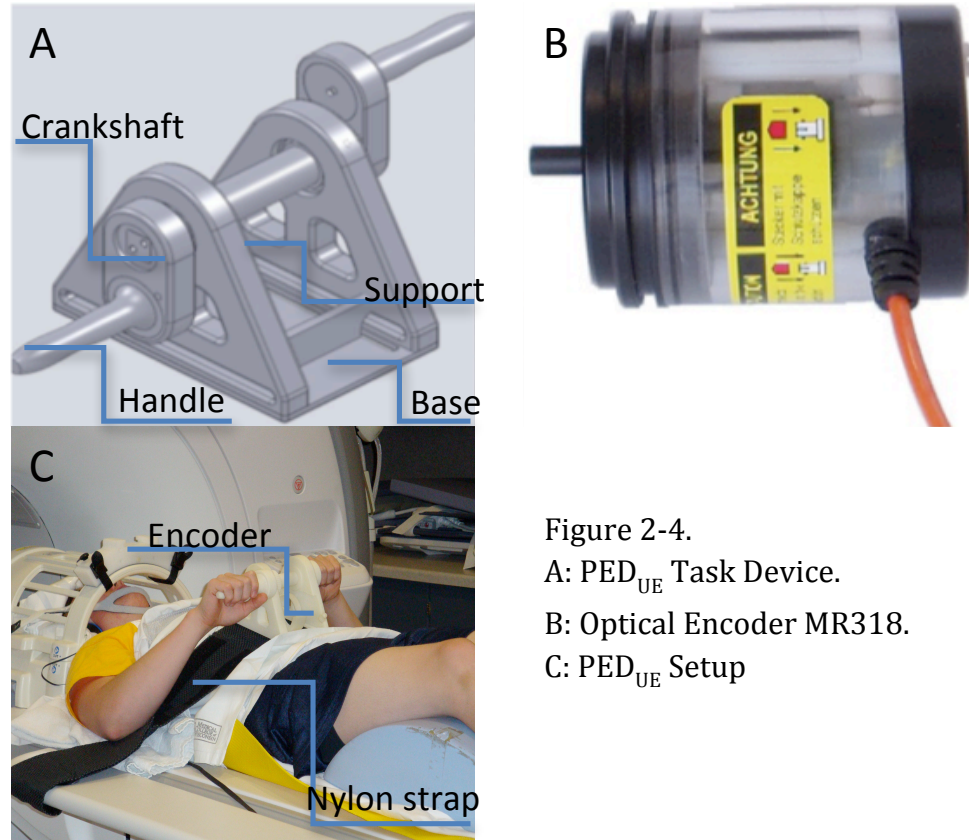


Figure 2-4.

A: PED<sub>UE</sub> Task Device.

B: Optical Encoder MR318.

C: PED<sub>UE</sub> Setup

For the upper extremity-pedaling device, another MR compatible optical encoder with resolution of  $1.0^\circ$  was applied (Figure 2-4 B, model MR 318, Micronor Inc., CA). The encoder was enclosed in a housing fixed on the base, and coupled to the crankshaft by plastic gears assembly arranged in a ratio 3:2. The data was recorded using the same acquisition system applied as the PED<sub>LE</sub> device.

## 2.2 MR Compatibility Experiment

The purpose of the phantom scanning experiment was to determine whether the PED<sub>UE</sub> device, the optical encoder, and the movement of the device in the MR environment would produce extra signal changes that would disturb the fMRI signal. We

recorded fMRI signals from a spherical silicone GE 3.0 Tesla (T) MRI head phantom (GE model 2359877) under a series of conditions. The phantom was a specially designed object that was used to evaluate the effects of imaging devices. In this experiment, we recorded fMRI signals in the conditions as listed in Table 2.1. In task 1, 2, 3, 4 and 15, the device was placed outside the scanning room, so that there was no device effect on the images. We repeatedly collected the data in five tasks, so that we could determine if the phantom images remained the same without noise-effect. In task 5 and 14, devices were placed in the scanner while electronics disconnected, so that device effect was introduced to the phantom images; in task 6 and 13, devices were placed in the scanner with electricity connected, but the power was turned off; in task 7 and 12 the power was turned on. In task 8 and 9, the experimenter who stood outside the 10 Gauss (G) line drove the device through a cotton string; in task 10 and 11, the experimenter stood nearby the device and pedaled the device by hand directly. These two conditions were designed to examine the effect of device motion with/without extremity movement in the magnetic field.

fMRI images were obtained using a gradient echo, echo planar imaging (EPI) pulse sequence (36 contiguous slices in the sagittal plane, 4 mm slice thickness, echo time (TE) = 25 ms, interscan period (TR) = 2 s, flip angle =  $77^\circ$ , field of view (FOV) = 24 cm, and 64 x 64 matrix). The resolution of the images was 3.75 x 3.75 x 4 mm. The raw DICOM files from scanner were converted to 3D + time images by Analysis of Functional NeuroImages (AFNI) software (AFNI; Cox 2011). The functional data were registered to the first slice of image in Task 1 to compensate for displacement that occurred during the experiment.

Task #	Scanning Room Conditions
1	Phantom only
2	Phantom only
3	Phantom only
4	Phantom only
5	Phantom+Bike+Encoder+Cable
6	Phantom+Bike+Encoder+Cable+Plug in
7	Phantom+Bike+Encoder+Cable+Plug in+power
8	Pedal with String
9	Pedal with String
10	Pedal with Hand
11	Pedal with Hand
12	Phantom+Bike+Encoder+Cable+Plug in+Power
13	Phantom+Bike+Encoder+Cable+Plug in
14	Phantom+Bike+Encoder+Cable
15	Phantom Alone

Table 2-1. The Phantom Scanning Protocol

In order to quantify the brightness through all the task conditions, we performed direct voxel-wise subtraction of each task from the “phantom alone”, and examining the changes visually. To understand the noise introduced by the equipment and movement, we calculated the signal to noise ratio for each task as performed in the following equation 1 (Mehta, et al. 2009; Khanicheh, et al. 2005).

$$\text{SNR} = S / (0.655 \times \text{SD}_{\text{noise}});$$

where SNR represents the signal to noise ratio, S is the mean value of the signal in a 36000 uL area inside phantom and  $\text{SD}_{\text{noise}}$  is the average of the standard deviation of

a 36000uL region outside the phantom. The scaling factor 0.655 was used to correct changes in the distribution of Gaussian noise present on the raw dataset caused by calculation of the magnitude image from original complex MR data. For each task, we chose 7 different areas to compute the value of S.

### 2.3 Results

The results of the phantom scanning suggested that the device, the electronics and the movement did not produce significant signal changes inside the phantom. Figure 2-5A showed the image recorded from the phantom alone (Task 4), and Figure 2-5B corresponded to the images from task 5, 6, 7, 8 and 10 (Table 2-1). When the device, electronics, and movement were introduced in steps, the brightness increased by the scale of -0.01%, -0.02%, -0.09%, -0.45%, and -0.77% in task 5, 6, 7, 8, and 10 respectively as compared to task 4. These changes were indiscernible on the scale as the original phantom image (Figure 2-5C). Column C in Figure 2-5 reflected the signal change, which was determined by subtracting column B from column A. The signal changes were visually indiscernible since they were displayed in the same intensity scale of column A and B, but were clear enough to be observed when the contrast was enhanced by 20 times (Figure 2-5 D).

We computed SNR changes within seven phantom ROIs caused by the PED<sub>UE</sub> device, wire connected, electricity turned on, pedaling outside by string and pedaling by hand. Values of SNR varied across the seven ROIs, all supporting that the setup of the experiment induced no significant changes to the functional signal. As shown in Figure 2-6, the values of SNR remained stable across all the conditions, while only limited scale of shift existed. We only observed significantly change in the condition that experimenter

pedaled the device (Task 10 and 11), indicating that the arm movement could result in movement-related noise to the images.

Task	Scanning Room Conditions	Image Brightness	SNC (Region 1)
1	Phantom Alone	339.8	177.4
2	Phantom Alone	339.0	177.1
3	Phantom Alone	338.4	175.7
4	Phantom Alone	337.7	175.4
5	Phantom+Bike+Encoder+Cable	338.3	175.7
6	Phantom+Bike+Encoder+Cable+Plug in	338.0	175.4
7	Phantom+Bike+Encoder+Cable+Plug in+power	338.1	175.1
8	Pedal with String	336.9	174.8
9	Pedal with String	336.8	174.9
10	Pedal with Hand	335.8	173.1
11	Pedal with Hand	336.4	173.0
12	Phantom+Bike+Encoder+Cable+Plug in+Power	335.6	173.8
13	Phantom+Bike+Encoder+Cable+Plug in	335.0	173.6
14	Phantom+Bike+Encoder+Cable	337.1	173.2
15	Phantom Alone	336.4	173.3

Table 2-2. Changes in Brightness and SNCs across Experimental Conditions

## 2.4 Discussion

An upper extremity bilateral pedaling device has been designed for fMRI experiments in this study. The compatibility test demonstrated that our PED<sub>UE</sub> device was MR safe and compatible. We observed slight brightness change across different conditions in the range from 0.01% to 0.77%. The device-related change could be considered negligible, because the values of change were no larger than that of other devices deemed compatible for MRI (Mehta, et al. 2009). The SNR suggested that the device introduced little noise to the image; however, the pedaling movement made by the

subject inside the scanner might induce extra noise to the fMRI signal ( $P < 0.05$ ). However, the decrease in SNR was very small. Previous studies also provided the parameters of other MR compatible devices, and the decrease of SNR ranged to 3% (Chinzei, et al. 2000), but we only observed a decrease of 0.74% during Task 10 and 11. In conclusion, the PED<sub>UE</sub> device and the experiment setup was MR and compatible. Although there were changes in the brightness of the image and the value of SNR in different scanning tasks, the scale was limited and acceptable, and we would apply a special method to minimize the noise effect that was introduced by the head movement (See Chapter 3).

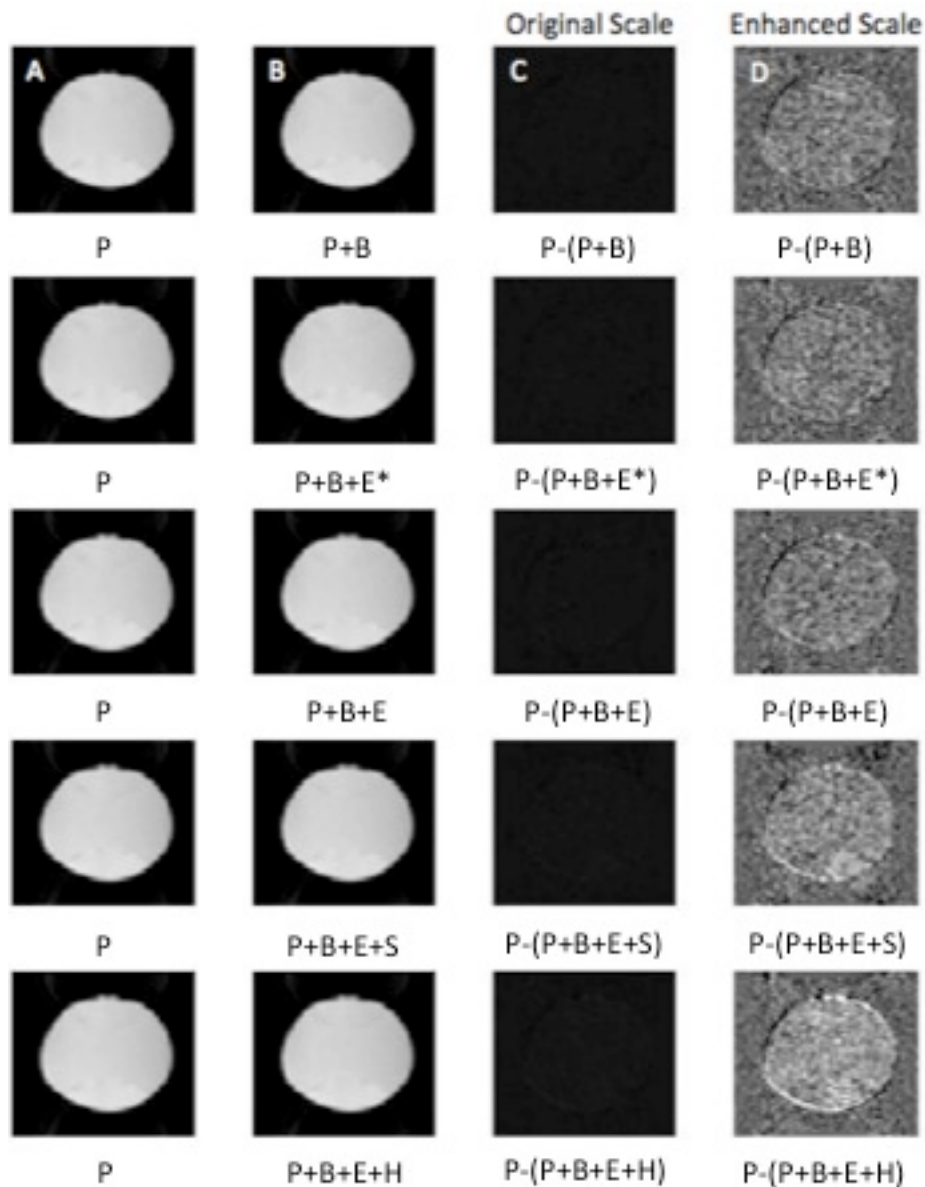


Figure 2-5. Image of Phantom Scanning.

Images of the phantom alone (P) are shown in A. Images of the phantoms plus, the pedaling device (B), plug in with electronics off (E\*), electronics on (E), movement (M), driven by string (S), and driven by hand (H) are shown in B. Columns C and D show the difference in images between each task condition on the original (column C) and 5% of the original (column D) scale.

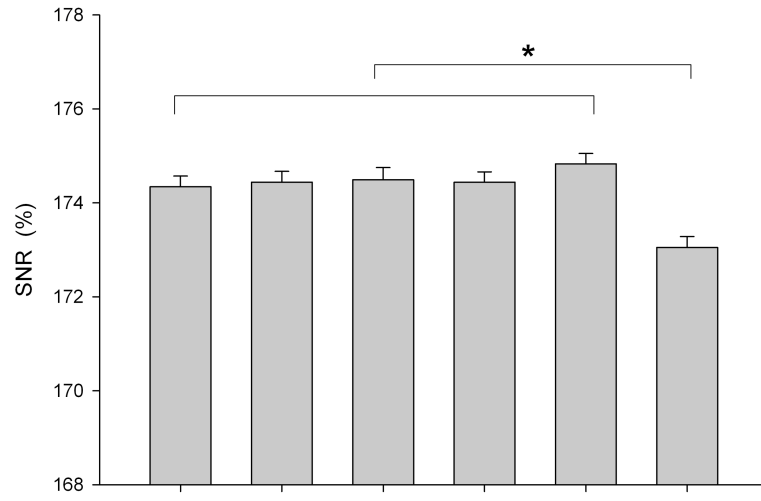


Figure 2-6. Ratio of Signal to Noise (SNC) of one region across varied conditions.



## **CHAPTER 3: SIMILARITY AND DIFFERENCE IN SUPRASPINAL CONTROL OF UPPER AND LOWER EXTREMITY MOVEMENT**

### 3.1 Introduction

In stroke rehabilitation, therapeutic protocols are sometimes used interchangeably between retraining of upper and lower limb movements. For example, constraint induced movement therapy (CIMT) is usually employed for upper limb rehabilitation (Miltner, et al. 1999), although some investigators began to adapt it for rehabilitation of walking as well (Marklund et al. 2006; Numata et al. 2008). While these studies demonstrated positive effects of CIMT on lower limb rehabilitation, it is unclear whether the neural mechanisms underlying the beneficial effects of CIMT are similar between upper and lower limb rehabilitation. This is an important question because therapeutic approaches primarily designed for functional recovery of upper limb movements may be suboptimal when used for that of lower limb movements, or vice versa, unless the neural processes activated during the given therapies are similar between upper and lower limb movements. In fact, the neuroscience literature suggests that the two types of movement may involve distinct neural processes. Upper limb movements, such as reaching and manipulating objects, are heavily controlled by supraspinal structures such as primary motor cortex (M1), cerebellum and supplementary motor area (SMA) (Moran and Schwartz 1999). Lower limb movements, such as walking and running, rely heavily on pattern generating circuits in the spinal cord and may be less strongly influenced by the brain (Duysens, et al. 1998).

While these observations may suggest fundamentally different neural control schemes for the upper and lower limbs, differences in task demands may also have an

important influence over neural control. Many (although not all) upper limb movements are discrete in nature and performed unilaterally (e.g., reaching for a coffee cup), whereas many (but not all) lower limb movements are continuous and bilateral (e.g., walking to the restroom after consuming too much coffee). Thus, in order to understand the way in which the brain controls upper and lower limb movements, or how it controls limb movement in general, it is important to separate limb effects (i.e., upper vs. lower) from task effects (e.g., bilateral vs. unilateral, discrete vs. continuous). This argument is supported by the neuroscience literature, which suggests that unilateral and bilateral movements are controlled by distinct neural processes (Kelso, et al. 1979; Swinnen 2002), and that continuous and discrete movements activate distinct neural pathways (Schaal, et al. 2004). In addition, there is a discrepancy regarding whether bilateral training can facilitate unilateral performance, or vice versa (Nozaki et al. 2006; Wang et al. 2009, 2010).

### 3.2 Purpose

The purpose of this study was to investigate supraspinal contributions to the control of upper and lower limb movements. We used functional MRI (fMRI) to examine human brain activity during upper and lower limb movements in healthy young adults. There are previous studies that have examined brain activity during upper and lower limb movements, and demonstrated neural activities in the motor cortices such as M1 and SMA (Mehta, et al. 2009; Sahyoun, et al. 2004; Miyai, et al. 2001; Luft, et al. 2002). However, further investigations are necessary because the previous studies focused on examining brain activity during unilateral movements. In addition, bilateral movements, especially those involving locomotor patterns, were seldom investigated in fMRI studies,

mainly due to the difficulty of examining locomotor patterns in the MRI scanner. We recently developed an MRI-compatible device that allowed us to study a bilateral pedaling task performed by the lower limbs (Mehta, et al. 2009, 2012). We also developed a similar device that can be used by the upper limbs for the present study (see Chapter 2), which allowed us to compare brain activity between upper and lower limb movements during the same bilateral task. In this study, we also examined brain activity during unilateral tasks performed by the upper and lower limbs (hand squeezing and foot tapping) to investigate the similarities and/or differences in supraspinal contributions to the control of upper and lower limbs during bilateral and unilateral tasks.

### 3.3 Functional magnetic resonance Imaging (fMRI)

fMRI is a non-invasive imaging technique for measuring neural activity. It utilizes the magnetic properties of blood to reflect the neuron activation in specific areas. Images are reconstructed from the blood oxygenated level dependent (BOLD) signal, which is related to the metabolic activity neurons. Brain activities cause the oxygen consumption, which results in an increase in blood flow to the neighborhood regions. More oxygenated hemoglobins are delivered to the neighbor region of activated neurons, so that the density of deoxygenated hemoglobin decreases; as a result, the BOLD response increases. During a continuous limb movement, the correlated brain regions demand extra blood supply, which produces a significantly high plateau BOLD signal, indicating that the brain regions are highly correlated to the movement.

### 3.3.1 Experimental Design

Participants performed two sets of tasks: bilateral and unilateral movement tasks. The former set consisted of lower extremity bilateral pedaling ( $PED_{LE}$ ) and upper extremity bilateral pedaling ( $PED_{UE}$ ). The latter set consisted of ankle flexion/extension (FOOT) and finger flexion/extension (FING), with each task performed by both dominant and non-dominant limbs separately. Pedalling tasks were presented in a block design consisting of 3 runs of each pedaling condition. Each run lasted 4 minutes. In a single run, subjects pedaled for 30 s, then rested for 30 s. This sequence was repeated 4 times. FING and FOOT were presented in another block design consisting of only 1 run which lasted 3 minutes and 28 seconds. Subjects moved their feet or fingers for 16 s, then rested for 16 s; and this sequence was repeated 6 times. Throughout the experiment, subjects' pedaling performance was visually monitored through the control room window and by examining the position data from the optical encoder. We also had access to real time information about head position. If the subject did not perform the task as instructed or if their head moved more than 2 mm, we checked the subject for comfort, repeated the instructions, and restarted the run.

A 3.0T MR scanner (General Electric Healthcare, Milwaukee, WI) and a single channel transmit/receive split head coil assembly (GE model 2376114) were used for all experiments. Audacity (open source software) and Presentation (Neurobehavioral Systems, CA) software were used to deliver audio output to the subjects via MR-compatible earphones (model SRM 212, Stax, Japan). fMRI images were obtained using a gradient echo, echo planar imaging (EPI) pulse sequence (36 contiguous slices in the sagittal plane, 4 mm slice thickness, echo time (TE) = 25 ms, interscan period (TR) = 2 s,

flip angle =  $77^\circ$ , field of view (FOV) = 24 cm, and  $64 \times 64$  matrix). The resolution of the images was  $3.75 \times 3.75 \times 4$  mm. High resolution spoiled GRASS (gradient-recalled at steady state) anatomical images were collected with TE = 3.9 ms, TR = 9.5 ms, flip angle =  $76^\circ$ , matrix of  $256 \times 244$ , and slice thickness of 1 mm.

### 3.3.2 Subject Selection and Preparation

Nine healthy individuals (4 males, mean ( $\pm$ STD) age of 22 ( $\pm$ 3) years) with no elite training in pedaling volunteered to participate. Each subject gave written informed consent according to the Declaration of Helsinki and institutional guidelines at Marquette University and the Medical College of Wisconsin. All of them were right hand dominant as evidenced by scores  $\geq 80$  on the Edinburgh handedness inventory (Oldfield, 1971). Prior to their participation, subjects underwent two fMRI safety screenings and were excluded if they were claustrophobic, pregnant, or had any implants or foreign bodies incompatible with fMRI. Subjects were also excluded if they had a history of neurological impairments or physical conditions contraindicative to pedaling. Eight subjects completed all the procedures; one completed only the pedaling tasks due to insufficient time in the scanner. All data from one male subject were discarded after high-resolution anatomical imaging revealed a previously undocumented anatomical anomaly of the brain. One female subject's PED<sub>UE</sub> and PED<sub>LE</sub> data were discarded due to head movement  $>2$  mm. At last, we have 7 individuals' data throughout the four tasks.

During fMRI scanning, subjects lay supine on the scanner bed. The head was placed in the head coil and adjusted to achieve symmetry in all 6 planes of movement (superior-inferior, left-right, anterior-posterior, roll, pitch, and yaw). To minimize head movement, the head rested in a beaded vacuum pillow that enveloped the entire head

(except the face) and created a firm, comfortable “brace” around the head. A chinstrap was used to prevent inferior-superior head movement. The torso was stabilized with a wide Velcro strap to minimize trunk movement. Additional padding under the buttocks and shoulders was provided for comfort. Each subject wore MR-compatible earphones, through which audio cues were delivered, and an additional set of headphones on top of the ear phones to protect against scanner noise. An emergency squeeze ball was placed near the subject’s hands and could be used at any time to signal a problem. Participants were monitored for safety and comfort and were able to communicate via intercom with the scanner technician.

During the PED<sub>LE</sub> task, the feet were secured to the PED<sub>LE</sub> device by pedal-mounted sandals (see Chapter 2). The position of the pedaling device was adjusted until subjects were able to pedal comfortably and their legs did not touch the scanner. During the PED<sub>UE</sub> task, the UE pedaling device (see Chapter 2) was placed on the subject’s abdomen and fixed to the edge of the scanning bed by a nylon strap and Velcro fasteners (Figure 2-4 C). During the FING task, an air bladder that was used to record the finger movements was placed in the subject’s right or left hand, which rested comfortably on the abdomen. During the FOOT task, the legs were positioned over a foam bolster such that the hip and knees were flexed and the feet were approximately 15 cm above the surface of the scanner table. A tapping button, used to record the ankle movements, was placed under the ball of the left or right foot.

### 3.4 Data Analysis

Processing of fMRI signals was completed using the Analysis of Functional NeuroImages (AFNI) software. The signal processing procedures have been described in

our previous study (Mehta, et al. 2009). Dicom files containing fMRI signals were converted into 3 dimensional images. Individual voxels were aligned to the same temporal origin within each TR. The first 4 TRs within each run were removed to eliminate magnetization artifact. Multiple runs of data were concatenated. Function data were registered to the anatomical scan. To identify voxels containing BOLD signal associated with PED<sub>LE</sub>, PED<sub>UE</sub>, FING, and FOOT, general linear modeling (GLM) was performed. Since the subject's movement could introduce extra noise to the signal (see Chapter 2), only the portion of the BOLD time-series after movement stopped was used in processing, as described in the previous publications (Mehta, et al. 2009; Mehta, et al. 2012). To identify significantly active voxels at  $P < 0.05$  (familywise error rate), we used AFNI program "AlphaSim" to set an appropriate cluster size for a given individual voxel P-value. AlphaSim performs Monte Carlo (alpha) simulation, which constitutes of image generation, spatial correlation of voxels, masking, and cluster identification (Douglas, 2000). The output of this procedure estimates the probability of a false detection of Type II error, so that the minimal cluster sizes of active clusters can be determined.

Percent signal change was calculated as the change in amplitude from baseline. Significantly correlated voxels outside of the brain and negatively correlated voxels were ignored. Any voxels with percent signal change  $> 10\%$  were also ignored, as these large changes were likely due to edge effects.

Values for volume and intensity of activation were calculated for each subject in M1, S1 and Brodmann's area 6 (BA6) on the left and right side of the brain. These regions were consistently active across tasks and subjects. The anatomical boundaries for each of these regions of interest (ROI) were defined from the  $T_1$ -weighted images as

previously described (Wexler et al. 1997). M1 was defined as the anterior bank of the central sulcus extending anteriorly to the precentral sulcus. S1 comprised the posterior bank of the central sulcus extending posterior to the postcentral sulcus. BA6 included the pre-supplemental, supplemental, and premotor areas. In the sagittal plane, this region extended from the medial border of each hemisphere spanning laterally over the dorsolateral frontal lobe. BA6 was bordered posteriorly by M1, extending anteriorly to cover approximately the posterior half of the superior frontal gyrus.

In order to quantify the activation pattern during each task, we computed three performance measures: laterality index, and activation volume and intensity in each ROI. The lateral index (LI) was calculated using the equation shown below (Seghier 2008):

$$LI = (Q_C - Q_I) / (Q_C + Q_I);$$

where  $Q_C$  is the quantity of voxels in the hemisphere contralateral to the moving limb, and  $Q_I$  is the quantity in the ipsilateral hemisphere of the movement. In  $PED_{UE}$  and  $PED_{LE}$ ,  $Q_C$  is the quantity in the right hemisphere, and  $Q_I$  is the quantity in the left hemisphere. The LI of 0 indicates absolutely bilateral activation while that of +/- 1 indicates absolutely contralateral/ipsilateral activation. The intensity of activation was calculated using the following equation (Chen, 2013):

$$Intensity = 100 * b/a * (1 - b/a);$$

Where 'a' is the baseline constant of the brain voxel, and 'b' is the 1<sup>st</sup> order regression coefficient of GLM of the voxel. The volume of activation was calculated based on the total volume of voxels that pass the threshold of p value.

These performance measures obtained from the bilateral and unilateral tasks were subjected to two separate repeated-measures ANOVA's, with Limb (upper, lower) and



Region (M1, S1, BA6) as two within-subject factors. With respect to the LI, our data indicated no significant differences between the left and right limbs during the unilateral tasks. Thus, we collapsed the LI data across the left and right limbs during the unilateral tasks, and subjected them to the above-mentioned ANOVA without considering the laterality (left vs. right) as another factor. For post-hoc comparisons, paired t-tests were used. The alpha level was set at 0.05 for statistical significance.

### 3.5 Results

#### 3.5.1 Pattern of brain activity during bilateral tasks

We observed correlated activation in S1, M1, and BA6 in both PED<sub>UE</sub> and PED<sub>LE</sub> tasks (Figure 3-1). PED<sub>LE</sub> produced activity in the medial area of S1 and M1, while the activity during PED<sub>UE</sub> was located in the lateral areas. In BA6, the activation was limited in the medial area, which corresponded to SMA, while the fMRI signal in the premotor cortex (PM) was not significantly correlated with the movement. In SMA, PED<sub>UE</sub> activated the areas that are more superior and posterior to the areas observed during PED<sub>LE</sub>. The activation of cerebellum was displayed in Appendix A.

The brain activities during both PED<sub>UE</sub> and PED<sub>LE</sub> were strongly bilateral in all the three cortical regions (S1, M1, and BA6) as indicated by low LI values ( $\leq 0.11$ , Figure 3-2 A). The symmetry of brain activity during pedaling was not affected by limb or brain region, as indicated by the lack of significant main or interaction effects (ANOVA limb effect  $P=0.513$ , region effect  $P=0.722$ , limb X region interaction  $P=0.562$ ). The intensity of brain activation as measured by percent signal change was higher during PED<sub>UE</sub> as compared to PED<sub>LE</sub> (limb effect  $P=0.024$ , Figure 3-2 B; interaction effect  $P =$

0.240). In terms of the activation volume, there was a significant interaction effect ( $P=0.022$ , Figure 3-2 C). The post hoc analyses indicated that the activation volume during PED<sub>UE</sub> was significantly larger than that during PED<sub>UE</sub> only in S1 ( $P < 0.035$ ).

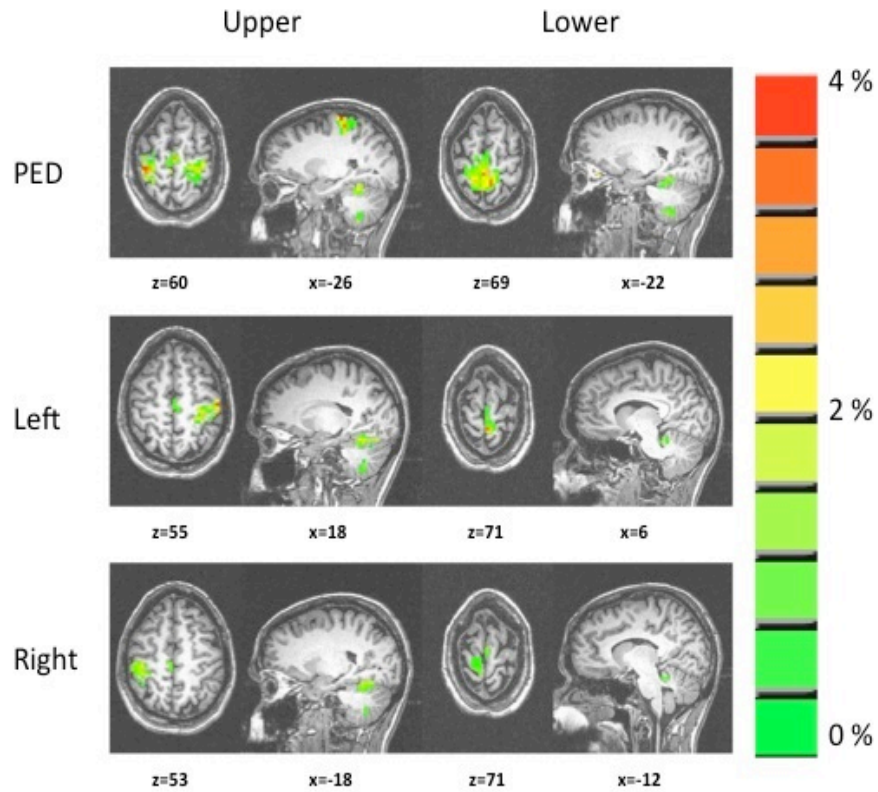


Figure 3-1. Functional Images of a Representative Subject (No.02) in PED<sub>UE</sub>, PED<sub>LE</sub>, FING and FOOT.

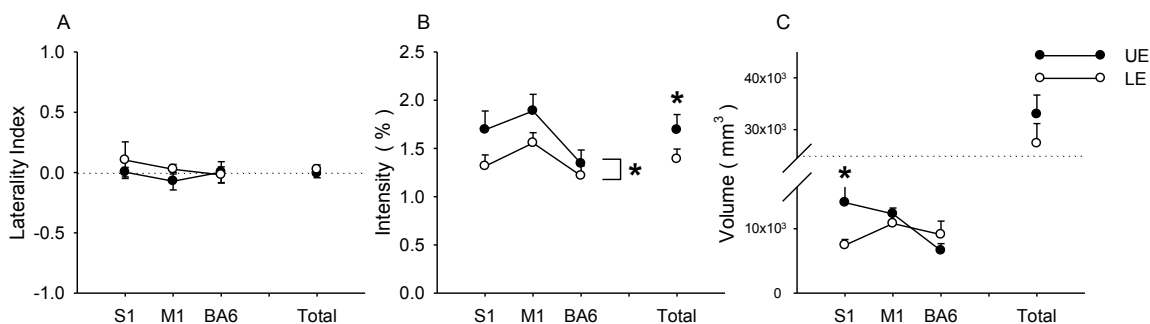


Figure 3-2. Bilateral extremity movement

### 3.5.2 Pattern of brain activity during unilateral tasks

The brain activities during FING and FOOT are also displayed in Figure 3-1.

Both FING and FOOT produced cortical activities in S1, M1 and BA6. In S1 and M1, the activation during both tasks was mainly observed in the hemisphere contralateral to the moving limb; and the areas activated during FING were more lateral than those observed during FOOT. The activation in BA6 was limited in the region of SMA, while other PM regions were not activated.

In terms of LI, no significant difference was observed between the left and the right limbs during either FING (side (left vs. right) effect  $P = 0.246$ , side x region interaction  $P = 0.972$ ) or FOOT (side effect  $P = 0.930$ , side x region interaction  $P = 0.522$ ). Thus, the LI values collapsed across the left and right limbs were subjected to further analyses. As illustrated in Figure 3-3A, the brain activation was strongly unilateral in all three regions during FING; and it was unilateral in S1 and M1, but bilateral in BA6 during FOOT. There was a significant interaction effect ( $P = 0.003$ ), which was caused by the fact that the LI in M1 and BA6 was significantly lower during FOOT than during FING (M1  $P = 0.046$ , BA6  $P = 0.004$ ).

Percent signal change showed a significant interaction effect ( $P=0.003$ ); and the post hoc analyses indicated that the intensity was significantly higher during the FING as compared to the FOOT task in S1 and M1 (S1  $P = 0.018$ , and M1  $P < 0.001$ ), but not in BA6 (BA6  $P = 0.298$ , Figure 3-3 B). Similarly, the activation volume also showed a significant interaction effect ( $P < 0.001$ ), with the higher volume observed during the FING task in S1 ( $P = 0.001$ ) and M1 ( $P = 0.043$ ), but not in BA6 ( $P = 0.139$ , Figure 3-3 C).

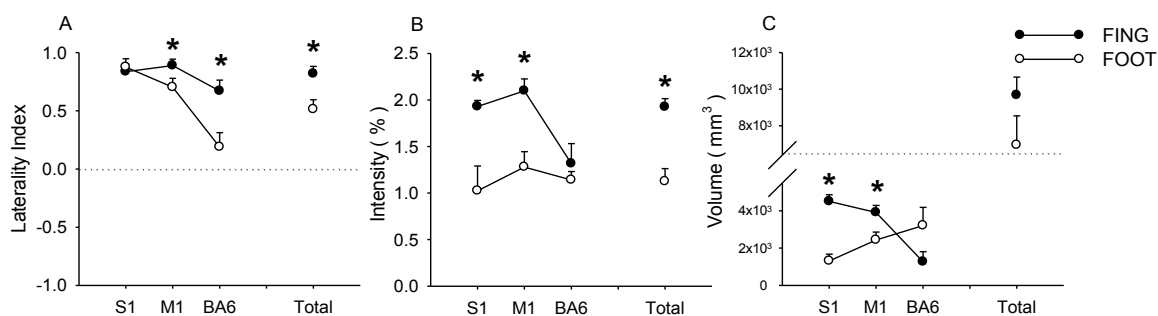


Figure 3-3. Unilateral extremity movement

### 3.6 Discussion

The aim of this project was to determine the similarities and differences in supraspinal control of the upper and lower extremities. To achieve this aim, we used fMRI to characterize the brain activities from 7 healthy subjects in two bilateral pedaling tasks (PED<sub>UE</sub> and PED<sub>LE</sub>) and two unilateral tasks (FING and FOOT). The cortical activity observed during our tasks was generally limited in three ROIs: S1, M1, and BA6. We described the data in terms of laterality index, and activation intensity and volume during each of the tasks. In the following section, we discuss how these data can help us

understand the key question of whether the upper and lower extremities use distinct control strategies or not.

### 3.6.1 Bilateral Movements

Our data add to the growing body of literature demonstrating that the cerebral cortices are involved in the control and production of human locomotion (Petersen, et al. 2002; Miyai, et al. 2001; Pyndt, et al. 2003). According to our results, both PED<sub>UE</sub> and PED<sub>LE</sub> demonstrated bilateral activity in S1, M1, and SMA. And to our knowledge, this is the first time that such an observation has been made for a locomotor-like task involving the upper extremities.

The difference in volume of activity in sensorimotor cortex might be related to the quantity of cortical neurons devoted to the motor or sensory representation of the hand and arm. This difference was also consistent with the somatotopic map reported by Penfield that upper extremity corresponding to larger area than the lower extremity (Penfield, et al. 1937). When the differences in activation volume were controlled for, the mean intensity of activation in M1 and S1 was statistically greater for PED<sub>UE</sub> than PED<sub>LE</sub>. The literature indicates several factors that are known to influence the level of intensity: (1) movement speed (Lutz, et al. 2005; Mehta, et al. 2012), (2) complexity of movement (Shibasaki H 1993; Gerloff, et al. 1998), and (3) level of force produced by the muscles (Kinoshita, et al. 2000). In our experiment, subjects chose their own comfortable speed in each task. The pedaling rate was higher for UE, but the diameter for PED<sub>LE</sub> was longer, and the exact speed for LE was significantly higher than UE ( $P=0.002$ ). In addition, we assumed that the complexity level was similar between PED<sub>UE</sub> and PED<sub>LE</sub> in that the pedaling tasks involved similar whole UE and LE movements. Both the UE and LE

pedaling devices rotated on friction-less bearings; thus the resistant force was negligible, which must have significantly minimized the level of joint force needed for both tasks. This suggests that the intensity differences observed between  $PED_{UE}$  and  $PED_{LE}$  in our study may not be attributed to the aforementioned factors, but rather to a difference in the neural processes underlying the two types of movements. Our finding of higher intensity during the upper limb movement is consistent with Luft et al.'s findings (2002), which indicated greater activation in S1 and M1 during finger-to-thumb opposition as compared to knee extension-flexion.

### 3.6.2 Unilateral Movements

During the unilateral tasks, S1 and M1 both showed higher intensity and larger volume of activation in FING as compared to FOOT. These results are similar to our results from the bilateral movements, and suggest that even though similar brain regions are involved in controlling the upper and lower limb movements, the pattern of supraspinal contribution is somewhat different depending on whether the upper or the lower limbs are involved.

With regard to the laterality of brain activation, both the FING and FOOT tasks showed strong contralateral activation to the moving limb in S1, but the activation in M1 was less lateralized during the FOOT than the FING task. This result is partially in agreement with previous studies, which suggested that the lower extremity is more bilaterally controlled by the motor cortex than the upper extremity (Luft, et al. 2002; Kapreli, et al. 2006). Luft et al. reported that the brain activity related to knee extension-flexion was less lateralized as compared to finger-thumb opposition (finger M1 LI > 0.75, knee M1 LI < 0.3; finger S1 LI > 0.5 knee S1 < 0.1). Kapreli et al. reported that the dominant

(right) ankle and knee extension-flexion produced less lateralized activity than finger-thumb opposition movement did in the sensorimotor cortex (finger LI=0.71, knee LI=0.45, ankle LI=0.46). While their findings are similar to ours in terms of the lateralization observed in M1, these two sets of findings (Luft et al. vs. our current data) are somewhat inconsistent in terms of the lateralization observed in S1. That is, Luft et al. observed less lateralized activation during the lower limb movement than the upper limb movement in S1, whereas we observed highly lateralized activation during both the upper and lower limb movements. A plausible explanation for this difference involves the use of proximal versus distal limbs. Previous studies suggested that the motor cortex activity is more lateralized during movement performed by the distal, as compared to the proximal, part of both the upper and lower limbs (Kapreli, et al. 2006; Nirikko, et al. 2001). Thus, the greater lateralization observed in our study might be due to the fact that the part of the leg used to perform our task was more distal than that used to perform Luft et al.'s task (ankle vs. knee, respectively).

### 3.6.3 Comparisons between Bilateral and Unilateral Movements

In the present study, we did not make statistical comparisons between bilateral and unilateral movements, for the following two reasons. First, the nature of our bilateral and unilateral movements was somewhat different in that the bilateral tasks involved continuous and cyclical movements, while the unilateral tasks involved a repetition of rather discrete movements. Second, we decided not to include the type of movement (bilateral vs. unilateral) as an independent factor in our ANOVA's, thereby minimizing the complexity of our data analyses and interpretation. Therefore, we cannot make any

direct, and quantitative, comparisons between the two types of movements tested in this study. Instead, we attempt to make a qualitative comparison between the two types of movements in this section.

Brain regions activated in this study were generally similar between the bilateral and unilateral movements (i.e., S1, M1, BA6), although some differences were observed between the upper and lower limb movements. The activity observed during PED<sub>LE</sub> and FOOT were located in the superior and medial portion of the paracentral cortex, while the activity during PED<sub>UE</sub> and FING were located more laterally from the areas observed during the upper limb movements. These differences between upper- and lower limb-associated activities are in agreement with the literature. For example, Penfield (1937) demonstrated, based on a technique that stimulated different parts of the body electrically, that along the cortical surface of paracentral cortex, the lower extremity lied in the medial portion, the head in the most lateral portion, and the upper extremity lied between the two portions. This finding was confirmed by recent fMRI studies that compared the brain activity between isolated upper and lower limb joint movements (Luft, et al. 2002; Kapreli, et al. 2006; Harirchian, et al. 2008). The activation observed in the BA6 was limited to the supplementary motor area (SMA) for all tasks in our study (i.e., no premotor cortex (PM) activation observed). This is consistent with previous findings, which also observed activations in the SMA, but not in the PM, during bilateral leg pedaling (Mehta, et al. 2009; Mehta, et al. 2012). Within the SMA, the areas activated during PED<sub>UE</sub> and FING were located more posteriorly and caudally to the areas observed during PED<sub>LE</sub> and FOOT. This is also consistent with a finding that from its



rostral to caudal portion, the SMA corresponds to the sequence of orofacial, forelimb and hindlimb representations (Andrew, et al. 1987).

With regard to the intensity of brain activity, our data indicated a significant interaction effect between the two factors of limb (upper vs. lower) and region (ROIs) for unilateral movements, but only the limb main effect for bilateral movements. Our post hoc analyses revealed significant limb differences in S1 and M1 for unilateral movements, whereas only the overall limb difference across all the brain regions was observed for bilateral movements. Despite these differences, however, the overall pattern of our data is very similar between bilateral and unilateral movements, in that the mean values for S1 and M1 from the upper limb tasks are substantially greater than those from the lower limb tasks in both bilateral and unilateral movements. Similar trends are also observed with respect to the brain activity volume. Significant limb differences were observed in both S1 and M1 for unilateral movements, but only in S1 for bilateral movements; and yet, the overall data pattern is similar between the two types of movement, in that the mean values for S1 and M1 are substantially greater than that in BA6 during the upper, but not the lower, limb tasks, in both bilateral and unilateral movements.

Collectively, our findings indicate that the general pattern of brain activation is similar between the bilateral and unilateral movements tested in our current study, although the differences between the upper and lower limb tasks are relatively more rigorous in the unilateral tasks.

### 3.7 Study limitations

The major findings must be interpreted with respect to several limitations. Every effort was made to correct for factors that might have affected data integrity.

In this study, we compared the cortical activation of movement of PED<sub>UE</sub> and PED<sub>LE</sub>, assuming that the subjects paid equal attention to perform the movements. Yet the only method to ensure the equality was to maintain a comfortable speed throughout the experiment, because we supposed that similar effort was required for a comfortable PED<sub>UE</sub> and PED<sub>LE</sub>. However, if the experiment could be more systematic designed, we would not rely on the subject's personal feeling only. For example, if the length of the crank-arm could be adjusted freely according to the subject's limb, and the force required for pedaling could be manually modified, the effort or attention to perform the movement could be controlled by the experimenter.

Another limitation which should be concerned was that the subjects needed to grab the handle themselves during PED<sub>UE</sub>, while a pair of shoes helped to fix the feet during PED<sub>LE</sub>, so that the PED<sub>UE</sub> and PED<sub>LE</sub> movement was not completely the same. If we could add a pair of gloves to the PED<sub>UE</sub> device, the finger would generate less force during the pedaling, and the comparison between UE and LE would be fairer.

The third factor was related to the data analysis: we drew the ROIs based on the landmark of anatomic MR image; then we aligned the functional images to the anatomic figure in order to locate activity in each region. However, it was not guaranteed that we could correctly separate the functional images into S1, M1 and BA6 activities, because the spatial resolution of functional images was larger than that of the anatomic images.

The best way to reduce the problem was to increase the spatial resolution of the functional images, yet it was not attainable without updating the scanner.

### 3.8 Conclusions

We investigated supraspinal contributions to the upper and lower limb movements during bilateral tasks, as well as during unilateral tasks. Our main results suggest that the cortical involvement is similar between the upper and lower extremities during both bilateral and unilateral tasks (i.e., similar brain regions involved). However, the pattern of supraspinal contribution appears to be somewhat different depending on whether the controlled movement involves the upper or the lower limbs. Such differential contributions are observed more rigorously during the bilateral, as compared to the unilateral, movements, although the overall patterns are quite similar between bilateral and unilateral movements. These findings suggest that the neural processes underlying motor control are somewhat different between the upper and lower limb movements, but similar between bilateral and unilateral movements. Based on these findings, we speculate that therapeutic protocols primarily developed for the recovery of upper limb function may not have the same effects when applied for the recovery of lower limb function, or vice versa. Further research is needed to understand how the pattern of supraspinal contributions to upper and lower limb control is influenced by brain injury (e.g., stroke).

## **CHAPTER 4: SUPRASPINAL CONTROL OF UPPER AND LOWER EXTREMITY MOVEMENT IN INDIVIDUALS WITH POST-STROKE HEMIPARESIS**

### 4.1 Introduction

Stroke is defined as a rapid loss of brain function due to a cerebrovascular abnormality and is the leading cause of serious, long-term disability in the United States (American Heart Association, 2012). Restoration of motor function after stroke is a multifaceted process (O'Dell, David Lin and Harrison 2009; Fisher 1992) that can be divided into passive recovery and active reorganization. Passive recovery occurs in the first few weeks after stroke (Teasell, et al. 2005; Rossini, et al. 2003), and it may be due to regression of ischemia (Raymond, 1986), reabsorption of perilesional edema (Seitz, et al. 1999), and resolution of diaschisis (Nudo, et al. 2001). Active reorganization requires more time and is associated with brain reorganization, which is usually accompanied by an increase in the number and density of synapses on dendrites (Turkstra, Holland and Bays 2003). The neurophysiological mechanisms might include changes in neuronal membrane excitability, synaptic strengthening, and recruitment of nearby and remote neuronal ensembles after focal brain injury (Dong et al. 2007; Weiller, 1998).

The intact hemisphere contributes importantly to recovery from stroke, and previous work suggests neural reorganization in the intact hemisphere after stroke. Several studies have found increased volume of activation in the intact hemisphere during ipsilateral, paretic limb movement (Johansen-Berg, et al. 2002; Cramer, et al. 1997; Cuadrado, et al. 1999; Fisher 1992). Weiller observed changes in regional cerebral blood flow in caudate nucleus, angular gyrus, and premotor cortex in the intact hemisphere of subjects with striatocapsular infarctions (Weiller, et al. 1992). Biernaskie and Corbett

reported enhanced dendritic complexity and length in the intact hemisphere of better-recovered rats that had undergone experimental stroke (Biernaskie and Corbett 2001).

The role of the intact hemisphere in motor recovery post-stroke is unclear, and competing explanations exist. For example, increase activity in the intact hemisphere might be due to increased attention to movement (Johansen-Berg, et al, 2002) or maladaptive disinhibition of the intact motor cortex due to reduced transcallosal influences (Meyer, et al. 1998; Shimizu, et al. 2002). Johansen-Berg provided a completely different opinion on this issue: he suggested that activation in the intact hemisphere during paretic limb movement is related to adaptive plasticity in the intact hemisphere (Johansen-Berg, et al. 2002). In his TMS experiment, inhibiting the output of the caudal premotor cortex in the intact hemisphere affected movement of the paretic hand. Fisher provided more evidence suggestive of adaptive plasticity based on a finding in two stroke survivors. He found that after the recovery from hemiplegia, a second stroke in the intact hemisphere led to re-paralysis of the recovered limb (Fisher 1992).

Brain activation in the lesioned hemisphere of stroke survivors may also contribute to motor recovery. Functional imaging studies have shown movement-related brain activity in the intact portion of the lesioned hemisphere (Serrien, et al. 2004). Dong *et al.* found that the magnitude of activation in the portion of the motor cortex surrounding the lesion was higher than that observed in healthy subjects. Activation in the lesioned hemisphere was considered as a sign of better recovery. Serrien found that cortical activation in the intact hemisphere that was ipsilateral to the paretic limb was more apparent among subjects with poor motor function. Dong and *et al.* reported that improved motor function after CIMT was associated with decreased magnitude of

activity in M1 and Cb of the intact hemisphere, which was ipsilateral to the paretic hand, and the M1 activation partially shifted from the intact to the lesioned hemisphere after the training (Dong, et al. 2007).

As discussed in Chapter 1 and 3, the literature suggests that the neural control strategies underlying UE and LE movement are not exactly the same (Luft, et al. 2002; Miyai, et al. 2001; Kapreli, et al. 2006). For example, functional imaging studies suggest that typical UE movements (e.g., reach-to-grasp) are controlled primarily by the motor cortex contralateral to the moving limb, while typical LE movements (e.g., locomotion) are controlled bilaterally (Luft, et al. 2002; Kapreli, et al. 2006). In addition, our study indicates that the supraspinal control to the UE and LE movement is somewhat different with regard to the volume and intensity of activation (See Chapter 3). If we accept the existence of different UE and LE control strategies, we should also believe that treatments designed to restore movement in the UE might not be appropriate or effective for the LE, and vice versa. However, interventions designed for the LE have been shown to be effective for the UE (Kim, et al. 2012; Johannsen, et al. 2010). This paradox suggests that rehabilitation may be enhanced by a better understanding of the similarities and differences in the way the UE and LE recover from stroke. Knowledge on this area may also shed light on the field of neurological rehabilitation and provide insight into ways in which post-stroke rehabilitation can be enhanced.

#### 4.2 Objectives and Expectations

The work presented here was a pilot study aimed at understanding supraspinal control of UE and LE movements after stroke. The aims were 1) to determine whether the UE pedaling device described in Chapter 2 was suitable for producing locomotor-like

movements of the UE during fMRI in people post-stroke, and 2) to examine brain activation patterns associated with UE pedaling, LE pedaling, FING, and FOOT in people post-stroke. Data collected from stroke survivors were also compared to control (Chapter 3) data to understand whether supraspinal control of these tasks observed in control subjects was affected by stroke. We expected to observe different activation patterns for stroke and control subjects. Specifically, we anticipated that stroke survivors with primary motor cortex involvement would display asymmetrical brain activity during bilateral movements and brain activation that was shifted toward the intact hemisphere. On the other hand, stroke survivors with sub-cortical strokes, or with little or no primary motor cortex involvement would display bilateral activations during bilateral movements with activation patterns that are more similar to the control data (Feydy et al 2002). Given our small sample and the pilot nature of this study, preliminary conclusions about brain activity are drawn.

### 4.3 Methods

Descriptive information about stroke subjects is presented in Table 4-1. Four individuals (2 males and 2 females, mean ( $\pm$ STD) age of 64 ( $\pm$ 8) years) with chronic post-stroke hemiparesis volunteered to participate. All subjects had experienced their stroke as least 1.9 years prior to testing. There were two subjects (S01 and S03) with right and two subjects (S02 and S04) with left hemiparesis. The lesion location, as evidenced by T-1 weighted MR images, showed that two subjects (S01 and S03) had cortical stroke (STc) and two subjects (S02 and S04) had subcortical stroke (STsc). See Figure 4-1. The Fugl Meyer (FM) test of sensorimotor function (Gladstone, et al. 2002) was used to assess stroke-related impairment, and values are shown in Table 4-1. FM

scores were divided into UE motor (max=66), UE sensory (max=66), LE motor (max=34), and LE sensory (max=60). Prior to participating, each subject gave written informed consent according to the Declaration of Helsinki and institutional guidelines at Marquette University and the Medical College of Wisconsin.

Subject ID	Sex	Age	Time post stroke (years)	FM (motor/sensory)		Lesion Location
				UE (max) 66/66	LE (max) 34/60	
S01	M	55	6	42/59	32/60	Left cortical
S02	F	64	8.9	58/62	32/60	Right subcortical
S03	M	64	6.3	66/64	21/56	Left cortical
S04	F	74	1.9	64/66	32/60	Right subcortical

Table 4-1. Information about stroke subjects.  
M=male, F=female, FM=Fugl-Meyer, max=maximum.



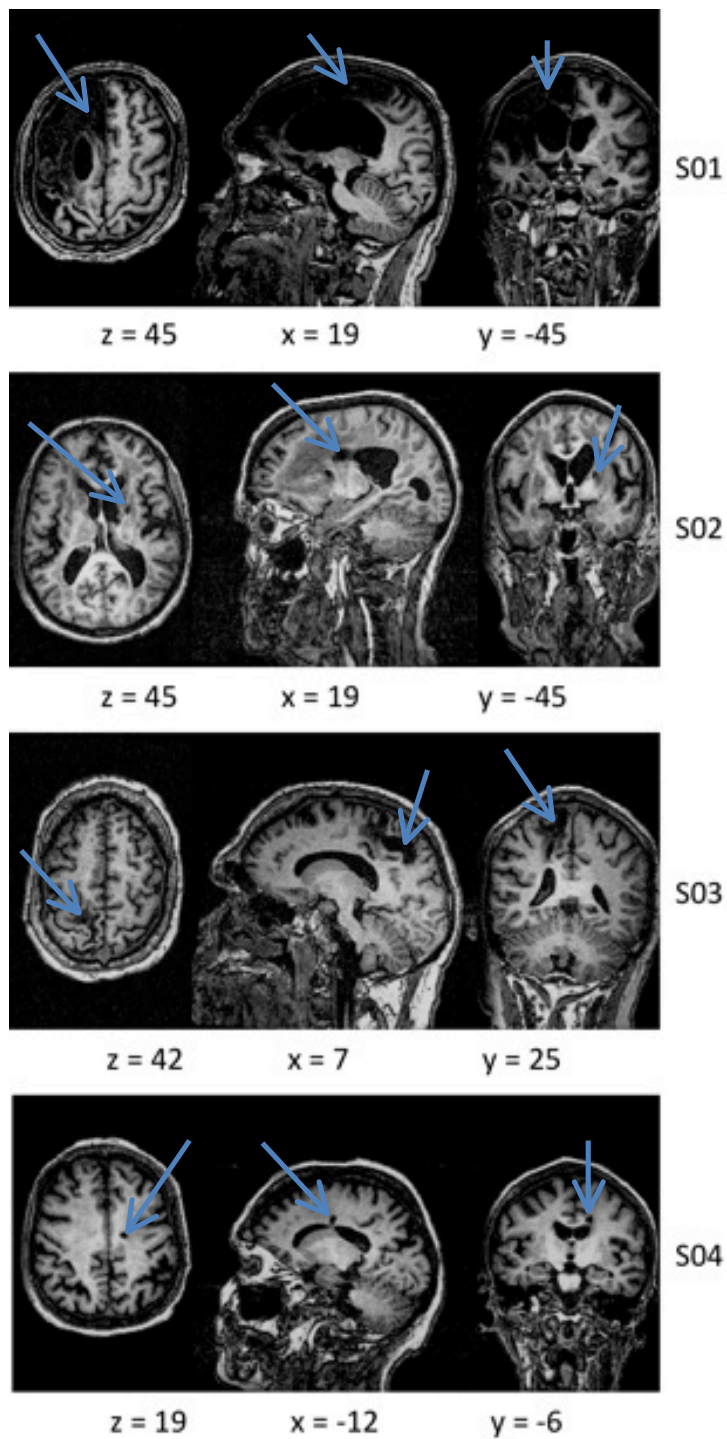


Figure 4-1. T-1 weighted images displaying lesion location. the lesion was pointed out by blue arrow

Experimental equipment, set-up, procedures, processing, and analysis were the same as those describe in Chapter 3 for control subjects. Prior to participating, subjects underwent two fMRI safety screenings and were excluded if they were claustrophobic, pregnant, or had any implants or foreign bodies incompatible with fMRI. All of the subjects participated in a familiarization session outside the MR environment where we explained the procedures and allowed them to practice the tasks until we were confident that they were able to do them correctly. The stroke subjects completed the same tasks that were performed by the control group and described in Chapter 3 (PED<sub>UE</sub>, PED<sub>LE</sub>, non-paretic FING, paretic FING, non-paretic FOOT, and paretic FOOT). One subject (S03), the dorsiflexion of the paretic ankle was not possible, so the subject was allowed to do knee flexion and extension.

We identified active brain regions and calculated the laterality index (LI) as well as the volume and intensity of activity in S1, M1, and BA6. The LI was determined based on the quantity of activated voxels in each ROI: in PED<sub>UE</sub> and PED<sub>LE</sub>, the positive value corresponded to the activation in the intact hemisphere (contra-lesion), and the negative value indicated ipsi-lesion activation; in paretic FING and FOOT, the positive value indicated greater activation in the ipsi-lesion side; and in non-paretic FING and FOOT, the positive value indicated greater activation in the contra-lesion hemisphere. To find the changes after stroke, we also displayed the volume, intensity, and LI from healthy subjects in Chapter 3.

## 4.4 Results

### 4.4.1 PED<sub>UE</sub> and PED<sub>LE</sub>

Of the four stroke subjects examined, only data for S01 and S03 are reported in bilateral pedaling part. In the other two stroke subjects, head-movement during PED<sub>LE</sub> exceeded 2 mm, so that the data were contaminated by movement artifact (see APPENDIX D, the results for PED<sub>UE</sub> and PED<sub>LE</sub> were contaminated, but their FING and FOOT data might be useful). fMRI data displaying brain activation during PED<sub>UE</sub> and PED<sub>LE</sub> for S01 and S03 are shown in Figure 4-2 (S01) and 4-3 (S03). Figure 4-4 shows the volume, intensity, and LI of pedaling-related brain activity in the three ROIs, and also provides a comparison to healthy subjects as described in Chapter 3. The movement paces were controlled internally by the subjects themselves throughout the experiment, and the mean rates were displayed in Table 4-2. As compared to the control group, S01 showed decreased pedaling rate in PED<sub>UE</sub> but increased rate in PED<sub>LE</sub>, and S03 showed faster PED<sub>UE</sub> but slower PED<sub>LE</sub> movement. The laterality index, intensity and volume of activation is described below and shown in table in APPENDIX H.

Subject ID	PED <sub>UE</sub> (RPM)	PED <sub>LE</sub> (RPM)	Paretic FING (Hz)	Non- paretic FING (Hz)	Paretic FOOT (Hz)	Non- paretic FOOT (Hz)
S01	46.1	62.6	62.1	43.7	146.3	63.8
S02	71.3	66.7	65.3	71.6	92.5	77.5
S03	90.9	49.6	60	59.7	112.5	77.5
S04	46.7	30.7	80.5	77.9	120	127.5
Control	71.2	56.99	89.9	92.2	120.0	133.7

Table 4-2. The movement rates for stroke and control group

The location of task-related brain activation in control subjects was described in Chapter 3. Recall that, in control subjects,  $PED_{UE}$  and  $PED_{LE}$  produced bilateral activity in S1, M1, and BA6. The location of activity in S1 and M1 in control subjects agreed with the somatotopic organization of the cerebral cortices, as described by Penfield (Penfield, et al. 1937).  $PED_{LE}$  activated the medial portion of S1 and M1, while  $PED_{UE}$  activated the lateral part of S1 and M1. In stroke subjects, brain activation was also located in S1, M1, and BA6; normal somatotopy (UE lateral, LE medial) was preserved in S01 but not S03.

S01 had a large cortical stroke affecting his left hemisphere, as shown in Figure 4-1. The injured areas of this subject's brain included the UE region of M1 and S1. As compared to control, the volume of pedaling-related brain activity observed in this subject during  $PED_{UE}$  was reduced in S1, M1, and BA6 (Figure 4-4A). Reduced pedaling-related brain activation volume was also observed during  $PED_{LE}$  in M1 and BA6, but not in S1 (Figure 4-4B). There was no reduction in the intensity of brain activity during  $PED_{UE}$  or  $PED_{LE}$ . In fact, in M1 and BA6, brain activation intensity during pedaling tended to be larger in S01 as compared to control. Pedaling-related brain activity in S01 was lateralized to the non-paretic (right) hemisphere in all active regions (Figure 4-4E and F). Lateralization was more robust during  $PED_{UE}$  as compared to  $PED_{LE}$ .

Subject S03 had a medially located cortical lesion in the left hemisphere that likely affected the portion of M1 controlling his right LE (Figure 4-1). This subject cannot perform FOOT with the paretic foot, so he made knee extension/flexion instead. As compared to control, the volume of pedaling-related brain activity observed in this

subject during  $PED_{UE}$  and  $PED_{LE}$  was reduced across all regions (Figure 4-4A and B). Most notably, there was no observable activity in BA6 during  $PED_{UE}$  (Figure 4-4 A). Most brain regions that showed activity in this subject had a larger intensity of activation than control. One exception was M1 during  $PED_{UE}$  which showed a lower than normal activation intensity. Pedaling-related brain activity in S03 was lateralized to the lesioned (left) hemisphere during  $PED_{UE}$  (Figure 4-4E). However, during  $PED_{LE}$  there was a mixed response. Activation in S1 was lateralized to the lesioned (left) hemisphere; BA6 was lateralized to the intact (right) hemisphere, and M1 displayed bilateral activity.

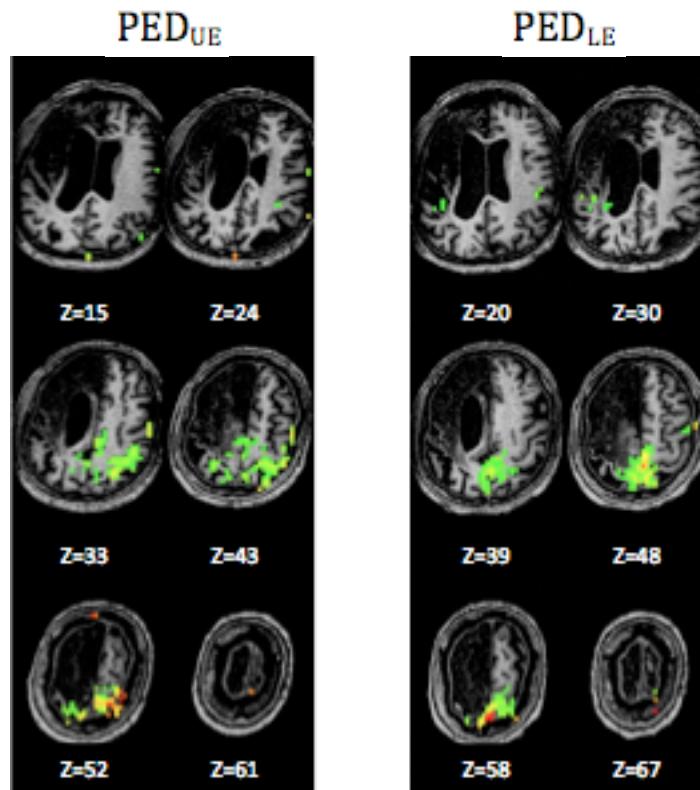


Figure 4-2. Subject S01. Pedaling-related brain activity.

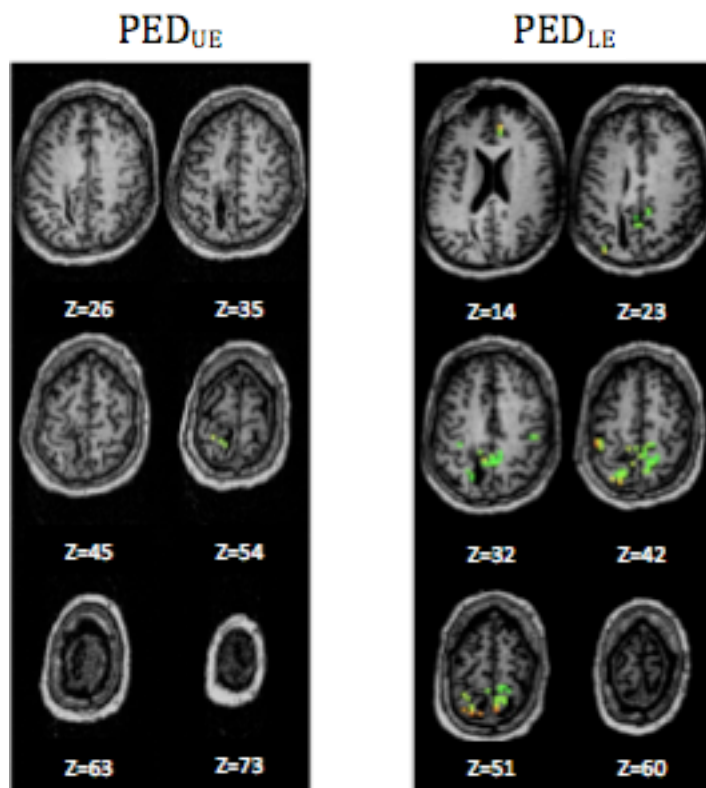


Figure 4-3. Subject S03. Pedaling-related brain activity.

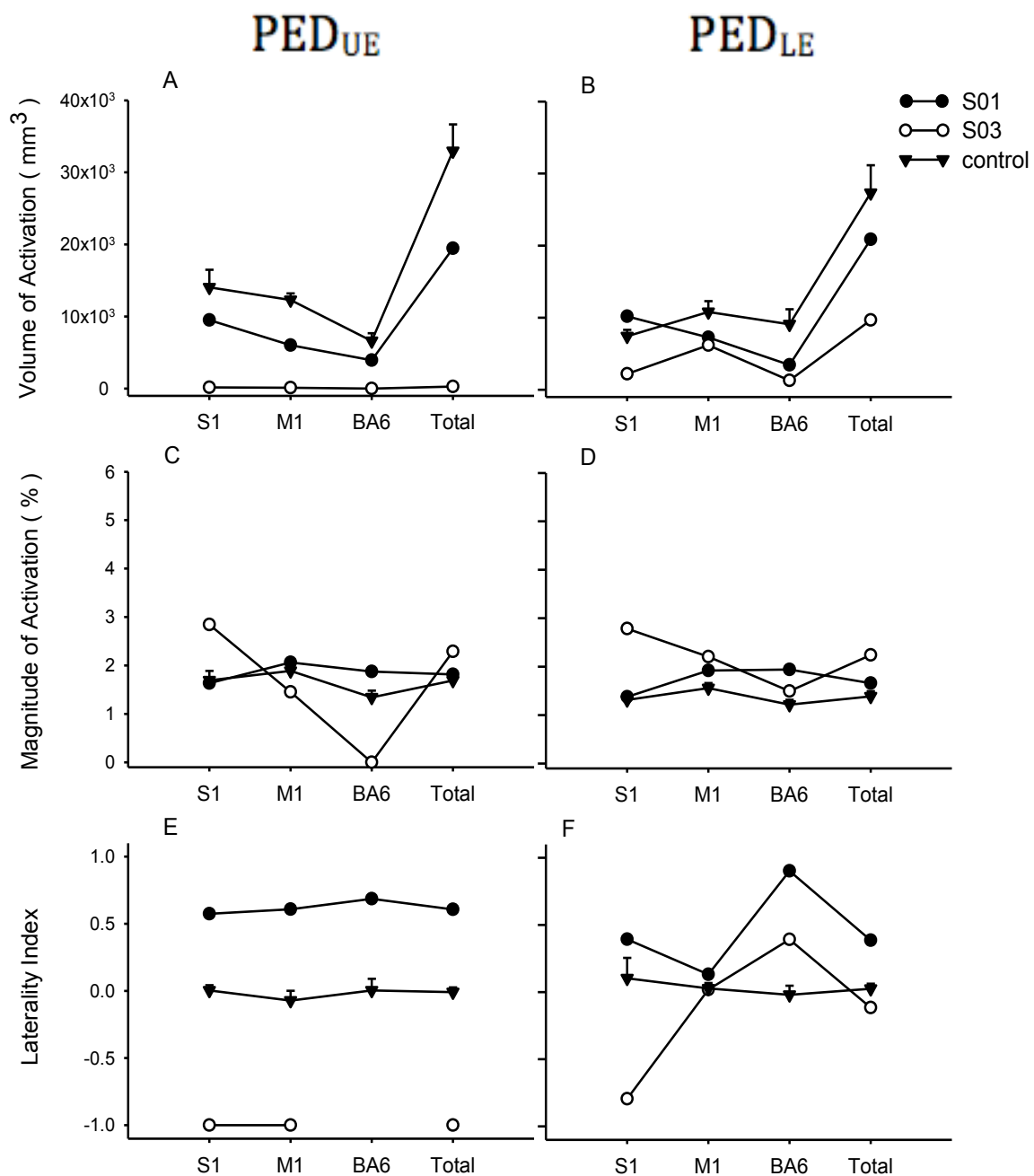


Figure 4-4. Volume, intensity and symmetry of pedaling-related brain activity in STc subjects S01 and S03. A: volume of activation in PED<sub>UE</sub>; B: volume of activation in PED<sub>LE</sub>; C: Intensity of activation in PED<sub>UE</sub>; D: Intensity of activation in PED<sub>LE</sub>; E: laterality index of PED<sub>UE</sub>; F: laterality index of PED<sub>LE</sub>. (Total = combination of S1, M1 and BA6)

#### 4.4.2 FING and FOOT

The FING/FOOT results of STc subjects (S01 and S03) and STsc subjects (S02 and S04) were displayed separately. The head movement for all the four subjects in FING and FOOT was displayed in APPENDIX D, while no subject showed extremely large scale of displacement. S03 could not perform paretic FOOT, so he made flexion/extension with the paretic knee instead. The brain activation related to FING was displayed in Figure 4-5, 4-6, 4-8 and 4-9. The head movement is limited in 2 mm for all the four subjects (APPENDIX D). Functional images corresponding to the paretic limb were placed on the left two columns, while the images corresponding to the non-paretic limb were placed on the right. Since we divided the subjects into STc and STsc group, we displayed the two groups of result separately.



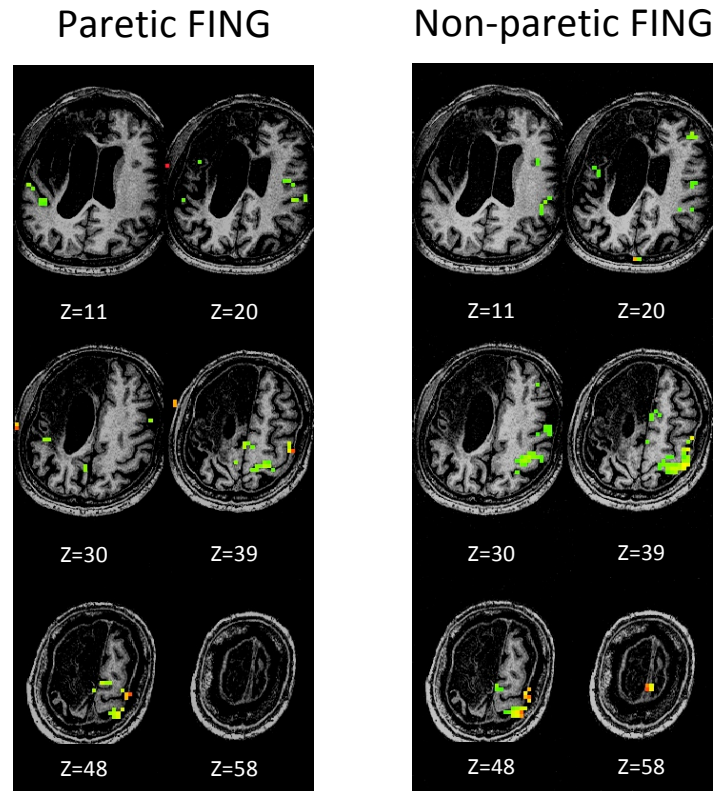


Figure 4-5. FING-related brain activation for S01.

The task related activation for S01 was displayed in Figure 4-5. The paretic limb (right hand and fingers) produced decreased volume of activation in S1 and M1, while the activation in BA6 was close to the control group (Figure 4-7A). The intensity of activation was higher than the control in M1 and BA6, while no apparent difference was observed in S1 (Figure 4-7C). The S1 activation was lateralized to the intact hemisphere, but the M1 and BA6 activation was bilateral according to the values of LI (Figure 4-7E). The activation produced by the non-paretic limb (left hand and fingers) was also lateralized to the contra-lesional hemisphere (Figure 4-5, Figure 4-7F). There was no apparent difference in volume or intensity between S01 and the control group according to Figure 4-7B, D.

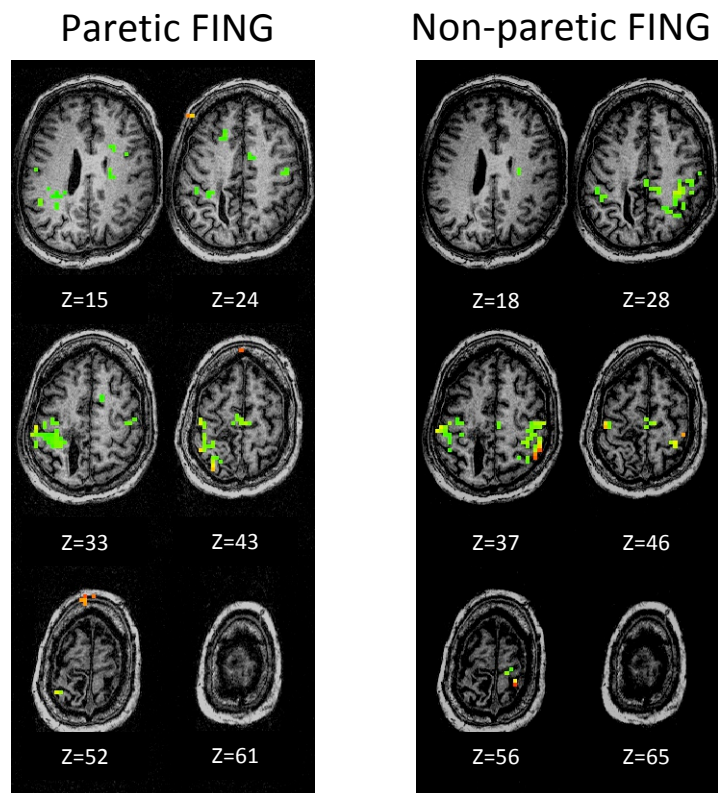


Figure 4-6. FING-related brain activation for S03.

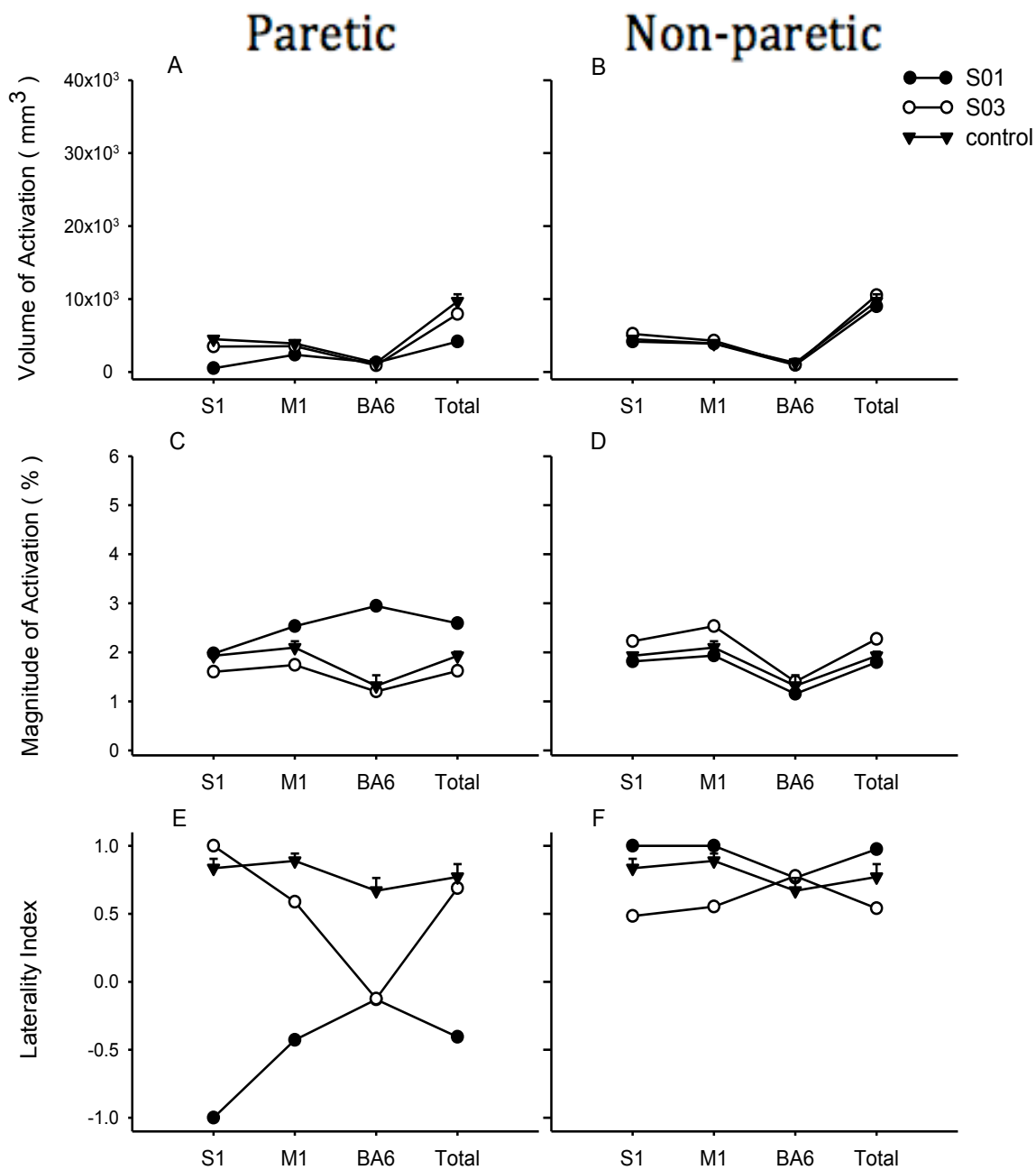


Figure 4-7. FING related brain activation of STc subjects S01 and S03.

A: volume of activation of paretic FING; B: volume of activation of non-paretic FING; C: Intensity of activation of paretic FING; D: Intensity of activation of non-paretic FING; E: laterality index of paretic FING; F: laterality index of non-paretic FING

For subject S03, the activation related to paretic (right) and non-paretic (left) FING was displayed in Figure 4-6. The paretic FING activation volume and intensity was close to the control group (Figure 4-7A, C), yet the activation was lateralized to the lesioned hemisphere that is also contralateral to the paretic limb (Figure 4-7E). The non-paretic FING produced activation in both lesioned and intact hemisphere (Figure 4-6), and the volume was close to the control group. The intensity in S1 and M1 is slightly higher than that of control group, while no apparent difference was observed in BA6. The activation tended to lateralize to the contra-lesional hemisphere (Figure 4-7F).

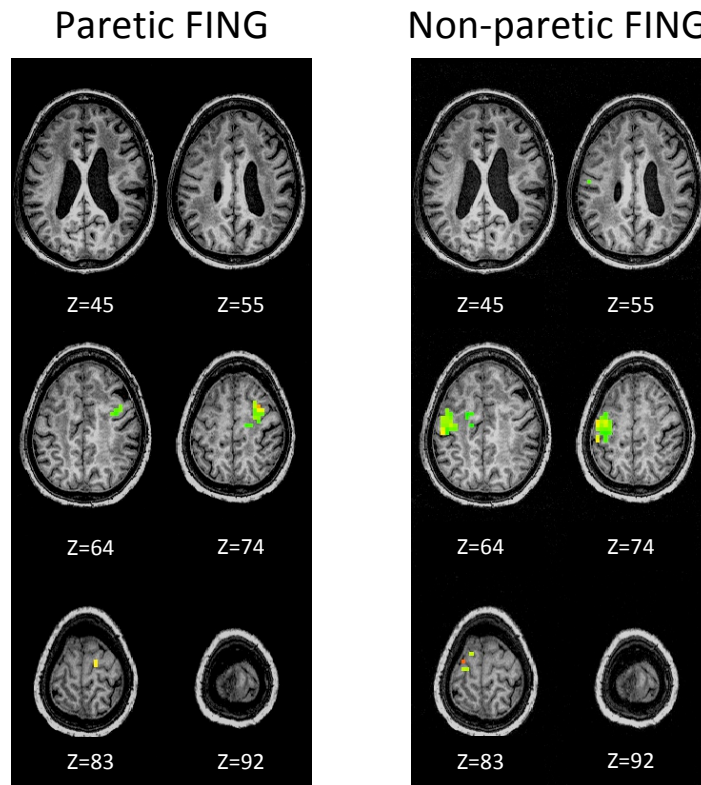


Figure 4-8. FING-related brain activation for S02.

In STsc group, subject S02 showed task related activation in S1, M1 and BA6 (Figure 4-8). Compared with the control group, S02 produced increased volume of activation in M1 with the paretic (left) limb, and the volume in S1 and BA6 was small (Figure 4-10A). The intensity was lower than control group in S1 and M1, but much higher in BA6 (Figure 4-10C). The activation was lateralized to the lesioned hemisphere (Figure 4-10E). The non-paretic FING (right FING) of S02 produced increased volume of activation in S1 and M1, and decreased volume in BA6 (Figure 4-10B). The intensity of activation in the three ROIs was relatively lower than the control group (Figure 4-10D), and the activation only existed in the intact (left) hemisphere according to the values of LI (Figure 4-10F).

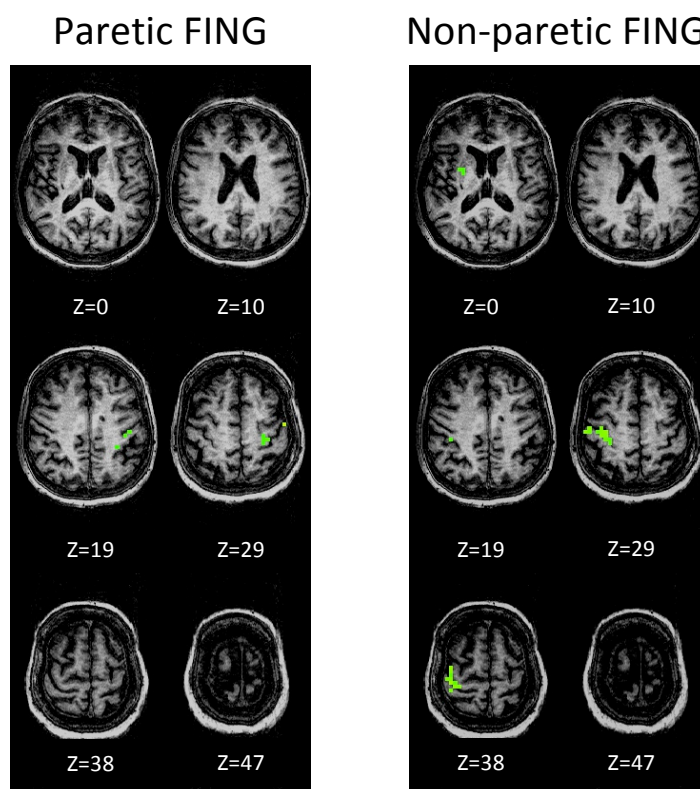


Figure 4-9. FING-related brain activation for S04.

The paretic FING related activation of S04 was displayed in Figure 4-9. No related activation was observed in BA6 in either contral- or ipsi-lesional hemisphere. The volume was lower than the control group in all the three ROIs (Figure 4-10A), and the intensity was also relatively lower (Figure 4-10C). According to the LI values, the activation was lateralized to the ipsi-lesional hemisphere (Figure 4-10E). The non-paretic FING produced larger volume of activation in M1 as compared to the control group, while the volume in S1 was comparable (Figure 4-10B); however, we failed to observe activation in BA6 (Figure 4-9, 4-10B, D). The intensity of activation was relatively lower than the control group, and the activation was lateralized to the contra-lesional hemisphere (Figure 4-9).

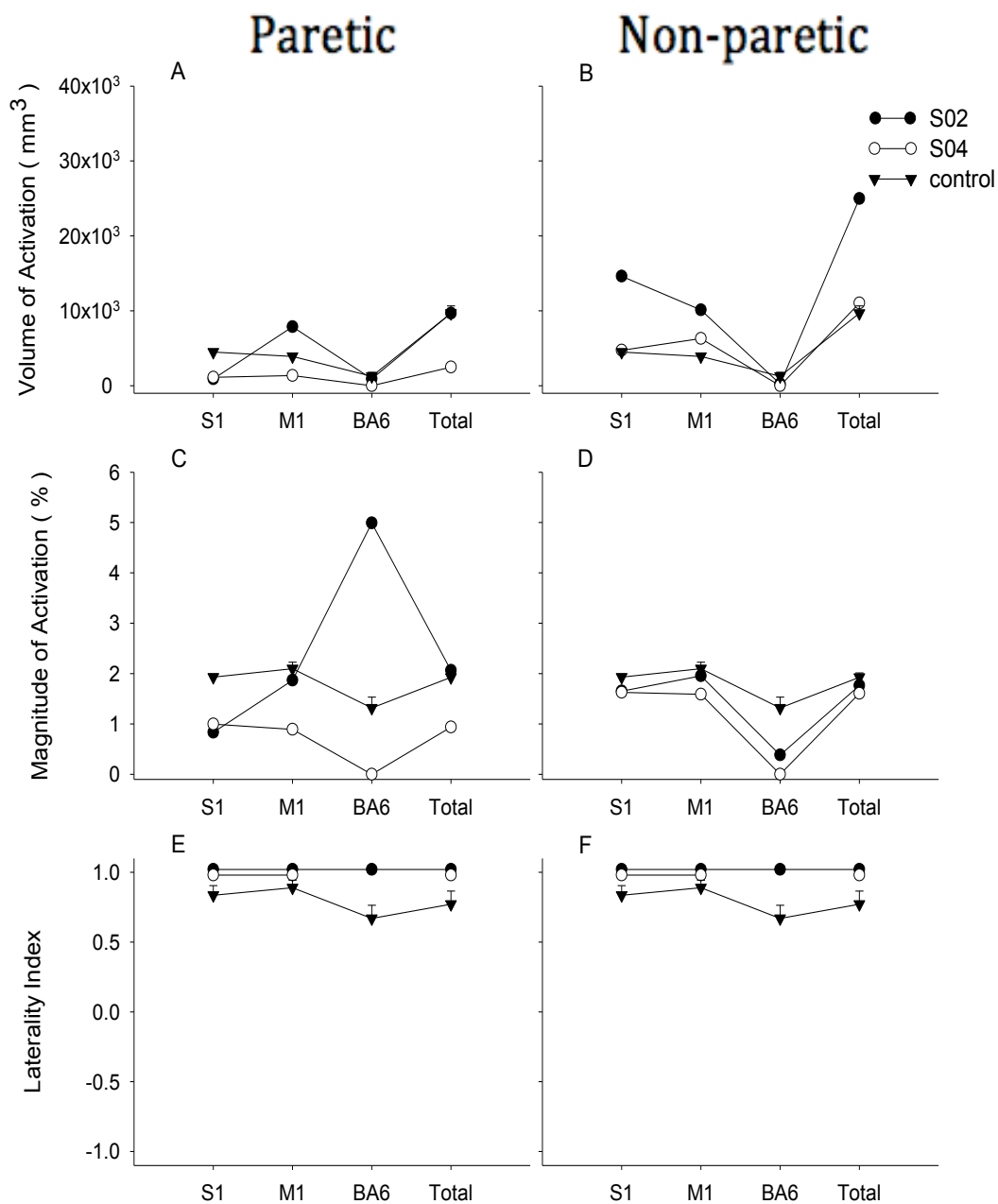


Figure 4-10. FING related brain activation of STsc subjects S02 and S04.  
 A: volume of activation of parietic FING; B: volume of activation of non-parietic FING;  
 C: Intensity of activation of parietic FING; D: Intensity of activation of non-parietic FING; E:  
 laterality index of parietic FING; F: laterality index of non-parietic FING

The FOOT related activation was displayed in Figure 4-11, 4-12, 4-14, and 4-15. S01 produced decreased volume of activation as compared to the control group with the paretic FOOT (Figure 4-13A). The intensity was relatively higher than the control group, and the activation only existed in the contra-lesional hemisphere (Figure 4-13C, E). The non-paretic FOOT related activation was shown in Figure 4-11. The volume was larger than the control group in M1, and comparable in S1, and smaller in BA6 (Figure 4-13B). The intensity of activation was slightly higher than the control group in M1 (Figure 4-13D), while the intensity in S1 and BA6 was comparable. The activation in S1 and M1 was lateralized to the contra-lesional hemisphere (Figure 4-13F), but the BA6 activation was bilateral.

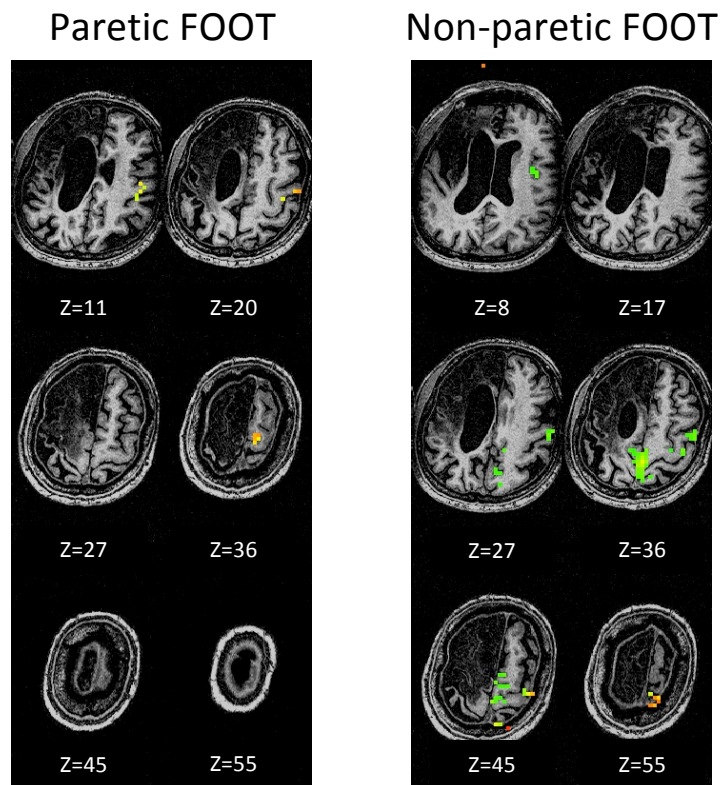


Figure 4-11. FOOT-related brain activation for S01.



Subject S03 could not perform FOOT with paretic limb, while the activation related to non-paretic FOOT was displayed (Figure 4-12). The volume was slightly larger than that of control group in M1, but smaller in BA6 (Figure 4-13B), and the intensity was higher than that of control group in all the ROIs (Figure 4-13D). The activation was lateralized to the contra-lesional hemisphere in BA6, but the activation tended to be bilateral in S1 and M1 (Figure 4-13F).

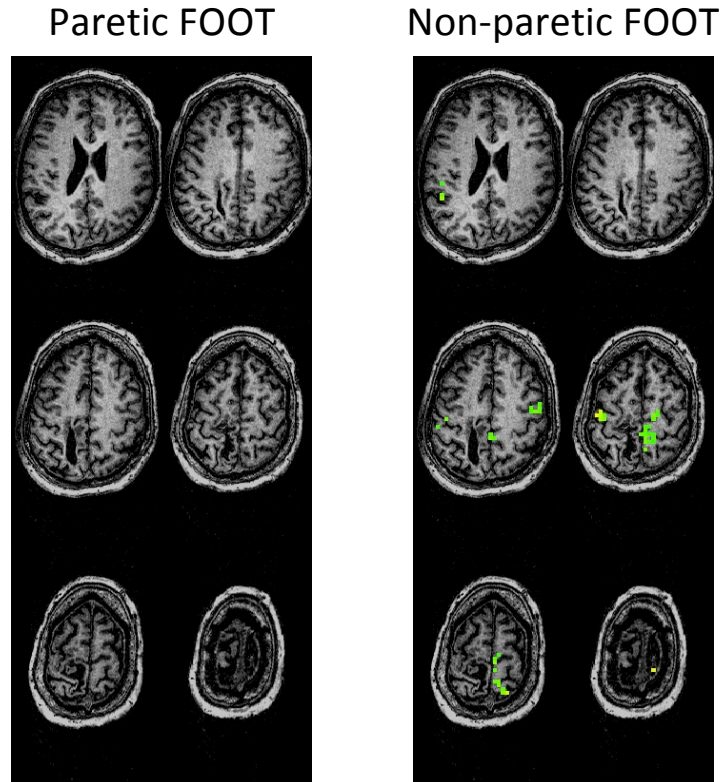


Figure 4-12. FOOT-related brain activation for S03.

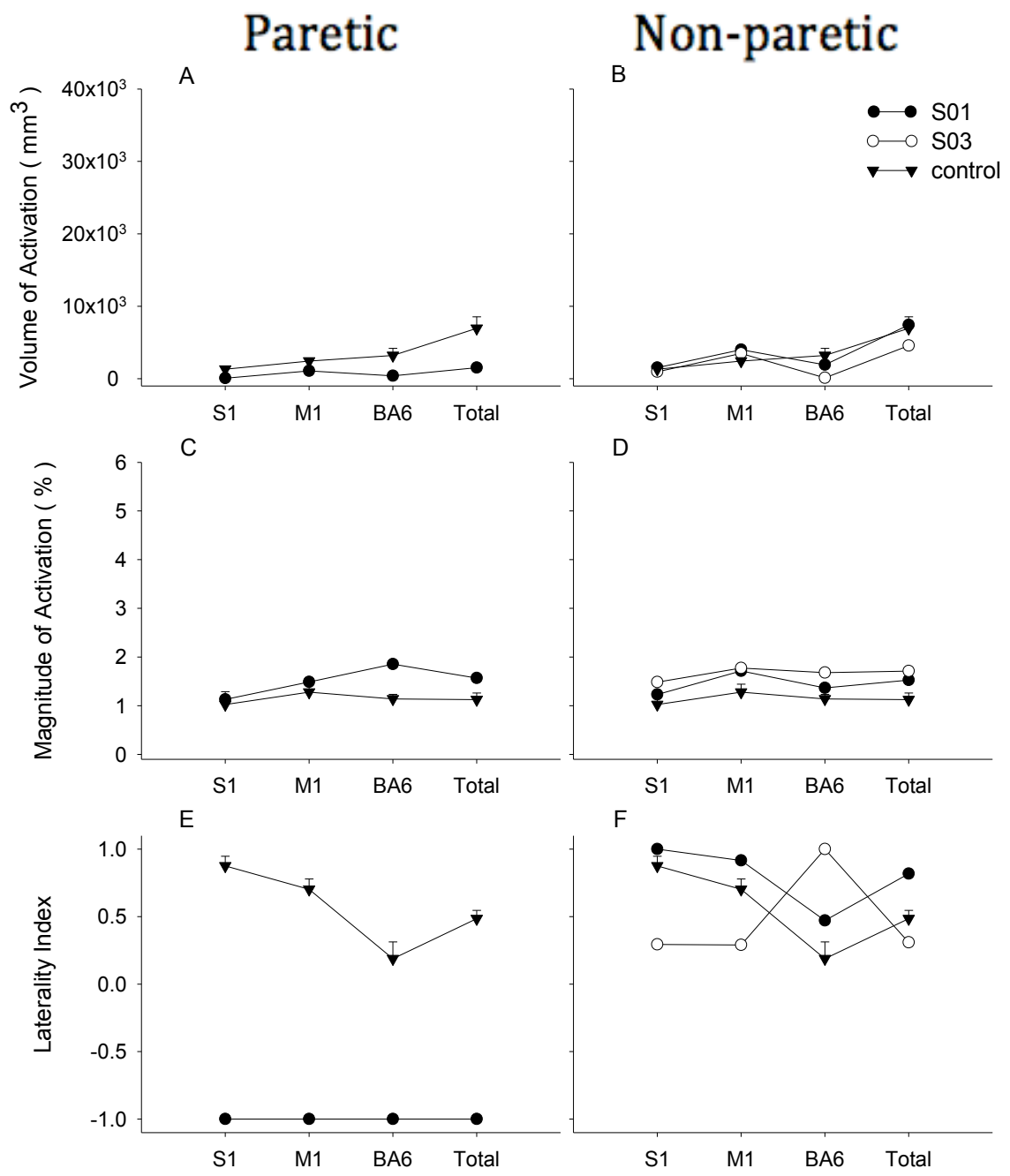


Figure 4-13. FOOT related brain activation of STc subjects S01 and S03. A: volume of activation of paretic FOOT; B: volume of activation of non-paretic FOOT; C: Intensity of activation of paretic FOOT; D: Intensity of activation of non-paretic FOOT; E: laterality index of paretic FOOT; F: laterality index of non-paretic FOOT

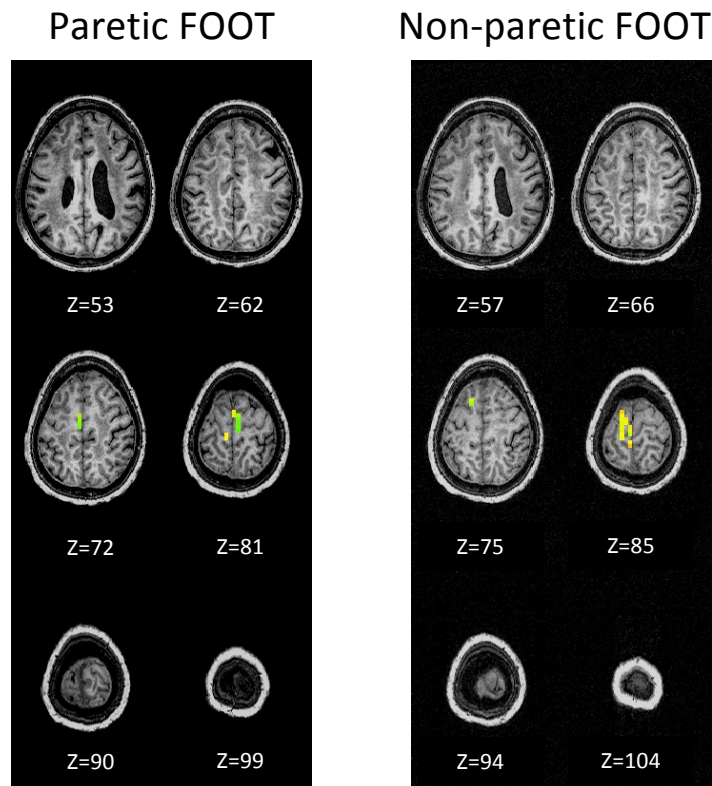


Figure 4-14. FOOT related brain activation for S02

In the STsc group, S04 did not show any consistent activation during either paretic or non-paretic FOOT task. The activation of S02 was shown in Figure 4-13. For paretic FOOT task, the volume in S1 and BA6 was relatively small, but was comparable in M1 as compared to the control group. The intensity of activation was higher than that of control in M1 and BA6 (Figure 4-16A), but lower in S1. The activation was lateralized to the paretic hemisphere in S1, and lateralized to the contra-lesional hemisphere in BA6, but the M1 activation was bilateral (Figure 4-16). The non-paretic FOOT produced slightly smaller volume of activation in S1 and BA6 (Figure 4-16B), but the intensity was higher than the control group. According to the values of LI, all the activation located in the contra-lesional hemisphere (Figure 4-15F).

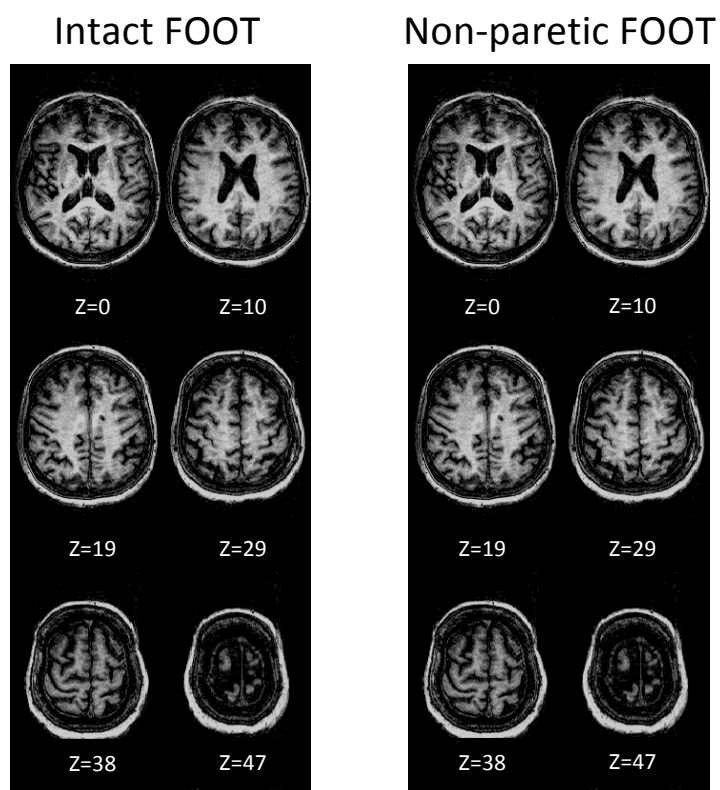


Figure 4-15. FOOT-related brain activation for S04.

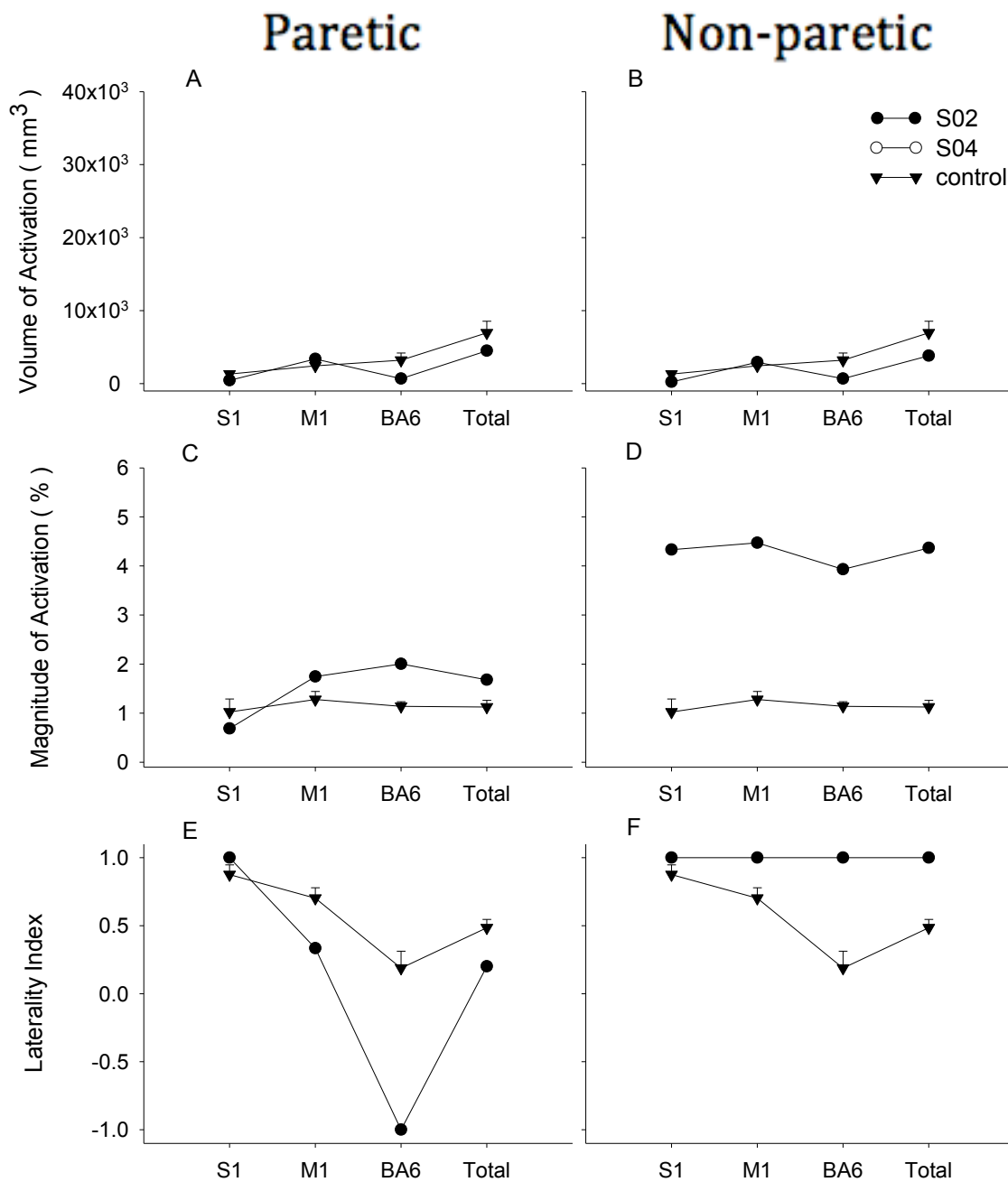


Figure 4-16. FOOT related brain activation of STsc subjects S02 and S04. A: volume of activation of paretic FOOT; B: volume of activation of non-paretic FOOT; C: Intensity of activation of paretic FOOT; D: Intensity of activation of non-paretic FOOT; E: laterality index of paretic FOOT; F: laterality index of non-paretic FOOT

## 4.5 Discussion

During both bilateral ( $PED_{UE}$ ,  $PED_{LE}$ ) and unilateral (FING, FOOT) movement, the cortical activation appeared in the regions of S1, M1, and BA6. Differed from the healthy subjects, the activation was asymmetric during  $PED_{UE}$  and  $PED_{LE}$ , and the lateralization of activation also changed in FING and FOOT tasks. The volume decreased as compared to the healthy group in  $PED_{UE}$  and  $PED_{LE}$ , but the decrease during unilateral movement was not apparent. The cortical recruitment after stroke, and the decrease in volume might reflect the contribution of supraspinal system to the bilateral (locomotion) movement.

### 4.5.1 Activation pattern after stroke

#### $PED_{UE}$ and $PED_{LE}$

Stroke subjects usually displayed asymmetrical activity in sensorimotor cortex (M1 and S1) and BA6 during bilateral movement, and the activity usually shifted to the contra-lesional hemisphere (Miyai, et al. 2002; Miyai et al. 2003; Miyai et al. 2006; Lin, et al. 2012). Our two subjects displayed opposite results during  $PED_{UE}$  and  $PED_{LE}$ : Subject S01 showed dominant activation in the contra-lesional hemisphere during both  $PED_{UE}$  and  $PED_{LE}$ , S03 showed only ipsi-lesional activation and no contra-lesional activation during  $PED_{UE}$ , and his lesioned hemisphere was more activated than the intact side during  $PED_{LE}$ . According to the literature, balanced activation plays an important role in locomotor recovery, and the LI of activation in sensorimotor cortex was a strong indicator of motor function after stroke (Miyai, et al. 2003; Lin, et al. 2012). The stroke survivors usually showed greater activation in the intact side, while improved motor

function was associated with increased activation in the ipsi-lesional hemisphere (Lin, et al. 2012). This theory was supported by the data from S01, who exhibited poor UE function and strong contra-lesional activation in  $PED_{UE}$ . Moreover, this subject had better LE function, while the M1 and S1 activation was more symmetric during  $PED_{LE}$ .

Subject S03 showed ipsi-lesional activation during  $PED_{UE}$ , which was inconsistent with the literature (Miyai, et al. 2003; Miyai, et al. 2005; Lin, et al. 2012). We suspect that the abnormal activation resulted of unbalanced contribution to the pedaling. If the non-paretic limb generated greater force than the paretic limb, or the subject paid all the attention to the paretic limb, the pedaling task was no longer a symmetric movement. However, we cannot tell the difference between two limbs based on current experimental design, so that we cannot determine the factor to the abnormal activation.

#### FING and FOOT

The functional images and laterality index reflected the reorganization during both paretic and non-paretic limb movements. Among our four subjects, S01 showed recruitment of activation in the contra-lesional hemisphere during the paretic FING and FOOT tasks, and S03 showed bilateral activation during paretic FING. The two STsc subjects (S02 and S04) produced ipsi-lesional activation during paretic FING, and S02 produced bilateral activation during paretic FOOT.

Based on our current data, the activation patterns of paretic limbs after stroke varied, indicating multiple choices for cortical reorganization during motor recovery. The STc subjects with median FM scores showed greater contra-lesional activation than the healthy subjects in S1 and M1, which indicated the recruitment of corticospinal tract in

the ipsilateral side of the limb (Kwon, et al. 2007). The literature suggested that this type of motor pathway was inhibited in mature and intact brain (Muller, et al. 1997; Kwon, et al. 2007), and the recruitment of pathway in contra-lesional side was usually associated with poor motor ability (Kwon, et al. 2007; Luft, et al. 2004; Turton, et al. 1996). By contrast, ipsi-lesional activation (or contralateral activation) was the activation pattern applied by the healthy subjects as described in Chapter 3. According to previous longitudinal studies, the stroke survivors showed decreasing volume of activation in contra-lesional S1 and M1 in the procedure of motor recovery (Feydy et al. 2002), and increasing activation in ipsi-lesional hemisphere (Miyai, et al. 2003). This theory complied with our current data: the two STsc subjects showed high motor function in FM test, and they also showed greater ipsi-lesional activation than contra-lesional activation.

In conclusion, the varied activation patterns suggested the tendency that activation shifted from the ipsi-lesional hemisphere to the contra-lesional side, reflecting the compensation of function from the opposite hemisphere. Yet ipsi-lesional recruitment might correspond to a better strategy for reorganization.

#### 4.5.2 Decreased volume of activation in stroke survivors

The cortical activation related to the PED<sub>UE</sub>, PED<sub>LE</sub>, FING and FOOT were limited in the regions of M1, S1, and BA6, which is the same to the healthy subjects. But according to the only two subjects' data for PED<sub>UE</sub> and PED<sub>LE</sub>, the volume of activation associated with PED<sub>UE</sub> and PED<sub>LE</sub> decreased as compared to the healthy subjects in the three ROIs, while no apparent difference in the intensity of activation was observed. In the FING and FOOT task, the volume and intensity of activation from four subjects varied. The changes in volume or intensity had been reported in previous studies (Luft, et



al. 2004). The literature suggested that the motor recovery of the upper limb is associated with enlarged activation in M1 in the lesioned hemisphere during unilateral movement (Luft, et al. 2004, Cao et al. 1998), but in locomotion tasks, the stroke subjects usually showed decreased volume of activation as compared to the healthy people.

The decrease in volume suggested that the number of neurons associated with movement control decreased. This phenomenon in our study could be partially explained by the assumption that CPGs contribute more to the movement after stroke than the healthy subjects (Miyai, et al. 2006). The literature suggested that CPGs contribute to the movement control as well as the supraspinal system (Duysens, et al. 1998; Dimitrijevic, et al. 1998). Although cortical regions contribute more to the locomotion than other neural centers (Armstrong, et al. 1993; Duysens, et al. 1998), it is possible that the CPGs take over some of the functions after stroke (Miyai, et al. 2006). Our result agreed with the idea that the movement related neurons is reduced in M1 and S1, thus it is possible that the original functions of those neurons have been taken by other neural centers.

The spinal CPG was supposed to generate rhythmic patterned output, especially the locomotion (Armstrong, et al. 1993; Duysens, et al. 1998; Leon, et al. 1998; Leon, et al. 1999). This theory can explain why we could observe larger scale of decrease in  $PED_{UE}$  and  $PED_{LE}$ , but no consistent decrease occurred in FING and FOOT.  $PED_{UE}$  could be considered as the 'arm locomotion' as compared to  $PED_{LE}$ , and the decrease in volume suggested that CPG adopt  $PED_{UE}$  easier than FING and FOOT.

Bhasin and et al. (2003) listed the volume and laterality index of M1 and SMA during wrist movement after stroke, while more than one third of the subjects showed no activation in M1 or SMA. He also found that the inactivated M1 returned to be active

after several weeks' training (Bhasin, et al. 2003). Bhasin's report supported our finding from two subjects, because S03 and S04 showed no activation during paretic FOOT.

There are two potential reasons to the disappearance of activation. (1) The disappearance of activation corresponds to impairment of motor ability. If so, the subjects should exhibit impaired movement because the required cortex stopped working, leading to less-controlled movement. (2) The function of the disappeared activation was replaced by the subcortical or spinal neural systems (e.g., CPG). If so, the subjects should not display serious impairment in movement since the motor control never ceased, but translated to other regions. However, we have no information more than the FM scores from the subjects, so that we cannot make sure whether the disappearance was related to motor impairment or CPG replacement.

Taken together, we suspect that the decrease in volume should be attributed to the novel strategies for locomotion control, but the limited number of samples could not provide convincing support to the hypothesis. If we want to consolidate this hypothesis, we should prove that stroke subjects truly displayed decreased volume of activation in bilateral pedaling, and the decrease was unique in pedaling task; in addition, we also need the subjects' movement data to prove the assumption that the function of the cortex never ceased, but translated to the spinal cord or other neural centers.

#### 4.6 Limitation

This study examined the brain activation from four individual with post-stroke hemiparesis. Functional images indicated multiple choices for neural reorganization, but it is not ready to argue if the brain use novel strategies for UE and LE control based on our current data. There are several limitations in this study. First, the head displacement

during  $PED_{UE}$  is a serious challenge to the experimenters. The stroke subject had greater difficulty in keeping the head still during UE pedaling, while large scale of head movement might result in the inaccurate output. There are several methods to prevent large scale of displacement. For example, we could remind the subject of the head movement during the experiment, or we can fix the head with larger strap if the subject could accept. Moreover, the head displacement might result of the momentum generated by the moving limbs, so that reducing the speed of the pedaling might be a good solution to this problem. After all, we believe that varied methods should all be applied to reduce the head displacement, making sure that we could get reliable data in future studies.

Another limitation of the experiment was related to subjects' motor performance. For example, we were not sure whether the two arms contribute equally to the movement, or the paretic limb was motivated by the non-paretic limb during pedaling. The potential issue of paretic and non-paretic limb might alter the activation patterns, and suppress the activation in one side of the hemisphere.

#### 4.7 Conclusion

In this project, we tested stroke subjects as a pilot study. Based on our current data, the activation pattern varied, while the volume of activation decreased in bilateral movement. These findings suggested that there were multiple choices for cortical reorganization after stroke. We suspect that the supraspinal system applies novel strategies for movement control with regard to the changes in volume, but if we need to make a more conclusive assertion, more subjects should be recruited to this study.

## CHAPTER 5: CONCLUSION AND FUTURE DIRECTIONS

### 5.1 Conclusion

In this study, we proved that the PED<sub>UE</sub> device was MR safe and compatible. Although the motion of the limbs could pollute the magnetic field, introducing extra noise to the signal (Chapter 2), we could exclude the noise by applying the ‘declined’ method as described in Chapter 3, because only the signal during the ‘rest’ period was extracted for data analyses (Mehta, et al. 2009).

We aimed to compare the difference of supraspinal contribution between UE and LE movement. Therefore, we designed four movement tasks: PED<sub>UE</sub>, PED<sub>LE</sub>, FING and FOOT, and two separated comparisons were made (PED<sub>UE</sub> vs. PED<sub>LE</sub>, FING vs. FOOT). We observed activity limited in the regions of S1, M1 and SMA, and the distribution of activation confirmed with the somatotopic order described by previous studies (Penfield, et al. 1937). The difference between UE and LE was twofold: (1) UE movement was associated with significantly greater intensity and larger volume of activation in M1 and S1; (2) the UE movement is strongly controlled by the contralateral hemisphere, while LE control is less contralateral in M1 and SMA. We concluded that the general controlling strategies for UE and LE were similar, but the supraspinal contribution to LE movement might be less than UE considering the volume and intensity of activation (Chapter 3).

We also tested 4 stroke subjects as a pilot study. The purpose was to determine whether the same setup for the healthy subjects was suitable for the people with post-stroke hemiparesis. The stroke subjects made relatively larger scale of head movement

during  $PED_{UE}$ , indicating that the original setup in Chapter 3 was not completely suitable for stroke subjects.

The activation patterns for stroke subjects diverged, which indicated multiple strategies for cortical reorganization. Due to the limited sampling size, we cannot make a conclusive assertion at this stage, but we suspected that the impaired brain applied different strategies for bilateral and unilateral movement control. Yet this assumption needs to be proved in future studies.

## 5.2 Future Directions

Our current result suggests that the intact brain use similar patterns of activation during UE and LE movement, but we are not sure if the strategies are the same for bilateral vs. unilateral movement, or for continuous vs. discrete movement. To completely understand the mechanisms underlying UE and LE movement, we should examine the activation of varied movement types.

There are several problems for the setup of the stroke subjects. As discussed in Chapter 4, the head movement should be reduced; otherwise, we would lose more data in the future. The stroke subjects displayed varied patterns of activity across different tasks, indicating novel strategies for movement control. So far, we assumed that decrease in volume occurs in  $PED_{UE}$  and  $PED_{LE}$ , but not in FING or FOOT; but we should recruit more subjects to this study before making any conclusive idea. Moreover, we are not sure if the paretic and non-paretic limbs make the same contribution to the pedaling movement, thus we are unaware whether bilateral pedaling was truly a symmetric task. We could add unilateral pedaling to our experiment, examining the activation for paretic and non-paretic movement separately.

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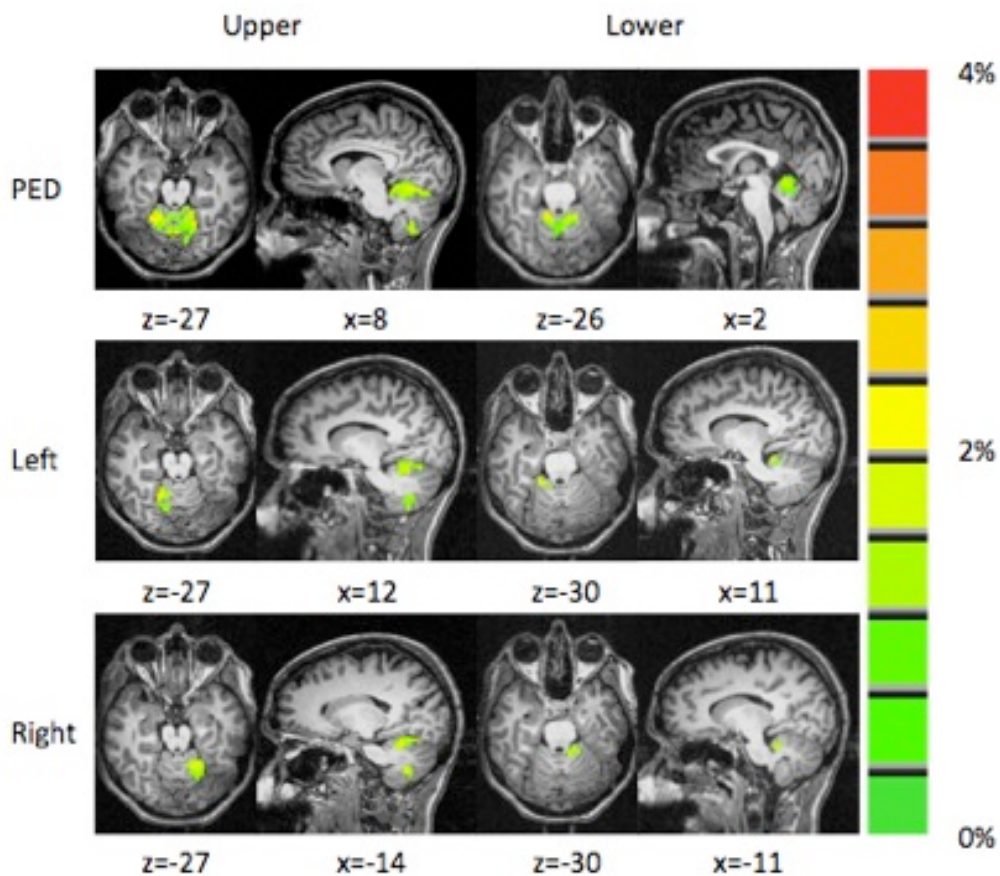
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## APPENDIX A      CEREBELLUM

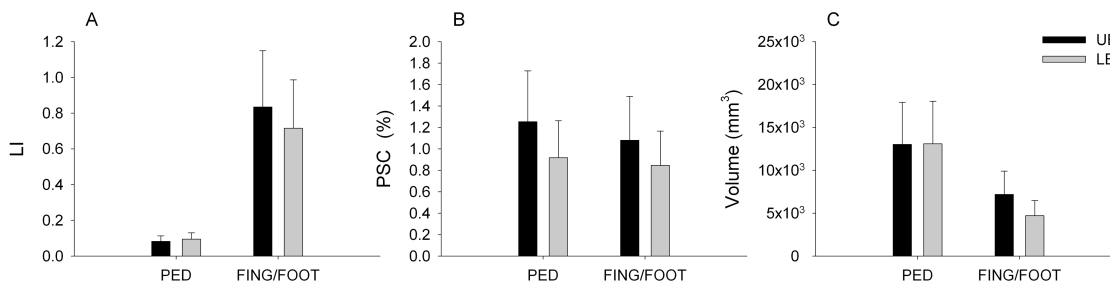
We observed cerebellum (Cb) activation from neurologically intact subject in all of our experiment conditions, and the figures were displayed bellow. The laterality index was determined by the formula bellow:

$$LI = (Q_I - Q_C) / (Q_I + Q_C);$$

Where  $Q_I$  is the quantity of activation in the ipsilateral hemisphere, and  $Q_C$  is the quantity in the contralateral hemisphere.  $PED_{UE}$  and  $PED_{LE}$  produced bilateral activation in Cb as evidenced by LI values that were  $\leq 0.10$ . The symmetry of brain activity during pedaling was not affected by limb (Paired-T test  $P=0.850$ ). FING/FOOT task produced activation, which was lateralized to the ipsilateral hemisphere to the moving limb as shown by values for LI that were  $\geq 0.71$ , while the limb effect does not contribute to the laterality of cerebellar activity (Paired-T test  $P=0.441$ ). The volume of activation was similar during  $PED_{UE}$  as compared to  $PED_{LE}$  (Paired-T test  $P=0.975$ ), but the intensity of activation was significantly higher for  $PED_{UE}$  (Paired-T test  $P=0.010$ ). FING and FOOT tasks produced similar volume and intensity of activation (Paired-T test  $P=0.235$  for volume, and  $P=0.144$  for intensity).



Functional Images of Representative Cerebellum Activity (No.02) in PED<sub>UE</sub>, PED<sub>LE</sub>, FING and FOOT.



The Laterality Index (A), Intensity of Activation (B), and the Volume of Activation (C) in the Cerebellum



## APPENDIX B      PARAMETER SHEET AND SCANNING PROTOCOL

This section illustrates the experimental protocol used during the pedaling experiment with all fMRI operating parameters

### fMRI Parameter Sheet

Expt Code: arm/leg pedaling

PI: Michelle Johnson, Ph.D., Sheila Shindler-Ivens, Ph.D., Jinsung Wang, Ph.D.

Start time (24-hr): \_\_\_\_\_

Technician: \_\_\_\_\_

Scanner: Short bore 3T

Gradient Coil: GE Head

RF Coil: GE head coil

### EPI Scan

Scan Type: GE-EPI TE (ms): 25 TR (ms): 2000 Flip: 77

NEX: 1

Plane: Sag FOV (mm): 240 Matrix: 64x64 Thickness (mm): 4

#Slices: 36

Location: First: \_\_\_\_\_ Last: \_\_\_\_\_

### SPGR Scan

Scan Type: SPGR TE (ms): 3.9 TR (ms): 9.6 Flip: 12

NEX: 1

Plane: Sag FOV (mm): 240 Matrix: 256x244

Thickness (mm): 1

#Slices: \_\_\_\_\_

Location: First: \_\_\_\_\_ Last: \_\_\_\_\_

PED<sub>UE</sub> and PED<sub>LE</sub> #reps: 128

FING and FOOT #reps: 104

## Experimental Protocol

Run #	Task condition	#reps	File name
1	PED <sub>LE</sub>	128	
2	PED <sub>LE</sub>	128	
3	PED <sub>LE</sub>	128	
4	SPGR		
5	PED <sub>UE</sub>	128	
6	PED <sub>UE</sub>	128	
7	PED <sub>UE</sub>	128	
8	SPGR		
9	Left FING	104	
10	Right FING	104	
11	Left FOOT	104	
12	Right FOOT	104	

**APPENDIX C      SCREENING FORM**

All subjects were screened for MR safety prior to the experiment; this section presents a copy of the MR screening form for human subjects.

### MAGNETIC RESONANCE IMAGING (MRI) SCREENING FORM FOR HUMAN SUBJECTS

*Note: If Participant /Subject has completed this form for previous MRI scanning session, indicate information has been reviewed by entering today's date and initials below*

Date \_\_\_\_/\_\_\_\_/\_\_\_\_ Participant Number \_\_\_\_\_

Name \_\_\_\_\_ Age \_\_\_\_\_ Height \_\_\_\_\_ Weight \_\_\_\_\_  
Last name First name Middle initial

Date of Birth \_\_\_\_/\_\_\_\_/\_\_\_\_ Male  Female  Body part to be examined \_\_\_\_\_

Address \_\_\_\_\_ Telephone (home) (\_\_\_\_) \_\_\_\_-\_\_\_\_

City \_\_\_\_\_ Telephone (work) (\_\_\_\_) \_\_\_\_-\_\_\_\_

State \_\_\_\_\_ Zip code \_\_\_\_\_

Reason for MRI and/or symptoms \_\_\_\_\_

Referring physician \_\_\_\_\_ Telephone (\_\_\_\_) \_\_\_\_-\_\_\_\_

1. Have you had prior surgery or an operation (e.g., arthroscopy, endoscopy, etc.) of any kind?  No  Yes

If yes, please indicate the date and type of surgery: Date \_\_\_\_/\_\_\_\_/\_\_\_\_ Type of surgery \_\_\_\_\_

2. Have you had a prior diagnostic imaging study or examination (MRI, CT, ultrasound, etc.)?  No  Yes

If yes, please list: Body part \_\_\_\_\_ Date \_\_\_\_/\_\_\_\_/\_\_\_\_ Facility \_\_\_\_\_

MRI \_\_\_\_\_

CT/CAT scan \_\_\_\_\_

X-ray \_\_\_\_\_

Ultrasound \_\_\_\_\_

Nuclear Medicine \_\_\_\_\_

Other \_\_\_\_\_

3. Have you experienced any problem related to a previous MRI examination or MR procedure?  No  Yes

If yes, please describe: \_\_\_\_\_

4. Have you had an injury to the eye involving a metallic object or fragment (e.g., metallic slivers, shavings, foreign body, etc.)?  No  Yes

If yes, please describe: \_\_\_\_\_

5. Have you ever been injured by a metallic object or foreign body (BB, bullet, shrapnel, etc.)?  No  Yes

If yes, please describe: \_\_\_\_\_

6. Are you currently taking or have you recently taken any medication or drug?  No  Yes

If yes, please list: \_\_\_\_\_

7. Are you allergic to any medication?  No  Yes

If yes, please list: \_\_\_\_\_

8. Do you have a history of asthma, allergic reaction, respiratory disease, or reaction to a contrast medium or dye used for an MRI, CT, or X-ray examination?  No  Yes

9. Do you have anemia or any disease(s) that affects your blood, a history of renal (kidney) disease, or seizures?  No  Yes

If yes, please describe: \_\_\_\_\_

For female participants:

10. Date of last menstrual period: \_\_\_\_/\_\_\_\_/\_\_\_\_ Post menopausal?  No  Yes

11. Are you pregnant or experiencing a late menstrual period?  No  Yes

12. Are you taking oral contraceptives or receiving hormonal treatment?  No  Yes

13. Are you taking any type of fertility medication or having fertility treatments?  No  Yes

If yes, please describe: \_\_\_\_\_

14. Are you currently breastfeeding?  No  Yes

*Information has been reviewed, and any and all changes since previous MR study are noted.*

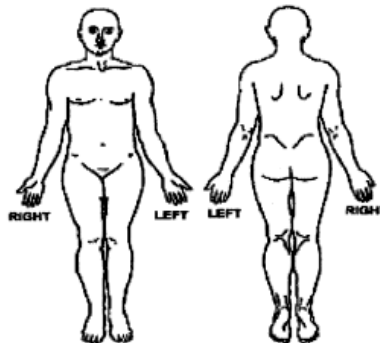
Date _____	Participant initials _____	Screener initials _____
Date _____	Participant initials _____	Screener initials _____
Date _____	Participant initials _____	Screener initials _____
Date _____	Participant initials _____	Screener initials _____
Date _____	Participant initials _____	Screener initials _____

**WARNING:** Certain implants, devices, or objects may be hazardous to you and/or may interfere with the MR procedure (i.e., MRI, MR angiography, functional MRI, MR spectroscopy). **Do not enter** the MR system room or MR environment if you have any question or concern regarding an implant, device or object. Consult the MRI Technologist or Radiologist **BEFORE** entering the MR system room. **The MR system magnet is ALWAYS ON.**

Please indicate if you have any of the following:

- Yes  No Aneurysm clip(s)
- Yes  No Cardiac pacemaker
- Yes  No Implanted cardioverter defibrillator (ICD)
- Yes  No Electronic implant or device
- Yes  No Magnetically-activated implant or device
- Yes  No Neurostimulation system
- Yes  No Spinal cord stimulator
- Yes  No Internal electrodes or wires
- Yes  No Bone growth/bone fusion stimulator
- Yes  No Cochlear, otologic, or other ear implant
- Yes  No Insulin or other infusion pump
- Yes  No Implanted drug infusion device
- Yes  No Any type of prosthesis (eye, penile, etc.)
- Yes  No Heart valve prosthesis
- Yes  No Eyelid spring or wire
- Yes  No Artificial or prosthetic limb
- Yes  No Metallic stent, filter, or coil
- Yes  No Shunt (spinal or intraventricular)
- Yes  No Vascular access port and/or catheter
- Yes  No Radiation seeds or implants
- Yes  No Swan-Ganz or thermodilution catheter
- Yes  No Medication patch (Nicotine, Nitroglycerine)
- Yes  No Any metallic fragment or foreign body
- Yes  No Wire mesh implant
- Yes  No Tissue expander (e.g., breast)
- Yes  No Surgical staples, clips, or metallic sutures
- Yes  No Joint replacement (hip, knee, etc.)
- Yes  No Bone/joint pin, screw, nail, wire, plate, etc.
- Yes  No IUD, diaphragm, or pessary
- Yes  No Dentures or partial plates
- Yes  No Tattoo or permanent makeup
- Yes  No Body piercing jewelry
- Yes  No Hearing aid  
*(Remove before entering MR system room)*
- Yes  No Other implant \_\_\_\_\_
- Yes  No Breathing problem or motion disorder
- Yes  No Claustrophobia

Please mark on the figure(s) below the location of any implant or metal inside of or on your body.



**IMPORTANT INSTRUCTIONS**

Before entering the MR environment or MR system room, you must remove **all** metallic objects including hearing aids, dentures, partial plates, keys, beeper, cell phone, eyeglasses, hair pins, barrettes, jewelry, body piercing jewelry, watch, safety pins, paperclips, money clip, credit cards, bank cards, magnetic strip cards, coins, pens, pocket knife, nail clipper, tools, clothing with metal fasteners, and clothing with metallic threads.

Please consult the MRI Technologist or Radiologist if you have any questions or concerns **BEFORE** you enter the MR system room.

**NOTE:** You are required to wear earplugs or other hearing protection during the MR procedure to prevent possible problems or hazards related to acoustic noise.

I attest that the above information is correct to the best of my knowledge. I read and understand the contents of this form and had the opportunity to ask questions regarding the information on this form and regarding the MR procedure that I am about to undergo.

Signature of Person Completing Form: \_\_\_\_\_ Date / / \_\_\_\_\_  
Signature

Form completed by:  
 Participant  Relative  Nurse  Other \_\_\_\_\_  
 Print name Relationship to participant

Form Information Reviewed By: \_\_\_\_\_  
 Print name Signature  
 MRI Technologist  Nurse  Radiologist  Other \_\_\_\_\_

## APPENDIX D HEAD MOVEMENT --- HEALTHY SUBJECTS

### Head Movement for Neurologically Intact Subjects

This section provides a pictorial representation of head movement averaged across 7 neurologically intact subjects during the 6 tasks. The movement is expressed in six directions: roll, pitch, yaw, superior-to-inferior, left-to-right, and anterior-to-posterior. The graphs display mean and standard deviation of the head movement between subjects during the six tasks.

X-axes in the figure represent the number of TRs with all 3 runs concatenated together. Y-axes are the amount of movement (degrees for rotational movement and mm for translational movement) with negative values implying movement in the inferior, right and posterior directions. Figures are presented in the following order:

Head movement during PED<sub>UE</sub>

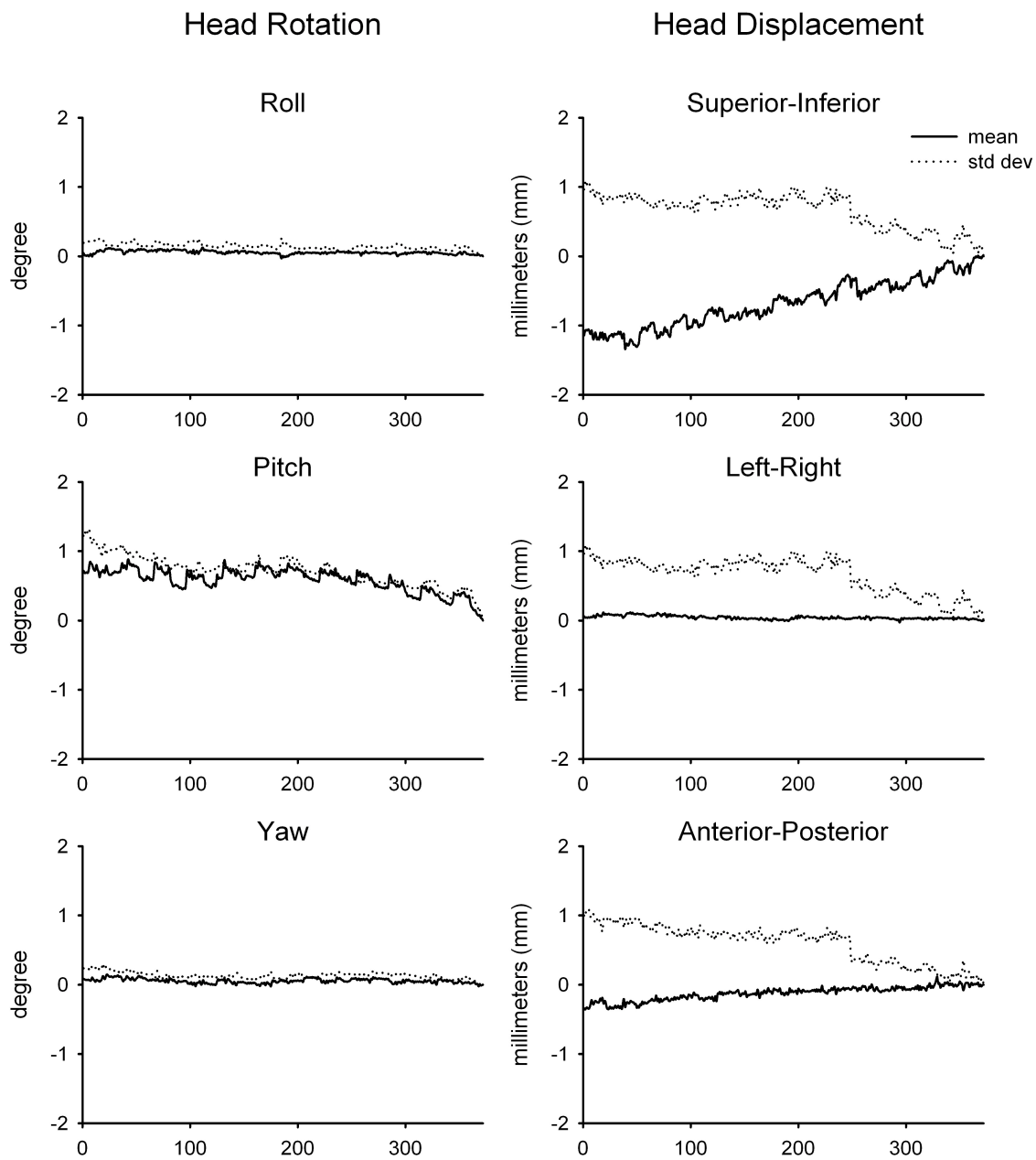
Head movement during PED<sub>LE</sub>

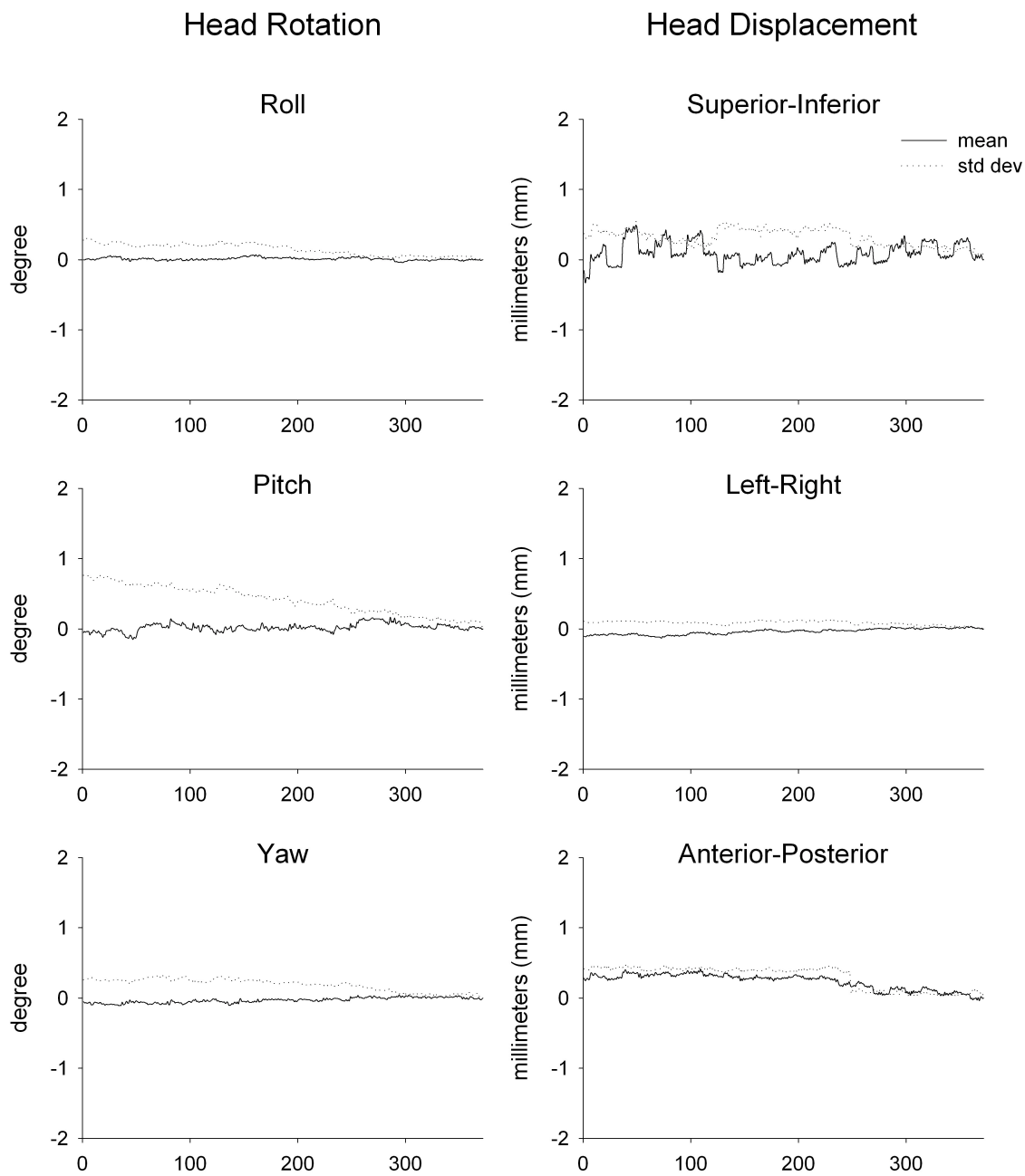
Head movement during left FING

Head movement during right FING

Head movement during left FOOT

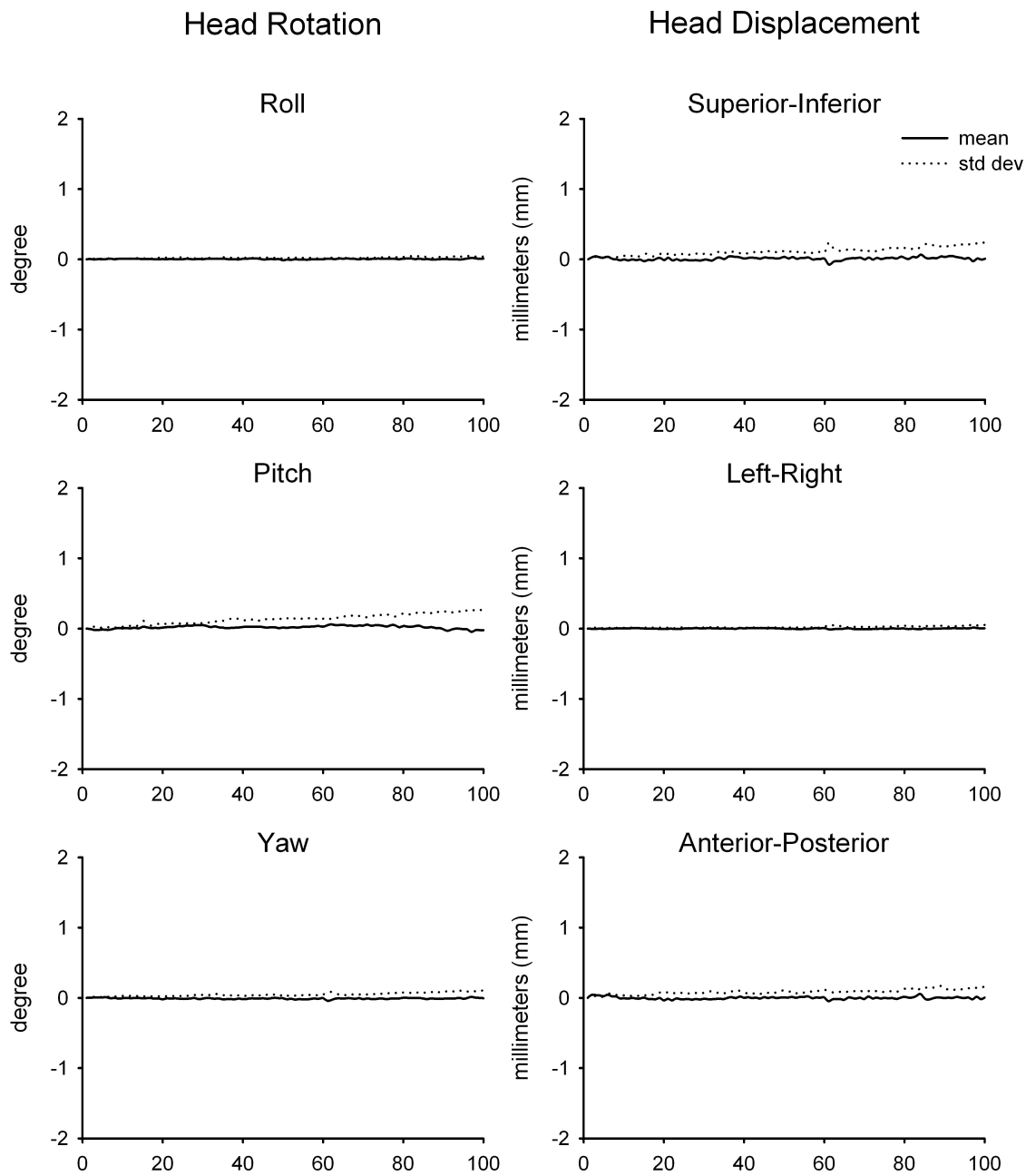
Head movement during right FOOT

Head movement during PED<sub>UE</sub>

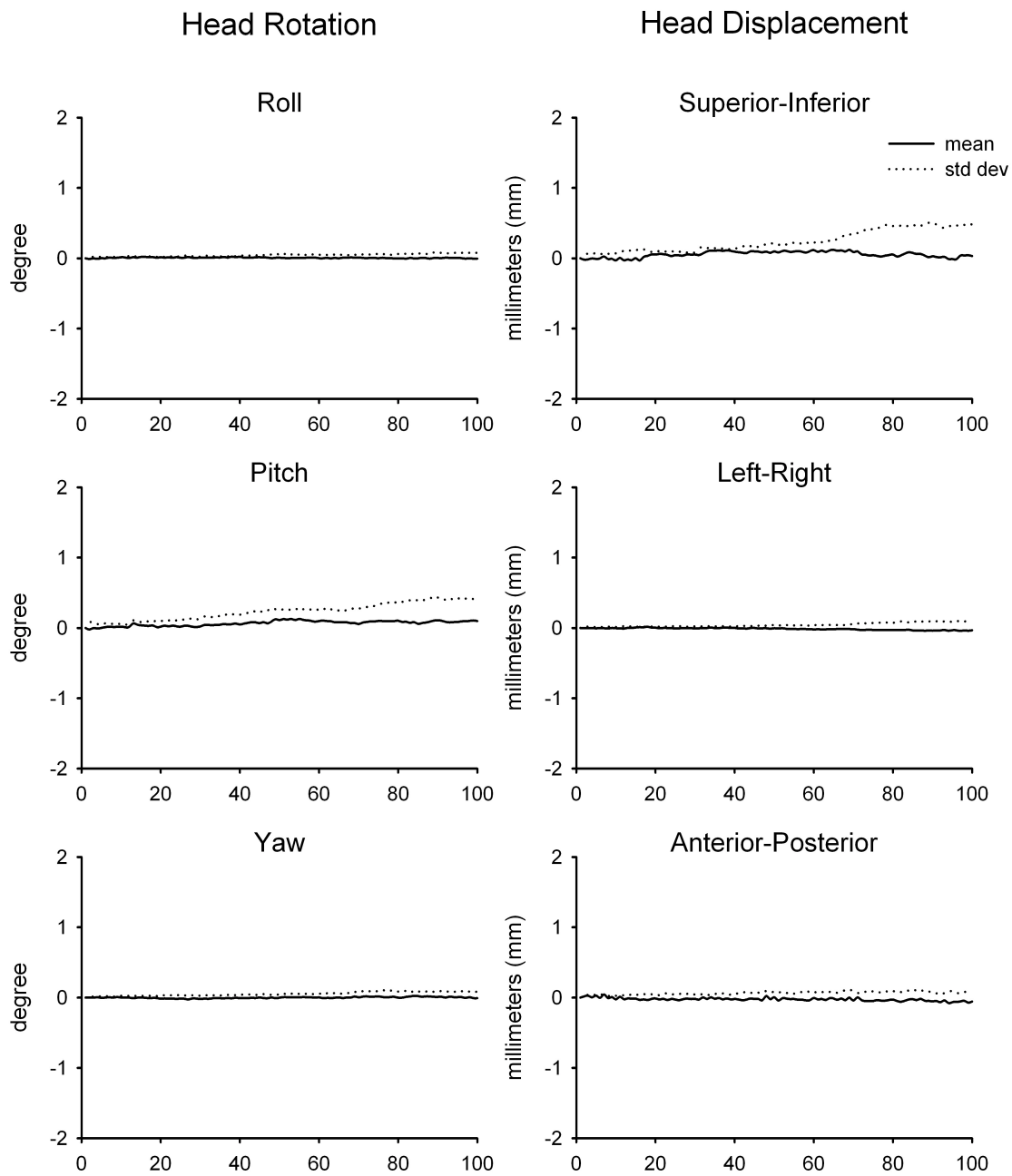
Head movement during PED<sub>LE</sub>



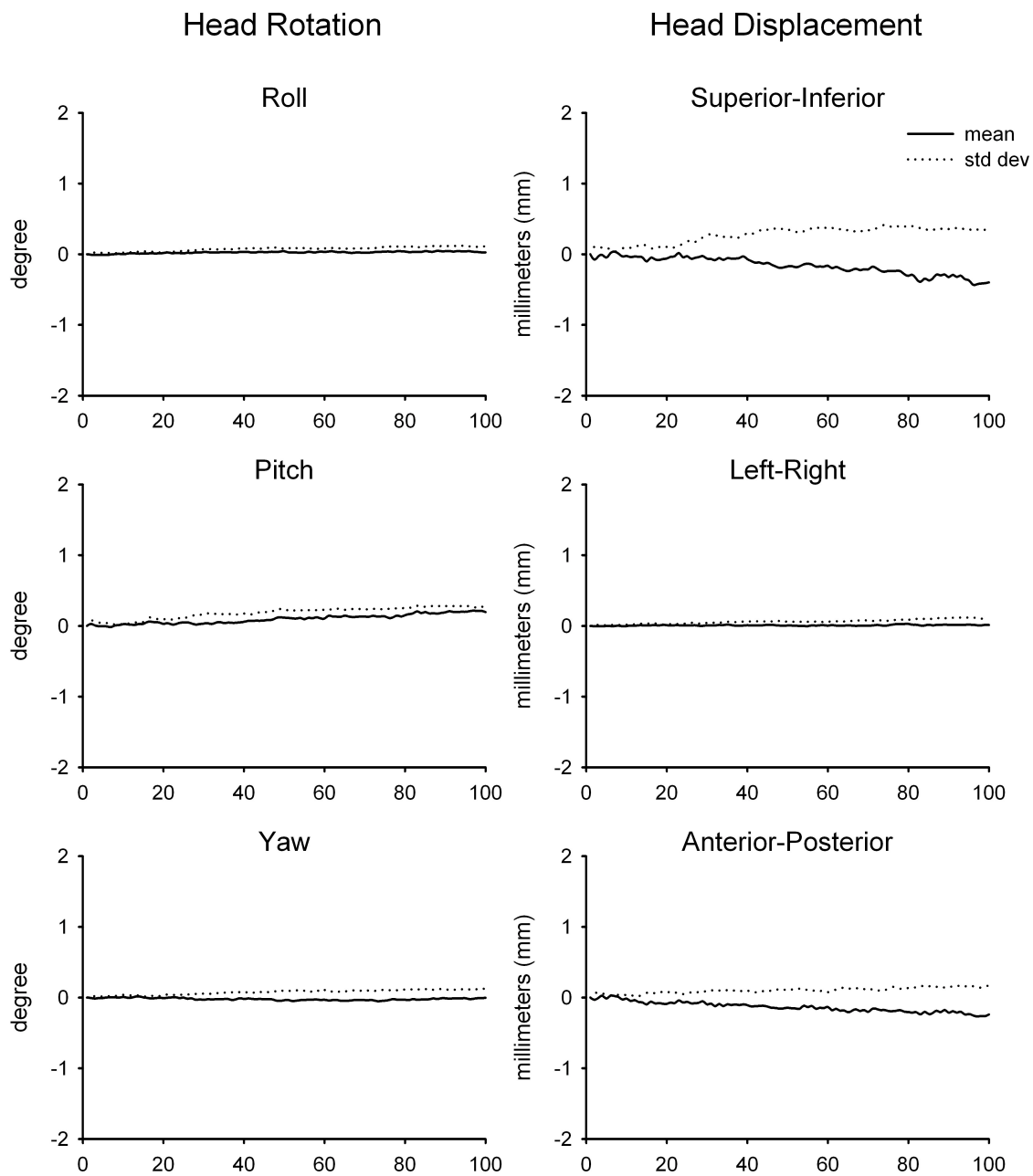
## Head movement during left FING



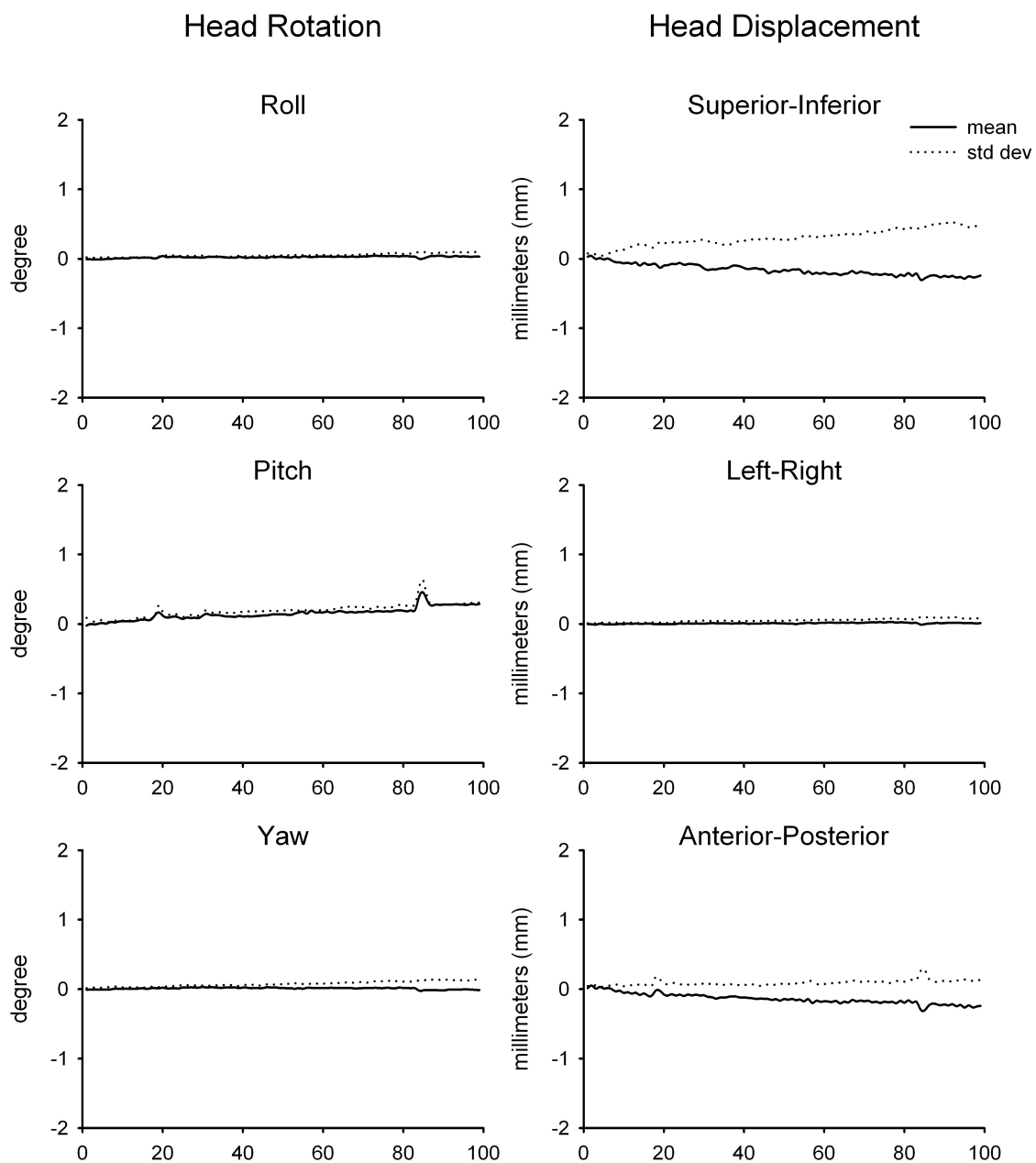
## Head movement during right FING



## Head movement during left FOOT



## Head movement during right FOOT



**APPENDIX E      HEAD MOVEMENT FOR STROKE SUBJECTS**

This section provides head movement for each of the 4 stroke subjects during the 6 tasks. The movement is expressed in six directions as shown in APPENDIX D: roll, pitch, yaw, superior-to-inferior, left-to-right, and anterior-to-posterior. Since the head movement of stroke subjects varied, figures for each subject are presented.

Head movement during PED<sub>UE</sub>

Head movement during PED<sub>LE</sub>

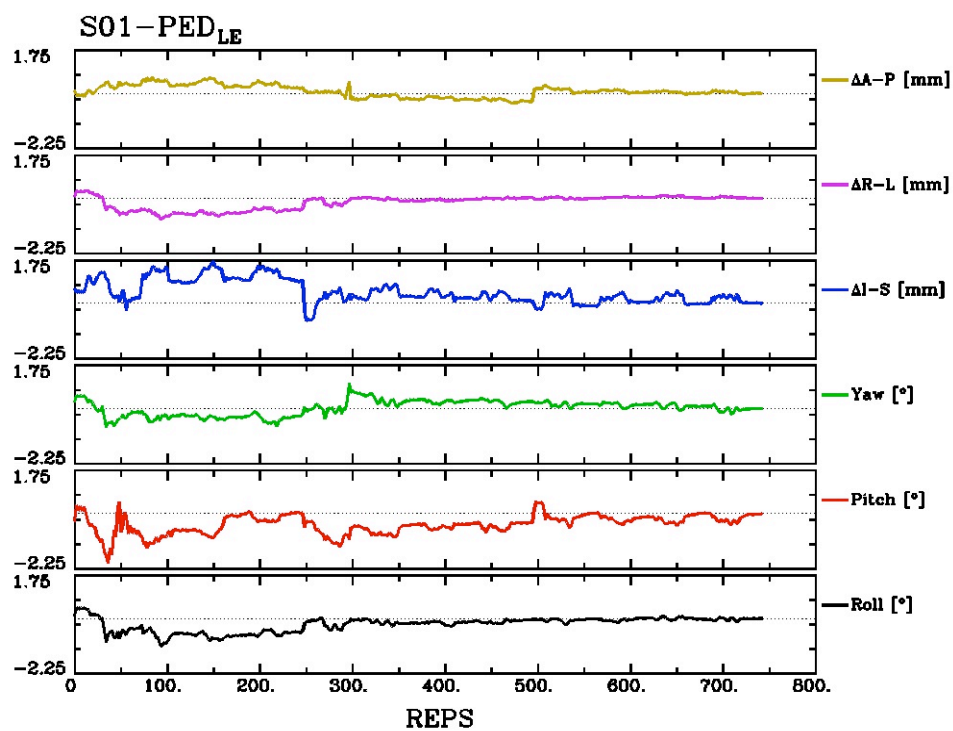
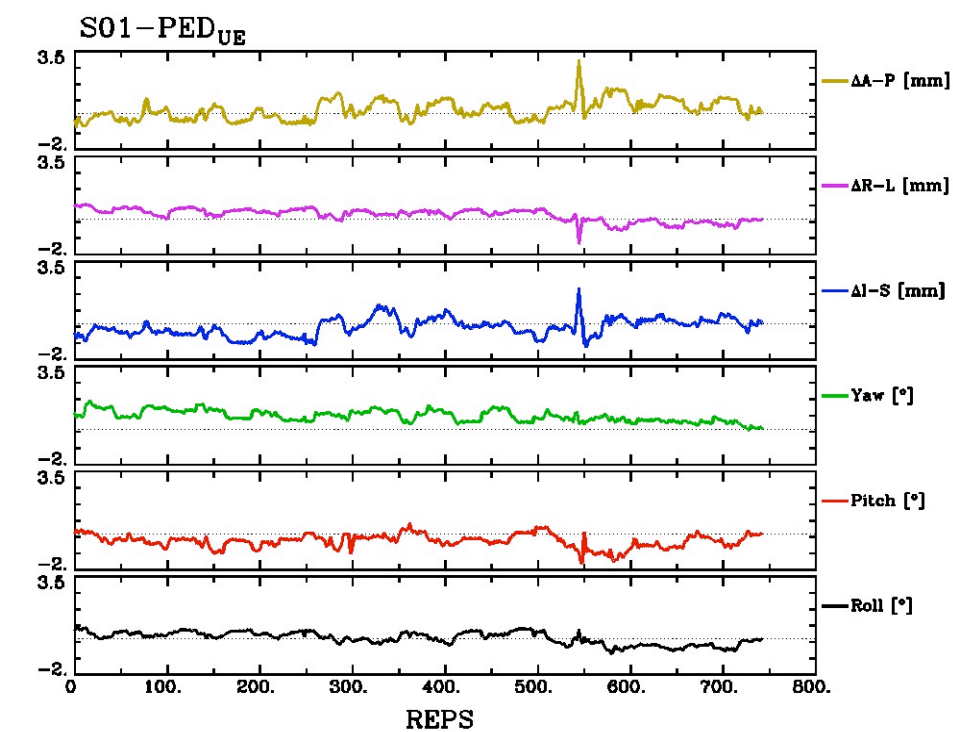
Head movement during paretic FING

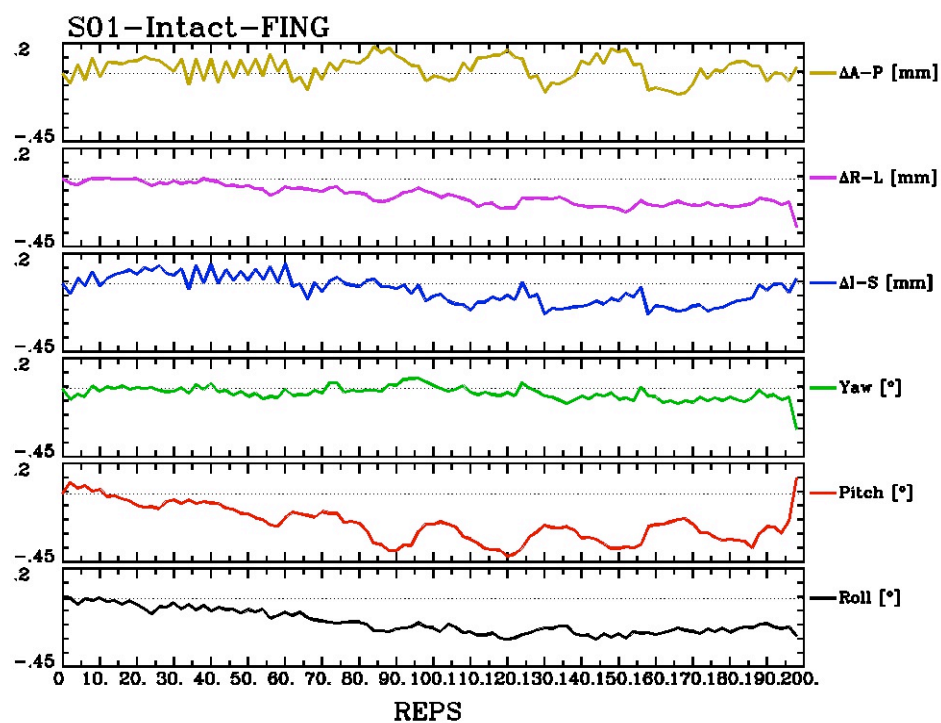
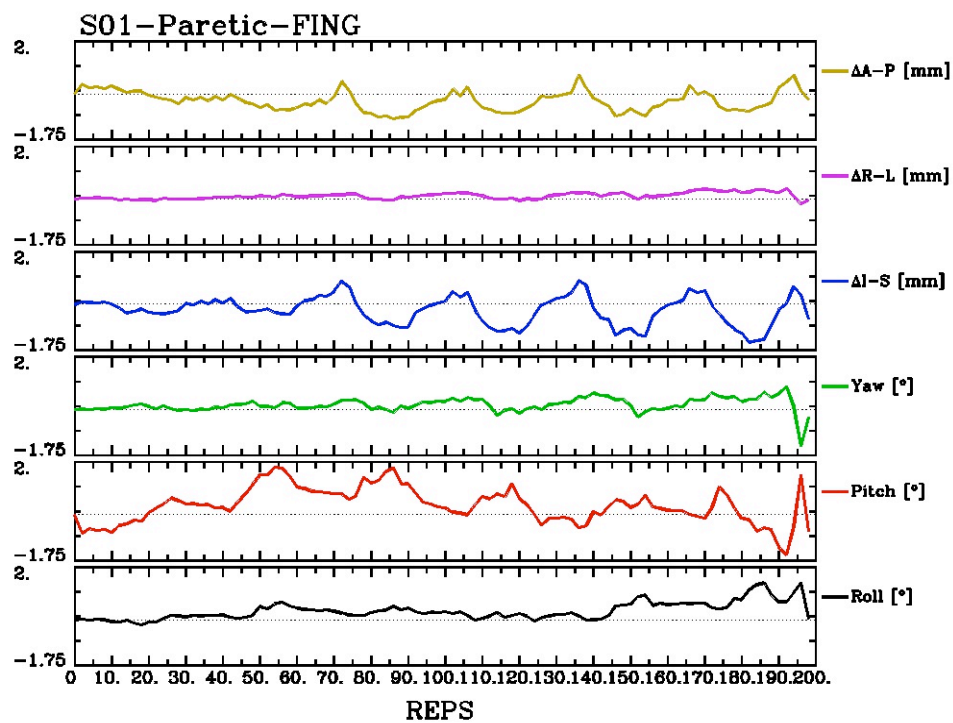
Head movement during non-paretic FING

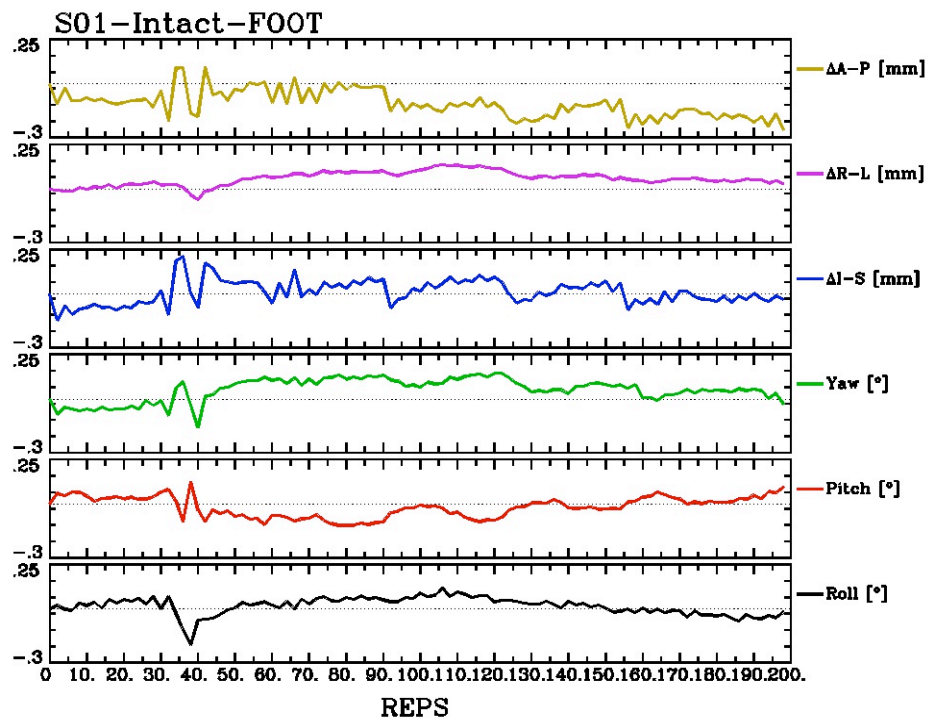
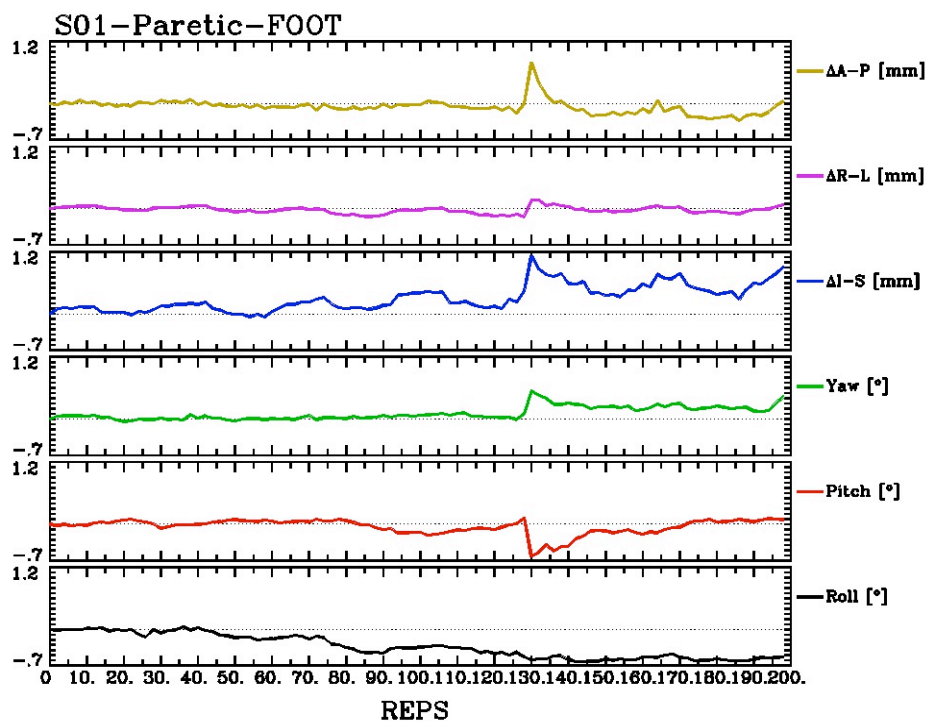
Head movement during paretic FOOT

Head movement during non-paretic FOOT

## Head movement (S01)

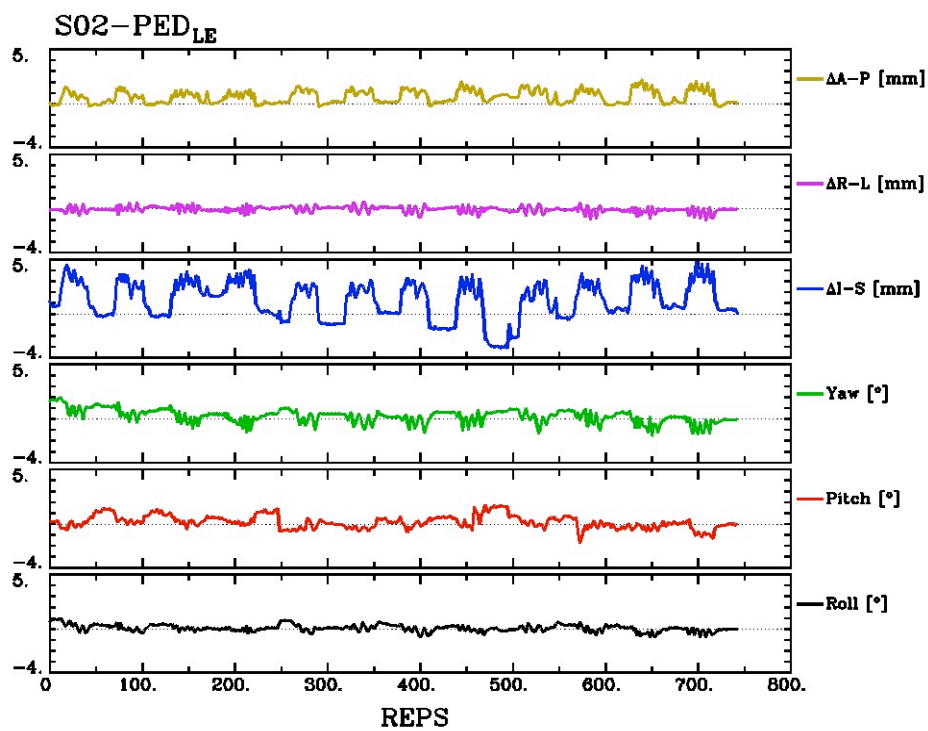
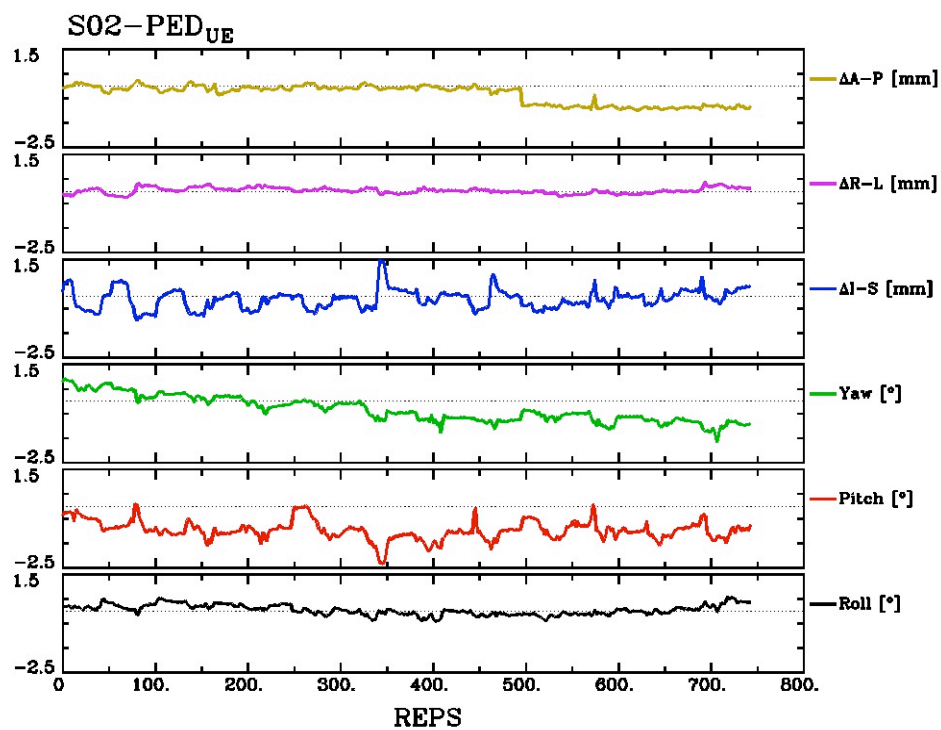


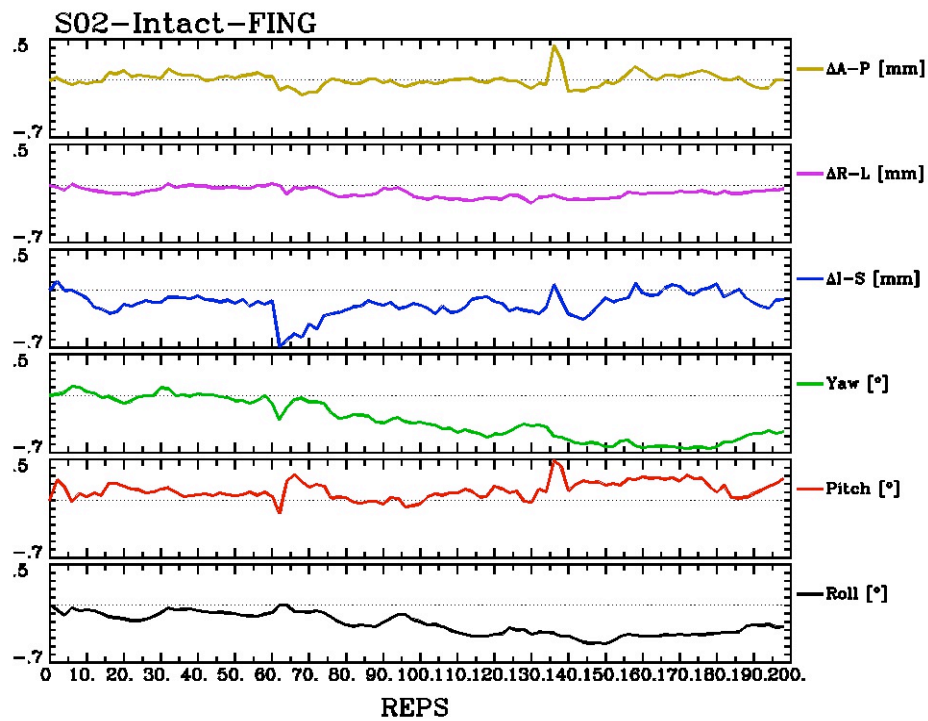
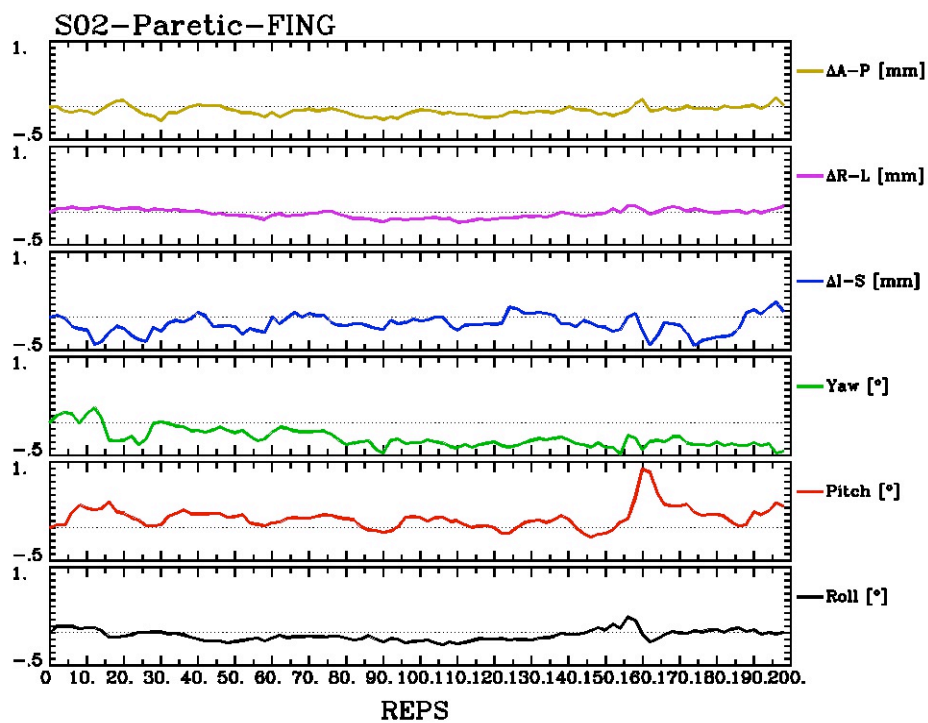


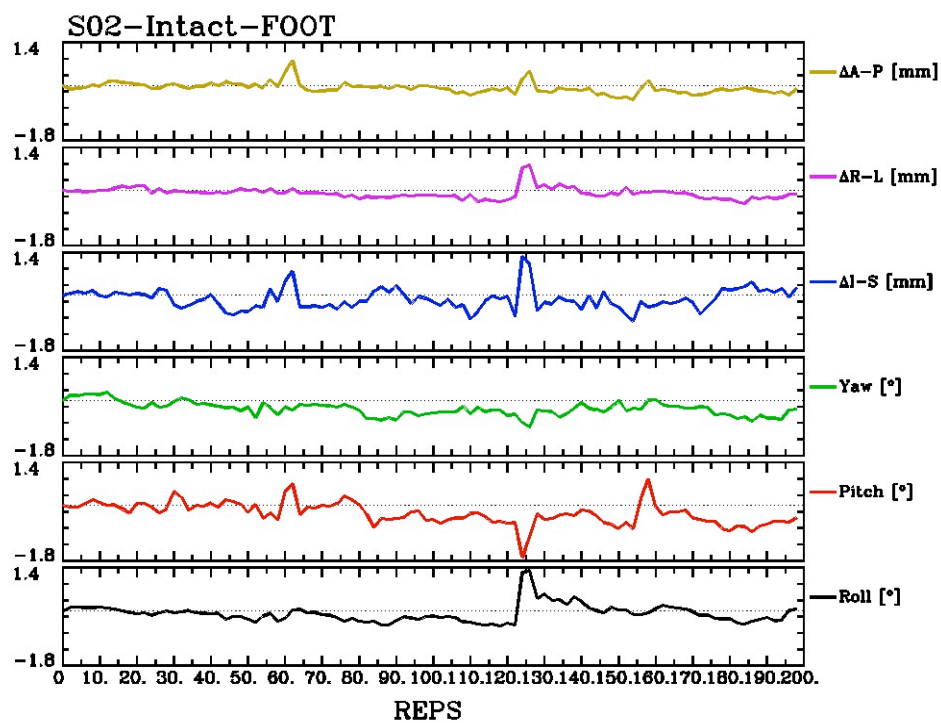
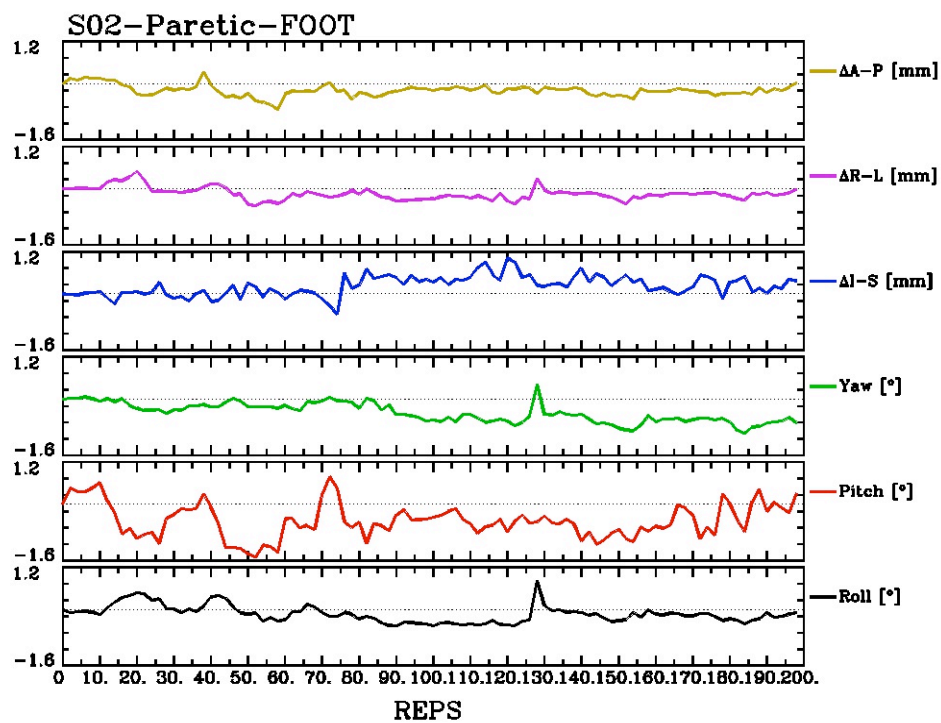




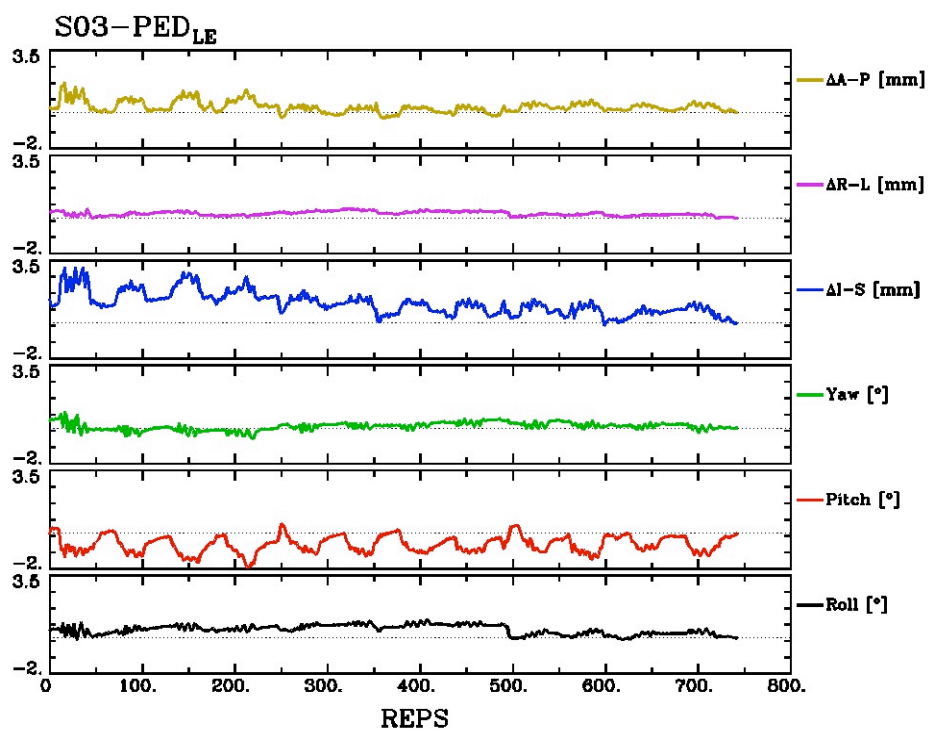
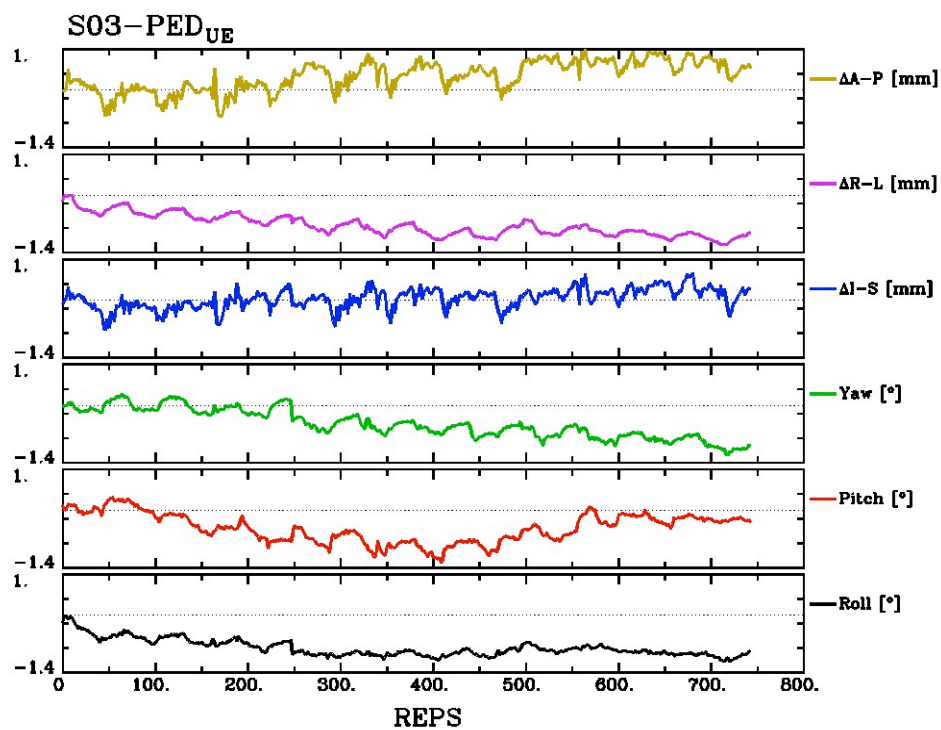
## Head movement (S02)

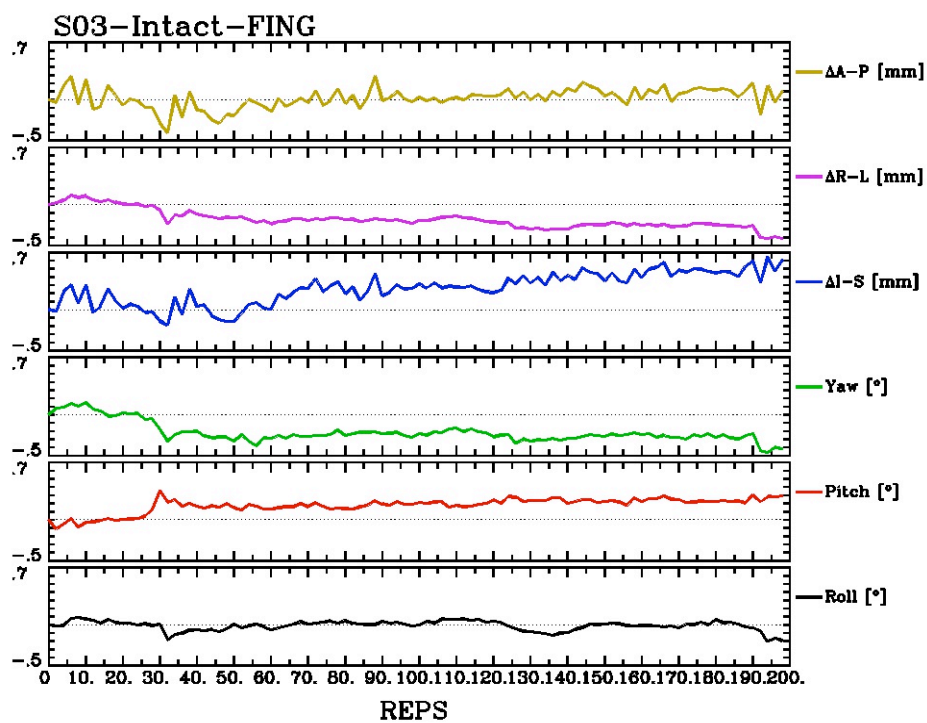
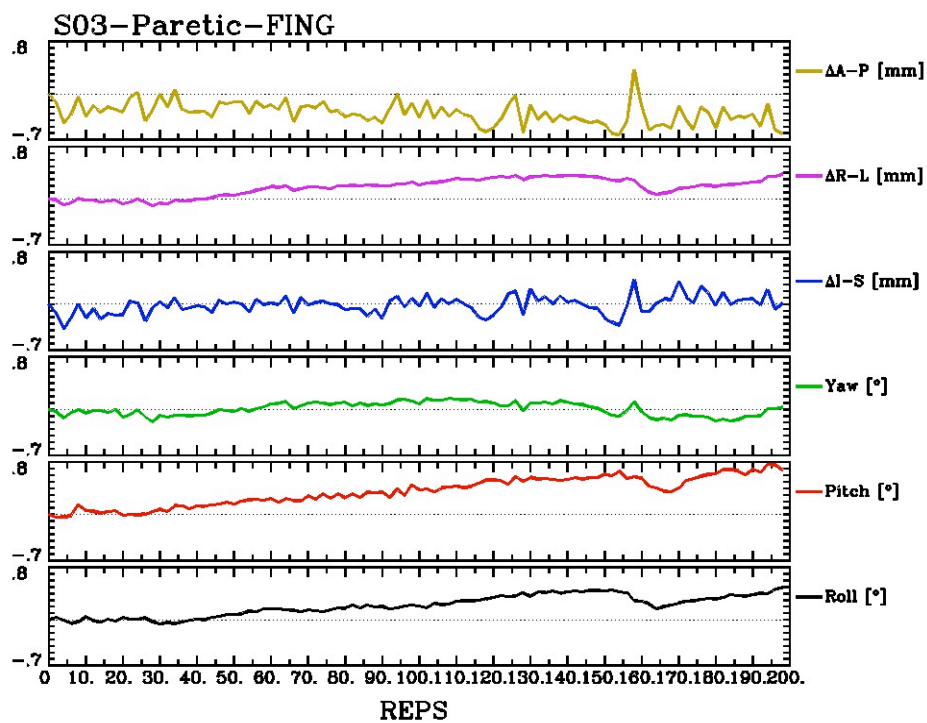


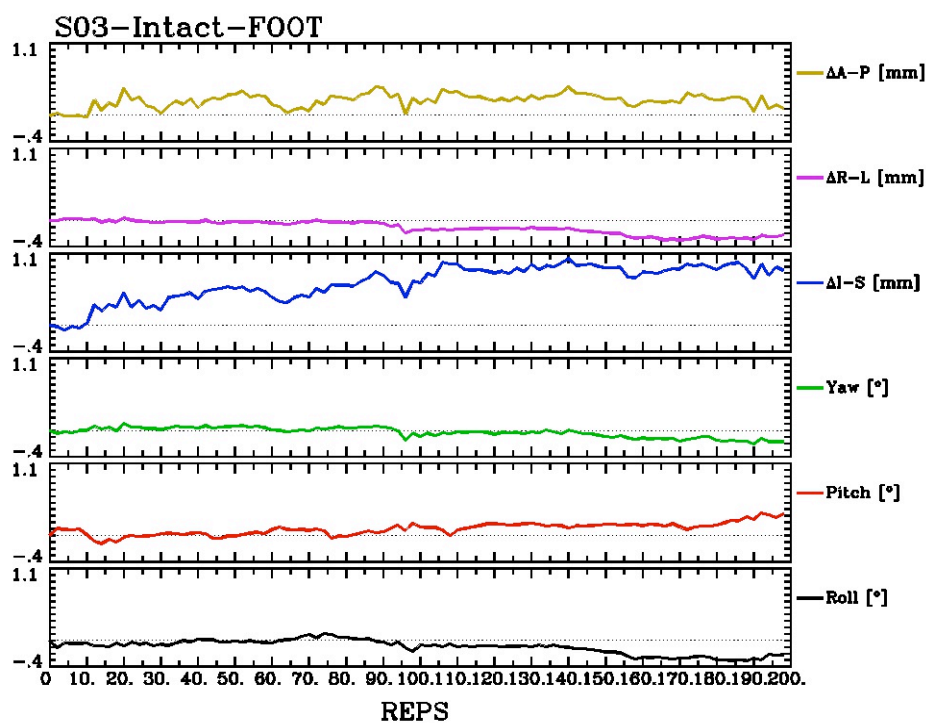
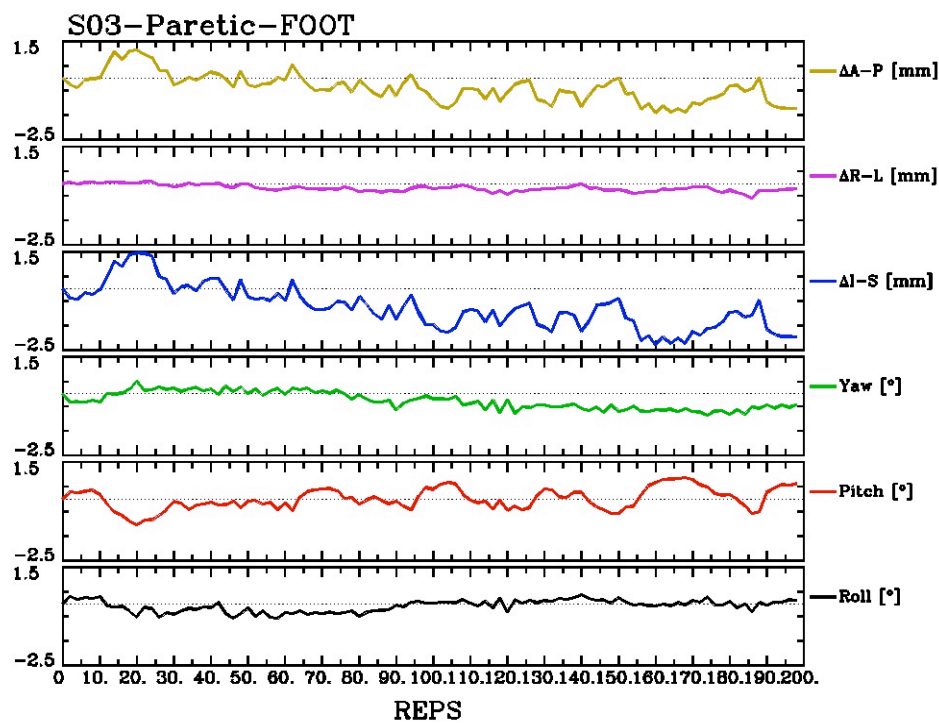




## Head movement (S03)

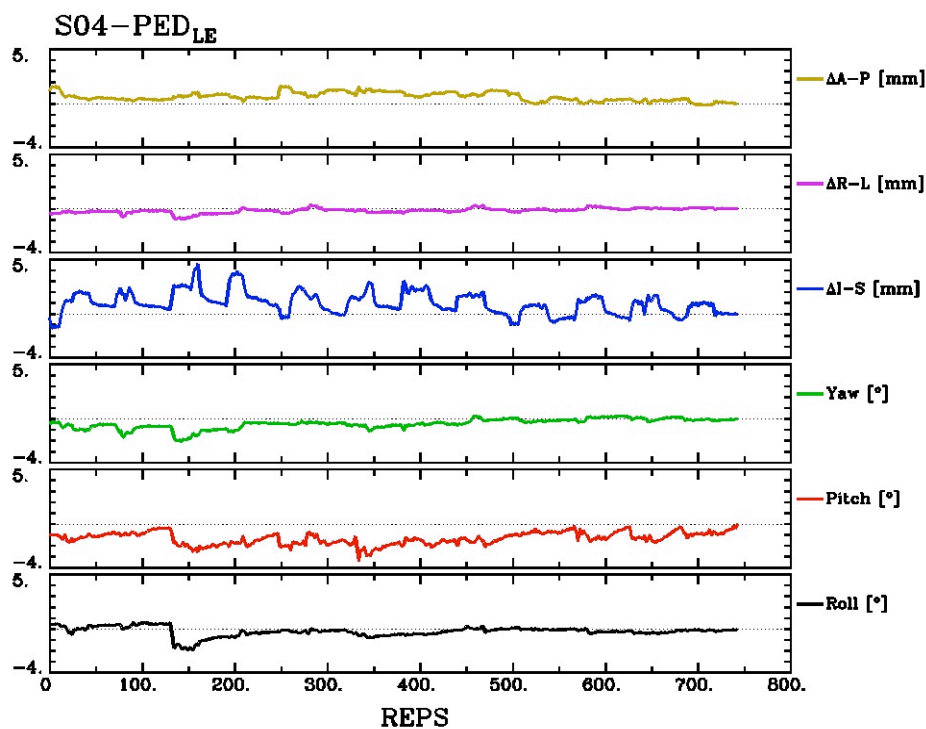
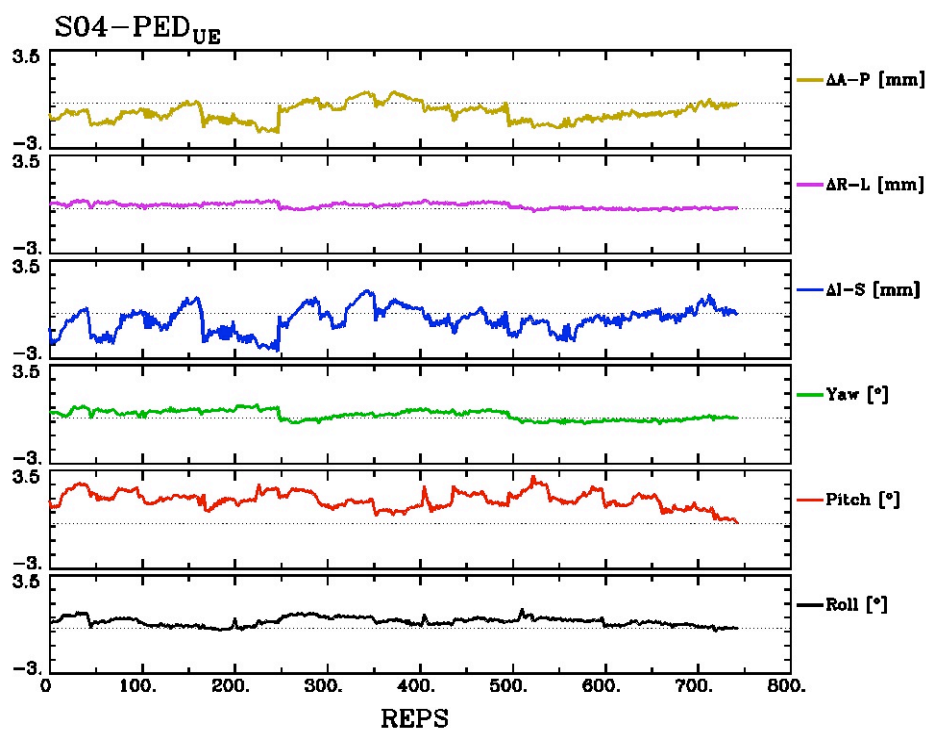


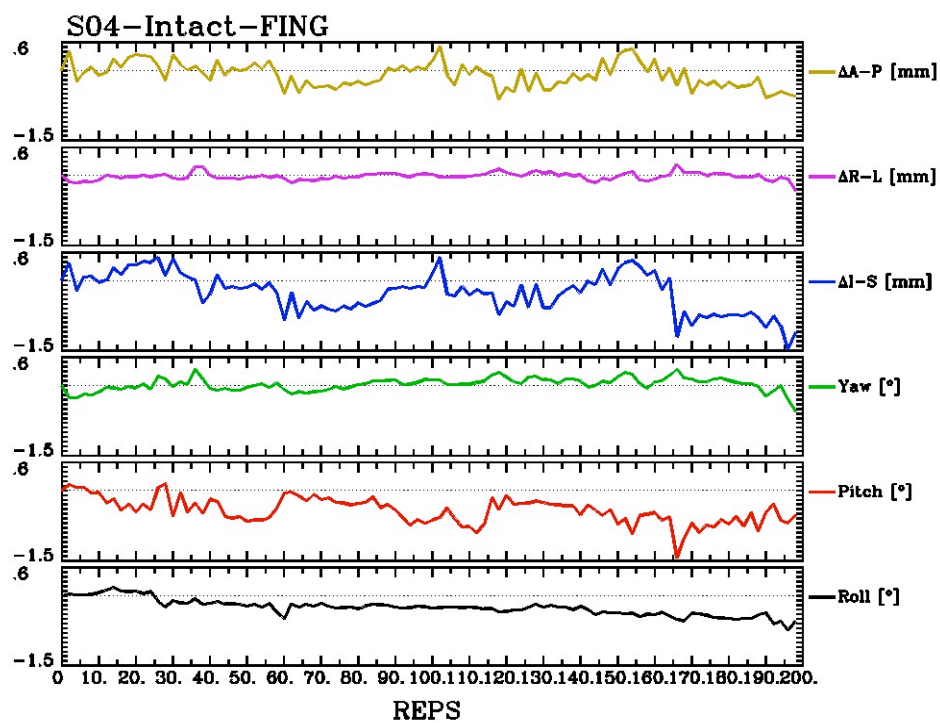
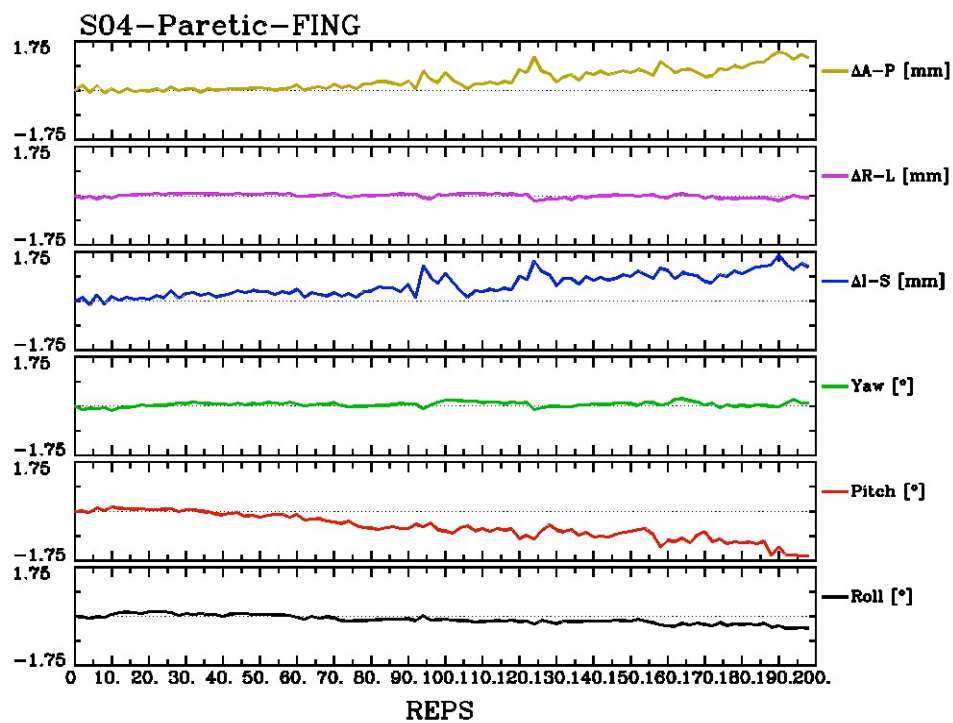




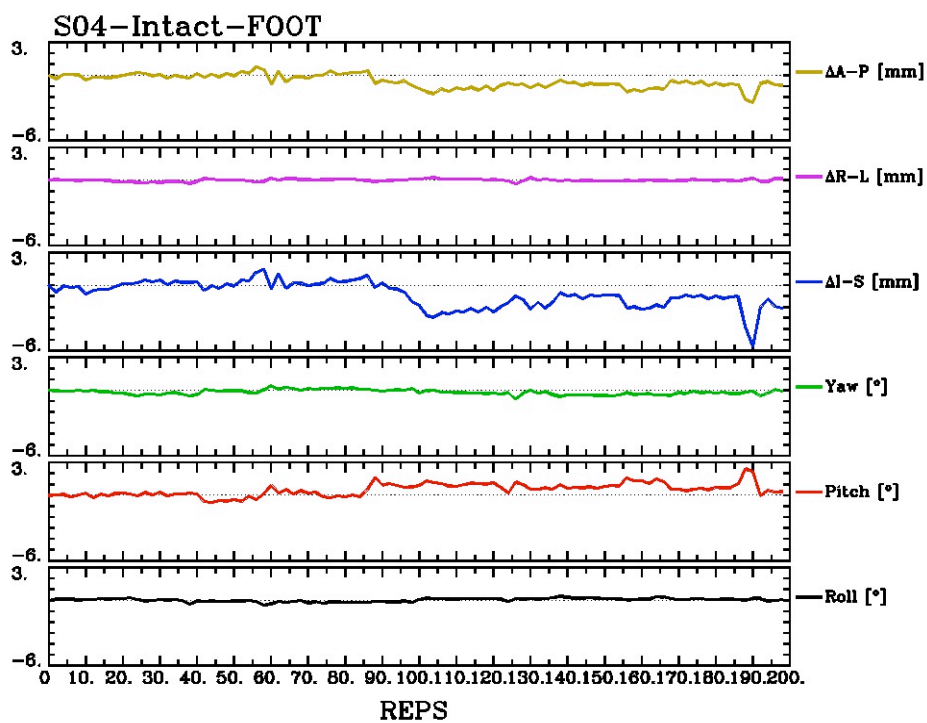
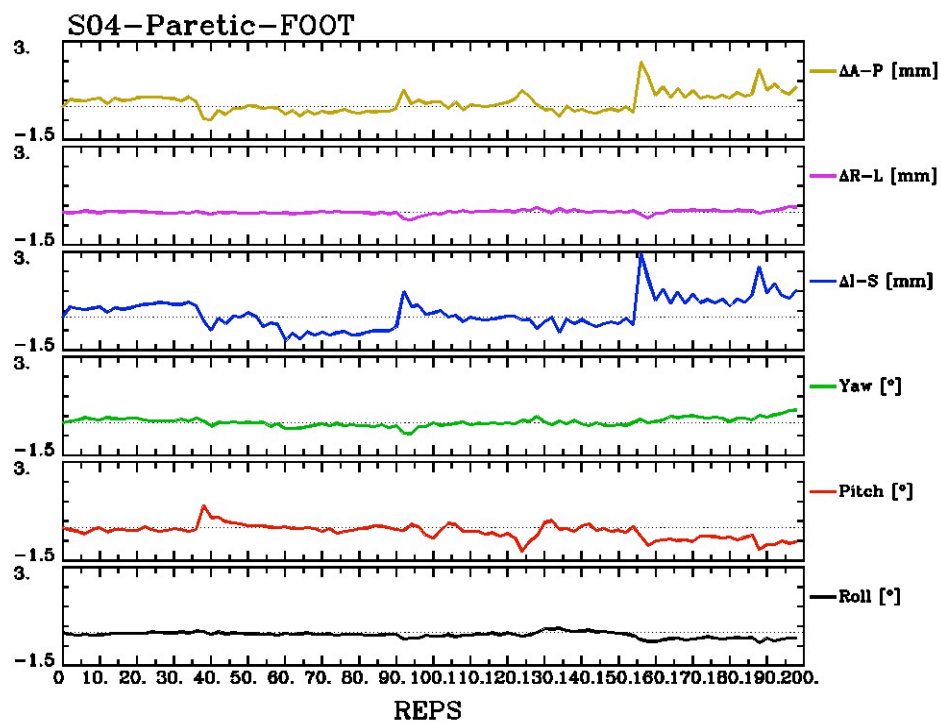


## Head movement (S04)









**APPENDIX F            CODES USED IN AFNI TO PROCESS FMRI DATA**

```
#!/bin/csh

cd
cd documents/ctsi/Nov2

set sub_IDs = (sub_1 sub_2 sub_3 sub_5 sub_6 sub_7 sub_9)
foreach condition ( $sub_IDs )

cd $sub_ID

3dTshift \
-verb \
-tzero 0 \
-prefix Arm_pedal_tshift_01 \
-ignore 4 \
-Fourier \
arm_pedal_01+orig

3dTshift \
-verb \
-tzero 0 \
-prefix Arm_pedal_tshift_02 \
-ignore 4 \
-Fourier \
arm_pedal_02+orig

3dTshift \
-verb \
-tzero 0 \
-prefix Arm_pedal_tshift_03 \
-ignore 4 \
-Fourier \
arm_pedal_03+orig

3dTcat \
arm_pedal_tshift_01+orig'[4..127]' \
arm_pedal_tshift_02+orig'[4..127]' \
arm_pedal_tshift_03+orig'[4..127]' \
-prefix arm_pedal_tshift
```

```

align_epi_anat.py \
-epi arm_pedal_tshift+orig \
-anat anat_pedal+orig \
-epi_base 371 \
-epi2anat \
-tshift off \
-volreg on

```

```

3dDeconvolve \
-float \
-input arm_pedal_tshift_al+orig \
-polort A \
-num_stimts 7 \
-concat concat.pedal.372 \
-censor Mcensor372.1D \
-stim_file 1 Mcanonical372.1D \
-stim_minlag 1 0 \
-stim_maxlag 1 0 \
-stim_label 1 arm_pedal \
-stim_file 2 arm_pedal_tshift_vr_motion.1D'[0]' -stim_base 2 -stim_label 2 roll \
-stim_file 3 arm_pedal_tshift_vr_motion.1D'[1]' -stim_base 3 -stim_label 3 pitch \
-stim_file 4 arm_pedal_tshift_vr_motion.1D'[2]' -stim_base 4 -stim_label 4 yaw \
-stim_file 5 arm_pedal_tshift_vr_motion.1D'[3]' -stim_base 5 -stim_label 5 dS \
-stim_file 6 arm_pedal_tshift_vr_motion.1D'[4]' -stim_base 6 -stim_label 6 dL \
-stim_file 7 arm_pedal_tshift_vr_motion.1D'[5]' -stim_base 7 -stim_label 7 dP \
\
-fitts arm_pedal_tshift.fitts_decline \
-errts arm_pedal_tshift.errts_decline \
-fout \
-tout \
-bout \
-full_first \
-bucket arm_pedal_tshift.bucket_decline

```

```
sh arm_pedal_tshift.REML_cmd
```

```

3dFWHMx \
-dset arm_pedal_tshift.errts_decline+orig \
-mask anat_pedal_1500_bigvoxels.mask+orig \
-out arm_pedal_censor.tshift.cat.FWHMx.

```

```

3dmerge \
-1thresh 2.839 \

```

```
-lclust 6.6 393 \
-lindex 1 \
-ltindex 2 \
-prefix arm_pedal_cluster \
arm_pedal_tshift.bucket_decline_REML+orig
```

```
3dcalc \
-fscale \
-a arm_pedal_tshift.bucket_decline+orig'[1]' \
-b arm_pedal_tshift.bucket_decline+orig'[7]' \
-c arm_pedal_tshift.bucket_decline+orig'[13]' \
-g arm_pedal_tshift.bucket_decline+orig'[19]' \
-expr "100 * (g/((a+b+c)/3)) * step( 1 - abs( (g/((a+b+c)/3)) ) )" \
-prefix arm_pedal"$sub_ID"._tshift.bucket_decline.PSC
```

```
3dcalc \
-a arm_pedal"$sub_ID"._tshift.bucket_decline.PSC+orig \
-b arm_pedal_tshift.bucket_decline_REML+orig \
-expr "b/b*a" \
-prefix arm_pedal"$sub_ID"._tshift.bucket.figure
```

```
3dcalc \
-a arm_pedal"$sub_ID"._tshift.bucket_decline.PSC+orig \
-expr "a*within(a,0,10)" \
-prefix arm_pedal"$sub_ID"._tshift.bucket_decline.cutoff.PSC
```

```
3dcalc \
-a left_M1_second_bigvoxels.mask+orig \
-b arm_pedal"$sub_ID"._tshift.bucket_decline.cutoff.PSC+orig \
-c arm_pedal"$sub_ID"._tshift.bucket_decline_REML_3dmerge+orig \
-expr 'a*b*c/c' \
-prefix arm_pedal"$sub_ID"._tshift.bucket_decline.PSC.left.M1
```

```
3dcalc \
-a right_M1_second_bigvoxels.mask+orig \
-b arm_pedal"$sub_ID"._tshift.bucket_decline.cutoff.PSC+orig \
-c arm_pedal"$sub_ID"._tshift.bucket_decline_REML_3dmerge+orig \
-expr 'a*b*c/c' \
-prefix arm_pedal"$sub_ID"._tshift.bucket_decline.PSC.right.M1
```

```
3dcalc \
```

```

-a left_S1_second_bigvoxels.mask+orig \
-b arm_pedal"$sub_ID"._tshift.bucket_decline.cutoff.PSC+orig \
-c arm_pedal"$sub_ID"._tshift.bucket_decline_REML_3dmerge+orig \
-expr 'a*b*c/c' \
-prefix arm_pedal"$sub_ID"._tshift.bucket_decline.PSC.left.S1

3dcalc \
-a right_S1_second_bigvoxels.mask+orig \
-b arm_pedal"$sub_ID"._tshift.bucket_decline.cutoff.PSC+orig \
-c arm_pedal"$sub_ID"._tshift.bucket_decline_REML_3dmerge+orig \
-expr 'a*b*c/c' \
-prefix arm_pedal"$sub_ID"._tshift.bucket_decline.PSC.right.S1

3dcalc \
-a left_area_6_second_bigvoxels.mask+orig \
-b arm_pedal"$sub_ID"._tshift.bucket_decline.cutoff.PSC+orig \
-c arm_pedal"$sub_ID"._tshift.bucket_decline_REML_3dmerge+orig \
-expr 'a*b*c/c' \
-prefix arm_pedal"$sub_ID"._tshift.bucket_decline.PSC.left.area_6

3dcalc \
-a right_area_6_second_bigvoxels.mask+orig \
-b arm_pedal"$sub_ID"._tshift.bucket_decline.cutoff.PSC+orig \
-c arm_pedal"$sub_ID"._tshift.bucket_decline_REML_3dmerge+orig \
-expr 'a*b*c/c' \
-prefix arm_pedal"$sub_ID"._tshift.bucket_decline.PSC.right.area_6

cd ..

end

set sub_IDs=( sub_1 sub_2 sub_3 sub_5 sub_7 sub_9 )
foreach condition ($sub_IDs)
cd $sub_ID

set areas = (M1 S1 area_6)
set hemis = (left right)
foreach area ($areas)
foreach hemi ($hemis)

3dBrickStat \
-volume \
-max \
-mean \

```

```
-non-zero \  
arm_pedal"$sub_ID"._tshift.bucket_decline.PSC."$hemi"."$area"+orig \  
>"$sub_ID"."$area"."$hemi".count.txt
```

```
end  
end  
cd ..  
end
```

## APPENDIX G      The movement information of healthy subjects

This section provides the values of pedaling rates (RPM), and FING/FOOT frequencies for each subject.

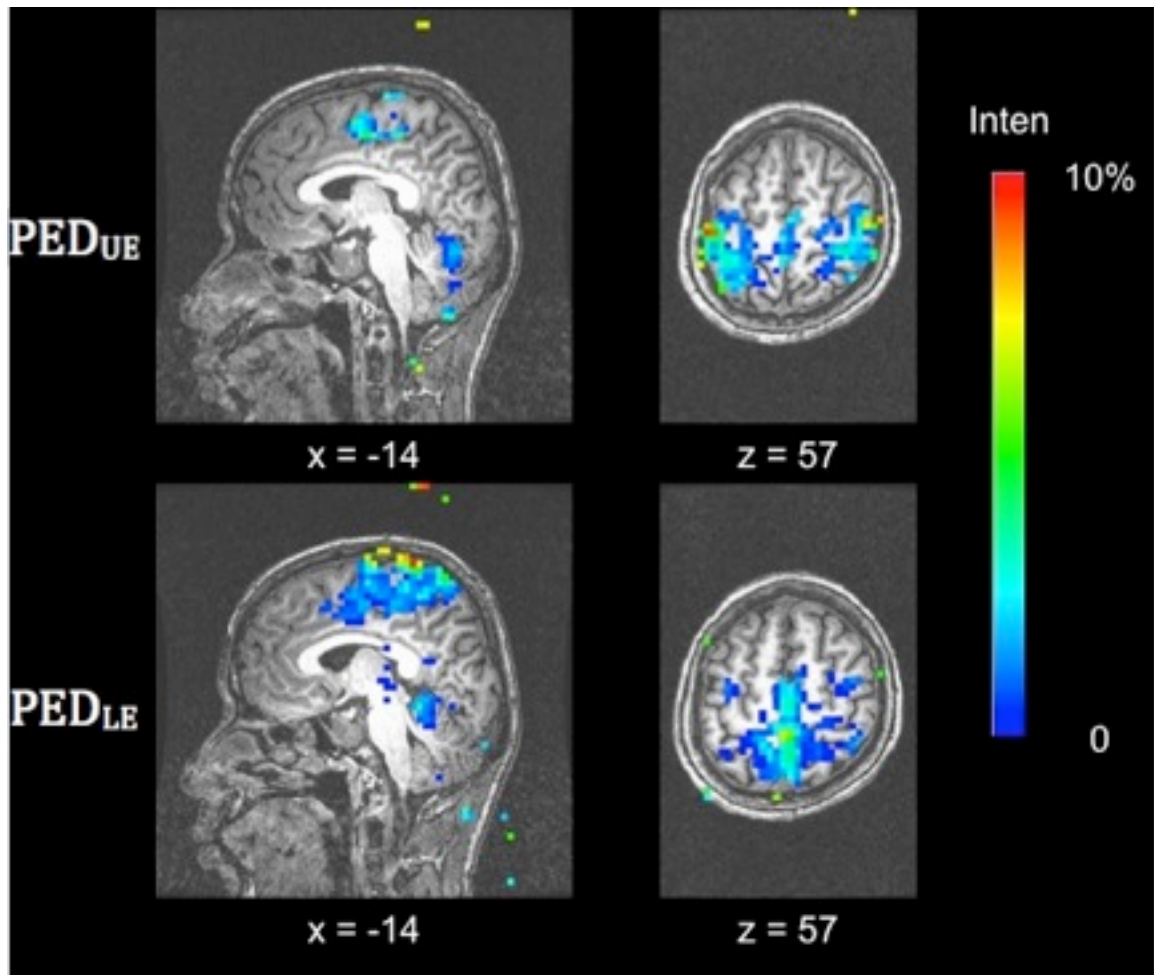
Subject ID	PED <sub>UE</sub> (RPM)	PED <sub>LE</sub> (RPM)	left FING (Hz)	right FING (Hz)	left FOOT (Hz)	right FOOT (Hz)
Sub_01	67.4	94.7	119.5	122.1	153.1	168.1
Sub_02	55.0	59.6	68.2	64.9	117.5	122.5
Sub_03	55.7	63.9	213.9	209.4	153.1	168.1
Sub_05	77.1	114.8	68.9	70.2	169.4	211.9
Sub_06	68.0	66.2	45.3	44.3	58.1	60.6
Sub_07	24.9	29.8	46.4	46.9	72.5	73.1
Sub_08	50.1	69.1	66.9	87.2	115.6	131.3
Sub_09	56.9	71.2	89.9	92.2	119.9	133.7
Mean	67.4	94.7	119.5	122.1	153.1	168.1

## **APPENDIX H      BRAIN ACTIVITY OF INDIVIDUALS**

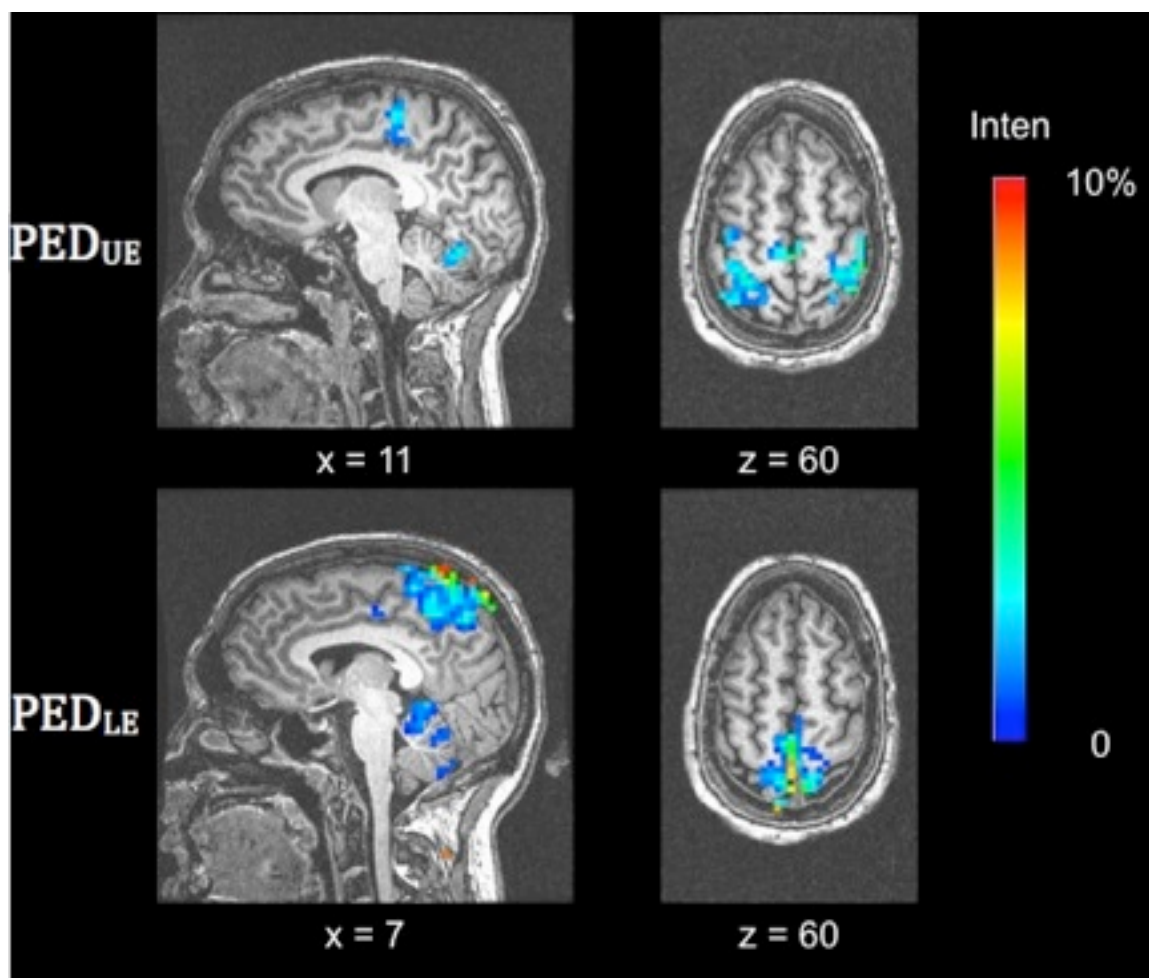
This section provides an overview of the brain activity for neurologically intact subjects during different experimental tasks, and the images are taken in sagittal and axial directions. The color bars indicate the intensity of activation with red being the maximum value (10%).



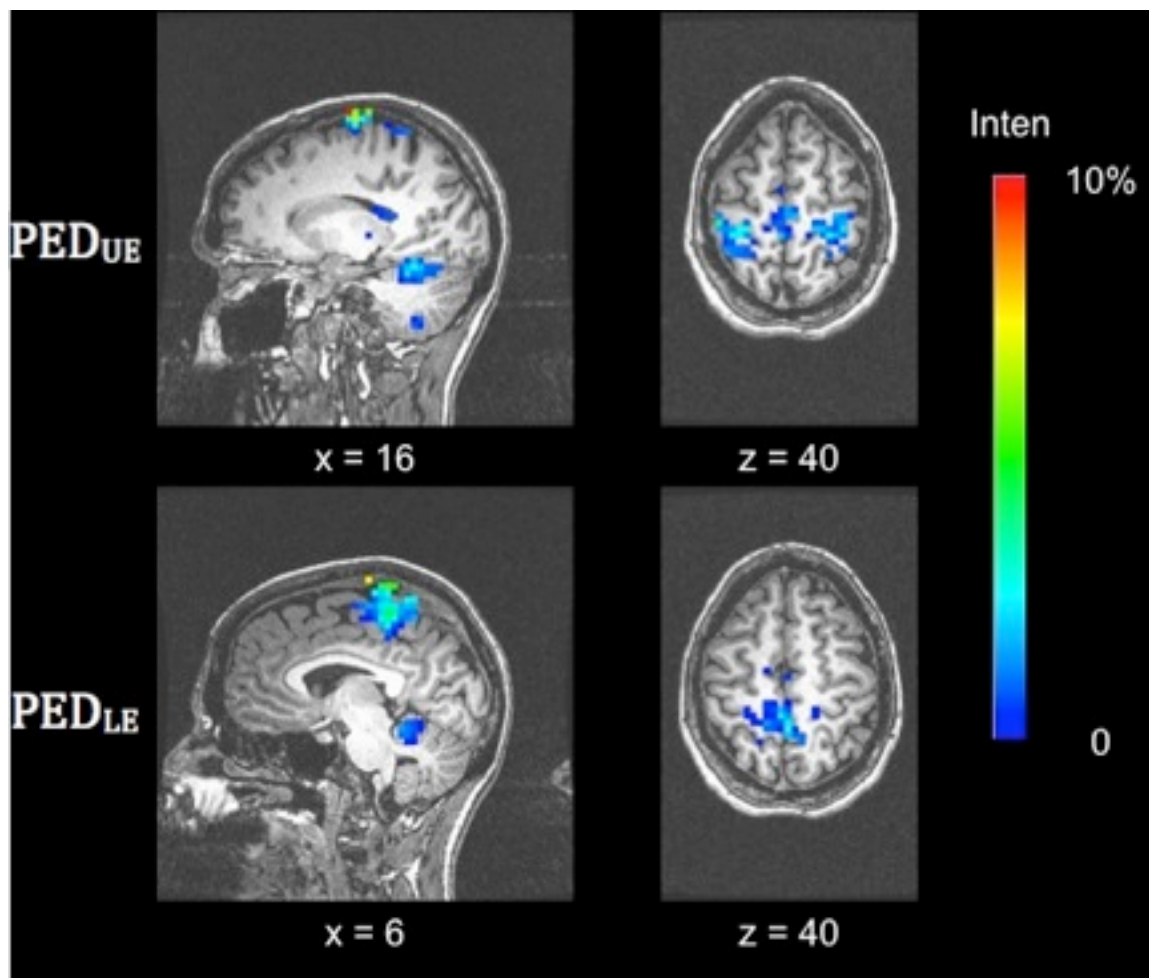
Pedaling related activity for subject No.01



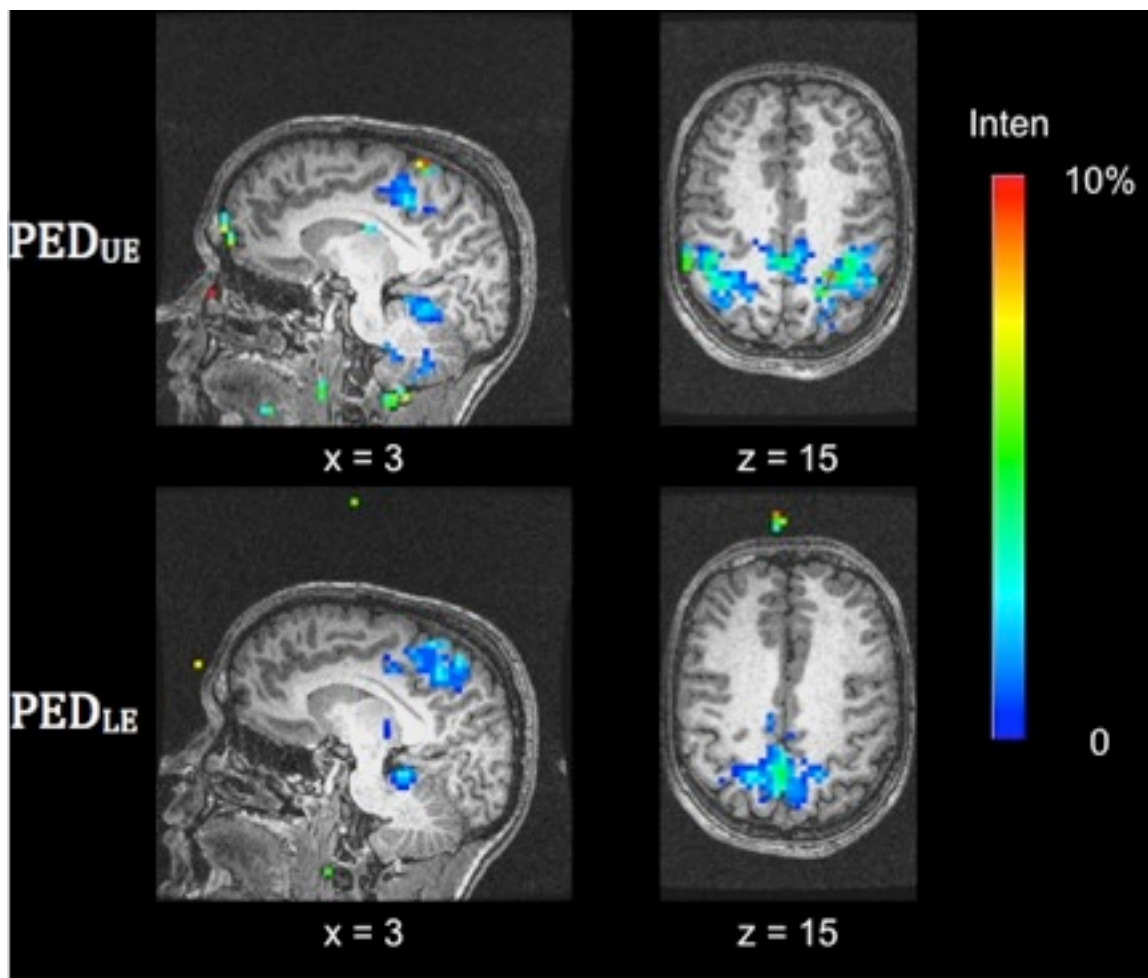
Pedaling related activity for subject No.02



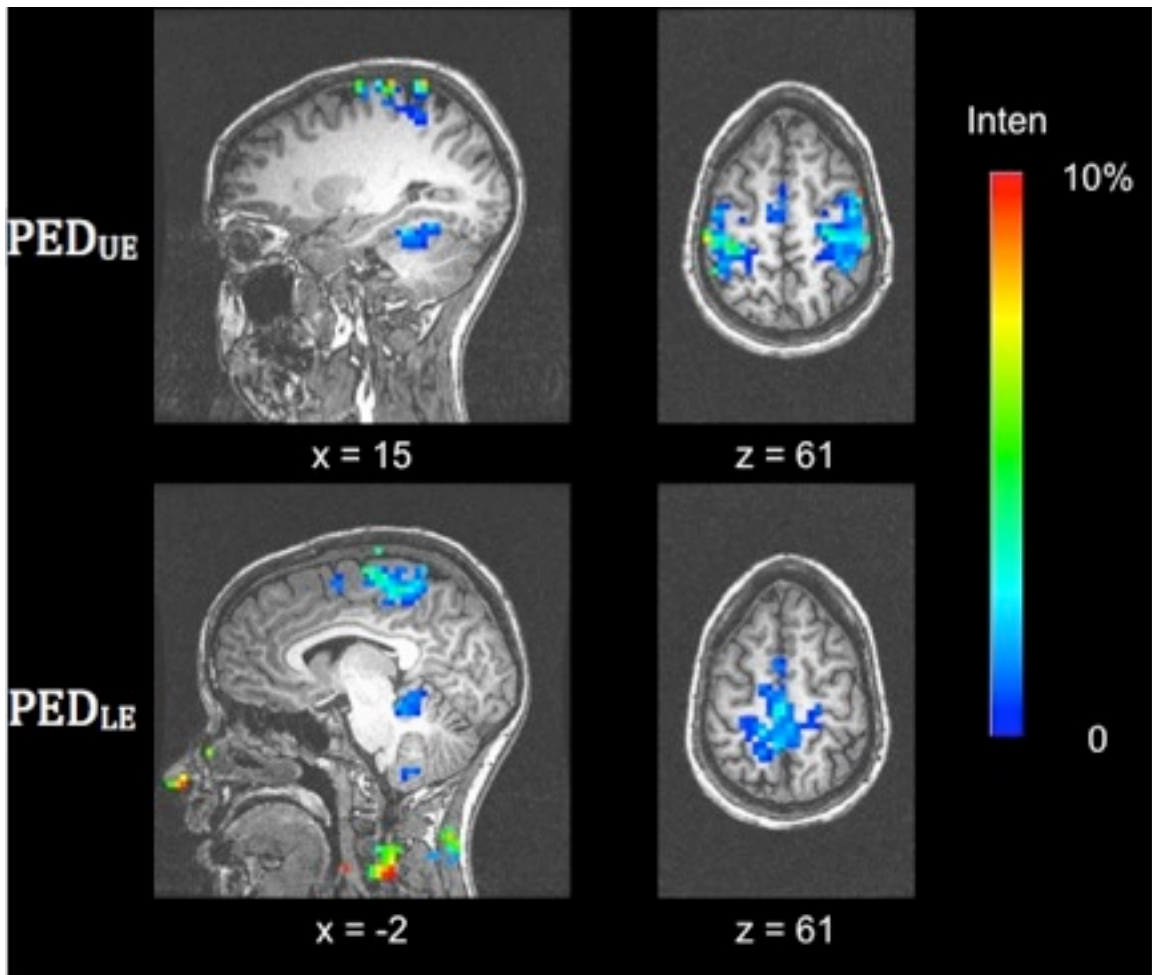
Pedaling related activity for subject No.03



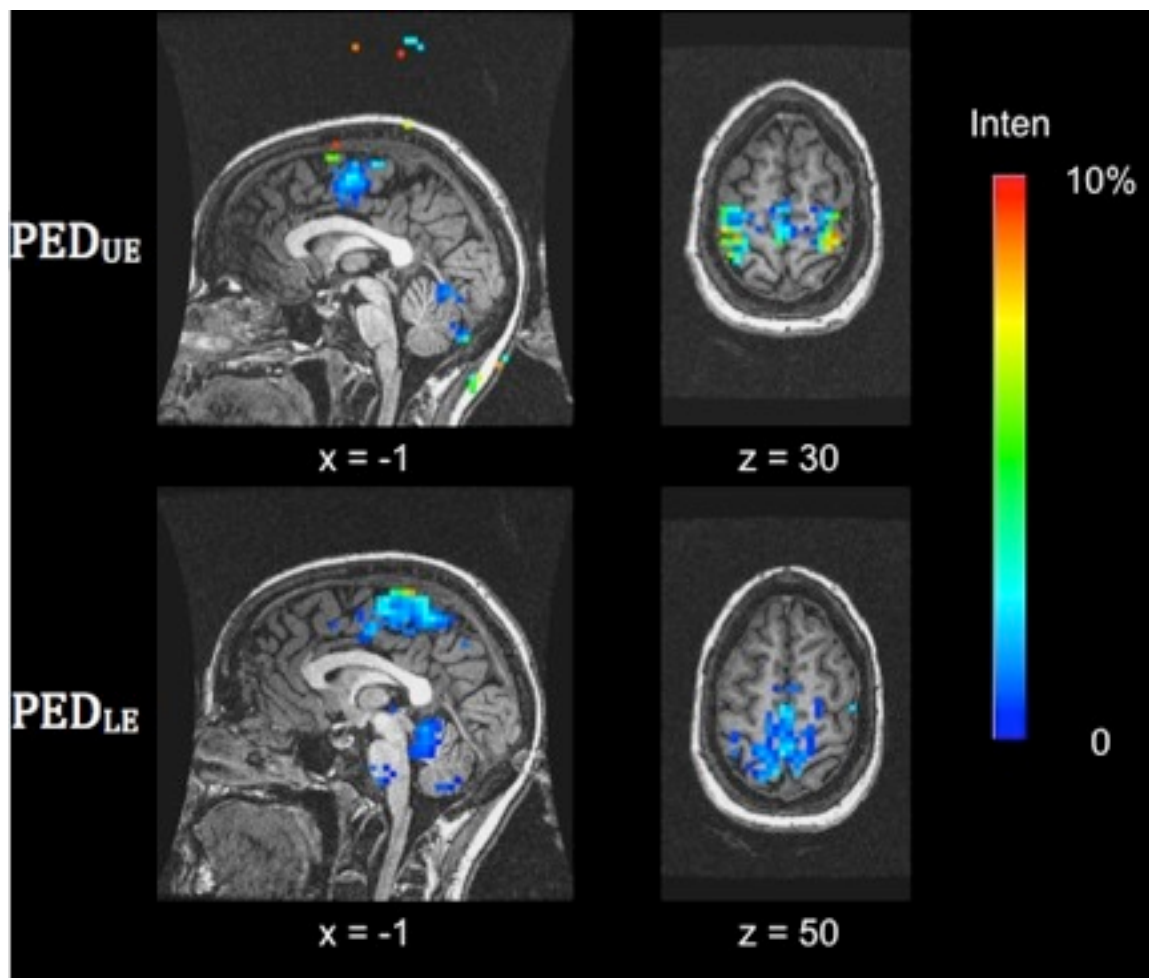
Pedaling related activity for subject No.05



## Pedaling related activity for subject No.06

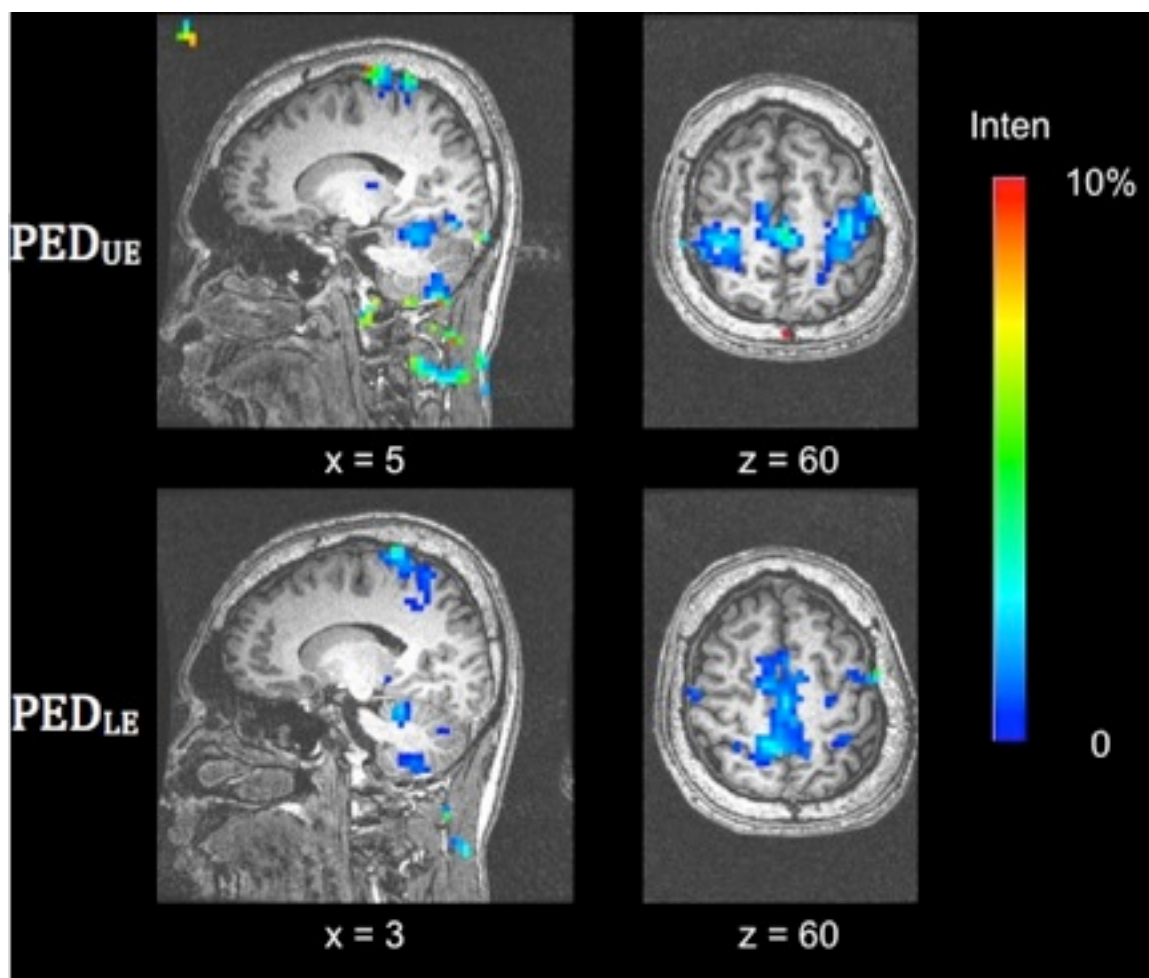


Pedaling related activity for subject No.07

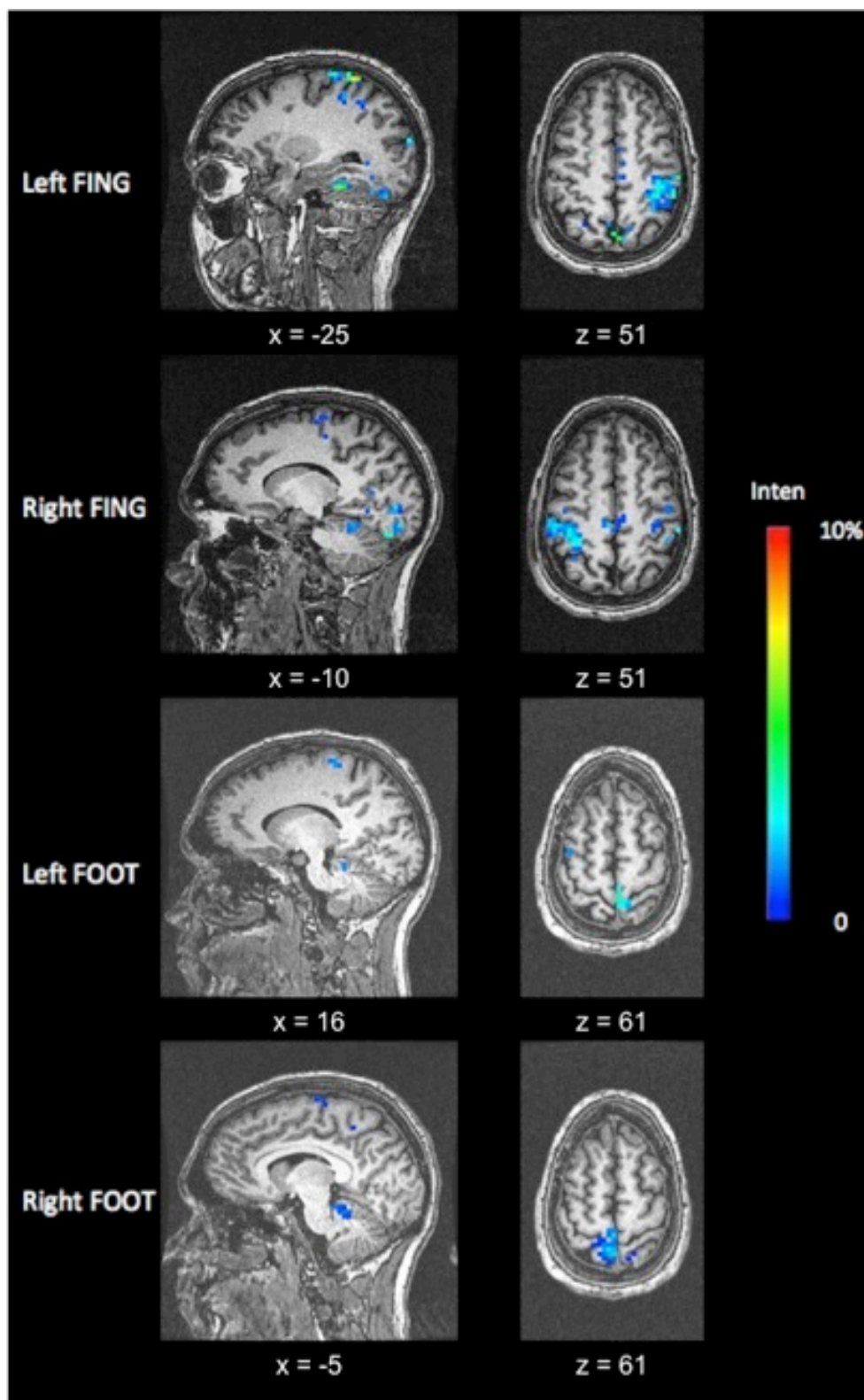




Pedaling related activity for subject No.09

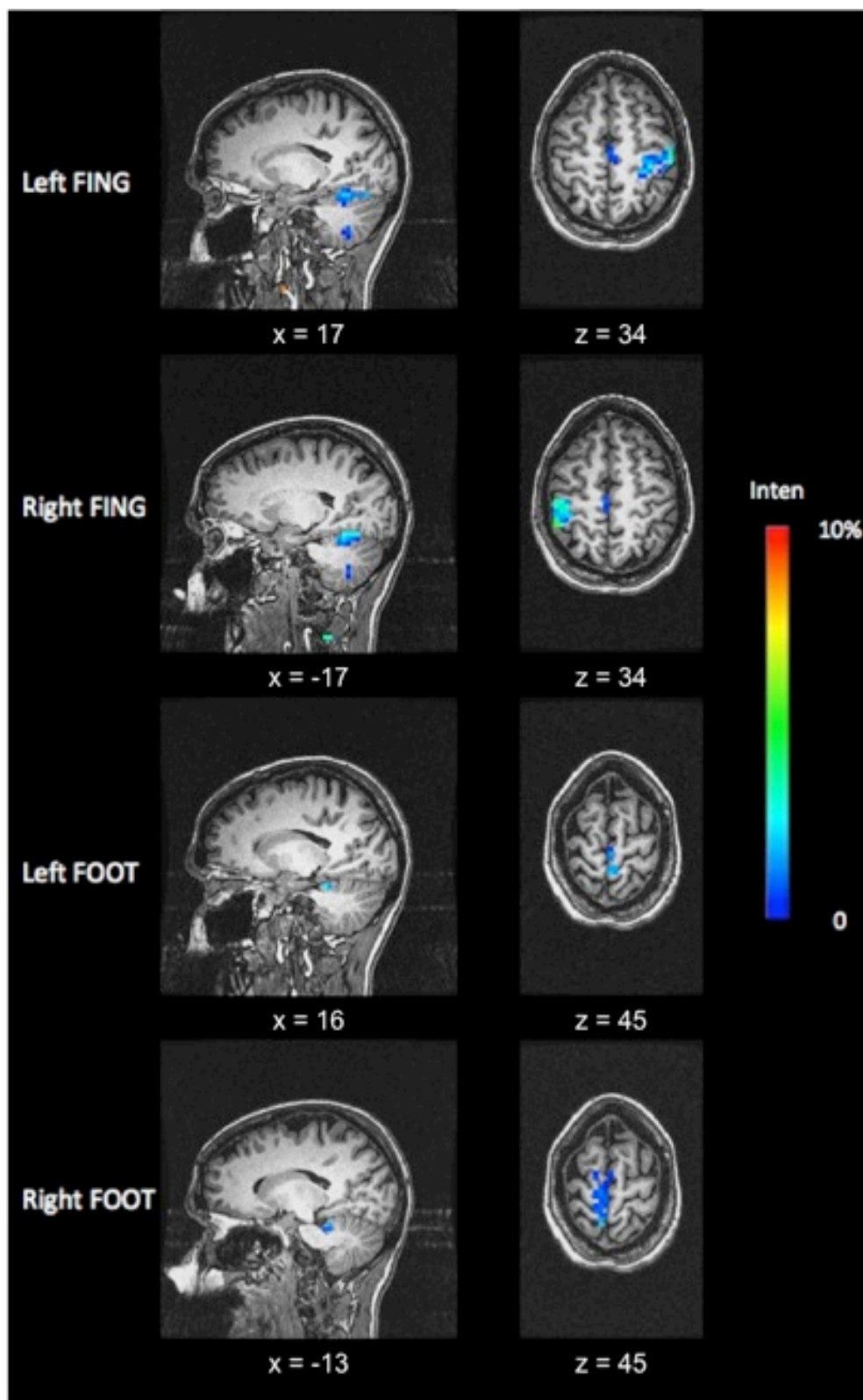


FING and FOOT related activity for subject No.02

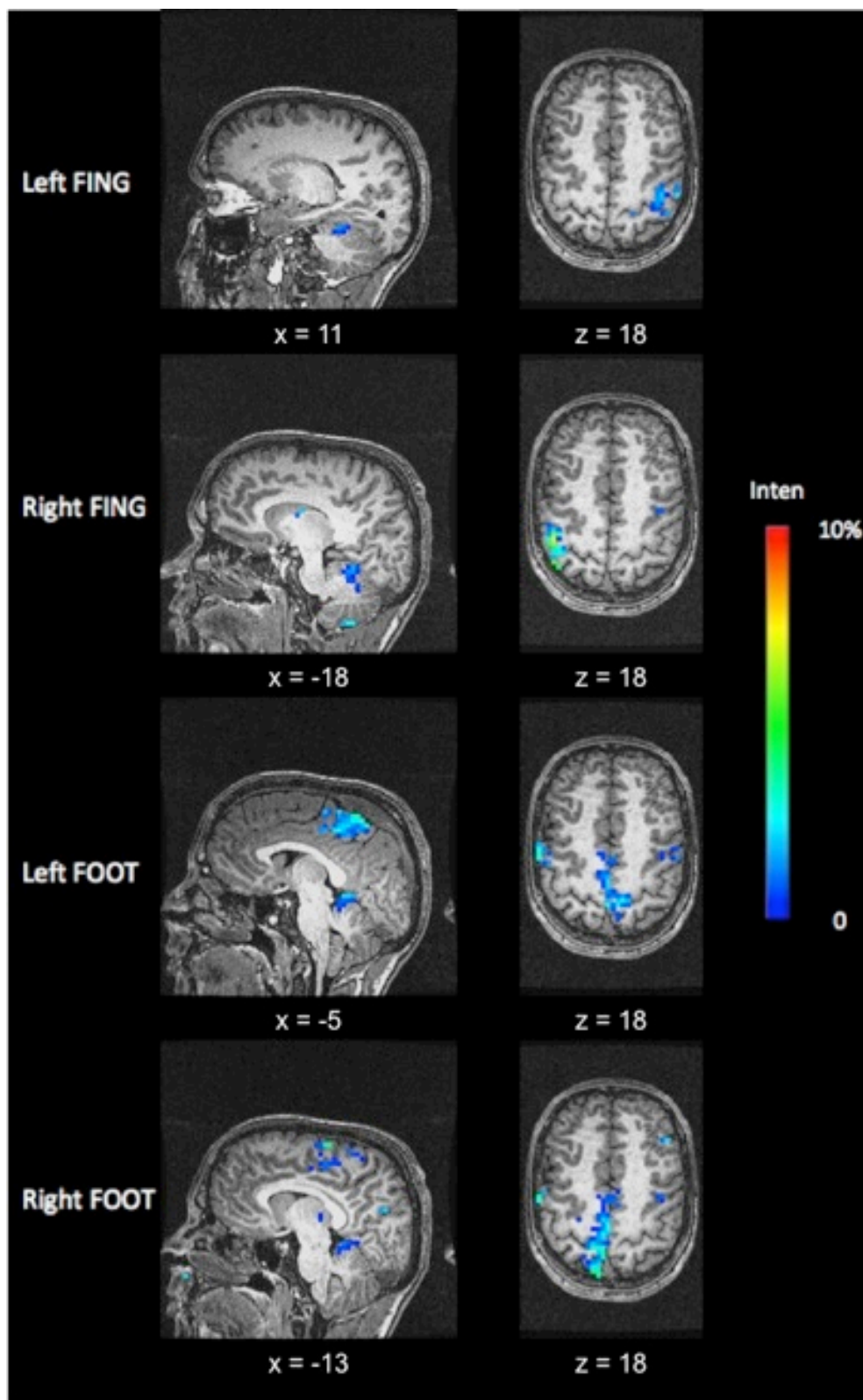




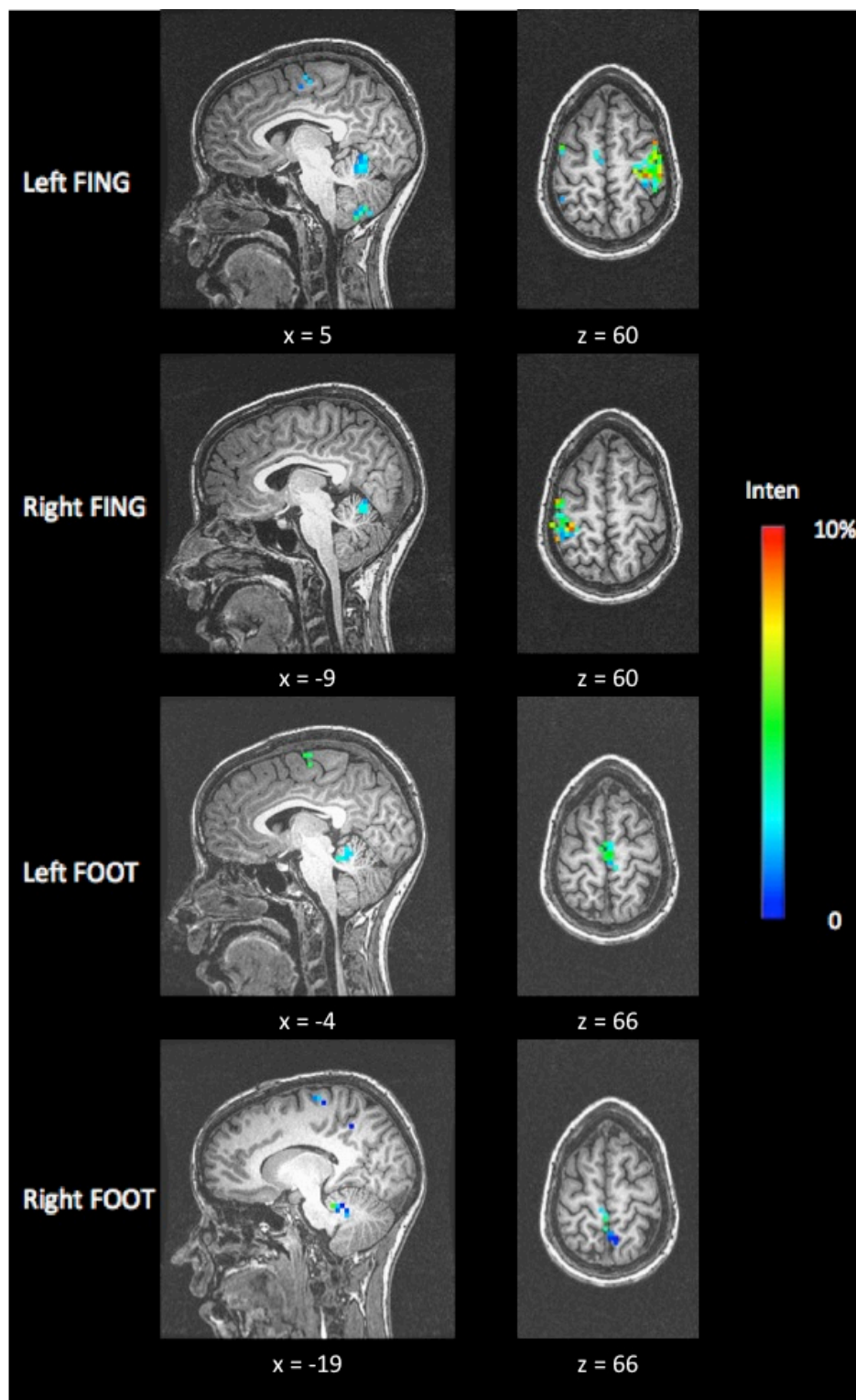
FING and FOOT related activity for subject No.03



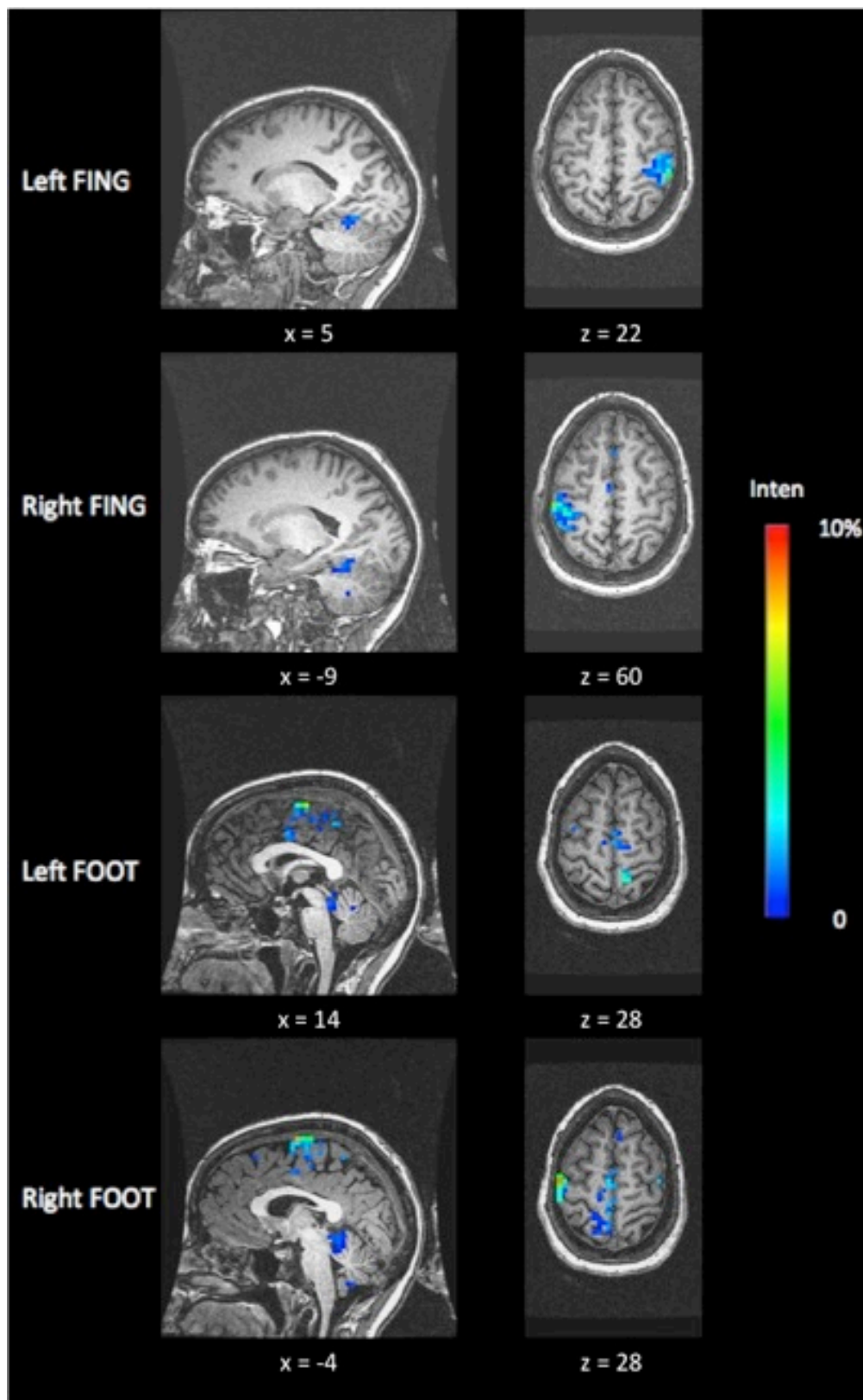
FING and FOOT related activity for subject No.05



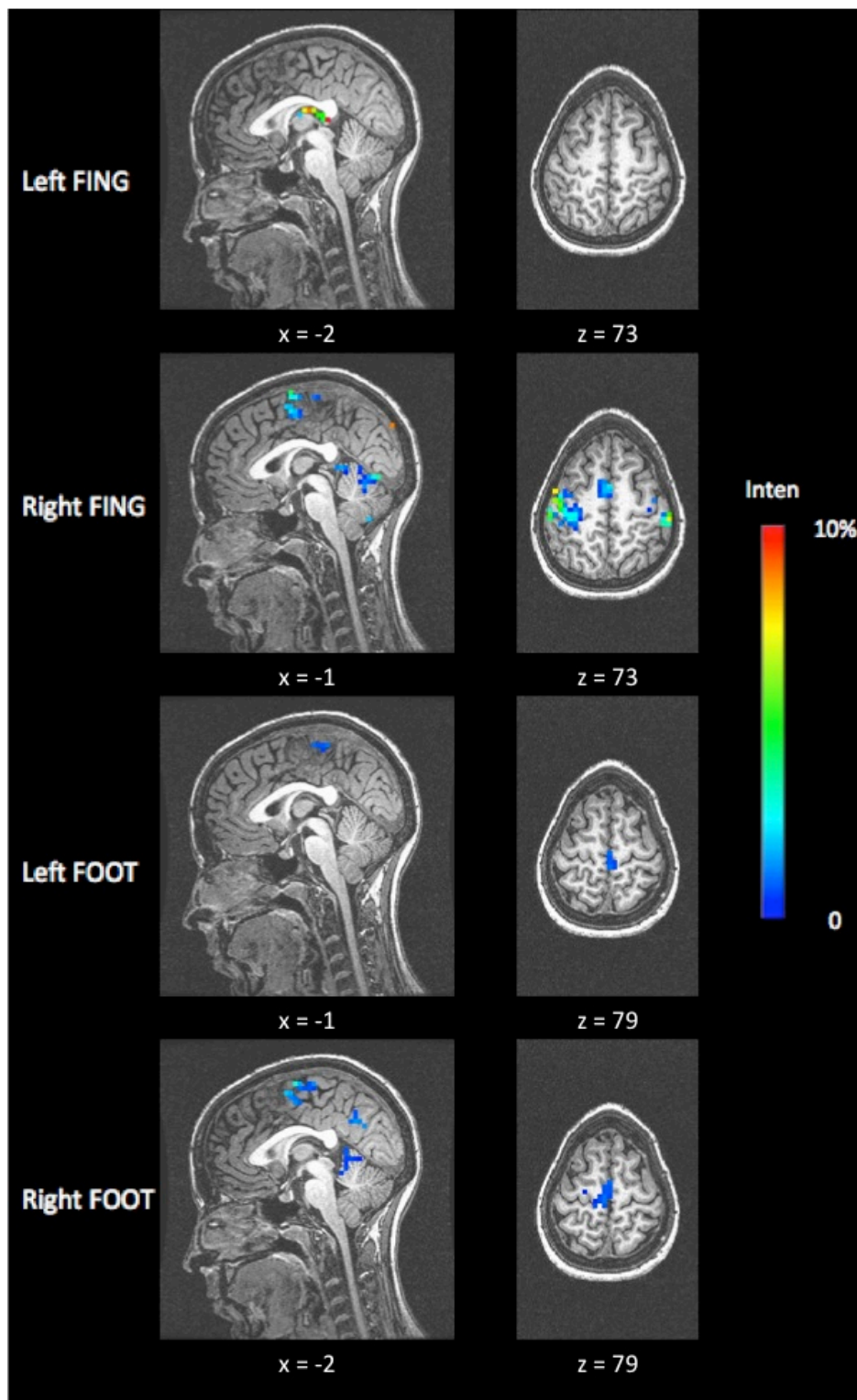
## FING and FOOT related activity for subject No.06



## FING and FOOT related activity for subject No.07

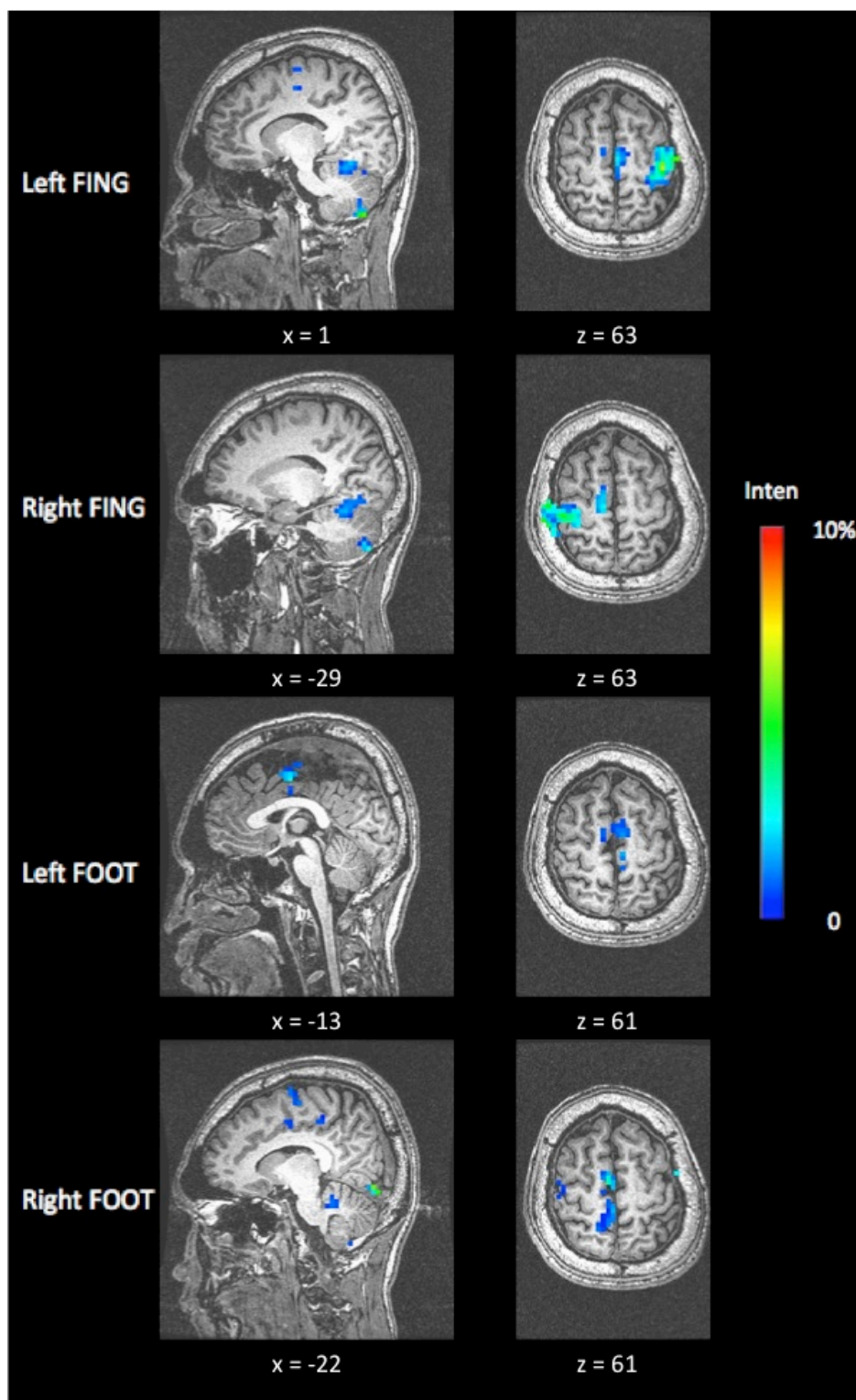


FING and FOOT related activity for subject No.08





## FING and FOOT related activity for subject No.09



**APPENDIX I THE ACTIVATION RESULTS FOR STROKE SUBJECTS**

This section provides the values of laterality index, intensity, volume of activation for each subject. The mean value from the neurologically intact subjects is provided for comparison.

Laterality index = LI, Intensity = Int, Volume = Vol. Units: Int (%), Vol (mm<sup>3</sup>)

Cortical activity during PED<sub>UE</sub> and PED<sub>LE</sub>:

Subject ID		S1			M1			BA6			Total		
		LI	Int	Vol	LI	Int	Vol	LI	Int	Vol	LI	Int	Vol
<b>S01</b>	UE	0.57	1.6	9506	0.61	2.1	6018	0.69	1.9	3937	0.61	1.8	19462
	LE	0.39	1.4	10181	0.13	1.9	7256	0.90	1.9	3431	0.39	1.7	20868
<b>S03</b>	UE	-1	2.8	169	-1	1.4	113	---	---	0	-1	2.3	281
	LE	-0.79	2.8	2194	0.02	2.2	6188	0.39	1.5	1294	-0.12	2.2	9675
<b>Control</b>	UE	0.01	1.7	14062	-0.07	1.9	12295	0.01	1.3	6597	-0.01	1.7	32954
	LE	0.1	1.3	7433	0.03	1.6	10792	-0.02	1.2	9080	0.02	1.4	27305



## Cortical activity during paretic and non-paretic FING:

Subject ID		S1			M1			BA6			Total		
		LI	Int	Vol	LI	Int	Vol	LI	Int	Vol	LI	Int	Vol
S01	Paretic	1	2.0	506	0.43	2.5	2363	0.13	2.9	1294	0.41	2.6	4163
	Intact	1	1.8	4163	1	1.9	3881	0.76	1.2	956	0.98	1.8	9000
S03	Paretic	-1	1.6	3488	-0.58	1.7	3544	-0.68	1.2	900	-0.69	1.6	7931
	Intact	0.48	2.2	5231	0.55	2.5	4275	0.54	1.4	1012	0.54	2.3	10519
<b>Control</b>		0.84	1.9	4504	0.89	2.1	3909	0.67	1.3	1261	-0.05	1.9	9675
<hr/>													
		LI	Int	Vol	LI	Int	Vol	LI	Int	Vol	LI	Int	Vol
S02	Paretic	-1	0.8	900	-1	1.9	7875	-1	5.0	900	-1	2.1	9675
	Intact	1	1.7	14625	1	2.0	10125	1	0.4	225	1	1.8	24975
S04	Paretic	-1	1.0	1125	-1	0.9	1350	---	---	0	-1	0.9	2475
	Intact	1	1.6	4725	1	1.6	4275	---	---	0	1	1.6	11025
<b>Control</b>		0.84	1.9	4504	0.89	2.1	3909	0.67	1.3	1261	-0.05	1.9	9675

## Cortical activity during paretic and non-paretic FOOT:

Subject ID		S1			M1			BA6			Total		
		LI	Int	Vol	LI	Int	Vol	LI	Int	Vol	LI	Int	Vol
S01	Paretic	1	1.1	56	1	1.5	2363	1	1.9	394	1	1.6	1519
	Intact	1	1.2	1519	0.92	1.7	3881	0.47	1.4	1913	0.82	1.5	7425
S03	Paretic	---	---	0	---	---	0	---	---	0	---	---	0
	Intact	0.48	2.2	956	0.55	2.5	3488	0.54	1.4	112	0.54	2.3	4556
<b>Control</b>		0.88	1.0	1306	0.70	1.3	2435	0.19	1.1	3206	-0.20	1.1	6947
		LI	Int	Vol	LI	Int	Vol	LI	Int	Vol	LI	Int	Vol
S02	Paretic	-1	0.7	450	-0.33	1.7	3375	1	2.0	675	-0.2	1.7	4500
	Intact	1	4.3	225	1	4.5	2925	1	3.9	675	1	4.4	3825
S04	Paretic	---	---	0	---	---	0	---	---	0	---	---	0
	Intact	---	---	0	---	---	0	---	---	0	---	---	0
<b>Control</b>		0.88	1.0	1306	0.70	1.3	2435	0.19	1.1	3206	-0.20	1.1	6947