

MAGNETIC RESONANCE IMAGING OF PLASTIC CHANGES IN THE  
HUMAN BRAIN FOLLOWING A MOTOR TASK

APPROVED BY SUPERVISORY COMMITTEE

---

Kimberly Huber, Ph.D.

---

Kevin Gardner, Ph.D.

---

Craig Malloy, M.D.

## **DEDICATION**

To my beloved wife Katy, whose unconditional love, support, patience, kindness, and goodness enable me to complete my pursuit of advanced education.

To my parents Jerry and Helen, whose words of wisdom still resonate within me throughout all my works and endeavors.

To my mentor Professor Hanzhang Lu, PhD, whose guidance, insights, and inputs have forever transformed my knowledge and understanding of science and scientific process.

MAGNETIC RESONANCE IMAGING OF PLASTIC CHANGES IN THE  
HUMAN BRAIN FOLLOWING A MOTOR TASK

by

KUANG-CHI TUNG

DISSERTATION

Presented to the Faculty of the Graduate School of Biomedical Sciences

The University of Texas Southwestern Medical Center at Dallas

In Partial Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

The University of Texas Southwestern Medical Center at Dallas

Dallas, Texas

December, 2012

Copyright

by

KUANG-CHI TUNG, 2012

All Rights Reserved

## **Abstract**

# **MAGNETIC RESONANCE IMAGING OF PLASTIC CHANGES IN THE HUMAN BRAIN FOLLOWING A MOTOR TASK**

Kuang-Chi Tung, Ph.D.

The University of Texas Southwestern Medical Center at Dallas,

December, 2012

Mentor: Hanzhang Lu, Ph.D.

Brain plasticity forms the basis of many of our daily functions including memory and learning. Evidence of brain plasticity in humans mostly consists of morphological and functional changes following days, weeks, or years of specific usage. On a time scale of minutes, on the other hand, it is not yet clear whether such changes are detectable and what the nature of these changes is. If detected and understood, then these changes have the potential of becoming diagnostic or predictive parameters towards treatments or therapies.

The experiments I performed showed that significant changes in brain's organization can be detected within a single session using functional MRI technique. Here human volunteers were subject to a 23-minute button-press motor task and their resting-state brain activity before and after the task was assessed with functional connectivity MRI (fcMRI). It was found that, compared to the

pre-task *resting* period, the post-task *resting* fcMRI revealed a significantly higher cross-correlation coefficient (CC) between left and right motor cortices. These changes were region-specific and required the motor task to take place as sham control study did not show CC changes. Furthermore, the amplitude of fcMRI signal fluctuation (AF) also demonstrated an increase in the post-task period compared to pre-task. These changes were observed using both right-hand-only task and two-hand task, and were demonstrated in two separate subject cohorts. The left-hand task group did not show significant changes in motor cortex CC. The recovery time-course of these changes was also investigated, and it was found that the CC change lasted for about 5 minutes while the AF change lasted for at least 15 minutes. Voxel-wise analysis revealed that pre/post-task differences were also observed in auditory cortex, visual areas, and thalamus. Finally, network analysis showed that simple motor tasks result in the strengthening of functional connectivity between these areas. My data suggest that elevated CC and AF in fcMRI may be potentially used as markers for brain plasticity. Further, these imaging parameters can be used to delineate network wide changes in the brain by the task.

## **PRIOR PUBLICATIONS**

Tung, K.C., Mao, D., Xu, F., Uh, J., Lu, H. Alterations in resting functional connectivity due to recent motor task. *NeuroImage*. In Peer Review.

## TABLE OF CONTENTS

Chapter 1	Introduction.....	1
	Lifetime Training .....	2
	Brain’s evoked activity in response to stimulation .....	5
	Resting brain and the training footprint.....	6
	Spontaneous activity in the resting brain.....	10
	Changes in the resting brain by training .....	12
	Magnetic Resonance Imaging.....	17
	Functional MRI.....	19
Chapter 2	Specific Aim 1: Plastic Changes in Motor Cortex After Dominant	
	(Right) Hand Task.....	23
	Introduction.....	24
	Material and Methods .....	30
	Sham experiment .....	31
	Region of Interest (ROI) selection – Motor Cortex .....	32
	Region of Interest (ROI) selection – Default Mode Network.....	32
	Region of Interest (ROI) selection – Auditory Network.....	34
	Data Processing.....	34
	Results.....	36
	CC between bilateral motor cortices was significantly greater in post-task	
	fcMRI.....	36



Sham control experiment showed no changes in CC in motor cortices .....	39
The plastic changes were region-specific .....	40
Plastic changes in brain regions stimulated by MRI noise – primary auditory cortex.....	42
Amplitude of Fluctuation (AF) of fcMRI signal also increased in post-task period .....	43
Discussion .....	46
Comparison with previous plasticity literature .....	47
Imagery activation during the post-task period?.....	50
Chapter 3 Specific Aim 2: Plastic Changes in Motor Cortex After Bilateral Hand Task 52	
Introduction.....	53
Material and Methods .....	54
Data Processing.....	55
Results.....	56
Discussion .....	61
Chapter 4 Specific Aim 3: Plastic Changes in Motor Cortex After Non-Dominant (Left) Hand Task..... 64	
Introduction.....	65
Materials and Methods.....	65
Data Processing.....	67

Results.....	68
Discussion.....	73
Chapter 5    Voxel Based Analysis and Network Functional Connectivity	
Analysis    75	
Introduction.....	76
Materials and Methods.....	79
Post-processing .....	80
Results.....	87
Amplitude of Fluctuation.....	87
Functional Connectivity.....	90
Discussion.....	98
Chapter 6    Conclusion .....	105
Summary .....	106
Spatial distribution of the plastic changes .....	106
Neural underpinnings of the CC and AF changes in the fcMRI data .....	107
Brain network analysis.....	111
Future Works.....	115
References.....	123

## **List of Figures**

Figure 1.....	3
Figure 2.....	4
Figure 3.....	11
Figure 4.....	15
Figure 5.....	30
Figure 6.....	37
Figure 7.....	38
Figure 8.....	39
Figure 9.....	41
Figure 10.....	41
Figure 11.....	43
Figure 12.....	44
Figure 13.....	45
Figure 14.....	46
Figure 15.....	55
Figure 16.....	57
Figure 17.....	58
Figure 18.....	59
Figure 19.....	60
Figure 20.....	60
Figure 21.....	61
Figure 22.....	66
Figure 23.....	69
Figure 24.....	70
Figure 25.....	71
Figure 26.....	72
Figure 27.....	72
Figure 28.....	73
Figure 29.....	79
Figure 30.....	84
Figure 31.....	88

Figure 32 ..... 92

Figure 33 ..... 93

Figure 34 ..... 96

Figure 35 ..... 97

Figure 36 ..... 97

**List of Tables**

Table 1 ..... 89

Table 2 ..... 95

## **List of Appendix**

<b>Appendix 1</b> .....	118
-------------------------	-----

## **Chapter 1    Introduction**

## **Lifetime Training**

The brain drives behavior. Behaviors in turn modify the brain. The modification of brain structures and functions based on previous experience is the basis to the learning process throughout our lives. This feature is known as the brain's plasticity. A well known example of how learning modifying the human brain is provided by a study conducted by Maguire et al. in 2000 (Maguire et al., 2000). The researchers found that the only area of the London taxi drivers' brains that was different for other control subjects was the size of the left and right hippocampus grey matter. While the overall hippocampi sizes are not different from the control subjects, the posterior part of the hippocampus was larger, while the anterior part was smaller in the taxi drivers. Further, the longer they had been in their experience, the larger their posterior hippocampus was. The posterior part of the hippocampus is associated with navigation skills, while the anterior part is associated with information encoding by new environment. The authors suggested these results reflect how these drivers' brains had adapted to hold the knowledge

required by the job.

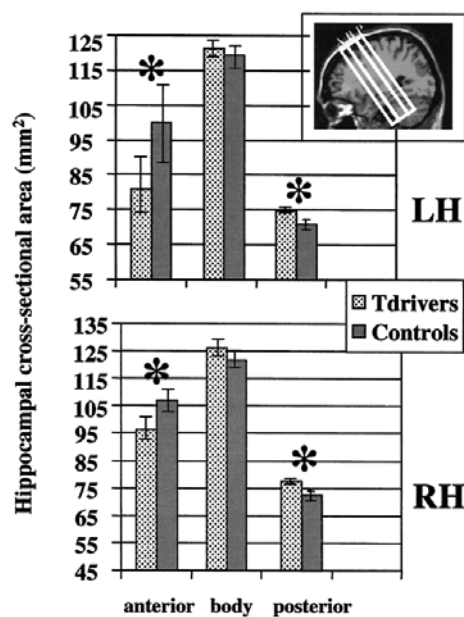


Figure 1. Hippocampus size differences between the taxi drivers and controls. The three dimension structural MRI image was reformatted into contiguous section in a tilted coronal plane, which was perpendicular to the long axis of the hippocampus: anterior (6 slices), body (12 slices), and posterior (6 slices). Each slice is 1.5mm (Maguire et al., 2000).

The example of brain's modification by long-term learning can also be found in musicians. Professional musicians were found to have larger grey matter volume in their motor and auditory cortices comparing to that in the non-musicians(Figure 2) (Gaser and Schlaug, 2003). Also in professional



musician's internal capsule (an area of white matter), which consists of ascending and descending axonal tracts connecting between neocortex and limbs, the structural organization of these fiber tracts were shown to be higher than that of non-musicians (Bengtsson et al., 2005).

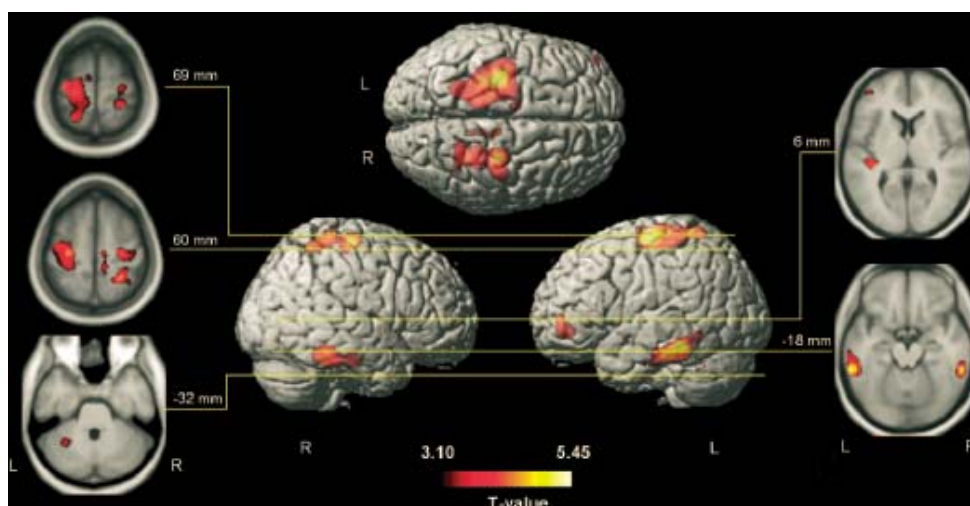


Figure 2. Regions where grey matter sizes are correlated with music skills. The three levels of skills are modeled as professional, amateur, and non-musician. Voxels with significant positive correlation between the skill grade and the increase in grey matter volume are shown.

Also, as a less specialized example, Taubert et al. showed that just after two weeks of dynamic balancing task, they were able to detect grey matter volume expansion in bilateral supplementary motor area (Taubert et al., 2010). Taken

together, it is clear that the brain can be modified by the repeated use and these plastic changes are specific to the nature of such use. Further, these structural modifications can take place even in the adulthood. Demands by function are coupled with the plastic changes observed in anatomical structures.

### **Brain's evoked activity in response to stimulation**

When the brain is being stimulated or performing a task, the evoked changes in blood flow as well as energy consumption can be detected in the specific region of the brain (Fox et al., 1988). Stimulation of the human visual cortex with a flashing checkerboard produced significant increases in blood flow and glucose use in the visual cortex when compared with a simple fixation on crosshair.

If trainings were applied to a specific region of the brain in the length of weeks, the magnitude of the evoked response and area of activation also increased. For example, after practicing a motor sequence learning (MSL) task for two weeks, the subjects showed not only an increase in the area of motor region that were activated by the task, but also the magnitude of the evoked response (Karni

et al., 1995; Xiong et al., 2009).

Since the skills obtained by practice are maintained by the brain even during rest, it is not surprising that the effects of practicing task could also be detected in the resting brain's spontaneous activity in this time scale (Lewis et al., 2009; Kilpatrick et al., 2011; Ma et al., 2011; Taubert et al., 2011).

### **Resting brain and the training footprint**

In the results by Karni et al., it was also reported that when the subject was learning a new MSL task, there is an initial habituation-like effect within a 30-minutes training session, such that the evoked response was larger in the earlier execution than in the later execution (Karni et al., 1995). Such confounding factor by habituation highlights one of the shortcomings of using evoked response to evaluate brain plasticity. Therefore, the experiment design which detects changes in the resting brain's activity became widely used. The benefit of detecting changes in resting activity is that unlike detecting changes in the evoked neural activity, detecting changes in the resting activity requires less

subject cooperation and thus signal is less dependent on their habituation, effort or attention. Resting state image data also allow the assessment of all brain regions, not just the task-evoked brain regions. The ability to detect the plastic changes under resting state permits a demonstration that the neural substrate of the training is present in the brain even it is not being used. Another reason for the interest in the spontaneous activity is that it may account for the variability in the evoked activity. Fox et al showed that the variability in the evoked responses in left motor cortex during a right-hand motor task is mostly attributed by the concurrent spontaneous activity in the motor network (Fox et al., 2006; Fox et al., 2007).

There is also a theoretical consideration for analyzing the brain's resting state in order to understand neuroplasticity. The changes in the energy demand during the task is usually small ( $< 5\%$ ) in comparison to the energy the brain consumed during rest (Raichle and Mintun, 2006). Thus most of the energy in the brain is consumed to support the spontaneous neuronal activities, and therefore it is important to understand the nature of these activities which consumes most of the energy. The spontaneous activities tend to be synchronous across hemispheres. It

was shown that these activities in the left sensorimotor cortex are specifically correlated with the spontaneous neural activities in the right sensorimotor cortex (Biswal et al., 1995). Because this finding was novel at its time, it was later replicated and confirmed (Lowe et al., 1998; Xiong et al., 1999; Cordes et al., 2000).

An index which characterizes the resting brain's spontaneous neural activity is the synchrony between a reference waveform, which originates in a region of interest (seed), and all other brain regions. The synchrony is typically measured as Pearson Correlation Coefficient  $r$  (Biswal et al., 1995):

$$r = \frac{n \sum_{t=1}^n x_t y_t - \sum_{t=1}^n x_t \sum_{t=1}^n y_t}{\sqrt{n \left[ \sum_{t=1}^n x_t^2 - \left( \sum_{t=1}^n x_t \right)^2 \right]} \sqrt{n \left[ \sum_{t=1}^n y_t^2 - \left( \sum_{t=1}^n y_t \right)^2 \right]}} \quad [1]$$

where  $x$  and  $y$  represent the two vectors (i.e., timeseries) of interest,  $n$  represents number of element in each vector.  $r$  is the Pearson Correlation Coefficient and it ranges from -1 to 1.

Another index commonly used to characterize spontaneous neural activity is

the amplitudes of fluctuation (AF) which is defined as (Yang et al., 2007; Luchinger et al., 2012):

$$AF = \frac{\sigma}{\mu} \cdot 100 \quad [2]$$

Where  $\sigma$  is the standard deviation of the signal,  $\mu$  is the mean (baseline) level of the signal. In eyes-open vs. eyes-closed experiment by Yang et al, it was shown that during AF of the visual cortex is higher in the eyes-closed resting state than in the eyes-open resting state. Thus AF was proposed to be another functional imaging marker for resting state experiments (Yang et al., 2007).

In a time scale of minutes, the brain's plastic changes have also been demonstrated. For example, after the subjects were exposed to 21 minutes of object-face and scene-face encoding task, it was found that during the post-task rest, the synchrony of spontaneous neural activities between their left posterior hippocampus and lateral occipital regions (evoked during the encoding task) is correlated with the subject's ability to recall the correct combination previously seen (Tambini et al., 2010). Similarly, in another study, after the subject

performed 11 minutes of visuomotor task, the spontaneous neural activity in their brain's frontal region and parietal region became more synchronous (Albert et al., 2009).

### **Spontaneous activity in the resting brain**

At the level of isolated neurons, spontaneous activities could be observed as spontaneous neuronal firings (Raman et al., 2000; Do and Bean, 2003; Mazzone et al., 2007). Spikes train generated by a group of neuron firing can be low-pass-filtered in 200Hz to obtain the so-called local field potential (LFP) (Logothetis, 2003). The LFP is considered slow fluctuations in the voltage of extracellular space, that reflect the group activity in a neural population in a diameter of 6mm around the probe (Mitzdorf, 1985). Further analysis on the time LFP timeseries revealed that the signal spectrum is dominated by the lower frequency contents, i.e., a '1/f' spectral profile, which means the coherence between the two time series decreases monotonically as a function of frequency (Leopold et al., 2003).

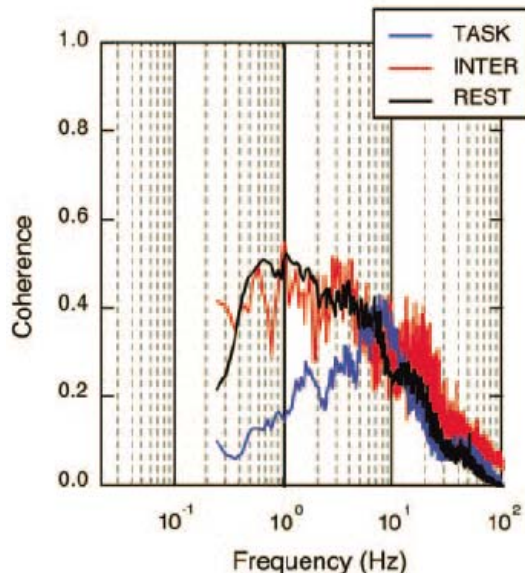


Figure 3 Mean pair-wise correlation of LFP signals during rest shows ‘1/f’ distribution. 15 electrodes were placed over the visual area of a rhesus monkey. (Leopold et al., 2003)

The data from Leopold et al show that the synchrony at the  $\gamma$ -band LFP signal shows a “1/f” distribution during both task and rests (Figure 3) (Shmuel and Leopold, 2008). Later, using bilateral direct electrode recording in human, Nir et al. showed that during rest, there are highly significant interhemispheric correlations in the spontaneous fluctuations of  $\gamma$ -band (40-100Hz) LFP in functional areas such as auditory as well as visual cortex (Nir et al., 2008). These studies confirmed that interregional coherence in neural activities is a feature of



functionally connected regions in the brain, and that it can be detected using either electrophysiological recordings or magnetic resonance imaging (MRI) techniques.

### **Changes in the resting brain by training**

The resting brain's activity has been shown to be associated with previous learning experience. Using  $\text{H}_2^{15}\text{O}$  Positron Emission Tomography (PET), Peigneux et al. showed that in humans, after learning a virtual navigation game for four hours, the subject's regional blood flows in hippocampus and parahippocampal space were increased during the subsequent sleep (Peigneux et al., 2004). In another study that evaluated the effect of sleep on learning (Huber et al., 2004), the subjects were instructed to perform rotation adaptation task with their dominant (right) hand for 18 minutes (contained 12 trials). Immediately after the task, their sleep electroencephalogram (EEG) was recorded. It is well known that slow wave activity (SWA) ( $< 4\text{Hz}$ ) of the EEG is an indicator of sleep intensity. SWA is thought to represent synaptic activity and it gradually decreases in the course of sleep (Tononi and Cirelli, 2003). During the first 30-minutes of

the non-REM sleep, the power density of SWA was found to be significantly elevated in the right parietal cortex (13% more than that of the untrained subjects). This area of the brain corresponds to the functional regions for visual and spatial inputs (Jonides et al., 1993; Cohen and Andersen, 2002). Within 90 minutes, the power density gradually recovered to the level of the untrained subjects. Further, the increase in the SWA power density during the sleep was positively correlated with performance improvement in the next day. A landmark study was carried out by Hoffman and McNaughton in 2002 using a rhesus monkey. They showed that synchrony in neural activities in multiple cortical regions (posterior parietal cortex, motor cortex, and somatosensory cortex) is enhanced after 30-minutes navigation motor reaching task. Further, the electrode pairs with high during the task also showed high synchrony during the subsequent rest (Hoffman and McNaughton, 2002).

Magnetic resonance imaging (MRI) technique such as BOLD (Ogawa et al., 1990) made it possible to study the spontaneous activity with whole brain coverage. When applied to the brain in the resting state, this technique is known

as functional connectivity MRI (fcMRI). Using motor cortex as an example, Biswal et al was the first to show that left and right motor cortices spontaneous fluctuation are highly synchronous (Biswal et al., 1995). It is now well known that the brain can be divided into functional networks based on the synchrony of spontaneous fluctuations observed using functional MRI, and the pattern derived is very consistent with respect to the pattern of activation, which means that regions that function together also rest together (Damoiseaux et al., 2006; van den Heuvel et al., 2008). Regions in a network become activated together during a task, but their spontaneous fluctuations are also synchronous during rest (Figure 4).

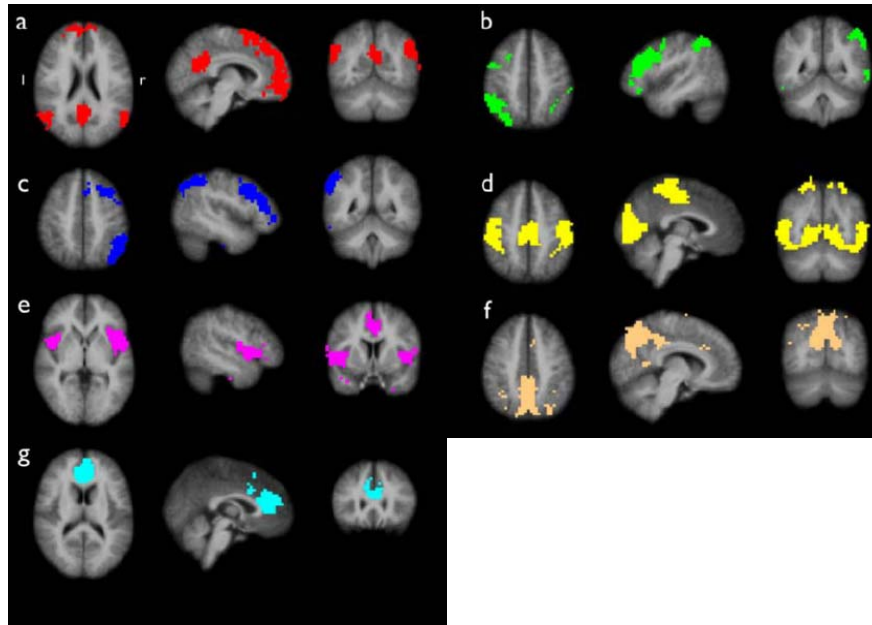


Figure 4 Resting state network in human brain. (a) Default Mode Network (b), (c) Attention Networks. (d) Sensorimotor and Visual Networks. (e) Saliency Network (f) Somatosensory Network (g) Executive Control Network (van den Heuvel et al., 2008).

The synchrony between the spontaneous fluctuations originated from the two regions of the brain, calculated as the Pearson Correlation Coefficient (CC), provides a measure of functional connectivity (FC) between two brain regions (Biswal et al., 1995). FC is a dynamic characteristic of the network. CC increase has been suggested as an evidence of learning. Several studies showed that after weeks of training, changes in functional connectivity (FC) between different

regions of the brain can be observed (Waites et al., 2005; Lewis et al., 2009; Stevens et al., 2010; Kilpatrick et al., 2011; Ma et al., 2011; Taubert et al., 2011).

For example, Taubert et al. showed that after six weeks of dynamic balance task (DBT) training, there is a significant FC increase between the supplementary motor area (SMA) and medial parietal cortex (mPL) in their trained subjects (Taubert et al., 2011). Lewis et al. conducted visual perception training for 2-9 days and compared the subject's FC pattern before and after the training. The authors observed a strengthening of connections between the visual and attention brain regions (Lewis et al., 2009). Ma et al. showed that after four weeks of daily practice of sequential finger movement, functional connectivity amongst left primary motor, right primary motor and supplemental motor area are significantly enhanced (Ma et al., 2011).

Training can also induce enduring changes in blood flows which can be detected in resting brain. Maquet et al. trained their subjects to perform right hand serial timing task (SRT). Their performance improved after a night of sleep. But a more important finding is that during the sleep, brain areas activated during the

execution of SRT such as left premotor cortex and cuneus showed more increases in regional blood flow during the sleep in the trained subjects than in the untrained subjects (Maquet et al., 2000).

### **Magnetic Resonance Imaging**

In order to create a magnetic resonance image, the human subject is first placed in a strong magnetic field. The strength of this field is 3 Tesla for magnet I used for my work. This field strength is 60 thousand times that of the earth's magnetic field. In the presence of such a strong field, atoms that have nuclear spin dipole moment will orient themselves with orientation either parallel or antiparallel to the main magnetic field ( $B_0$ ). More spin will be in the parallel than antiparallel orientation, resulting in a net magnetization that is parallel to the direction of the main magnetic field of the scanner. The nuclei will precess about  $B_0$  with a frequency, which is known as Larmor frequency ( $\nu_0$ ), which is directly proportional to  $B_0$ :

$$\nu_0 = \gamma B_0$$

$\gamma$  is gyromagnetic ratio, a fundamental physical constant for each nucleus.

Proton ( $^1\text{H}$ )  $\gamma$  is 42.58 MHz/Tesla. Due to its natural abundance, it is the most common nuclei of choice for MRI.

When a radiofrequency (RF) pulse is applied at Larmor frequency of the proton, resonance occurs as the proton nuclei spin is raised from the lower energy state to the higher energy state. Application of the RF pulse flips the magnetization into the transverse (with respect to the main magnetic field) plane. The RF pulse is then turned off as the magnetic moment of proton nuclei continues to precess about the main field. According to the Faraday's law of Induction, this time-varying precession induces a current in a receiver coil, the RF coil. This process results in an exponentially decaying voltage, which is referred as the free induction decay (FID), constitutes the MR signal.

When the magnetic moments are still in phase when it enters the transverse plane after an RF pulse. Because nuclei exchanges energy with each other as they collide, the magnetic moments begin to spread out in the transverse plane and they lose their phase coherence. In this process, the net transverse magnetization

(Mt) decays to zero exponentially with time. This is known as spin-spin relaxation.

The time constant that characterizes this decay is known as T2. Besides the spin-spin interactions, the inhomogeneities of the main magnetic field can contribute to the decay. This means that nuclei experiencing different main magnetic field will precess at different Larmor frequency.

Oxyhemoglobin is diamagnetic; it contains no unpaired electron and has zero magnetic moment. Deoxyhemoglobin has unpaired electrons and a significant magnetic moment; it is paramagnetic and thus reduces the magnetic field homogeneity in its environment. The presence of deoxyhemoglobin facilitates the proton spins in the environment to become out of phase more quickly. The time constant that describes combined effect of spin-spin interaction and magnetic field inhomogeneities is known as T2\*. As a result the MR signal intensity is reduced in the local environment where deoxyhemoglobin is present. Therefore deoxyhemoglobin can be thought as an endogenous contrast agent.

## **Functional MRI**



Functional MRI technique measures changes in the blood oxygenation levels in the circulation with respect to a baseline MR signal; therefore it is an indirect measure of neural activity (Bandettini et al., 1992). Blood supply in the capillary beds increases due to increasing neural activity in the surrounding tissues. It requires energy to maintain and restore neuronal membrane potentials. This energy is not stored in the brain, but must be continuously supplied by the vascular system through the delivery of glucose and oxygen. This increase in the blood supply overcompensates for neuronal oxygen extraction, thereby causing an increase in the oxyhemoglobin concentration and a decrease in the deoxyhemoglobin concentration. In the area of neural activation, increase in cerebral blood flow (CBF) results in an excess of oxygenated hemoglobin beyond the metabolic need, thus reducing the fraction of paramagnetic deoxyhemoglobin in the vasculature. (Fox and Raichle, 1986). The oxygen saturation of venous hemoglobin changes from 75% saturated to about 90% saturated. In other words, the net effect of elevated neural activity is a decrease in the local deoxyhemoglobin concentration, which results in a higher MR signal intensity. If

the MR signal is acquired overtime, then the temporal fluctuation of it can be interpreted as the fluctuation of neural activity at that site. The image acquired based on this type of contrast is known as blood oxygenation level dependent (BOLD) MRI (Ogawa and Lee, 1990).

This contrast can be detected in small veins, where the changes in oxygenation take place. Changes in venous oxygenation are functions of cerebral blood flow, cerebral metabolic rate of O<sub>2</sub>, and cerebral blood volume. Fluctuation in BOLD signal can be modeled as a percentage of the baseline BOLD signal level (Kim et al., 1999).

The main advantages of functional MRI (fMRI) include its noninvasive nature, relatively high spatial and temporal resolution and its ability to provide the whole brain coverage of the subjects. Therefore it has become a tool for the study of neural activities and their synchronies between different parts of the brain. The main disadvantage is that it is an indirect measure of neural mass activity, as an increase in BOLD signal could be contributed by the combination of excitatory and inhibitory activities between these neurons, such that there is still no net

functional output from that specific functional region (Logothetis, 2008).

**Chapter 2            Specific Aim 1: Plastic Changes in Motor Cortex After  
Dominant (Right) Hand Task**

## **Introduction**

To successfully adapt to the outside world, the brain is known to change continuously based on inputs from external stimuli (Rakic, 2002; Zeithamova et al., 2012). This feature is referred to as the brain's plasticity and forms the basis of many of our daily functions including memory and learning. Plastic changes on a time scale of months or years have been well documented. For example, it was reported that London taxi drivers showed a larger hippocampal volume compared to control subjects as this structure is used extensively in memorizing street names (Maguire et al., 2000). Similarly, professional pianists have larger motor and auditory cortices compared to non-musicians (Gaser and Schlaug, 2003). On a time scale of days to weeks, effects of training were shown in evoked response (Karni et al., 1995; Karni et al., 1998; Xiong et al., 2009; Debas et al., 2010) as well as in spontaneous activity in the resting brain (Lewis et al., 2009; Ma et al., 2010; Kilpatrick et al., 2011; Ma et al., 2011; Taubert et al., 2011).

On a time scale of minutes, brain plastic changes have been demonstrated in classic memory cortices such as hippocampus (Tambini et al., 2010) and frontal

regions (Albert et al., 2009; Hasson et al., 2009). However, it is unclear whether primary sensory and motor cortices can also manifest plastic changes following a short task. The goal of the present study is to provide evidence that a 23-minute motor task can leave behind a detectable “footprint” in human motor cortex, as shown by neuroimaging.

This study will focus on changes in resting state brain activity as assessed by functional connectivity MRI (fcMRI) (Biswal et al., 1995; Raichle et al., 2001). Unlike detecting changes in the evoked neural activity, detecting changes in the resting activity requires less subject cooperation and thus the fcMRI signal is less dependent on effort or attention. Resting state image data also allow the assessment of all brain regions, not just the task-activated brain regions as in evoked fMRI (van den Heuvel et al., 2008). Furthermore, the ability to detect the plastic changes under resting state permits a demonstration that the neural substrate of the memory is present in the brain even it is not being used.

In this study, I compared fcMRI data acquired before and after a 23-minute button-press task. Sham control experiments were performed to ensure

that the changes detected were not due to subject becoming drowsy or sleepy after being inside the scanner for a while. The results were further verified by additional studies on a new cohort with a two-hand (rather than right-hand only) button-press task. Moreover, in this cohort, three post-task fcMRI runs were performed to assess how long it takes for the plastic changes to dissipate. Voxel-wise comparison was conducted in the entire brain to examine whether brain areas other than a priori regions-of-interest (ROI) (i.e. motor cortices) showed the plastic changes.

Although it is well known that the brain's plasticity forms basis to our daily functions such as memory and learning, identifying potential biomarkers to brain's plasticity has been less straightforward. The main approach has been a standard task-activation paradigm in functional magnetic resonance imaging (fMRI), where spatial patterns of activation were compared across study groups or imaging sessions (Karni et al., 1995; Xiong et al., 2009; Debas et al., 2010). However, this paradigm has its limitations. First, practice effects, fatigue, and

habituation can limit the sensitivity and confound the interpretation of the results. Second, it relies on the participant being able to perform the task, which is not always feasible especially in patients.

Resting state functional connectivity MRI (fcMRI) can help circumvent these limitations. It uses the strength of correlations of a neural activity index between functionally connected regions during rest as a marker to the brain's organization (Biswal et al., 1995; Beckmann et al., 2005; Damoiseaux et al., 2006; van den Heuvel et al., 2008). The goal of my aim is to demonstrate that alterations in resting brain activity may be used as a potential biomarker for brain plasticity. Since neural events during rest in sensory cortex are known to be associated with previous experiences (Kenet et al., 2003; Huber et al., 2004; Foster and Wilson, 2006), the spontaneous neural activity in the resting brain has been used to demonstrate effects of training (Waites et al., 2005; Albert et al., 2009; Hasson et al., 2009; Lewis et al., 2009; Stevens et al., 2010). Taken together, these studies show that the strength of connection between nodes in a brain can be modulated across varying time scale. However, this renders observation of modulation by



training challenging, namely in understanding what the minimal requirements are for soliciting robust, detectable changes in the connections between nodes in a brain, and how soon such changes are being encoded in brain.

Effects of training have been shown in evoked response (Karni et al., 1995; Xiong et al., 2009; Debas et al., 2010), as well as the spontaneous activity in a resting brain (Waites et al., 2005; Albert et al., 2009; Hasson et al., 2009; Lewis et al., 2009; Stevens et al., 2010). Thus I hypothesize that since both evoked and spontaneous activities coexist during training (Liu et al., 1999; Fox et al., 2006; Fox et al., 2007), then once the evoked activity has ended, the spontaneous activity should still reflect the task effect. In other words, evidence should exist that strengthening of functional connectivity occurs within the network just evoked in association with the training.

Previous studies tend to focus on the connections between different networks of the brain. I sought to answer a more straight-forward question, that is, whether or not a robust change in functional connectivity can be detected in given brain regions after just repeated use. I chose human motor cortex as a model because

early adaptation and consolidation of previous motor experience takes place there first (Gandolfo et al., 2000; Muellbacher et al., 2002). I applied the classical resting-training-resting epoch to compare the brain's functional connectivity immediately following the task. The task only required the subject to click a button as soon as they observed the white cross in the middle of the display changing to grey. The training consists of 40 such trials and spans 23 minutes. A five-minute resting state fcMRI were scanned before and after the training, and they were compared for differences in their functional connectivity.

I utilized two defining characteristics of spontaneous activity measured by BOLD functional connectivity Magnetic Resonance Imaging (BOLD fcMRI) in this study: their tendency to be correlated across hemisphere (Biswal et al., 1995; Lowe et al., 1998; Cordes et al., 2000; Greicius et al., 2003; Fox et al., 2005; Damoiseaux et al., 2006; Nir et al., 2006; Fox and Raichle, 2007; Golland et al., 2007; Vincent et al., 2007), and their amplitude of fluctuation (AF) (Yang et al., 2007). My analysis is based on comparing changes in Pearson correlation coefficient (CC) between left motor cortex (LMC) and right motor cortex (RMC)

before and after training, and the corresponding changes in their ALFF.

## Material and Methods

BOLD fMRI data ( $3.4 \times 3.4 \times 5 \text{ mm}^3$  voxels, TE 25ms, TR 1000ms, flip angle 60 degrees) were acquired using a 3T Philips MR scanner. Healthy *right-handed* adults were recruited for the motor task using their right hand ( $n=24$ ,  $25 \pm 14 \text{ y.o.}$ , 13 male). The scan session included the pre-task fcMRI scan (under resting state), followed by the task, and then concluded with a post-task fcMRI scan (Figure 5).

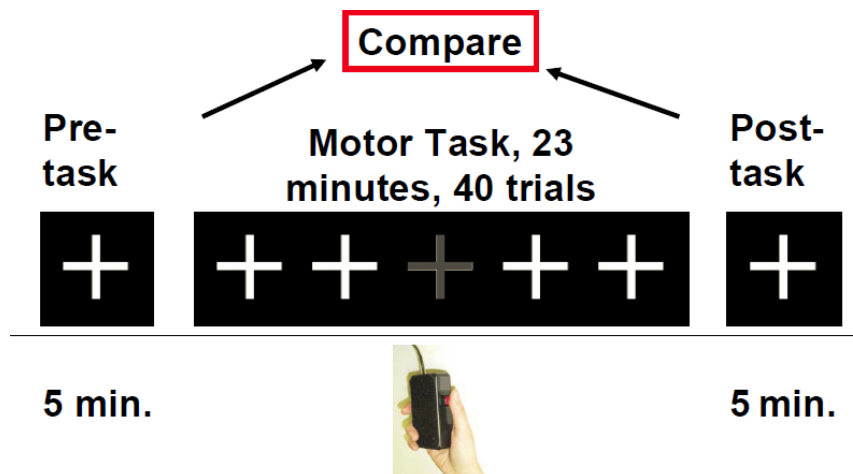


Figure 5 Experiment design. Within a single imaging session, after a five minutes pre-task fcMRI, the subject performed 23 minutes of button-clicking motor task with their right hand based on a visual queue. Then they were scanned for a post-task rest fcMRI. The two fcMRI scans were compared.

The pre-task and post-task fcMRI were five minutes. During the 23 minute task period, the subject performed unilateral motor task, in which they fixated on a white crosshair and, when the crosshair occasionally changed color to grey for 1000ms, they are supposed to press a button three times with their right index finger as soon as they saw the crosshair dim. The color change occurs every 27-32 seconds with randomized intervals. The two fcMRI runs before and after the motor task were performed with identical protocols (fixation on a white crosshair, 21 axial slices).

### **Sham experiment**

Ten subjects underwent scan session consisted of seven five-minute resting state runs with (1) a white cross in the center of their view, and (2) a button box in their right hand. They were instructed to remain awake with their eyes open. At the end of each run the subject were asked and responded to inquiry of their overall status.

All subjects reported to have complied with the instructions.

### **Region of Interest (ROI) selection – Motor Cortex**

The brain masks corresponding to left/right motor cortices were defined by the following procedure. I recruited back the 24 subjects from the one-hand task group for a separate scan session (at least 24 hours later), in which they performed a simple bilateral finger tapping task (40 seconds OFF, 20 seconds ON, eight repetitions, imaging parameters were identical to the plasticity sessions, total duration 8'40"). The data were processed with standard procedures including image realignment, spatial transformation into Talairach space, general linear model on individual subject, group-level analysis on regression coefficients, and delineation of activation clusters, which included left/right motor (sensory) areas and supplemental motor area (SMA). The final left (right) motor mask is then defined as the top 1000 voxels according to the one-sample t score in the left (right) motor cluster. These template ROIs were then transformed to individual subject space for spatial averaging.

### **Region of Interest (ROI) selection – Default Mode Network**

The parietal cortices of the Default Mode Network (DMN) were used as

the control regions where no plastic changes are expected as these regions are considered to be unrelated to the motor task used in the present study.

The brain masks corresponding to left/right parietal cortices were defined by the following procedure. The pre-task and post-task fcMRI data of the one-hand task group (N=24) were transformed into the Talairach space. A seed ROI (size=0.73 cm<sup>3</sup>) were positioned at bilateral posterior cingulate cortices based on Talairach coordinates (Hong et al., 2009; Xu et al., 2011). The cross-correlation coefficient (CC) between these seed voxels and all other voxels was calculated to generate a correlation map (using both pre-task and post-task fcMRI data). Then, a Fisher-z transform was employed and a group analysis was performed on the z-maps of all subjects to identify the DMN, which included posterior cingulate cortex, medial frontal cortex, and left/right parietal cortex. The final left (right) parietal mask is then defined as the top 500 voxels according to the one-sample t score in the left (right) parietal cluster. These template ROIs were then transformed to individual subject space for spatial averaging. Note that, since the ROIs were defined on the group data, they can be used for both

one-hand and two-hand data sets. It is also important to note that the goal of this study is to compare between pre-task and post-task, thus the definition of ROI is not expected to cause bias in my results as long as the same ROIs are applied to both pre and post data.

### **Region of Interest (ROI) selection – Auditory Network**

Since the auditory cortex is expected to be continuously stimulated by the magnet noise throughout the experiment, it is logical to examine whether this brain region also shows plastic changes comparing the post-task to pre-task fcMRI data. ROIs corresponding to left/right primary auditory cortex (A1) were delineated by anatomic masks (BA 41) defined on the Talairach template; the masks were transformed to individual space for spatial averaging. The rest of the ROI analysis steps were identical to those used for the motor cortex.

### **Data Processing**

All image volumes were co-registered to the first volume of the first fcMRI run. Physiologic fluctuations in the signal time course were removed by regressing out time courses of the whole-brain white matter, cerebral spinal fluid,

and six motion vectors. The time series were then band-pass-filtered to 0.01-0.1 Hz, which is the bandwidth commonly used in fcMRI processing (Damoiseaux et al., 2006). To further identify the bandwidth in which the plastic changes are most pronounced, I further band-pass-filtered the time-series to 0.01-0.05 Hz for a lower band, and from 0.05-0.1 Hz for a higher band.

Spatially averaged time courses (after removal of white matter, CSF, and motion vectors, and band-pass filtered as stated above) were obtained for each ROI. Two fcMRI indices were computed. CC between bilateral ROIs was calculated using Pearson correlation. Amplitude of fluctuation (AF) of the time course was calculated as the temporal standard deviation divided by mean signal intensity x 100% (Yang et al., 2007). This index is defined for each of the left and right sides.

Two-tail paired Student t tests were used for comparisons of pre-task and post-task indices. For the sham control fcMRI data, linear mixed effect model and one-way ANOVA were used since multiple time points were available.



## Results

### **CC between bilateral motor cortices was significantly greater in post-task fcMRI**

CC between left and right motor BOLD time courses was  $0.75 \pm 0.02$  (mean  $\pm$  SEM,  $N=24$ ) in the pre-task fcMRI data, consistent with previous literature that bilateral motor cortices show strong resting-state connectivity (Biswal et al., 1995; Damoiseaux et al., 2006; van den Heuvel et al., 2008). The post-task fcMRI data showed a CC value of  $0.83 \pm 0.02$ , which was significantly greater ( $p=0.002$ , two-tail paired t test) than that of the pre-task data (Figure 6). Because these CC were calculated using a fairly large range of signal frequencies (0.01-0.1 Hz), I further examined which frequency range contributed most to the correlation increase by splitting the frequency components into a lower (0.01-0.05 Hz) and a higher band (0.05-0.1 Hz) (Figure 7). It was found that the increase of CC was specific to the higher frequency band ( $p=0.02$ ), whereas the lower frequency band showed no changes in CC ( $p=0.77$ ) (Figure 8). I therefore focused on the higher frequency band in the remainder of the analyses.

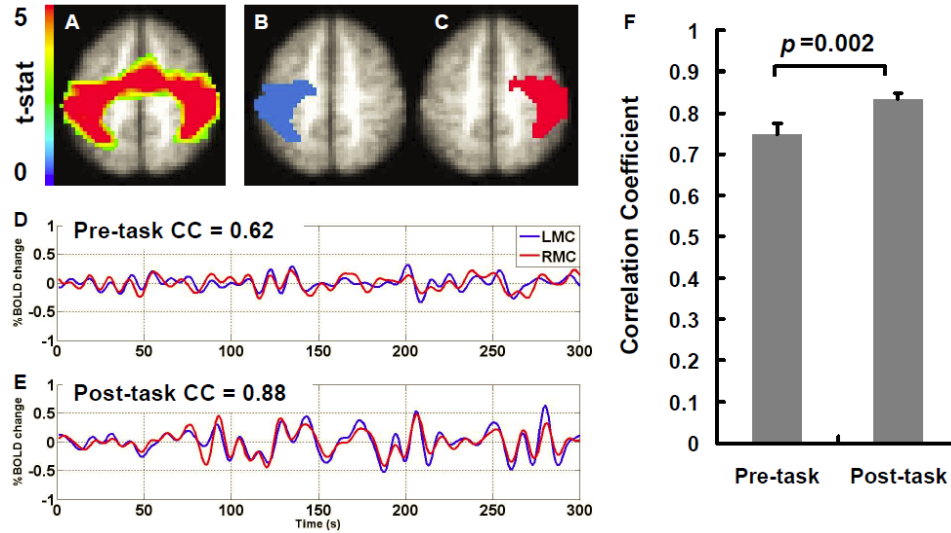


Figure 6 Motor cortex CC increases significantly after right-hand motor task. (A) Activation map from bilateral finger tapping experiment which identified motor cortices. (B) Top 1000 voxels based on the activation score in the left side that constitutes Left Motor Cortex (LMC) Region of Interest (ROI). (C) Top 1000 voxels based on the activation score in the right side that constitutes Right Motor Cortex (RMC) Region of Interest (ROI) (D) The time series of the LMC and RMC in an example subject pre-task rest and their correlation coefficient (CC). (E) The post-task rest time series of the same subject and CC. (F) Average CC of 24 subjects showing significant CC increases in the post-task rest (n=24, error bar = standard error).

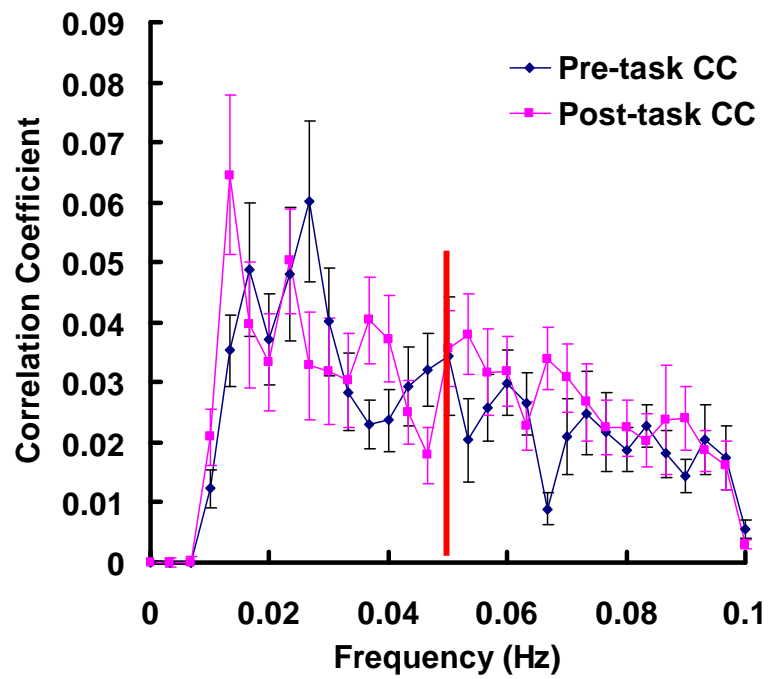


Figure 7 Spectral decomposition of CC. Contribution by each frequency bin to the overall CC is shown. The spectrum is divided at middle, 0,05 Hz, into the low band (0.01-0.05Hz) and the high band (0.05-0.1Hz). n=24, Error bar = standard err.

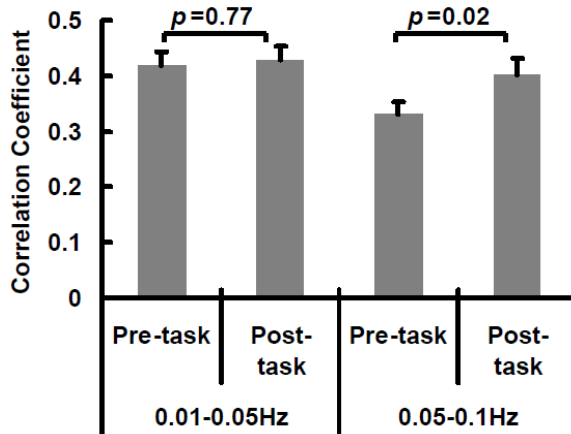


Figure 8 High band CC shows significant increase but not the low band.

### Sham control experiment showed no changes in CC in motor cortices

To provide evidence that the motor task was causal of the observed CC changes, I performed a sham experiment where the subject remained rest during the entire duration of the experiment (no motor task) while seven fMRI runs were performed consecutively. CC values between the bilateral motor cortices showed no changes with time regardless the type of statistical analysis used (linear mixed effect model on all seven runs,  $p=0.86$ ; one-way ANOVA on all seven runs,  $p=0.73$ ; paired t test between run 1 and run 7,  $p=0.96$ ). This finding also suggested that the observed CC increase was not due to the subject becoming

drowsy or sleeping inside the scanner.

### **The plastic changes were region-specific**

To examine whether the plastic changes were spatially specific or they were a whole-brain phenomenon, I studied another brain region that also has strong bilateral connectivity but is unrelated to the motor task, specifically the left and right parietal cortices, which are parts of the DMN. The left and right parietal cortices showed a significant correlation as expected, but there was no difference between the pre-task and post-task CC values (0.01-0.1 Hz band:  $0.68 \pm 0.02$  and  $0.67 \pm 0.03$  for pre- and post-task ( $p=0.86$ ), respectively; 0.01-0.05 Hz band:  $0.42 \pm 0.02$  and  $0.41 \pm 0.02$  for pre- and post-task ( $p=0.78$ ), respectively; 0.05-0.1 Hz band:  $0.26 \pm 0.02$  for both pre- and post-task,  $p=0.72$ ) (Figure 9, Figure 10).

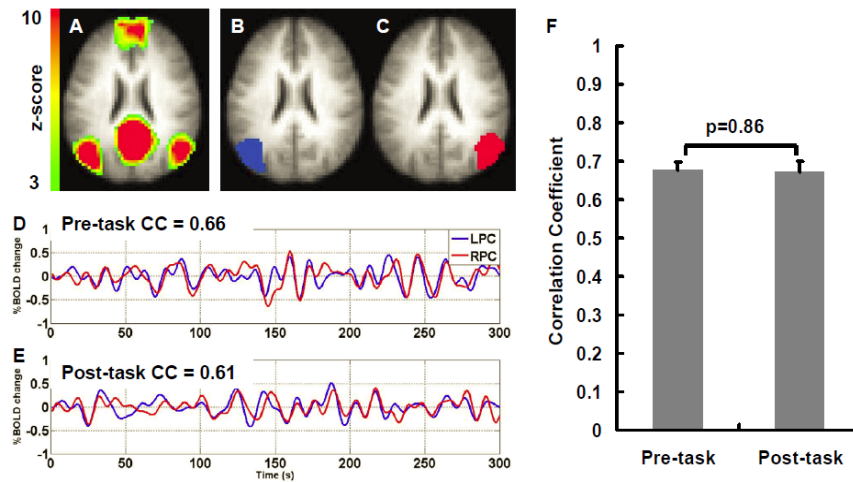


Figure 9 CC between the left and right parietal cortices of the Default Mode Network did not change significantly after motor task. (A) The average Default Mode Network of all subjects. (B) The top 500 voxels selected at the left parietal cortex (LPC) (C) The top 500 voxels selected at the right parietal cortex (RPC). (D) The time series of the LPC and RPC in an example subject pre-task rest and their correlation coefficient (CC). (E) The post-task rest time series of the same subject and CC. (F) Average CC of 24 subjects showing no significant CC changes in the post-task rest

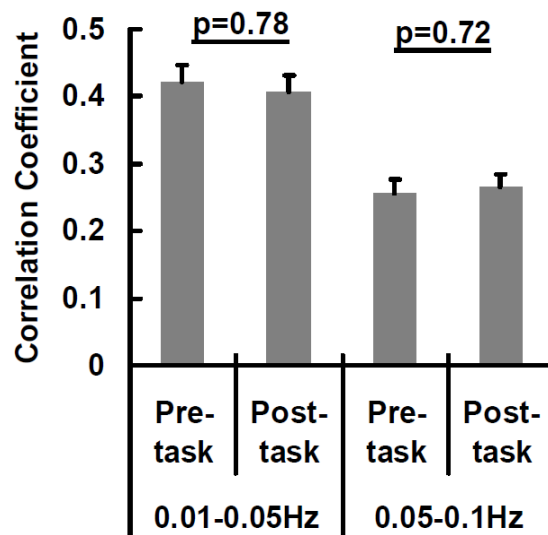


Figure 10 Neither high band nor low band CC between LPC and RPC showed significant changes after motor task.

### **Plastic changes in brain regions stimulated by MRI noise – primary auditory cortex**

If plastic changes can occur in the motor cortex due to motor activation, such changes may also be present in the auditory cortex due to strong MRI noise. Therefore, as an exploratory analysis, I examined fcMRI indices in the primary auditory cortex (BA41). CC between left and right auditory cortices during the post-task period was found to be significantly greater than that during the pre-task period. In this cohort, the pre- and post-task CC were  $0.319 \pm 0.027$  (mean  $\pm$  SEM, N=24) and  $0.415 \pm 0.035$ , respectively ( $p=0.02$  for pre/post comparison) (Figure 11).

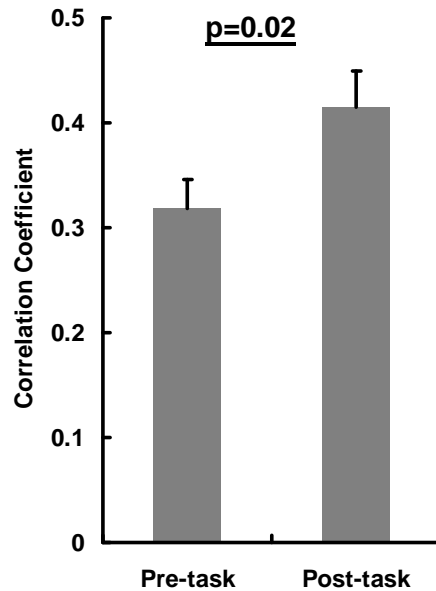


Figure 11 Auditory cortex CC shows significant increase in post-task rest after right-handed motor task.

### **Amplitude of Fluctuation (AF) of fcMRI signal also increased in post-task period**

AF is another quantitative index from the fcMRI data. When physiologic fluctuations have been removed by WM/CSF/motion regressors and random noise is minimized by spatial averaging, AF is thought to be predominantly originated from spontaneous neural activity (Yang et al., 2007; Luchinger et al., 2012).

Figure 12 shows the AF indices during the pre-task and post-task periods. It was



found that AF increased following the motor task. Interestingly, both left motor cortex (LMC) ( $p < 0.001$ , paired t test,  $N=24$ ) and right motor cortex (RMC) ( $p = 0.002$ ) showed a significant task-related AF increase although the right-hand task used in this study was expected to primarily activate the LMC. In terms of the effect size, LMC did manifest a significantly ( $p = 0.003$ , paired t test,  $N=24$ ) greater effect (51% increase comparing post-task AF to pre-task AF) compared to RMC (35% increase comparing post-task AF to pre-task AF).

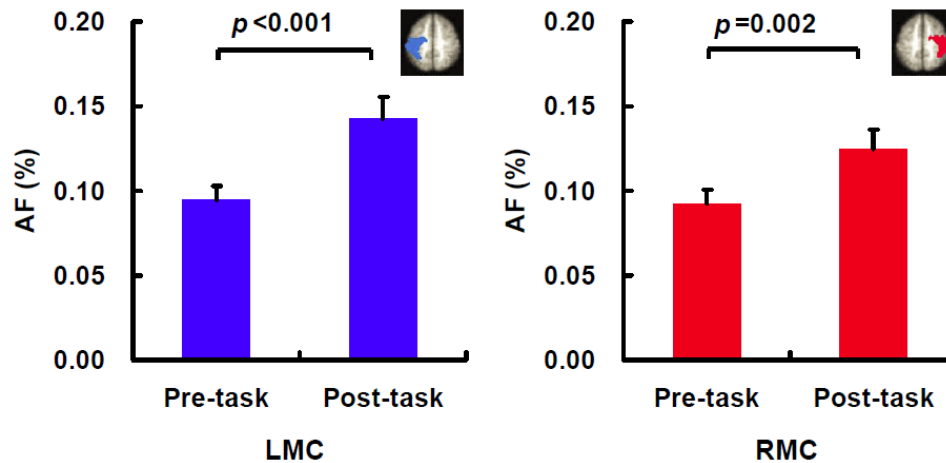


Figure 12 Motor cortex high band AF shows significant increases in the post-task rest.

AF data in auditory cortices showed similar results (Figure 13). In the

one-hand-task cohort, AF in the left auditory cortices increased from  $0.137 \pm 0.008\%$  (pre-task) to  $0.196 \pm 0.015\%$  (post-task) ( $p < 0.001$  for pre/post comparison). The values were  $0.116 \pm 0.007\%$  (pre-task) to  $0.162 \pm 0.009\%$  (post-task) ( $p < 0.001$  for pre/post comparison) in the right auditory cortex.

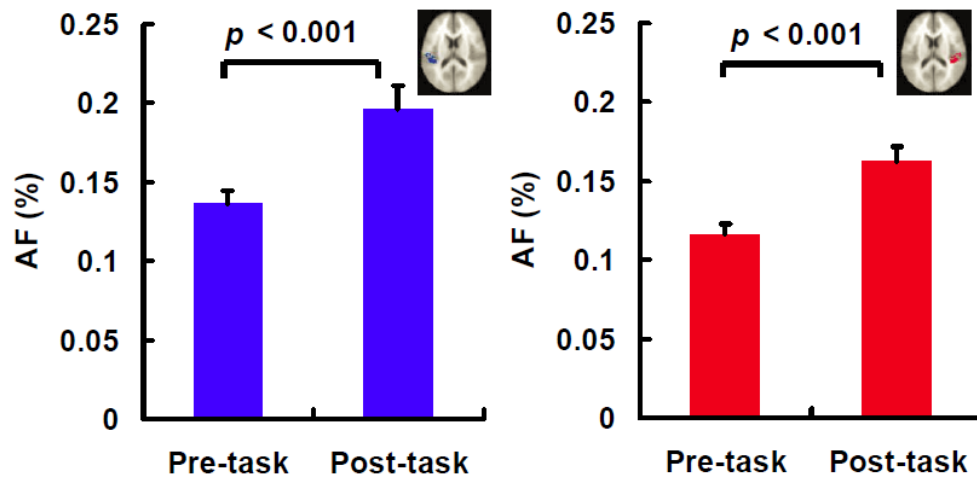


Figure 13 Auditory cortex high band AF increased significantly in post-task rest after the right-hand task.

Neither parietal cortices of the Default Mode Network showed significant changes in AF (Figure 14).

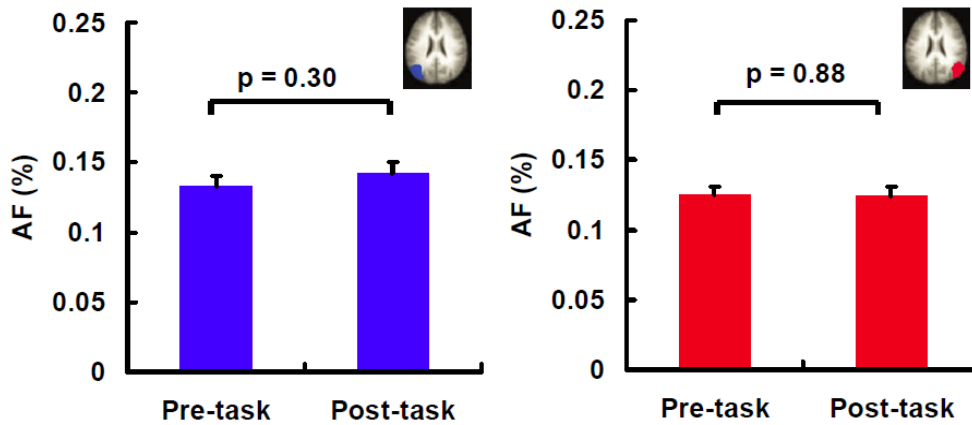


Figure 14 LPC and RPC of the Default Mode Network did not show significant AF changes in post-task rest.

## Discussion

My results show that human brain is being modified continuously during everyday life. This effect can be detected *in vivo* after merely minutes of usage. The plastic changes appear to be specific to the brain regions stimulated. These changes do not appear to be related to adaptation. The results here also show that although the task required right hand only, both left and right motor cortices were affected as shown by their post-task AF increases. This could be expected, as based on anatomical evidence, there are 10 to 15% of fibers in lateral cortical spinal tracts of human are uncrossed (Nyberg-Hansen and Rinvik, 1963).

My results also show that the effect of simple motor task is not just a “volume effect”. It did not increase the spontaneous activity across spectral profile. Rather, there is a selective enhancement in the 0.05-0.1Hz components of the post-task fcMRI. This is the main contribution to the elevated CC in the post-task resting state. Not only did the post-task spontaneous fluctuations of LMC and RMC become more synchronous, but their amplitudes also increased significantly. At this point however, it is not clear how long such post-task enhancement may persist. Future experiment will be designed to address the temporal trajectories of post-task fcMRI signals.

The present study demonstrated that a 23-min motor task can alter post-task motor functional connectivity. These data suggest that the brain is constantly re-organizing itself based on life experience and that a short-duration task is sufficient to leave a “foot-print” on the brain.

### **Comparison with previous plasticity literature**

The brain’s plastic changes as a consequence of use or experience have been documented in previous literature. It is known that structural changes can

take place after months or years of intensive usage (Maguire et al., 2000; Gaser and Schlaug, 2003; Bengtsson et al., 2005). Functional plastic changes can occur earlier and such evidence have been shown following days or weeks of task training, using a variety of techniques including functional MRI (Karni et al., 1995; Xiong et al., 2009; Debas et al., 2010; Ma et al., 2010), resting-state functional connectivity MRI (Lewis et al., 2009; Ma et al., 2011; Taubert et al., 2011), and Positron Emission Tomography (PET) (Maquet et al., 2000; Sidtis et al., 2004; Treyer et al., 2006). For example, Karni and colleagues conducted five weeks of sequential finger tapping training in young healthy human subjects and observed increased evoked fMRI response in motor cortices during the post-training period compared to the pre-training (Karni et al., 1995). Lewis et al. conducted visual perception training for 2-9 days and compared the subject's functional connectivity pattern before and after the training. The authors observed a strengthening of connections between the visual and attention brain regions (Lewis et al., 2009). There is also evidence that the plastic changes became particularly pronounced during rapid-eye-movement (REM) sleep on the same

night following the task (Maquet et al., 2000). The present study extends these previous findings to an even shorter time scale by showing that plastic changes can be detected following a task session as short as 23 minutes. My study has a similar time scale to an earlier report conducted in primates. Hoffman and McNaughton employed a virtual navigation motor reaching task on rhesus monkeys (*Macaca mulatta*) for 30 minutes, and the resting neural activity in the ten minutes before and after the task were compared (Hoffman and McNaughton, 2002). It was found that neural synchronization induced by the task was preserved during the post-task resting period, a finding comparable to the observations in the present study. Albert et al. conducted target-tracking task for 11 minutes and observed an increased connectivity between frontal and parietal regions, but not motor cortex (Albert et al., 2009). One possible reason for this discrepancy from my results may be that, in Albert et al., the subjects performed the task with their non-preferred hand (e.g. left hand task for a right-handed person), whereas the preferred hand was used in my study. Also, Peltier et al. reported that after 20 minutes of right-hand contraction task which was designed to fatigue the muscles,

they observed a decrease in the left and right motor cortices CC (Peltier et al., 2005). One obvious distinction of their results with mine here is that task for my subjects were not as physically demanding as theirs and therefore has smaller motor “footprint”. A note of interest regarding their results is that they also show increases in the spectral amplitude of motor post-task rest at frequency band similar to the 0.05-0.1Hz band I used throughout my work.

### **Imagery activation during the post-task period?**

Imagery activation has been shown to share some similarities with actual execution in term of neural representation (Rao et al., 1993; Stephan et al., 1995; Deiber et al., 1998; Binkofski et al., 2000; Boecker et al., 2002; Hanakawa et al., 2002; Nair et al., 2003; Dechent et al., 2004; Sharma et al., 2006; Iseki et al., 2008; Kasess et al., 2008; Chen et al., 2009; Munzert and Zentgraf, 2009; la Fougere et al., 2010). However, several pieces of evidence in my data suggest that imagery activation is unlikely to be the reason for my results. First, the auditory cortices also show significant CC and AF increases during the post-task rest. Since the magnet noise was present throughout the MRI session and was not part of the task,

it is unlikely that the subject would think of the sound more in the post-task period than in the pre-task period. Second, in this one-hand-task group, plastic changes were observed in both left and right motor cortices. Since motor task (and imagery) predominantly activates the contralateral side of the cortex, imagery motor activation (of the right hand) cannot account for signal changes in the right motor cortex (Stinear et al., 2006). Third, the subjects were specifically instructed not to think of anything in particular during the resting scans, and any occasional thinking of the motor task could not have accounted for the large (35-51%) increase in signal fluctuation.



**Chapter 3                      Specific Aim 2: Plastic Changes in Motor Cortex After**  
**Bilateral Hand Task**

## **Introduction**

Brain's plasticity forms the basis of many of our daily functions including memory and learning. It is then intuitive to speculate that certain changes have occurred to the brain comparing before and after a task. However, the exact neuronal processes that are altered are poorly understood, especially for human studies in which available tools are limited. In the Specific Aim 1, I showed that functional connectivity, measured as the cross-correlation coefficient (CC) between the left and right motor cortices in Blood Oxygenation Level Dependent (BOLD) signals during resting acquired by functional connectivity MRI (fcMRI) technique, can be enhanced after merely 23 minutes of right-hand button press task. However, given the simplicity of the task used (i.e. no behavior improvement can be quantified) and the relatively short training duration, the finding is somewhat surprising. A follow-up question is, if both hands were used during the task, how will the CC change after task? Furthermore, another logical follow-up question is how long it takes for the post-task effect to disappear, i.e. CC value returning to pre-task level. In the present study, I replicated my previous

finding of enhanced functional connectivity in a new cohort of subjects and, with additional post-task fcMRI acquisitions, I will show that the CC value returns to the pre-task level 4-5 min after the termination of the task.

### **Material and Methods**

Twenty-four healthy right-handed subjects ( $30 \pm 10$  y.o., 9 male) were recruited for the two-hand button-press experiment. The experimental procedure was identical to that of the one-hand experiment with two exceptions. The MR and imaging parameters are also the same ( $3.4 \times 3.4 \times 5 \text{ mm}^3$  voxels, TE 25ms, TR 1000ms, flip angle 60 degrees). There are the following modifications for this study: First, the subject held one button in each hand and was instructed to press both buttons simultaneously for three times. Second, I performed three post-task fcMRI runs (five minutes each) in these subjects, which allowed us to examine how long the plastic changes may last (Figure 15).

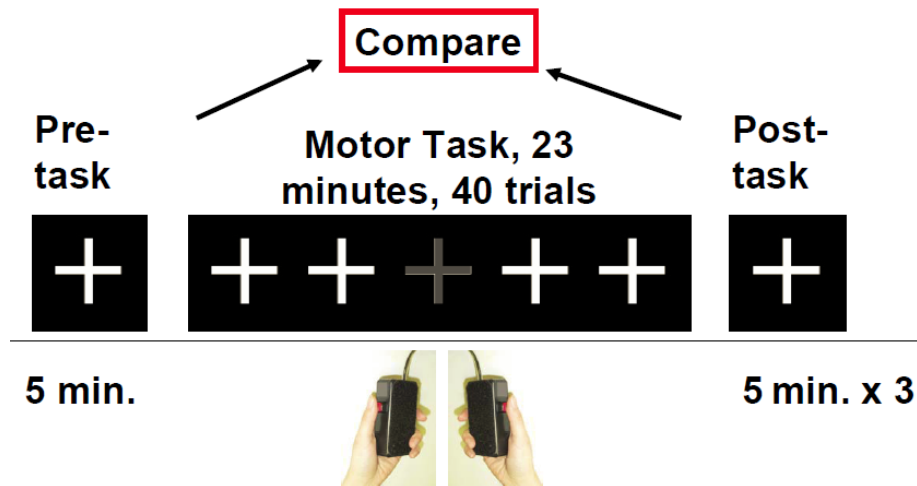


Figure 15 Experiment design. The five minutes pre-task rest is followed by the 23 minutes button-clicking motor task using both hands, followed by 15 minutes post-task rest.

### Data Processing

The methods used to process the fcMRI data is the same as reported in Aim 1. Briefly, all image volumes were realigned to the first volume of the first fcMRI run. Physiologic fluctuations in the signal time course were removed by regressing out time courses of the whole-brain white matter, cerebral spinal fluid, and six motion vectors (Fox et al., 2005; Hong et al., 2009; Chang and Glover, 2010). The time series were then band-pass-filtered to 0.01-0.1 Hz, which is the bandwidth commonly used in fcMRI processing (Damoiseaux et al., 2006). To further identify the bandwidth in which the plastic changes are most pronounced,

I further band-pass-filtered the time-series to 0.01-0.05 Hz for a lower band and from 0.05-0.1 Hz for a higher band.

Motor cortex ROI were derived from the motor cortex ROI template created during Aim 1. These ROI were transformed into the subject space. The Default Mode Network ROI were also derived from the average left and right parietal cortices ROI generated from Aim 1, then transformed into the subject space here.

Spatially averaged time courses (after removal of white matter, CSF, and motion vectors, and band-pass filtered as stated above) were obtained for each ROI. Two fMRI indices were computed. CC between bilateral ROIs was calculated using Pearson correlation. Amplitude of fluctuation (AF) of the time course was calculated as the temporal standard deviation divided by mean signal intensity x 100% (Yang et al., 2007). This index is defined for each of the left and right side ROI.

## **Results**

The lower frequency band (0.01-0.05 Hz) showed no changes in motor CC ( $p=0.229$ ), consistent with the results of the one-hand study. For the higher frequency band (0.05-0.1 Hz), the CC between bilateral motor cortices showed a significant increase ( $p=0.01$ , paired t test) following the task, from mean of  $0.30\pm0.02$  to  $0.38\pm0.03$ . However, it promptly returned to the pre-task level during the second post-task ( $0.27\pm0.02$ ) rest session and through the third session ( $0.27\pm0.02$ ) (Figure 16).

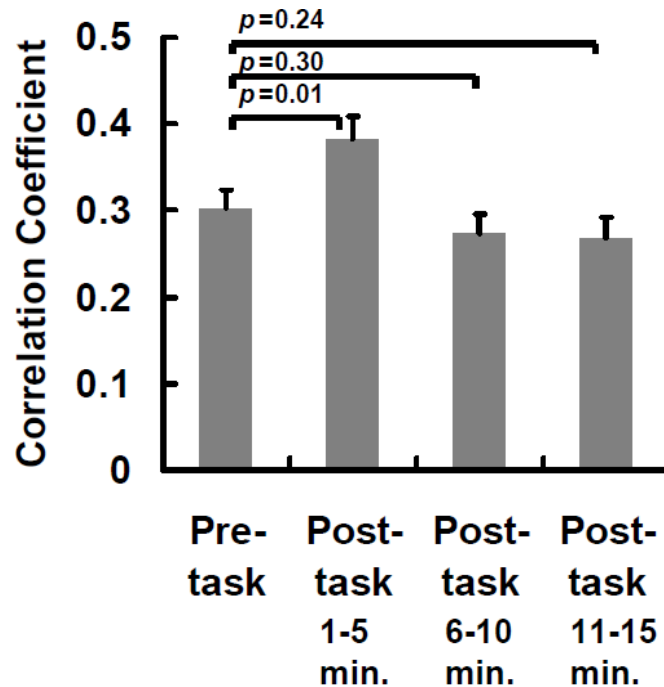


Figure 16 Left and right motor cortices CC changed significantly in the post-task rest after the

bilateral motor task, and returned to the pre-task level in the second post-task rest.

In the parietal cortex of the Default Mode Network, CC did not show significant change through the post-task scan (Figure 17).

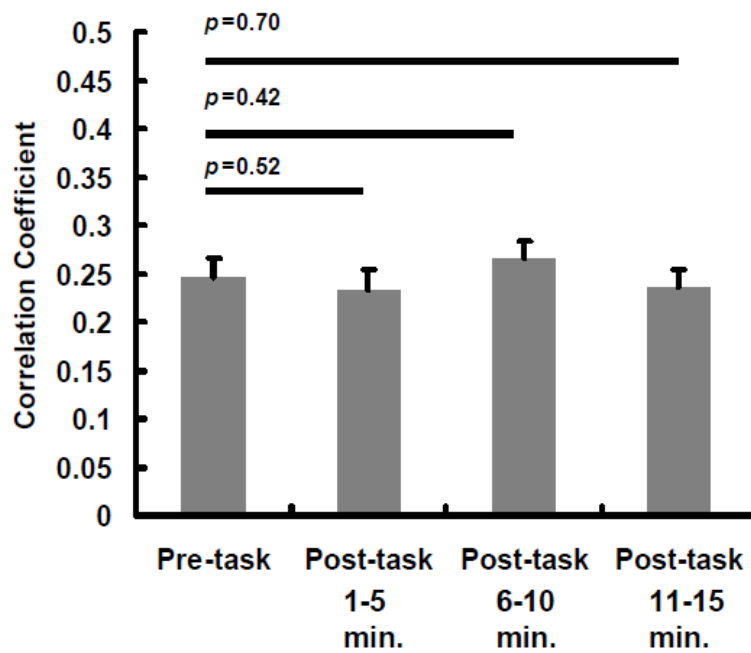


Figure 17 The Default Mode Network's left and right parietal cortices CC did not change significantly in the post-task rest after the bilateral motor task.

In the auditory cortex, however, CC increased significantly in the first five minutes of the post-task (Figure 18).

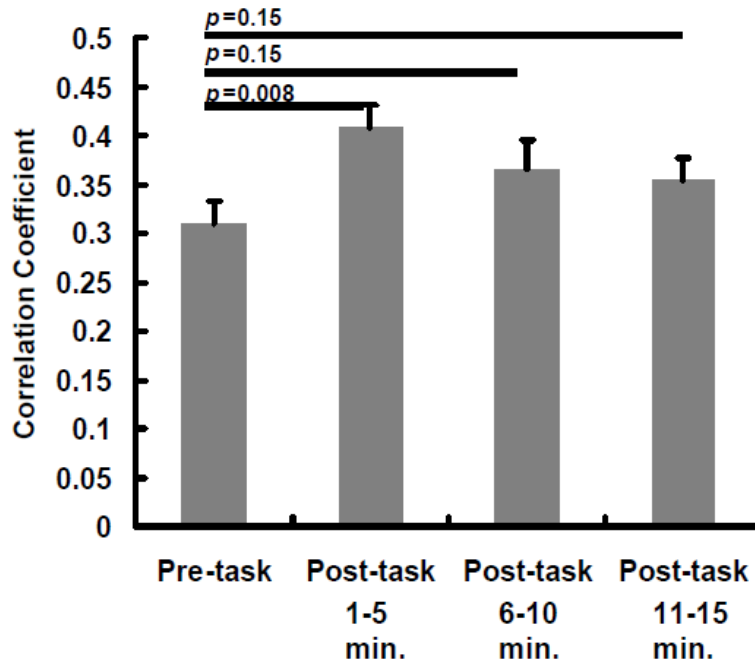


Figure 18 Left and right auditory cortices CC increased significantly in the first post-task rest after bilateral motor task, then return to the pre-task level.

AF showed an increase in both LMC ( $p<0.001$ ) and RMC ( $p<0.001$ ). The effect sizes in LMC and RMC were not different ( $p=0.233$ ) in the two-hand study, unlike the findings in the right-hand task, presumably because the two-hand task strongly activates both sides of the cortex (Figure 19).



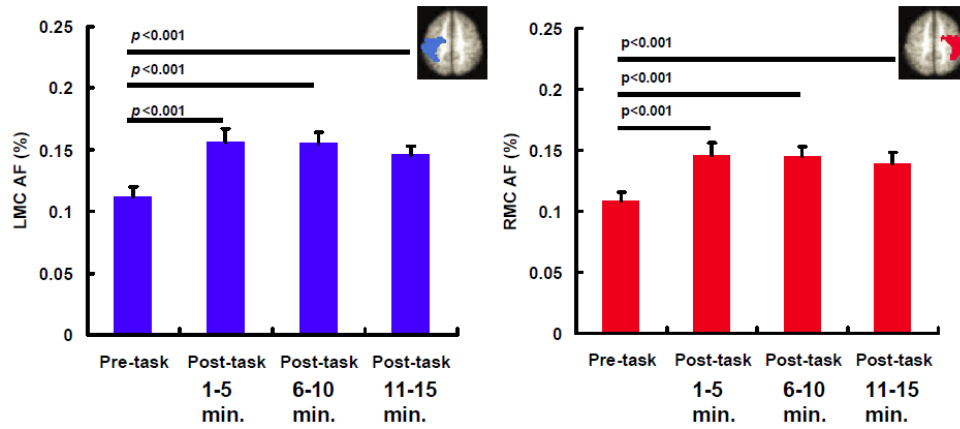


Figure 19 LMC and RMC AF increased significantly in the post-task rest after left-hand motor task and remained elevated through the third post-task rest.

Left and right parietal cortices showed no pre/post-task differences in AF

(Figure 20).

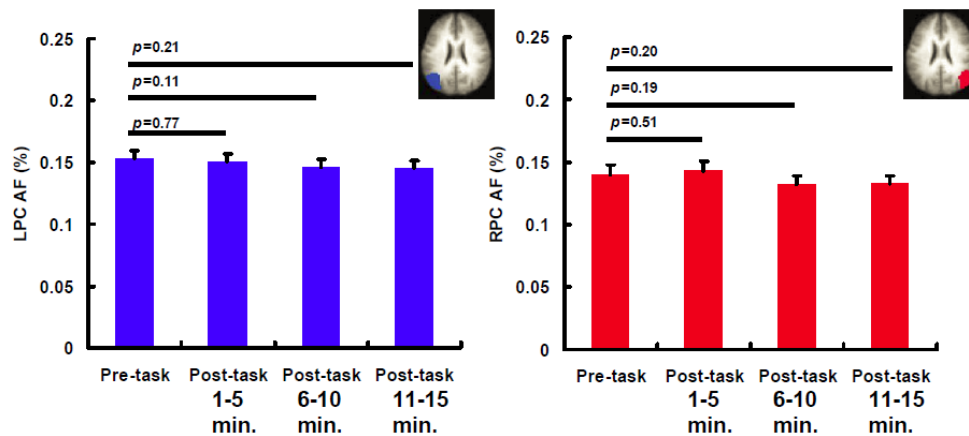


Figure 20 Left and right parietal cortices show no significant changes in AF in post-task rest after left-hand motor task.

However, both left and right auditory cortices showed significant increases in their AF during post-task rests (Figure 21).

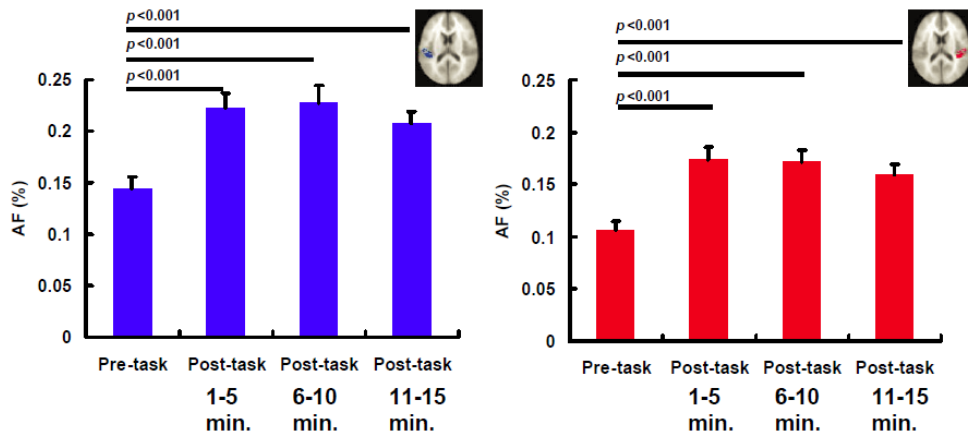


Figure 21 Left and right auditory cortices AF increased significantly in post-task rest after left-hand motor task, and remained elevated through the third post-task rest.

## Discussion

In this Aim, I successfully reproduced the results found in Aim1, even though the motor task included the left hand as well. At the BOLD signal level, frequency band of 0.05-0.1 Hz appear to consistently contain the signature, or “footprint”, of the plastic changes produced by the task. Specifically, in this frequency range, BOLD signals in a network impacted by the task became more synchronous and contain larger fluctuation amplitude. These changes also consist

of at least two components with different temporal behaviors. Functional connectivity, as measured by CC, can show a recovery effect by returning to the pre-task level, whereas the amount or intensity of the spontaneous activities, as measured by AF, persist through at least 15 minutes post-task. The results here shows that if the dominant part of the network were selectively invoked for the task, then the plastic changes observed will also appear in the remaining network.

The results here further underscore the sensitivity of fcMRI as a tool for measuring transient plastic changes in the brain. For the Default Mode Network, it was not expected to be invoked by the task, and its fcMRI signals showed no changes. In motor cortex and auditory cortex, however, task as well as the environment sound both provided stimuli that contributed to the changes in the resting state fcMRI signals.

Even though the results here appear similar in their magnitudes and general patterns when comparing to those of the Aim 1, these results do not imply that there is no difference between right-hand only and both-hand tasks. Therefore, the purpose of the next Aim is to examine how left-hand task impact the resting brain

functional connectivity in right-handed persons.

**Chapter 4                      Specific Aim 3. Plastic Changes in Motor Cortex After**  
**Non-Dominant (Left) Hand Task**

## **Introduction**

The results of Specific Aim 2 show that even if left hand was added to the motor task, the changes in the resting brain were similar to the case when only right hand was used. These results, while confirming my hypothesis that motor cortex can show transient changes in response to a short motor task, also raised a few questions. For example, did left hand contribute the increased Correlation Coefficient (CC) between left and right motor cortices and their amplitudes of fluctuation (AF)? As a model network, if a less dominant part of (left motor cortex) of the network were selected for the task, does the brain behave differently in the post-task rest?

## **Materials and Methods**

Subjects: 24 right-handed, healthy subjects were recruited for the motor task using their left hand (n=24, 29±9y.o., 10 male). BOLD fMRI data (3.4x3.4x5mm<sup>3</sup> voxels, TE 25ms, TR 1000ms, flip angle 60 degrees) were acquired using a 3T Philips MR scanner. The scan session included the pre-task fcMRI scan (under resting

state), followed by the task, and then concluded with a post-task fcMRI scan. The pre-task and post-task fcMRI were five minutes. During the 23 minute task period, the subject performed unilateral motor task, in which they fixated on a white crosshair and, when the crosshair occasionally changed color to grey for 1000ms, they are supposed to press a button three times with their left index finger as soon as they saw the crosshair dim. The color change occurs every 27-32 seconds with randomized intervals. The two fcMRI runs before and after the motor task were performed with identical protocols (fixation on a white crosshair, 21 axial slices) (Figure 22).

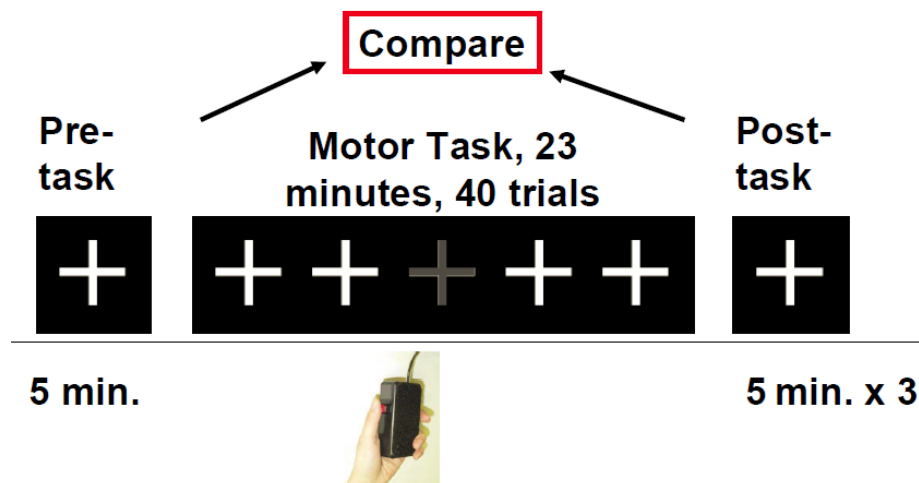


Figure 22 Experiment design. After the five minutes pre-task rest scan, subjects performed 23 minutes of button-clicking task with their left hand, followed by 15 minutes of post-task rest scan.

## **Data Processing**

Same methods were used to process the fcMRI data in this Aim as was in the previous Aims. Briefly, all images were realigned to the first volume of the first fcMRI run in order to calculate six degrees of motion vectors. All images were then spatially smoothed with 6mm FWHM. The time series contained in each voxel was further band-pass-filtered in the range of 0.01-0.1 Hz as this bandwidth is typically used for fcMRI (Damoiseaux et al., 2006). The motor cortex template ROIs created for Specific Aim 1 was used again on these subjects. The template ROIs were transformed to each subject's space. The left parietal cortex and right parietal cortex template ROIs created for Specific Aim 1 was also applied to these subjects. The auditory cortex ROIs were derived from the Brodmann Area 41 ROI in the TT\_Daemon atlas provided by AFNI. Similarly, these ROIs were transformed to each subject's space for this Aim.

Once these ROIs masks were transformed in the subject space, they were applied to the spatially smoothed fcMRI data to produce the average time series representing that ROI. As was in the previous Aims, after the artifacts (motion,



white matter, and CSF) were removed from the time series, the time series was also filtered in the 0.01-0.5Hz range as a low band, and 0.05-0.1Hz range as the high band.

## **Results**

The low band (0.01-0.05 Hz) time series showed no changes in their average motor cortex CC (pre-task CC = 0.41, post-task CC = 0.42,  $p=0.87$ ), which is consistent with the results shown in the previous two Aims. For the high band (0.05-0.1 Hz), however, there is difference with respect to right-hand and both-hand task results. Specifically, the increase in motor CC is not statistically significant (pre-task CC = 0.29, post-task CC = 0.33,  $p=0.45$ , second post-task CC = 0.30, third post-task CC = 0.29). Also, the post-task CC declined to the pre-task level during the second post-task rest. The transient changes observed here were smaller than in the both-hand experiment and thus the results here are not statistically significant (Figure 23).

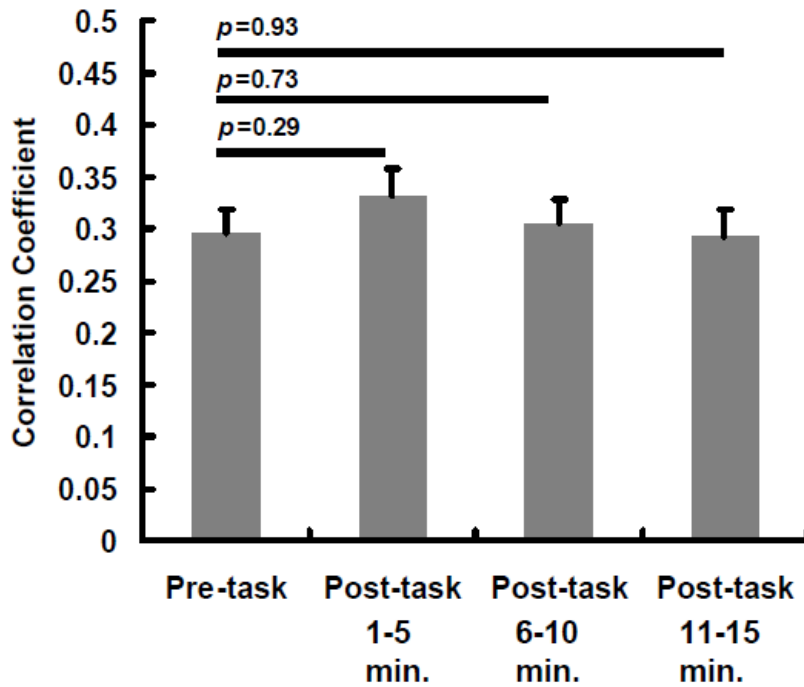


Figure 23 Left and right motor cortices CC did not change significantly in the post-task rest after left-hand motor task.

The Default Mode Network (DMN) was also analyzed for the CC between left and right hemispheres. The high band CC between the left parietal cortex (LPC) and right parietal cortex (RPC) did not show changes (pre-task CC = 0.24, first post-task CC = 0.23, second post-task CC = 0.24, third post-task CC = 0.24, no statistical significance found) (Figure 24).

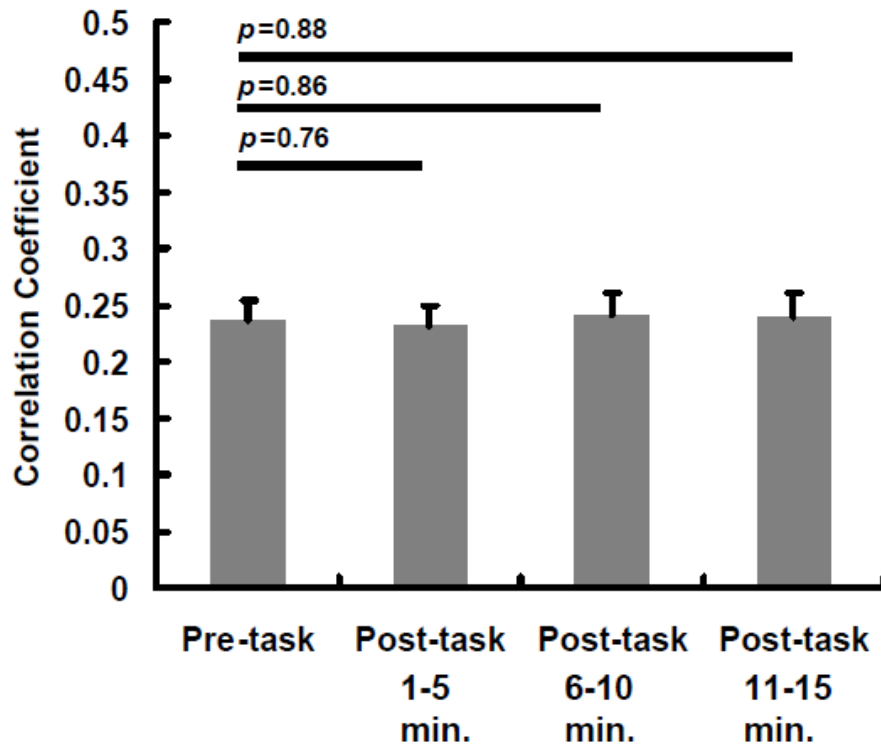


Figure 24 Left and right parietal cortices CC did not show significant changes after left-hand motor task.

I also examined the auditory cortex (Brodmann Area 41) for any CC changes.

The CC between left and right auditory cortices increased from 0.28 to 0.36,

$p=0.04$ , then in the second post-task, CC = 0.33, in the third post-task, CC = 0.31.

(Figure 25).

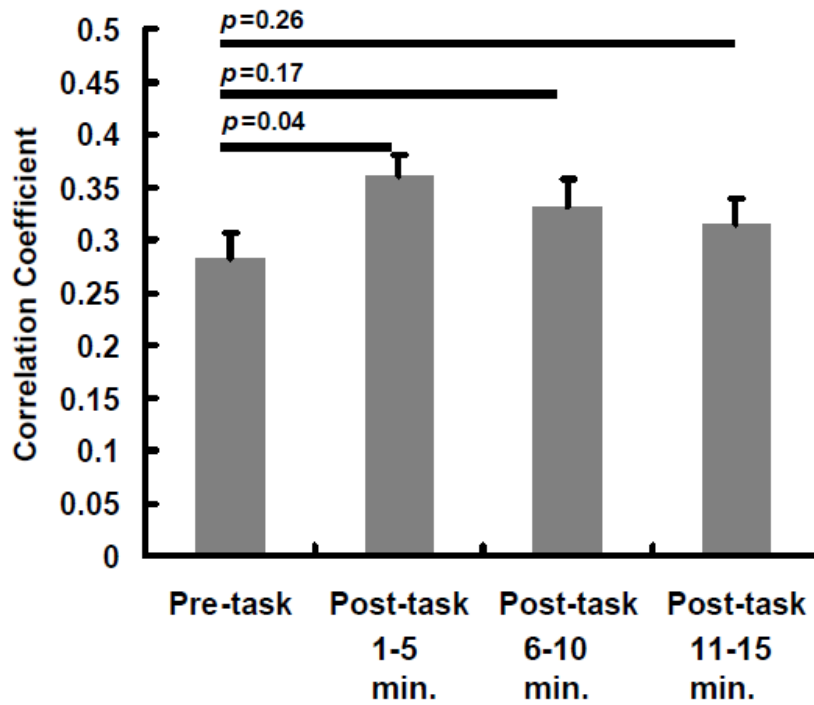


Figure 25 Left and right auditory cortices CC increased significantly in the first post-task rest after left-hand motor task, then return to the pre-task level.

In both left motor cortex (LMC) and right motor cortex (RMC), AF increased significantly in the first post-task rest and remained elevated through the third post-task rest (Figure 26).

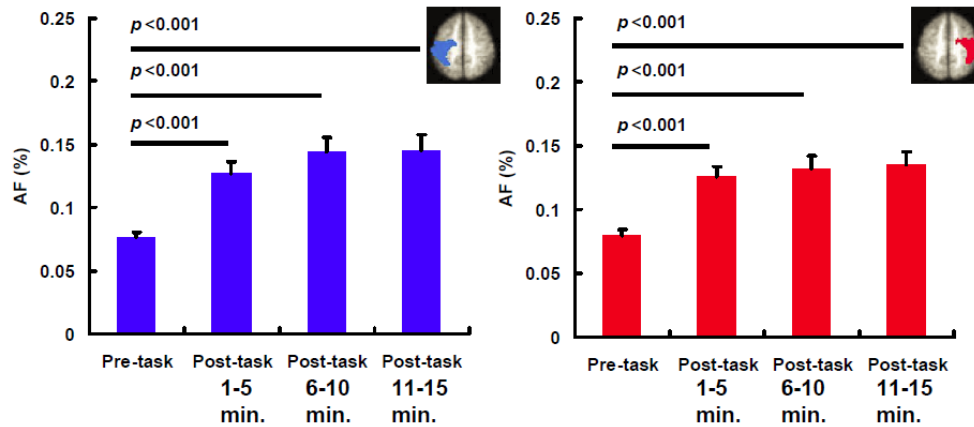


Figure 26 LMC and RMC AF increased significantly in the post-task rest after left-hand motor task and remained elevated through the third post-task rest.

As in the case of CC analysis, AF in the LPC and RPC of the Default Mode Network were examined and they show no significant changes through the post-task rest (Figure 27).

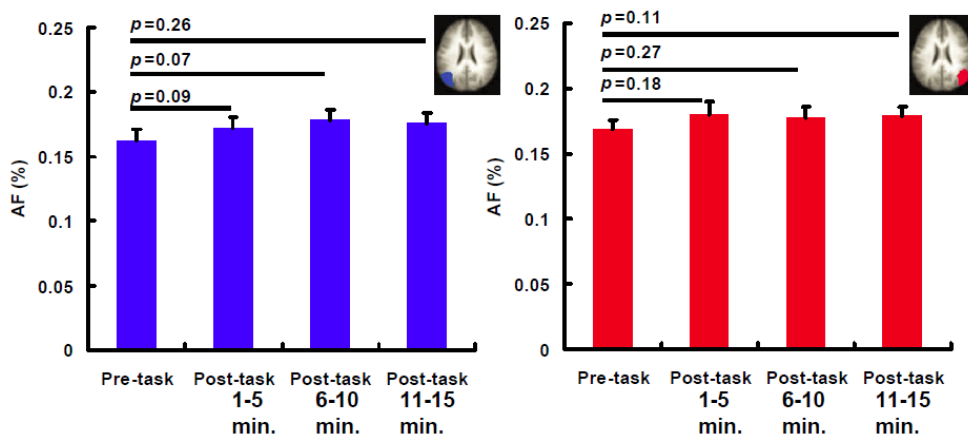


Figure 27 Left and right parietal cortices show no significant changes in AF in post-task rest after left-hand motor task.

For the auditory cortex, the AF increased significantly in post-task rest and remained elevated through the third post-task rest (left: Pre-task = 0.10%, post-task = 0.16%,  $p < 0.001$ . Right: Pre-task = 0.08%, Post-task = 0.13%,  $p < 0.001$ ) (Figure 28).

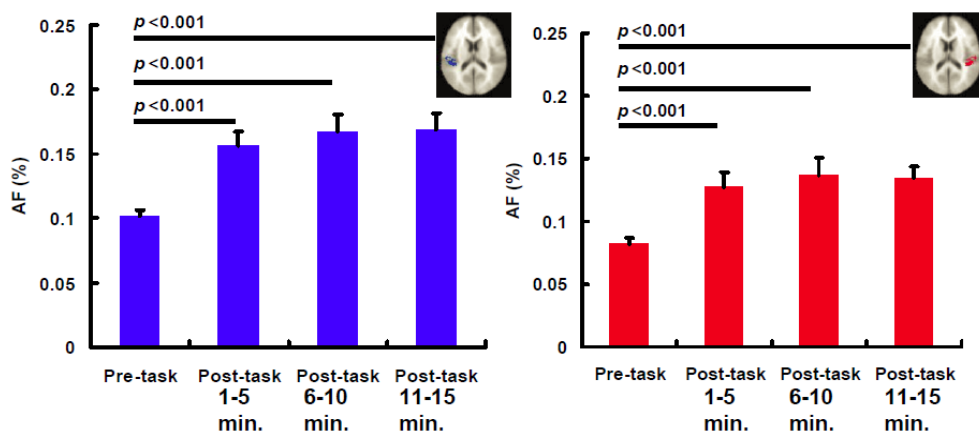


Figure 28 Left and right auditory cortices AF increased significantly in post-task rest after left-hand motor task, and remained elevated through the third post-task rest.

## Discussion

When the less dominant part (right motor cortex of the right-handed subjects) of the motor network was invoked by task, the “footprint” of the task is less than that observed in the previous Aims. The functional connectivity changes between

the two motor cortices measured by CC were not statistically significant. However, the post-task AF increased significantly in both motor cortices.

These results suggest that AF changes were sensitive to even slight experience or stimulation to the motor network, and that the less dominant part of the network can still impact the more dominant counterpart. This naturally leads into these questions: How different are the post-task resting brain amongst these different groups? To address this question, I used voxel based analysis and network analysis approaches to assess global differences in the entire brain, not just the network defined *a priori*. The results are reported in the following chapter.

## **Chapter 5      Voxel Based Analysis and Network Functional Connectivity Analysis**



## **Introduction**

The analyses presented thus far were based on spatial averaging of a pre-defined Region Of Interest (ROI). While this technique is useful in reducing random noise by averaging, it also restricted the analyses to those areas only. In this chapter, I used voxel based approach to address the question of what other regions of the brain showed plastic changes after the motor task? Further, since it is well known that the human brain is organized into functional networks (Damoiseaux et al., 2006; van den Heuvel et al., 2008), another important question to ask is whether or not other part of the brain were modified by my motor task. Also, to my knowledge, no one has shown whether or not functional connectivity in the entire brain can be modified by motor task within a single session.

As a large-scale system, the brain's organization can change over the timescale of decades. In a comparison of network organization between healthy young (mean age 24 y.o.) and old (67 y.o.) subjects, Meunier et al. found that in the old subjects, their cortical regions including motor network, default network,

and thalamus were less functionally connected to the rest of the brain than in their young subjects (Meunier et al., 2009). On a shorter time scale, Lewis et al. showed that after 2-9 days of visual perception task, functional connectivity between visual network and dorsal attention network increased significantly (Lewis et al., 2009). Tambini et al. showed that after 21 minutes of object-scene and face-scene encoding task, functional connectivity between left posterior hippocampus and right fusiform face area increased significantly (Tambini et al., 2010). However, it should not be generalized that performing tasks will automatically lead to detectable changes in functional connectivity. For example, Wang et al. conducted a semantic-matching task for 25 minutes, where a word was first presented by a picture, and the subjects were instructed to judge whether the picture matched the word or not. When they compared the pre- and post-task resting states, they did not detect significant changes in the functional connectivity of the Default Mode Network (DMN) with respect to other networks (Wang et al., 2012).

Based on the ROI results presented thus far, it is reasonable to expect that voxels in motor cortex and auditory cortex to show significant increases in post-task resting AF. But are there other regions of the brain with significant post-task AF increases? If so, do these regions show significant increases in their functional connectivity with one another?

In this chapter, I will first identify the locations of voxels that show significant changes in its post-task spontaneous amplitude of fluctuation (AF) in all three previous Aims, and then I will assess their changes in the organization of brain network in term of functional connectivity changes between all pairs of brain networks.

Calculation for AF is the same as in previous Aims, namely, AF is defined as  $\text{standard deviation} / \text{mean intensity} \times 100$  at each voxel time series. For network analysis, an anatomical template (atlas) is used to parcellate the voxel based fcMRI data. Voxel time series are spatially averaged based on the atlas. The pair-wise Pearson correlation is measured for all possible pairs to form a  $N \times N$  association matrix. This procedure is applied to both pre-task and post-task rests.

Then a comparison is made by taking the difference between the two association matrices (Figure 29).

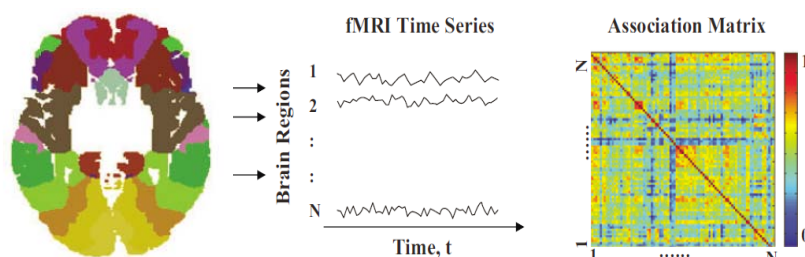


Figure 29 How brain networks connectivity is analyzed. A brain atlas is used to parcellate the voxel-level fMRI data into regions. The mean time series for each region is acquired by averaging all the voxel timeseries. The pair-wise association between two regions is calculated as Pearson correlation coefficient between the two time series. This is done for all possible pairs of nodes. The result is the association matrix, with the color being the magnitude of correlation coefficient between two nodes. (Bullmore and Bassett, 2011)

## Materials and Methods

BOLD fMRI data ( $3.4 \times 3.4 \times 5 \text{ mm}^3$  voxels, TE 25ms, TR 1000ms, flip angle 60 degrees) were acquired using a 3T Philips MR scanner. Healthy right-handed subjects were recruited for left-hand ( $n=24$ ,  $29 \pm 9$  y.o., 10 male) motor tasks.

The scan session included the pre-task fMRI scan (resting state), followed by the task, and then concluded with a post-task fMRI scan (5 minutes for post right-hand task, 15 minutes for post both-hand task, 15 minutes for post

left-hand task). During the 23 minute task period, the subject performed motor task, in which they fixated on a white crosshair and, when the crosshair occasionally changed color to grey for 1000ms, they are supposed to press a button three times with their index finger of their assigned hand as soon as they saw the crosshair dim. Subjects in Aim One only had a button box held in their right hand, subjects in Aim Two had a button box held in each hand, and subjects in Aim Three had a button box held in their left hand. The color change occurs every 27-32 seconds with randomized intervals. The two fcMRI runs before and after the motor task were performed with identical protocols (fixation on a white crosshair, 21 axial slices).

## **Post-processing**

### ***Voxel Based Amplitude of Fluctuation***

All images were co-registered to the first image volume of the first fcMRI run. Images were normalized to the TT\_avg152 template in Talairach space provided by the Analysis of Functional NeuroImages (AFNI) software package. After band-pass filtering (0.05-0.1Hz), correcting for motion, white matters and

CSF, the temporal signal remained is considered to reflect the resting state brain activity. Amplitude of Fluctuation (AF) of each voxel timeseries is calculated as standard deviation/baseline\*100.

The purpose of voxel based analysis is to examine the whole brain for any clusters with significant pre/post-task differences. Since in all three Aims, the pre-task fcMRI data were 300s long, only the first 300s of the post-task fcMRI data were used in both-hand and left-hand post-task scans. All image volumes were co-registered to the first volume of the first fcMRI. Each image was normalized to the TT\_avg152 template in Talairach space provided by AFNI. Motion, white matter, and cerebral spinal fluid fluctuations removed from the data. AF was calculated on a voxel-by-voxel basis to generate spatial maps, which were then compared between pre-task and post-task conditions. To limit the number of false positive voxels, I only displayed clusters that showed significantly pre/post-task difference in the right-hand task, both-hand task, and left-hand task datasets. Specifically, a voxel-wise threshold of  $p < 0.005$  was applied on the

one-hand-task group comparison to generate a preliminary mask. Another preliminary mask was generated for the both-hand-task data, and another mask was similarly generated for the left-hand-task data. An “AND” operation was performed amongst all three masks and a cluster size of  $1350\text{mm}^3$  (corresponding to a FDR  $p < 0.05$ ) were used to delineate significant clusters (Xu et al., 2007).

### ***Network Correlation Analysis***

fcMRI data were processed in SPM5 (Statistic Parametric Mapping, <http://www.fil.ion.ucl.ac.uk/spm>) using Matlab. First, all images were realigned to the first volume of the first fcMRI. These images were then spatially smoothed with 6mm FWHM. Then all the images were spatially normalized to the Montreal Neurological Institute (MNI) EPI template and were resampled to 3mm cubic voxels. Then the time series in each voxel is band pass filtered from 0.05-0.1Hz, and linearly detrended. After these steps, I used an automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) to parcellate the brain into 90 regions of interest (ROIs) (45 in each hemisphere) The time series of each ROI were extracted by averaging that of all voxels within the ROI. Artifact correction

(motion, white matter, cerebral spinal fluid) were applied to each time series. Correlation coefficient between all pairs of the 90 time series were calculated and presented as a 90x90 color matrix. The index and name of ROIs are in the Appendix.

### ***Network Functional Connectivity Statistical Analysis***

In each experiment group (right-hand task, both-hand task, and left-hand task), paired t-test between pre- and post-task rest matrices were performed for the case of post-task > pre-task. A binary mask was acquired by setting the threshold at uncorrected p-value < 0.005. Then the matrix elements that meet this threshold in all three groups were identified by AND operation amongst the binary masks of all three groups. There were 24 elements (ROI pairs) identified, consists of 16 unique ROIs. The reverse case comparison of pre-task > post-task were also performed. There was no element which meets the same threshold in all three groups.

### ***Concept of Network Analysis***

The results aforementioned indicate which pair-wise relationship between



two given regions was significantly altered in the post-task rest. However, these results do not provide information about each region specifically. For example, which regions become more functionally connected to the rest of the brain, and thereby become more integrated in the whole brain's network? Which regions become less integrated or more isolated from the whole brain's network? To answer these questions, I conducted network analysis. A network can be considered as a set of nodes and their connected edges. Each node represents a location. Each edge represents the strength of connection between two given nodes.

Consider an example network:

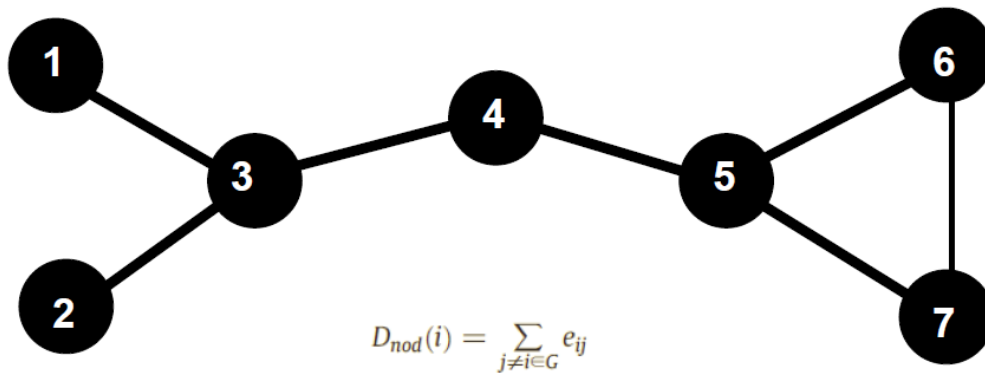


Figure 30 An example network with seven nodes and their connections. Node 3 and 5 has the

highest degree. Node 4 has the highest efficiency, and node 3 has the highest betweenness.

In this example network, the number of connections that links a given node to its neighbors can be defined as the degree of that node. In this example, node 3 and node 5 have most neighbors.

Another parameter that can be defined for each node is pathlength. It is defined as the number of edges that must be traversed from a given node to another node. In the example network shown in Figure 30, from node 6, there are two ways for to reach node 5. My interest is in the shortest way, which is from node 6 to node 5 directly. For the convenience, the efficiency of a node is defined as the sum of the inverse of all the shortest paths between a given node and all other nodes. In this example, node 4 has the highest efficiency.

Another parameter of interest is known as betweenness of a node. It measures how many shortest paths between all other nodes which pass through this node. In this example, node 3 has the highest betweenness because there are more shortest paths going through node 3 than any other nodes.

Given the association matrix, I conducted network analysis first by

thresholding the matrix from top 10% of the values in the association matrix.

Each value that survived the thresholding is replaced with a value of 1. Those did not meet the threshold is replaced with a value of 0. This means that each association matrix now becomes a binary matrix. I then relaxed the thresholding at the increment of 1%, up to the top 46% of the values in the association matrix (Tian et al., 2011). Then I sum up all these results across the thresholds. This is necessary because setting the threshold is arbitrary.

Mathematically, the nodal degree of a node  $i$  is defined as:

$$D_{nod}(i) = \sum_{j \neq i \in G} e_{ij}$$

Where  $e_{ij}$  is the  $(i,j)$ th element in the binary matrix. It's either 1 or 0.

The nodal efficiency of a node  $i$  is defined as:

$$E_{nod}(i) = \frac{1}{N-1} \sum_{j \neq i \in G} \frac{1}{L_{ij}}$$

And the betweenness of a node  $i$  is defined as

$$N_{bc}(i) = \sum_{j \neq i \neq k \in G} \frac{\delta_{jk}(i)}{\delta_{jk}}$$

Where  $\delta_{jk}(i)$  is the number of shortest path from  $j$  to  $k$  that passes through  $i$ .  $\delta_{jk}$  is

the total number of shortest path from j to k (Achard and Bullmore, 2007).

For these calculations, I used the GRETNA toolbox designed by Wang et al for Matlab (Wang et al., 2011).

The time series from the ROI results of motor cortex used in the previous chapters were used as the time series of the Precentral Gyrus and Postcentral Gyrus nodes in the network analysis.

## **Results**

### **Amplitude of Fluctuation**

Figure 31 illustrates clusters that showed significant post-task AF increase in all (right-hand-task, both-hand-task and left-hand task) data. Consistent with the ROI results, sensorimotor and auditory cortices were detected in the voxel-wise map. Other major brain regions included cuneus, thalamus, secondary and tertiary visual cortex, and medial frontal gyrus (including premotor cortex and supplemental motor area). No brain regions showed a significant decrease in AF.

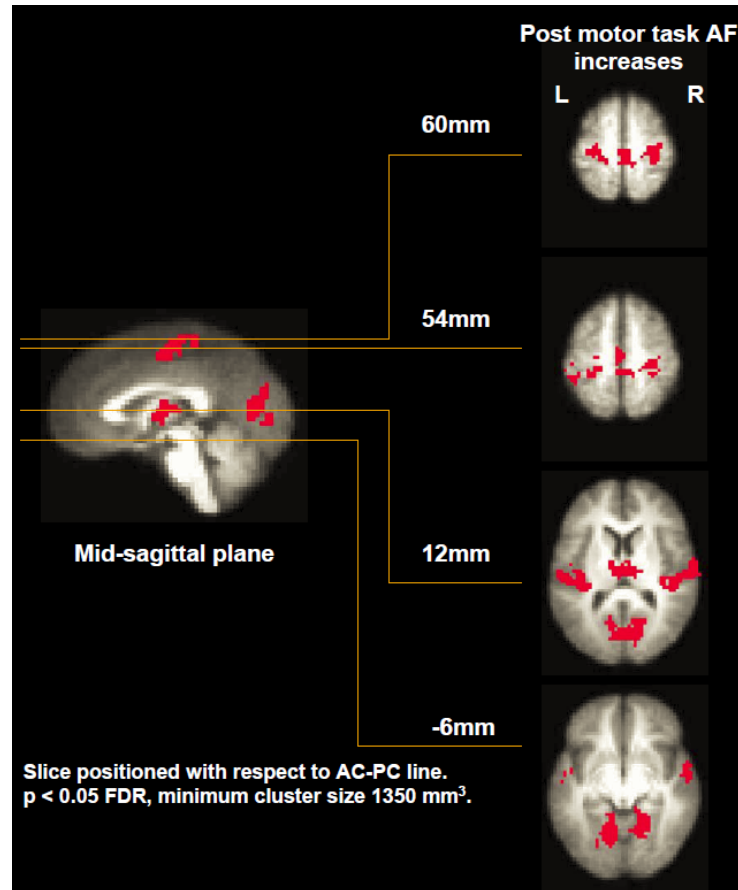


Figure 31 Voxel-based map illustrating regions in which AF during post-task fcMRI (first five minutes) was significantly greater than that during pre-task. Statistical threshold:  $p < 0.05$  FDR corrected, minimum cluster size 1350 mm<sup>3</sup>. Only voxels delineated in right-hand, both-hand and left-hand experiments are shown. The label next to each slice denotes its location relative to anterior commissure-posterior commissure (AC-PC) line.

The name and center-of-mass coordinate of the regions indicated above are in Table 1. Eight regions were identified and their corresponding Brodmann Area

designations were indicated.

Table 1 Brain regions with significant increases in AF comparing post-task to pre-task periods as was shown in the previous figure.

<b>Region</b>	<b>x (mm)</b>	<b>y (mm)</b>	<b>z (mm)</b>
Left primary motor cortex (BA4) and sensorimotor area (BA3)	23.5	27.5	57.9
Right primary motor cortex (BA4) and sensorimotor area (BA3)	-30.7	26.6	55
Left and right premotor and supplementary motor area (BA6)	-1.7	20.1	53.1
Left primary auditory cortex (BA41)	47.5	18.7	6
Right primary auditory cortex (BA41)	-58.3	15.5	5.5
Left and right thalamus	-1.9	14.2	9
Left secondary and tertiary visual cortex (BA18, BA19)	2.4	6.8	5.7
Right secondary and tertiary visual cortex (BA18, BA19)	-18.3	50	-5.5

RAI/DICOM coordinates of the center-of-mass correspond to the space of TT-Daemon atlas provided by AFNI. Voxel size  $3 \times 3 \times 3 \text{ mm}^3$ .  $p < 0.05$  FDR corrected. Minimum cluster size:  $1350 \text{ mm}^3$ . Brodmann Area designations are indicated in parenthesis.

Based on Table 1, it is clear that the regions showing significant AF increases were functionally related to motor, auditory and visual functions.

## **Functional Connectivity**

Inter-regional functional connectivity changes in the entire brain were also examined. Brodmann Areas 1-6 can be thought as motor network regions, while the Brodmann Areas 21 and 41 can be thought as auditory network regions. The results here suggest that the most significant increases in functional connectivity were between the motor-auditory node pairs (Figure 32, Figure 33). For example, left Precentral gyrus (which includes the primary motor cortex designated by Brodmann Area 4) and the right superior temporal gyrus (which includes the primary auditory cortex designated by Brodmann Area 41) show significant increases in their functional connectivity in all three post-task rests. Also, left Precentral gyrus shows increased functional connectivity with Heschl gyrus, which is functionally known to be a central part of the auditory cortex. As expected, left Precentral gyrus also shows significant increases in its functional connectivity with other motor network nodes such as right Precentral gyrus, right Postcentral gyrus, right supplementary motor area and right Rolandic operculum (Figure 32 A-D).

For the right Precentral gyrus, where the right primary motor cortex is located, it shows a similar pattern in the functional connectivity enhancement. Namely, it's functional connectivity with auditory network nodes such as Heschl gyrus and superior temporal gyrus increased significantly, and it's functional connectivity with other motor network nodes such as left Rolandic operculum, right supplementary motor area, and Postcentral gyrus also increased significantly (Figure 32 E-H).

There are five edges that represent significant decreases in functional connectivity with respect to the two primary motor network nodes (Figure 33). These edges indicate that functional connectivity between motor and thalamus, as well as motor and caudate nuclei, are decreased in the post-task rest. Specifically, for the left Precentral gyrus, its functional connectivity with respect to right caudate nuclei, and left and right thalamus decreased significantly (Figure 33 A-D). For the right Precentral gyrus, its functional connectivity with respect to the left and right thalamus decreased significantly (Figure 33 E-H).



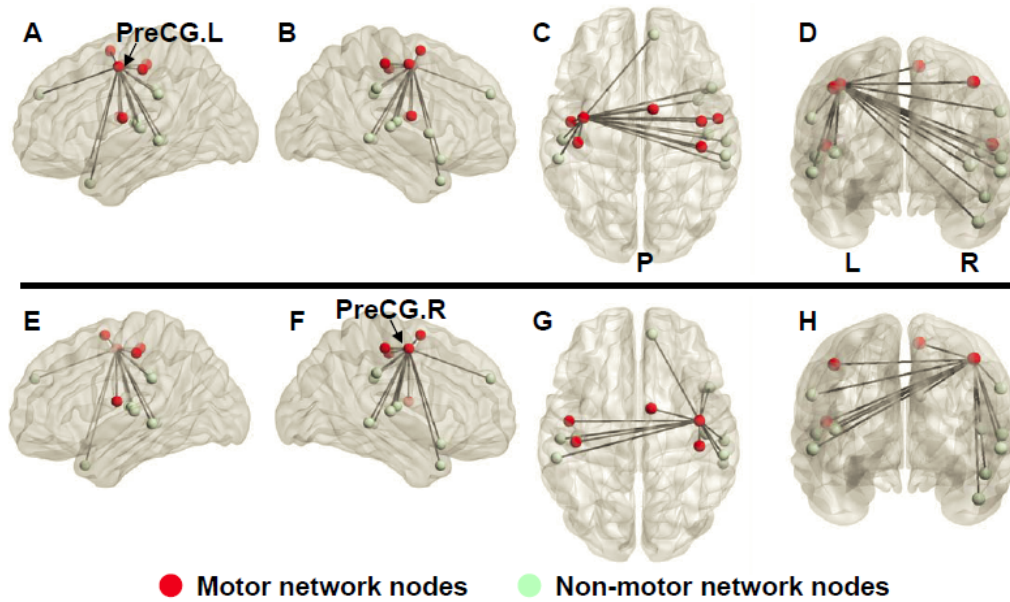


Figure 32 Nodes showing functional connectivity *increases with respect to the primary motor cortices (PreCG.L and PreCG.R)* in the post-right-hand rest and post-both-hand rest cohorts. In each cohort, the significance of increase in FC was assessed at uncorrected  $p < 0.05$ . Then with the surviving edges in each cohort, an AND operation was performed. The edges shown represent the significant increases of FC in both cohorts. The red nodes indicate motor network related nodes, while the grey nodes are outside of the known motor network area of the brain. Top panel (A) – (D) shows FC changes with respect to *left* primary motor cortex. Bottom panel (E) – (H) shows FC changes with respect to the *right* primary motor cortex. (A) Sagittal view from left side (B) Sagittal view from right side (C) Axial view from top of the brain. (D) Coronal view from the back of the brain. (E) – (H) follow the same convention.

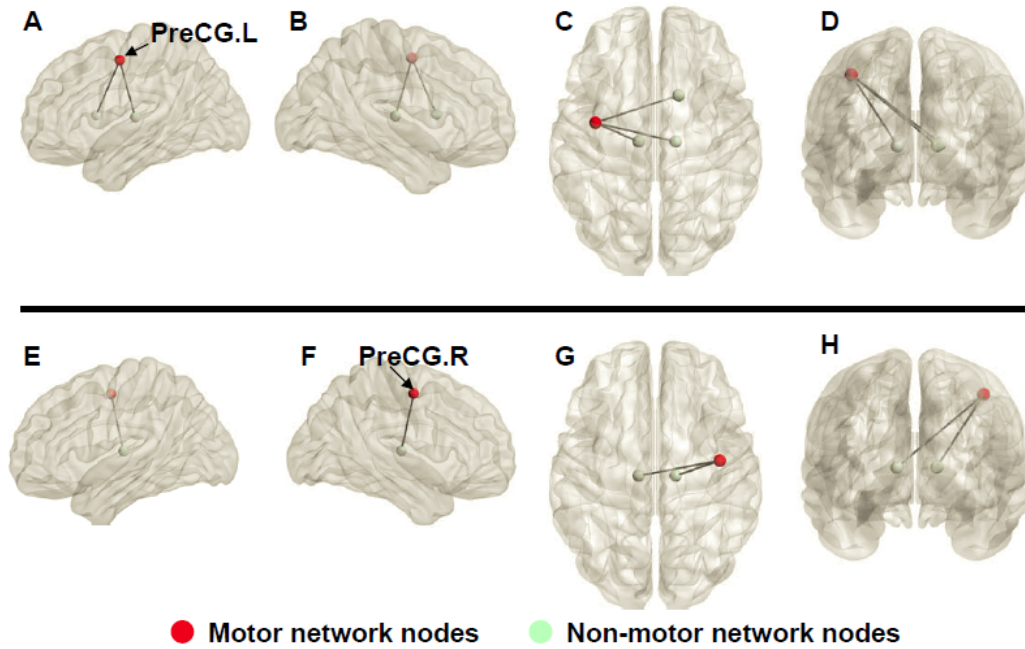


Figure 33 Nodes showing functional connectivity *decreases with respect to the primary motor cortices (PreCG.L and PreCG.R)* in the post-right-hand rest and post-both-hand rest cohorts. In each cohort, the significance of increase in FC was assessed at uncorrected  $p < 0.05$ . Then with the surviving edges in each cohort, an AND operation was performed. The edges shown represent the significant increases of FC in both cohorts. The red nodes indicate motor network related nodes, while the grey nodes are outside of the known motor network area of the brain. Top panel (A) – (D) shows FC changes with respect to *left* primary motor cortex. Bottom panel (E) – (H) shows FC changes with respect to the *right* primary motor cortex. (A) Sagittal view from left side (B) Sagittal view from right side (C) Axial view from top of the brain. (D) Coronal view from the back of the brain. (E) – (H) follow the same convention.

The names of all nodes in Figure 32 and Figure 33 are listed in Table 2. It can be noted that for both left and right primary motor cortices, their functional

connectivity increased not only with each other, but also with the nodes such as superior and middle temporal gyri in both ipsilateral and contralateral sides. Further, it is notable that midbrain regions such as thalamus show decrease in its functional connectivity with respect to either primary motor cortex.

Table 2 Nodes with significant FC changes with respect to the primary motor cortex Precentral Gyrus (L and R, respectively). Grey shades indicate increases in FC, while the uncolored indicate decreases. NC: No Change. NA: Not Applicable. Threshold was set at uncorrected  $p < 0.05$  in both right-hand **AND** both-hand cohorts.

Nodes	Precentral Gyrus L	Precentral Gyrus R
Precentral Gyrus L	NA	↑
Precentral Gyrus R	↑	NA
Rolandic Operculum L	↑	↑
Rolandic Operculum R	↑	NC
Supplementary Motor Area R	↑	↑
Superior Frontal Gyrus Medial R	↑	↑
Insula R	↑	NC
Postcentral Gyrus L	↑	↑
Postcentral Gyrus R	↑	↑
SupraMarginal Gyrus L	↑	↑
SupraMarginal Gyrus R	↑	↑
Caudate Nuclei R	↓	NC
Thalamus L	↓	↓
Thalamus R	↓	↓
Heschl Gyrus L	↑	↑
Heschl Gyrus R	↑	↑
Superior Temporal Gyrus L	↑	↑
Superior Temporal Gyrus R	↑	↑
Superior Temporal Gyrus Pole R	↑	↑
Middle Temporal Gyrus L	↑	↑
Middle Temporal Gyrus R	↑	↑
Middle Temporal Gyrus Pole R	↑	↑

### *Network analysis – first and second cohorts*

Since the right-hand and both-hand task cohorts showed significant increases in their motor cortex FC while the left-hand task cohort did not, I performed the network analysis first based on the first two cohorts only.

In each cohort, the changes in the nodal parameters – degree, efficiency, and betweenness – were assessed at uncorrected  $p < 0.05$ . The results then were compared using AND operation between the two cohorts. Therefore these are changes that are common in the both cohorts.

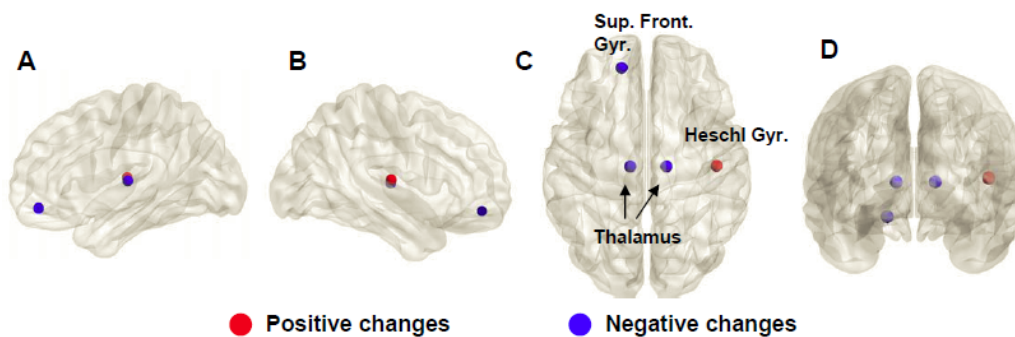


Figure 34 Nodes with significant changes in the nodal **degree** during the post-task rest for both right-hand task and both-hand task cohorts. Within each cohort, the significance was assessed at uncorrected  $p < 0.05$ . The results were then combined via AND operation. (n=22 in right-hand cohort, n=24 in both-hand cohort). Red nodes show positive changes in nodal degree, whereas blue nodes show negative changes. (A) Sagittal view from left side (B) Sagittal view from right side (C) Axial view from top of the brain. (D) Coronal view from the back of the brain.

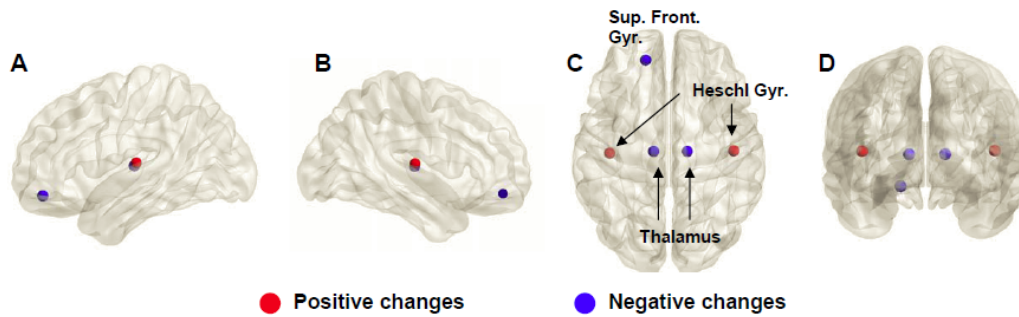


Figure 35 Nodes with significant changes in the nodal **efficiency** during post-task rest for both right-hand task and both-hand task cohorts. Within each cohort, the significance was assessed at uncorrected  $p < 0.05$ . The results were then combined via AND operation. (n=22 in right-hand cohort, n=24 in both-hand cohort). Red nodes show positive changes in nodal efficiency, whereas blue nodes show negative changes. (A) Sagittal view from left side (B) Sagittal view from right side (C) Axial view from top of the brain. (D) Coronal view from the back of the brain.

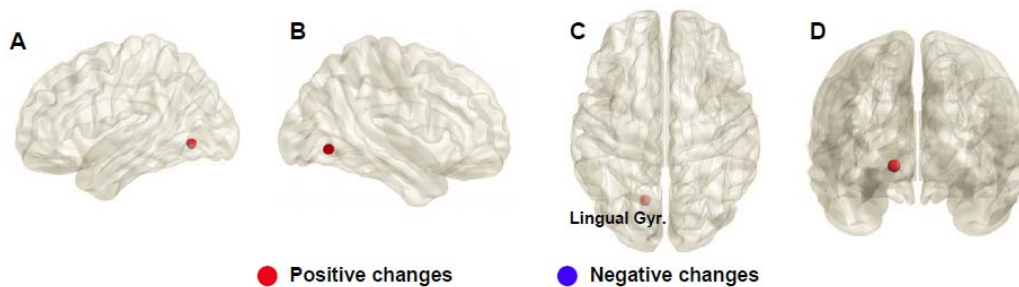


Figure 36 Nodes with significant changes in the nodal **betweenness** during post-task rest for both right-hand task and both-hand task cohorts. Within each cohort, the significance was assessed at uncorrected  $p < 0.05$ . The results were then combined via AND operation. (n=22 in right-hand cohort, n=24 in both-hand cohort). Red nodes show positive changes in nodal betweenness, whereas blue nodes show negative changes. (A) Sagittal view from left side (B) Sagittal view from right side (C) Axial view from top of the brain. (D) Coronal view from the back of the brain.

## Discussion

These voxel based results are consistent with the ROI analyses done in the Aims 1-3. Namely, the plastic changes in the motor and auditory cortices were observed regardless of analysis methods used, as indicated by the spatial pattern of the voxels clusters with significant AF increases. Further, the inter-regional functional connectivity analysis shows that there is a strong interaction between regions of the brain where motor and auditory networks are.

Table 2 shows the nodes that are involved in significant functional connectivity increases with respect to the motor cortex. There are seven nodes that can be categorized as a part of motor network (Precentral Gyri, Rolandic Operculum, Supplementary Motor Area, and Postcentral Gyri), and ten nodes that can be categorized as a part of auditory network (Supramarginal Gyri, Heschl Gyri, Superior Temporal Gyri, Superior Temporal Gyrus Pole and Middle Temporal Gyri), and four nodes that can be categorized as the regions that serve as sensory relay (Thalamus and Caudate Nuclei). Of the nodes that show significant increases in their functional connectivity with respect to the Precentral

gyrus on either side, Precentral gyrus, Postcentral gyrus, Rolandic Operculum, Supplementary Motor Area were grouped to the sensorimotor network (BA1, 2, 3, 4, 5, 6). More specifically, the Precentral gyrus can be further assigned to the primary motor network (BA4). And the nodes such as Heschl Gyrus, Superior Temporal Gyrus, Superior Temporal Gyrus Pole, Middle Temporal Gyrus and Supramarginal Gyrus (which includes Wernicke's area) are grouped to be the auditory network.

Because these changes were not present in the sham cohort, these results provide strong evidence for the transient plasticity due to motor task. So how did motor task footprint transfer into auditory network? Auditory-motor interactions are well known given that it is the basis to musical training in musicians. When a musician plays an instrument, the motor network controls the manual movements to create the sound. As the sound reaches the auditory cortex, the musician can adjust motor movements to achieve the desired sound output. Therefore motor and auditory networks are tightly coupled during activation (Zatorre et al., 2007).

Auditory cortices are anatomically connected to the motor system. Based on



data from non-human primates, it is known that direct connections exist from the auditory regions in the superior temporal gyrus to dorsal and lateral premotor area (Chavis and Pandya, 1976). And naturally both dorsal and lateral premotor areas are highly interconnected between them as well as with the primary motor cortex (BA4) and the supplementary motor area (BA6) (Dum and Strick, 2005).

The results of my conjunction analysis of the two experiment groups show that their functional connectivity is enhanced even after a 23 minutes simple motor task.

### ***Functional Connectivity Changes in Temporal Cortex***

Both correlation analysis and network analysis point to temporal cortex as a major location where significant changes took place. In these analyses, Superior Temporal Cortex (ST) and Middle Temporal Cortex (MT) showed significant changes in their functional connectivity with motor network nodes in the brain, as indicated by the comparison of pre-task and post-task association matrices (Figure 32). Also, nodes in the auditory network such as Heschl Gyrus became more

functionally connected to the rest of the brain as indicated by its increase in nodal degree and efficiency (Figure 34, Figure 35). What is the role of this part of the brain in the context of the motor task in my experiments?

A possible explanation is that ST and MT are the regions where multisensory (sensorimotor, auditory and visual pathways) convergence takes place (Karnath, 2001; Stein and Stanford, 2008). It has been shown using direct electrode recording in primate that temporal cortex consists of neurons receiving visual, somatosensory and auditory inputs (Baylis et al., 1987). Later, using fMRI, Stevenson et al showed that the BOLD evoked response in ST in humans, when combination of audio and visual stimuli were presented, surpassed the sum of the BOLD response to audio or visual stimuli presented independently (Stevenson et al., 2007). Although it is well known that ST and MT are parts of the auditory network (Kaas and Hackett, 2000; Poremba et al., 2003), there are cells in this region which can also be activated by visual stimuli (Baylis et al., 1987; Schroeder and Foxe, 2002; Schroeder et al., 2003). Using direct electrode recording in macaques, Ledberg et al showed that perception of visual queue and

the motor response selection were the results of concurrent processes in visual, motor and executive areas (Ledberg et al., 2007). Their results showed that neural activities in the superior temporal regions are associated with both visual stimuli and motor response. It is possible that the changes I observed were the result of attention to the visual queue during the task.

Another possible explanation for the role of ST and MT can be ascribed to the functional connectivity of motor and auditory networks (Zhang et al., 2012). It is also well known that motor and auditory network may be co-activated during either motor or sounds stimulation. For example, Using fMRI technique, Baumann et al found that when non-musicians moved their fingers using their right hand on a mock keyboard without auditory feedback, their auditory cortex was activated. When they were listening to a piece of music, their supplementary motor area and premotor cortex in both hemispheres were also activated (Baumann et al., 2005). Chen et al showed that both superior temporal gyrus and premotor cortex showed evoked response proportional to the level of sound (Chen et al., 2006). Foxe et al showed that superior temporal cortex was activated in

both auditory and somatosensory stimulation conditions. Specifically, they showed that both left and right superior temporal gyri, the region where auditory cortex is mapped, could be activated by either a motor task (moving fingers in right hand) or sound (Foxe et al., 2002). Kawashima et al showed that superior temporal cortex responded to finger tapping task (Kawashima et al., 2000). Lahav et al showed activation in the frontoparietal motor related network when their subjects listen to music (Lahav et al., 2007). Meta analysis showed that during finger tapping task, motor and auditory networks often were co-activated (Witt et al., 2008). In the resting state, Zhang et al showed that posterior supplementary motor area (SMA) is functionally connected to auditory cortex (Zhang et al., 2012). Taken together, these studies suggest that either motor or auditory experience can activate both motor and auditory networks.

The two explanations aforementioned – multisensory convergence and motor-auditory network functional connectivity - need not to be mutually exclusive. By integrating information from inputs via visual, auditory, and somatosensory pathways together, the brain will be able to enhance the

identification of the stimuli in terms of its spatial and temporal relationship with the individual, and also enhance the response accuracy to the stimuli. This is consistent with the analogy to the musical performance by professional musicians (Zatorre et al., 2007). For example, a pianist during a performance is constantly integrating the fine somatosensory (tactile/vibratory feedback), auditory (tone or pitch) and visual (reading notes or hand position on the keyboard) inputs during their musical performance.



**Summary**

It is well known that certain changes have occurred to the brain comparing before and after a task/learning. However, the exact neuronal processes that are altered are poorly understood, especially for human studies in which available tools are limited. The present study demonstrated that a 23-min motor task can alter post-task motor functional connectivity and further elucidated the temporal course of its return to pre-task level. These data suggest that the brain is constantly re-organizing itself based on life experience and that a short-duration task is sufficient to leave a “foot-print” on the brain. However, if not maintained or strengthened, such alterations will dissipate with time.

**Spatial distribution of the plastic changes**

From the voxel-wise map, it is clear that the pre/post-task differences are not a whole-brain phenomenon. Instead, they are distributed in specific brain regions. The plastic changes were primarily observed in areas activated by the task, such as primary sensorimotor cortices, supplementary motor areas, thalamus,

and auditory cortices. Visual areas also showed changes, which can be attributed to the color change of the fixation crosshair during the task period.

In the voxel-wise results, I display only the clusters that showed a change in right-hand, two-hand and left-hand task datasets in order to reduce false positive clusters. More spurious voxels could be seen when examining the map in each group. One can expect that in the three different groups, their maps may show systematical differences due to slight different neural circuits involved in the tasks. I focus on the common regions in this study because the purpose of this initial report is to establish that there is a detectable plastic change in the motor cortex.

### **Neural underpinnings of the CC and AF changes in the fcMRI data**

Recent evidence suggests that resting-state BOLD signal fluctuation in fcMRI most likely reflects a corresponding fluctuation in gamma-band local field potential (LFP) of the spontaneous neural activity (Logothetis et al., 2001; Mukamel et al., 2005; Niessing et al., 2005; Nir et al., 2007; Privman et al., 2007;



Nir et al., 2008; Shmuel and Leopold, 2008). Therefore, an increased fcMRI CC value during the post-task period could indicate a higher synchronization of LFP between left and right motor cortices, a finding previously suggested by a direct neural recording study (Hoffman and McNaughton, 2002). Note that, because fcMRI is a slow hemodynamic signal, it cannot distinguish whether the connection between bilateral motor cortices is excitatory or inhibitory (Ferber et al., 1992). Instead, this signal only suggests that, during time periods when there is a greater gamma-band LFP fluctuation in the left motor cortex, the fluctuation in the right motor cortex is also greater.

The AF data indicate that the bilateral motor cortices are not only more synchronized, but each of them also manifested a greater spontaneous neural activity during the post-task period. Both the AF and CC results could be due to an aggregation of neurotransmitter receptors in the synaptic terminal or enlargement in dendritic spine due to the recent use (Cingolani et al., 2008; Lushnikova et al., 2009; Yoshida et al., 2009), which may be the source of the “footprint” observed in the present study. This may also explain the presence of

the effect in the right motor cortex following the right-hand-only task. It is possible that even though the right motor cortex was not activated during the right-hand task, the enhanced inhibitory inputs from the left cortex may have resulted in a higher GABA concentration in the synaptic terminals in the right cortex. However, further experimental work is needed to confirm this conjecture.

It is also interesting to note that the recovery of CC seemed to precede the recovery of AF. That is, the bilateral motor cortices lost synchrony while still maintaining a high spontaneous fluctuation. The high fluctuation is present for at least 15 minutes after the termination of the task, and may continue into the sleep period on the same night. Future study should evaluate the AF on the next day to examine whether the AF has returned to baseline level.

Consistent with my hypothesis (that resting brain can provide meaningful information regarding its previous use), my results identified significant strengthening in human brain networks. Through these results, it is clear that: (1) The brain's plastic changes in its spontaneous activity during rest can be considered as the "footprint" of previous task. (2) This footprint is specific to the

functional networks of the brain stimulated by the task. (3) This footprint can be consistently imaged using fMRI technique. Therefore, even within the time as short as an hour, where fundamental structural changes at a neuronal level are not expected, brain can exhibit remarkable and significant reconfiguration and strengthening of functional connection after the task. In other words, human brain's organized pattern is a dynamic property that can be a biomarker to plastic changes in the brain. This finding can be a basis of a method for predicting the outcome of training and learning effect *in vivo*.

Using motor cortex as a model, I have shown that the strongest changes in the brain organization and connection are between motor and auditory networks. Functional connectivity between left and right motor cortices is shown to be sensitive to short task. Through my experiment design and statistical analysis, I was able to show that these changes are not due to the settling effect and these changes are likely the results of previous task. Further, my network analysis show that the effect of motor task extended to auditory cortex in such a way that not only motor-auditory functional connectivity is increased, but so is the functional

connectivity within the auditory cortex itself.

### **Brain network analysis**

The network analysis evaluated how the motor tasks change the functional connectivity in the entire brain, and how each region (node) of the brain was changed in their functional connectivity with respect to the rest of the brain. This analysis reveals that while the most of the brain were robust, there are nodes whose functional connectivity with the rest of the brain was modified.

The task required motor action based on a visual queue. Primary motor cortices show significant increases in their functional connectivity with each other, as well as with many other nodes in the brain. Most of these other nodes are located in the superior and middle temporal cortices (ST and MT), where multisensory convergence takes place (Karnath, 2001; Stein and Stanford, 2008). From the anatomical perspective, it is known that direct connections exist from auditory regions in the superior temporal gyrus to the premotor area (Chavis and Pandya, 1976), and premotor areas are highly connected to the primary motor

cortex (Dum and Strick, 2005). Neurons receiving visual, somatosensory and auditory inputs are known to converge in the temporal regions of the brain based on direct electrode recording in primates (Baylis et al., 1987; Schroeder and Foxe, 2002; Schroeder et al., 2003). Stevenson et al showed that evoked fMRI response in human ST, when both audio and visual stimuli were presented, surpassed the sum of the evoked response to either audio or visual stimuli presented alone (Stevenson et al., 2007). Clearly motor and auditory cortices are functionally connected. Therefore it is not surprising that the nodes such as Heschl Gyrus, where the auditory cortex is, show increases in the nodal degree and efficiency. This means its overall functional connectivity with the rest of the brain became higher in the post-task rest. An important aspect of the task was the demand of visual attention. Visual information travels via the ascending retinal ganglion cells, relaying through the lateral geniculate nuclei in the thalamus, then from optic radiation tract through the superior and middle the temporal cortex before it enters the primary visual cortex. In the higher visual area such as lingual gyrus, where the integration from primary visual and motor sensory areas took place, it shows

increased betweenness. This suggests that lingual gyrus node became more important in the routing of primary sensory inputs during the post-task rest.

The task also requires the subject's attention to make the decision for motor task execution. Orbital part of the superior frontal gyrus, which contains Brodmann Area 11, appears to fit this function. This node, along with thalamus, showed decreases in their nodal degree and efficiency. This suggests that for these nodes, their functional connectivity with the rest of the brain is reduced. It is possible that the reduction in functional connectivity can be thought as trimming of less relevant functional connections.

Another explanation for my observation of the significance of ST and MT in the functional connectivity changes during the post-task rest can be ascribed to the functional connectivity of motor and auditory networks (Zhang et al., 2012). Zhang et al used fcMRI in human to show that posterior supplementary motor area (SMA) is functionally connected to auditory cortex. Baumann et al showed that auditory cortex was activated even though their non-musician subjects were moving their right hand fingers on a mock keyboard without auditory feedback.

And when the subjects were listening to a piece of music, their motor and premotor areas in both hemispheres were activated (Baumann et al., 2005). Such pattern of coactivation may also be observed without using music as the auditory stimuli. For example, Chen et al used simple tone to show coactivation of superior temporal gyrus and premotor cortex (Chen et al., 2006). Lahav et al found that listening to the music alone is sufficient to activate motor related network including Broca's area, premotor cortex and parietal cortex (Lahav et al., 2007). But this needs not be limited to music. Foxe et al showed that ST was activated whether the sensorimotor or white noise stimulation were introduced (Foxe et al., 2002). Kawashima et al showed that ST was coactivated with motor network using a task requiring right hand finger click based on visual queues (Kawashima et al., 2000). Therefore based on their anatomical interconnections in the ST and MT regions, and their functional overlap, it is reasonable to suggest that motor experience can enhance motor network's functional connectivity with nodes that categorized as auditory network.

Primary motor area (M1) did not show significant nodal parameter changes.

This may be because M1 is simply a center for motor execution and feedback. And even though its functional connectivity with most of the ST and MT nodes were increased, it is not enough to have an impact on M1's overall functional connectivity with the rest of the brain. The two explanations aforementioned need not to be mutually exclusive. As the inputs via difference senses converges in ST and MT, the brain makes decisions based on the nature of the stimuli perceived, such as its spatial and temporal nature with the individual, and the motor execution is fine tuned accordingly.

### **Future Works**

The findings of the present study need to be interpreted in view of a few limitations. Given the low difficulty level of my button-press task, I do not have a behavioral measure to demonstrate any improvement in performance comparing post-task to pre-task period. Thus, the task used does not qualify to be considered as training and, consequently, it is not clear whether the fcMRI changes represent a learning process or they are simply a history of use in the neural circuits. Additionally, despite indirect evidence arguing against an imagery activation



effect, this issue should nonetheless be further considered in future studies using experimental designs such as a distraction task following the primary task.

Future studies can also take advantage of the current experiment design with modified task in such a way that is more challenging, so that all subject's performance can be stratified with a broader range. This will enable the determination of behavioral correlate between fcMRI parameters and their performance.

Another obvious application of my experiment design is for the comparison of changes post-task rest between patients and healthy control, or between young and old adults. In the former case, if a clear difference in their brain's post-task changes can be found, then my experiment design and analysis methods could be further extended to assess whether or not a single imaging session such as mine could be used to predict their recovery or treatment effect trajectories. In the latter case, my experiment design and analysis may help understand how functional connectivity between each region could change throughout life time, and identify the functional connectivity changes that are relevant to the task of interest, so that

early intervention or practice strategy can be implemented to deter functional decline.

## Appendix 1 List of ROI for network correlation analysis

Labels	Regions	Description	Abbreviation
1	Precentral_L	Precentral gyrus	PreCG.L
2	Precentral_R	Precentral gyrus	PreCG.R
3	Frontal_Sup_L	Superior frontal gyrus, dorsolateral	SFGdor.L
4	Frontal_Sup_R	Superior frontal gyrus, dorsolateral	SFGdor.R
5	Frontal_Sup_Orb_L	Superior frontal gyrus, orbital part	ORBsup.L
6	Frontal_Sup_Orb_R	Superior frontal gyrus, orbital part	ORBsup.R
7	Frontal_Mid_L	Middle frontal gyrus	MFG.L
8	Frontal_Mid_R	Middle frontal gyrus	MFG.R
9	Frontal_Mid_Orb_L	Middle frontal gyrus, orbital part	ORBmid.L
10	Frontal_Mid_Orb_R	Middle frontal gyrus, orbital part	ORBmid.R
11	Frontal_Inf_Oper_L	Inferior frontal gyrus, opercular part	IFGoperc.L
12	Frontal_Inf_Oper_R	Inferior frontal gyrus, opercular part	IFGoperc.R
13	Frontal_Inf_Tri_L	Inferior frontal gyrus, triangular part	IFGtriang.L
14	Frontal_Inf_Tri_R	Inferior frontal gyrus, triangular part	IFGtriang.R
15	Frontal_Inf_Orb_L	Inferior frontal gyrus, orbital part	ORBinf.L
16	Frontal_Inf_Orb_R	Inferior frontal gyrus, orbital part	ORBinf.R

17	Rolandic_Oper_L	Rolandic operculum	ROL.L
18	Rolandic_Oper_R	Rolandic operculum	ROL.R
19	Supp_Motor_Area_L	Supplementary motor area	SMA.L
20	Supp_Motor_Area_R	Supplementary motor area	SMA.R
21	Olfactory_L	Olfactory cortex	OLF.L
22	Olfactory_R	Olfactory cortex	OLF.R
23	Frontal_Sup_Medial_L	Superior frontal gyrus, medial	SFGmed.L
24	Frontal_Sup_Medial_R	Superior frontal gyrus, medial	SFGmed.R
25	Frontal_Med_Orb_L	Superior frontal gyrus, medial orbital	ORBsupmed.L
26	Frontal_Med_Orb_R	Superior frontal gyrus, medial orbital	ORBsupmed.R
27	Rectus_L	Gyrus rectus	REC.L
28	Rectus_R	Gyrus rectus	REC.R
29	Insula_L	Insula	INS.L
30	Insula_R	Insula	INS.R
31	Cingulum_Ant_L	Anterior cingulate and paracingulate gyri	ACG.L
32	Cingulum_Ant_R	Anterior cingulate and paracingulate gyri	ACG.R
33	Cingulum_Mid_L	Median cingulate and paracingulate gyri	DCG.L
34	Cingulum_Mid_R	Median cingulate and paracingulate gyri	DCG.R
35	Cingulum_Post_L	Posterior cingulate gyrus	PCG.L
36	Cingulum_Post_R	Posterior cingulate gyrus	PCG.R
37	Hippocampus_L	Hippocampus	HIP.L
38	Hippocampus_R	Hippocampus	HIP.R
39	ParaHippocampal_L	Parahippocampal gyrus	PHG.L

40	ParaHippocampal_R	Parahippocampal gyrus	PHG.R
41	Amygdala_L	Amygdala	AMYG.L
42	Amygdala_R	Amygdala	AMYG.R
43	Calcarine_L	Calcarine fissure and surrounding cortex	CAL.L
44	Calcarine_R	Calcarine fissure and surrounding cortex	CAL.R
45	Cuneus_L	Cuneus	CUN.L
46	Cuneus_R	Cuneus	CUN.R
47	Lingual_L	Lingual gyrus	LING.L
48	Lingual_R	Lingual gyrus	LING.R
49	Occipital_Sup_L	Superior occipital gyrus	SOG.L
50	Occipital_Sup_R	Superior occipital gyrus	SOG.R
51	Occipital_Mid_L	Middle occipital gyrus	MOG.L
52	Occipital_Mid_R	Middle occipital gyrus	MOG.R
53	Occipital_Inf_L	Inferior occipital gyrus	IOG.L
54	Occipital_Inf_R	Inferior occipital gyrus	IOG.R
55	Fusiform_L	Fusiform gyrus	FFG.L
56	Fusiform_R	Fusiform gyrus	FFG.R
57	Postcentral_L	Postcentral gyrus	PoCG.L
58	Postcentral_R	Postcentral gyrus	PoCG.R
59	Parietal_Sup_L	Superior parietal gyrus	SPG.L
60	Parietal_Sup_R	Superior parietal gyrus	SPG.R
61	Parietal_Inf_L	Inferior parietal, but supramarginal and angular gyri	IPL.L
62	Parietal_Inf_R	Inferior parietal, but supramarginal and angular gyri	IPL.R
63	SupraMarginal_L	Supramarginal gyrus	SMG.L
64	SupraMarginal_R	Supramarginal gyrus	SMG.R

65	Angular_L	Angular gyrus	ANG.L
66	Angular_R	Angular gyrus	ANG.R
67	Precuneus_L	Precuneus	PCUN.L
68	Precuneus_R	Precuneus	PCUN.R
69	Paracentral_Lobule_L	Paracentral lobule	PCL.L
70	Paracentral_Lobule_R	Paracentral lobule	PCL.R
71	Caudate_L	Caudate nucleus	CAU.L
72	Caudate_R	Caudate nucleus	CAU.R
73	Putamen_L	Lenticular nucleus, putamen	PUT.L
74	Putamen_R	Lenticular nucleus, putamen	PUT.R
75	Pallidum_L	Lenticular nucleus, pallidum	PAL.L
76	Pallidum_R	Lenticular nucleus, pallidum	PAL.R
77	Thalamus_L	Thalamus	THA.L
78	Thalamus_R	Thalamus	THA.R
79	Heschl_L	Heschl gyrus	HES.L
80	Heschl_R	Heschl gyrus	HES.R
81	Temporal_Sup_L	Superior temporal gyrus	STG.L
82	Temporal_Sup_R	Superior temporal gyrus	STG.R
83	Temporal_Pole_Sup_L	Temporal pole: superior temporal gyrus	TPOsup.L
84	Temporal_Pole_Sup_R	Temporal pole: superior temporal gyrus	TPOsup.R
85	Temporal_Mid_L	Middle temporal gyrus	MTG.L
86	Temporal_Mid_R	Middle temporal gyrus	MTG.R
87	Temporal_Pole_Mid_L	Temporal pole: middle temporal gyrus	TPOmid.L

88	Temporal_Pole_Mid_R	Temporal pole: middle temporal gyrus	TPOmid.R
89	Temporal_Inf_L	Inferior temporal gyrus	ITG.L
90	Temporal_Inf_R	Inferior temporal gyrus	ITG.R

## References

- Achard S, Bullmore E (2007) Efficiency and cost of economical brain functional networks. *PLoS Comput Biol* 3:e17.
- Albert NB, Robertson EM, Miall RC (2009) The resting human brain and motor learning. *Curr Biol* 19:1023-1027.
- Bandettini PA, Wong EC, Hinks RS, Tikofsky RS, Hyde JS (1992) Time course EPI of human brain function during task activation. *Magn Reson Med* 25:390-397.
- Baumann S, Koeneke S, Meyer M, Lutz K, Jancke L (2005) A network for sensory-motor integration: what happens in the auditory cortex during piano playing without acoustic feedback? *Ann N Y Acad Sci* 1060:186-188.
- Baylis GC, Rolls ET, Leonard CM (1987) Functional subdivisions of the temporal lobe neocortex. *J Neurosci* 7:330-342.
- Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005) Investigations into resting-state connectivity using independent component analysis. *Philos Trans R Soc Lond B Biol Sci* 360:1001-1013.
- Bengtsson SL, Nagy Z, Skare S, Forsman L, Forssberg H, Ullen F (2005) Extensive piano practicing has regionally specific effects on white matter development. *Nat Neurosci* 8:1148-1150.
- Binkofski F, Amunts K, Stephan KM, Posse S, Schormann T, Freund HJ, Zilles K, Seitz RJ (2000) Broca's region subserves imagery of motion: a combined cytoarchitectonic and fMRI study. *Hum Brain Mapp* 11:273-285.
- Biswal B, Yetkin FZ, Haughton VM, Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 34:537-541.
- Boecker H, Ceballos-Baumann AO, Bartenstein P, Dagher A, Forster K, Haslinger B, Brooks DJ, Schwaiger M, Conrad B (2002) A H(2)(15)O positron emission tomography study on mental imagery of movement sequences--the effect of modulating sequence length and direction. *Neuroimage* 17:999-1009.



- Bullmore ET, Bassett DS (2011) Brain graphs: graphical models of the human brain connectome. *Annu Rev Clin Psychol* 7:113-140.
- Chang C, Glover GH (2010) Time-frequency dynamics of resting-state brain connectivity measured with fMRI. *Neuroimage* 50:81-98.
- Chavis DA, Pandya DN (1976) Further observations on corticofrontal connections in the rhesus monkey. *Brain Res* 117:369-386.
- Chen H, Yang Q, Liao W, Gong Q, Shen S (2009) Evaluation of the effective connectivity of supplementary motor areas during motor imagery using Granger causality mapping. *Neuroimage* 47:1844-1853.
- Chen JL, Zatorre RJ, Penhune VB (2006) Interactions between auditory and dorsal premotor cortex during synchronization to musical rhythms. *Neuroimage* 32:1771-1781.
- Cingolani LA, Thalhammer A, Yu LM, Catalano M, Ramos T, Colicos MA, Goda Y (2008) Activity-dependent regulation of synaptic AMPA receptor composition and abundance by beta3 integrins. *Neuron* 58:749-762.
- Cohen YE, Andersen RA (2002) A common reference frame for movement plans in the posterior parietal cortex. *Nat Rev Neurosci* 3:553-562.
- Cordes D, Haughton VM, Arfanakis K, Wendt GJ, Turski PA, Moritz CH, Quigley MA, Meyerand ME (2000) Mapping functionally related regions of brain with functional connectivity MR imaging. *AJNR Am J Neuroradiol* 21:1636-1644.
- Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF (2006) Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A* 103:13848-13853.
- Debas K, Carrier J, Orban P, Barakat M, Lungu O, Vandewalle G, Hadj Tahar A, Bellec P, Karni A, Ungerleider LG, Benali H, Doyon J (2010) Brain plasticity related to the consolidation of motor sequence learning and motor adaptation. *Proc Natl Acad Sci U S A* 107:17839-17844.
- Dechent P, Merboldt KD, Frahm J (2004) Is the human primary motor cortex involved in motor imagery? *Brain Res Cogn Brain Res* 19:138-144.
- Deiber MP, Ibanez V, Honda M, Sadato N, Raman R, Hallett M (1998) Cerebral processes related to visuomotor imagery and generation of simple finger

- movements studied with positron emission tomography. *Neuroimage* 7:73-85.
- Do MT, Bean BP (2003) Subthreshold sodium currents and pacemaking of subthalamic neurons: modulation by slow inactivation. *Neuron* 39:109-120.
- Dum RP, Strick PL (2005) Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere. *J Neurosci* 25:1375-1386.
- Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992) Interhemispheric inhibition of the human motor cortex. *J Physiol* 453:525-546.
- Foster DJ, Wilson MA (2006) Reverse replay of behavioural sequences in hippocampal place cells during the awake state. *Nature* 440:680-683.
- Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 8:700-711.
- Fox MD, Snyder AZ, Zacks JM, Raichle ME (2006) Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. *Nat Neurosci* 9:23-25.
- Fox MD, Snyder AZ, Vincent JL, Raichle ME (2007) Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. *Neuron* 56:171-184.
- Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A* 102:9673-9678.
- Fox PT, Raichle ME (1986) Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci U S A* 83:1140-1144.
- Fox PT, Raichle ME, Mintun MA, Dence C (1988) Nonoxidative glucose consumption during focal physiologic neural activity. *Science* 241:462-464.
- Foxe JJ, Wylie GR, Martinez A, Schroeder CE, Javitt DC, Guilfoyle D, Ritter W,

- Murray MM (2002) Auditory-somatosensory multisensory processing in auditory association cortex: an fMRI study. *J Neurophysiol* 88:540-543.
- Gandolfo F, Li C, Benda BJ, Schioppa CP, Bizzi E (2000) Cortical correlates of learning in monkeys adapting to a new dynamical environment. *Proc Natl Acad Sci U S A* 97:2259-2263.
- Gaser C, Schlaug G (2003) Brain structures differ between musicians and non-musicians. *J Neurosci* 23:9240-9245.
- Golland Y, Bentin S, Gelbard H, Benjamini Y, Heller R, Nir Y, Hasson U, Malach R (2007) Extrinsic and intrinsic systems in the posterior cortex of the human brain revealed during natural sensory stimulation. *Cereb Cortex* 17:766-777.
- Greicius MD, Krasnow B, Reiss AL, Menon V (2003) Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A* 100:253-258.
- Hanakawa T, Honda M, Sawamoto N, Okada T, Yonekura Y, Fukuyama H, Shibasaki H (2002) The role of rostral Brodmann area 6 in mental-operation tasks: an integrative neuroimaging approach. *Cereb Cortex* 12:1157-1170.
- Hasson U, Nusbaum HC, Small SL (2009) Task-dependent organization of brain regions active during rest. *Proc Natl Acad Sci U S A* 106:10841-10846.
- Hoffman KL, McNaughton BL (2002) Coordinated reactivation of distributed memory traces in primate neocortex. *Science* 297:2070-2073.
- Hong LE, Gu H, Yang Y, Ross TJ, Salmeron BJ, Buchholz B, Thaker GK, Stein EA (2009) Association of nicotine addiction and nicotine's actions with separate cingulate cortex functional circuits. *Arch Gen Psychiatry* 66:431-441.
- Huber R, Ghilardi MF, Massimini M, Tononi G (2004) Local sleep and learning. *Nature* 430:78-81.
- Iseki K, Hanakawa T, Shinozaki J, Nankaku M, Fukuyama H (2008) Neural mechanisms involved in mental imagery and observation of gait. *Neuroimage* 41:1021-1031.
- Jonides J, Smith EE, Koeppe RA, Awh E, Minoshima S, Mintun MA (1993)

- Spatial working memory in humans as revealed by PET. *Nature* 363:623-625.
- Kaas JH, Hackett TA (2000) Subdivisions of auditory cortex and processing streams in primates. *Proc Natl Acad Sci U S A* 97:11793-11799.
- Karnath HO (2001) New insights into the functions of the superior temporal cortex. *Nat Rev Neurosci* 2:568-576.
- Karni A, Meyer G, Jezard P, Adams MM, Turner R, Ungerleider LG (1995) Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature* 377:155-158.
- Karni A, Meyer G, Rey-Hipolito C, Jezard P, Adams MM, Turner R, Ungerleider LG (1998) The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex. *Proc Natl Acad Sci U S A* 95:861-868.
- Kasess CH, Windischberger C, Cunnington R, Lanzenberger R, Pezawas L, Moser E (2008) The suppressive influence of SMA on M1 in motor imagery revealed by fMRI and dynamic causal modeling. *Neuroimage* 40:828-837.
- Kawashima R, Okuda J, Umetsu A, Sugiura M, Inoue K, Suzuki K, Tabuchi M, Tsukiura T, Narayan SL, Nagasaka T, Yanagawa I, Fujii T, Takahashi S, Fukuda H, Yamadori A (2000) Human cerebellum plays an important role in memory-timed finger movement: an fMRI study. *J Neurophysiol* 83:1079-1087.
- Kenet T, Bibitchkov D, Tsodyks M, Grinvald A, Arieli A (2003) Spontaneously emerging cortical representations of visual attributes. *Nature* 425:954-956.
- Kilpatrick LA, Suyenobu BY, Smith SR, Bueller JA, Goodman T, Creswell JD, Tillisch K, Mayer EA, Naliboff BD (2011) Impact of Mindfulness-Based Stress Reduction training on intrinsic brain connectivity. *Neuroimage* 56:290-298.
- Kim SG, Rostrup E, Larsson HB, Ogawa S, Paulson OB (1999) Determination of relative CMRO<sub>2</sub> from CBF and BOLD changes: significant increase of oxygen consumption rate during visual stimulation. *Magn Reson Med* 41:1152-1161.

- la Fougere C, Zwergal A, Rominger A, Forster S, Fesl G, Dieterich M, Brandt T, Strupp M, Bartenstein P, Jahn K (2010) Real versus imagined locomotion: a [ $^{18}\text{F}$ ]-FDG PET-fMRI comparison. *Neuroimage* 50:1589-1598.
- Lahav A, Saltzman E, Schlaug G (2007) Action representation of sound: audiomotor recognition network while listening to newly acquired actions. *J Neurosci* 27:308-314.
- Ledberg A, Bressler SL, Ding M, Coppola R, Nakamura R (2007) Large-scale visuomotor integration in the cerebral cortex. *Cereb Cortex* 17:44-62.
- Leopold DA, Murayama Y, Logothetis NK (2003) Very slow activity fluctuations in monkey visual cortex: implications for functional brain imaging. *Cereb Cortex* 13:422-433.
- Lewis CM, Baldassarre A, Committeri G, Romani GL, Corbetta M (2009) Learning sculpts the spontaneous activity of the resting human brain. *Proc Natl Acad Sci U S A* 106:17558-17563.
- Liu Y, Gao JH, Liotti M, Pu Y, Fox PT (1999) Temporal dissociation of parallel processing in the human subcortical outputs. *Nature* 400:364-367.
- Logothetis NK (2003) MR imaging in the non-human primate: studies of function and of dynamic connectivity. *Curr Opin Neurobiol* 13:630-642.
- Logothetis NK (2008) What we can do and what we cannot do with fMRI. *Nature* 453:869-878.
- Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412:150-157.
- Lowe MJ, Mock BJ, Sorenson JA (1998) Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *Neuroimage* 7:119-132.
- Luchinger R, Michels L, Martin E, Brandeis D (2012) Brain state regulation during normal development: Intrinsic activity fluctuations in simultaneous EEG-fMRI. *Neuroimage* 60:1426-1439.
- Lushnikova I, Skibo G, Muller D, Nikonenko I (2009) Synaptic potentiation induces increased glial coverage of excitatory synapses in CA1 hippocampus. *Hippocampus* 19:753-762.

- Ma L, Narayana S, Robin DA, Fox PT, Xiong J (2011) Changes occur in resting state network of motor system during 4 weeks of motor skill learning. *Neuroimage* 58:226-233.
- Ma L, Wang B, Narayana S, Hazeltine E, Chen X, Robin DA, Fox PT, Xiong J (2010) Changes in regional activity are accompanied with changes in inter-regional connectivity during 4 weeks motor learning. *Brain Res* 1318:64-76.
- Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RS, Frith CD (2000) Navigation-related structural change in the hippocampi of taxi drivers. *Proc Natl Acad Sci U S A* 97:4398-4403.
- Maquet P, Laureys S, Peigneux P, Fuchs S, Petiau C, Phillips C, Aerts J, Del Fiore G, Degueldre C, Meulemans T, Luxen A, Franck G, Van Der Linden M, Smith C, Cleeremans A (2000) Experience-dependent changes in cerebral activation during human REM sleep. *Nat Neurosci* 3:831-836.
- Mazzoni A, Broccard FD, Garcia-Perez E, Bonifazi P, Ruaro ME, Torre V (2007) On the dynamics of the spontaneous activity in neuronal networks. *PLoS One* 2:e439.
- Meunier D, Achard S, Morcom A, Bullmore E (2009) Age-related changes in modular organization of human brain functional networks. *Neuroimage* 44:715-723.
- Mitzdorf U (1985) Current source-density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. *Physiol Rev* 65:37-100.
- Muellbacher W, Ziemann U, Wissel J, Dang N, Kofler M, Facchini S, Boroojerdi B, Poewe W, Hallett M (2002) Early consolidation in human primary motor cortex. *Nature* 415:640-644.
- Mukamel R, Gelbard H, Arieli A, Hasson U, Fried I, Malach R (2005) Coupling between neuronal firing, field potentials, and fMRI in human auditory cortex. *Science* 309:951-954.
- Munzert J, Zentgraf K (2009) Motor imagery and its implications for understanding the motor system. *Prog Brain Res* 174:219-229.
- Nair DG, Purcott KL, Fuchs A, Steinberg F, Kelso JA (2003) Cortical and

- cerebellar activity of the human brain during imagined and executed unimanual and bimanual action sequences: a functional MRI study. *Brain Res Cogn Brain Res* 15:250-260.
- Niessing J, Ebisch B, Schmidt KE, Niessing M, Singer W, Galuske RA (2005) Hemodynamic signals correlate tightly with synchronized gamma oscillations. *Science* 309:948-951.
- Nir Y, Hasson U, Levy I, Yeshurun Y, Malach R (2006) Widespread functional connectivity and fMRI fluctuations in human visual cortex in the absence of visual stimulation. *Neuroimage* 30:1313-1324.
- Nir Y, Fisch L, Mukamel R, Gelbard-Sagiv H, Arieli A, Fried I, Malach R (2007) Coupling between neuronal firing rate, gamma LFP, and BOLD fMRI is related to interneuronal correlations. *Curr Biol* 17:1275-1285.
- Nir Y, Mukamel R, Dinstein I, Privman E, Harel M, Fisch L, Gelbard-Sagiv H, Kipervasser S, Andelman F, Neufeld MY, Kramer U, Arieli A, Fried I, Malach R (2008) Interhemispheric correlations of slow spontaneous neuronal fluctuations revealed in human sensory cortex. *Nat Neurosci* 11:1100-1108.
- Nyberg-Hansen R, Rinvik E (1963) Some comments on the pyramidal tract, with special references to its individual variations in man. *Acta Neurologica Scandinavica* 29:1.
- Ogawa S, Lee TM (1990) Magnetic resonance imaging of blood vessels at high fields: in vivo and in vitro measurements and image simulation. *Magn Reson Med* 16:9-18.
- Ogawa S, Lee TM, Nayak AS, Glynn P (1990) Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Med* 14:68-78.
- Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J, Phillips C, Degueldre C, Del Fiore G, Aerts J, Luxen A, Maquet P (2004) Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron* 44:535-545.
- Peltier SJ, LaConte SM, Niyazov DM, Liu JZ, Sahgal V, Yue GH, Hu XP (2005) Reductions in interhemispheric motor cortex functional connectivity after

- muscle fatigue. *Brain Res* 1057:10-16.
- Poremba A, Saunders RC, Crane AM, Cook M, Sokoloff L, Mishkin M (2003) Functional mapping of the primate auditory system. *Science* 299:568-572.
- Privman E, Nir Y, Kramer U, Kipervasser S, Andelman F, Neufeld MY, Mukamel R, Yeshurun Y, Fried I, Malach R (2007) Enhanced category tuning revealed by intracranial electroencephalograms in high-order human visual areas. *J Neurosci* 27:6234-6242.
- Raichle ME, Mintun MA (2006) Brain work and brain imaging. *Annu Rev Neurosci* 29:449-476.
- Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. *Proc Natl Acad Sci U S A* 98:676-682.
- Rakic P (2002) Neurogenesis in adult primate neocortex: an evaluation of the evidence. *Nat Rev Neurosci* 3:65-71.
- Raman IM, Gustafson AE, Padgett D (2000) Ionic currents and spontaneous firing in neurons isolated from the cerebellar nuclei. *J Neurosci* 20:9004-9016.
- Rao SM, Binder JR, Bandettini PA, Hammeke TA, Yetkin FZ, Jesmanowicz A, Lisk LM, Morris GL, Mueller WM, Estkowski LD, et al. (1993) Functional magnetic resonance imaging of complex human movements. *Neurology* 43:2311-2318.
- Schroeder CE, Foxe JJ (2002) The timing and laminar profile of converging inputs to multisensory areas of the macaque neocortex. *Brain Res Cogn Brain Res* 14:187-198.
- Schroeder CE, Smiley J, Fu KG, McGinnis T, O'Connell MN, Hackett TA (2003) Anatomical mechanisms and functional implications of multisensory convergence in early cortical processing. *Int J Psychophysiol* 50:5-17.
- Sharma N, Pomeroy VM, Baron JC (2006) Motor imagery: a backdoor to the motor system after stroke? *Stroke* 37:1941-1952.
- Shmuel A, Leopold DA (2008) Neuronal correlates of spontaneous fluctuations in fMRI signals in monkey visual cortex: Implications for functional connectivity at rest. *Hum Brain Mapp* 29:751-761.
- Sidtis JJ, Strother SC, Rottenberg DA (2004) The effect of set on the resting state



- in functional imaging: a role for the striatum? *Neuroimage* 22:1407-1413.
- Stein BE, Stanford TR (2008) Multisensory integration: current issues from the perspective of the single neuron. *Nat Rev Neurosci* 9:255-266.
- Stephan KM, Fink GR, Passingham RE, Silbersweig D, Ceballos-Baumann AO, Frith CD, Frackowiak RS (1995) Functional anatomy of the mental representation of upper extremity movements in healthy subjects. *J Neurophysiol* 73:373-386.
- Stevens WD, Buckner RL, Schacter DL (2010) Correlated low-frequency BOLD fluctuations in the resting human brain are modulated by recent experience in category-preferential visual regions. *Cereb Cortex* 20:1997-2006.
- Stevenson RA, Geoghegan ML, James TW (2007) Superadditive BOLD activation in superior temporal sulcus with threshold non-speech objects. *Exp Brain Res* 179:85-95.
- Stinear CM, Fleming MK, Byblow WD (2006) Lateralization of unimanual and bimanual motor imagery. *Brain Res* 1095:139-147.
- Tambini A, Ketz N, Davachi L (2010) Enhanced brain correlations during rest are related to memory for recent experiences. *Neuron* 65:280-290.
- Taubert M, Lohmann G, Margulies DS, Villringer A, Ragert P (2011) Long-term effects of motor training on resting-state networks and underlying brain structure. *Neuroimage* 57:1492-1498.
- Taubert M, Draganski B, Anwander A, Muller K, Horstmann A, Villringer A, Ragert P (2010) Dynamic properties of human brain structure: learning-related changes in cortical areas and associated fiber connections. *J Neurosci* 30:11670-11677.
- Tian L, Wang J, Yan C, He Y (2011) Hemisphere- and gender-related differences in small-world brain networks: a resting-state functional MRI study. *Neuroimage* 54:191-202.
- Tononi G, Cirelli C (2003) Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull* 62:143-150.
- Treyer V, Buck A, Schnider A (2006) Effects of baseline task position on apparent activation in functional imaging of memory. *Neuropsychologia* 44:462-468.

- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002) Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15:273-289.
- van den Heuvel M, Mandl R, Hulshoff Pol H (2008) Normalized cut group clustering of resting-state fMRI data. *PLoS One* 3:e2001.
- Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, Van Essen DC, Zempel JM, Snyder LH, Corbetta M, Raichle ME (2007) Intrinsic functional architecture in the anaesthetized monkey brain. *Nature* 447:83-86.
- Waites AB, Stanislavsky A, Abbott DF, Jackson GD (2005) Effect of prior cognitive state on resting state networks measured with functional connectivity. *Hum Brain Mapp* 24:59-68.
- Wang JH, Zuo XN, Gohel S, Milham MP, Biswal BB, He Y (2011) Graph theoretical analysis of functional brain networks: test-retest evaluation on short- and long-term resting-state functional MRI data. *PLoS One* 6:e21976.
- Wang Z, Liu J, Zhong N, Qin Y, Zhou H, Li K (2012) Changes in the brain intrinsic organization in both on-task state and post-task resting state. *Neuroimage* 62:394-407.
- Witt ST, Laird AR, Meyerand ME (2008) Functional neuroimaging correlates of finger-tapping task variations: an ALE meta-analysis. *Neuroimage* 42:343-356.
- Xiong J, Parsons LM, Gao JH, Fox PT (1999) Interregional connectivity to primary motor cortex revealed using MRI resting state images. *Hum Brain Mapp* 8:151-156.
- Xiong J, Ma L, Wang B, Narayana S, Duff EP, Egan GF, Fox PT (2009) Long-term motor training induced changes in regional cerebral blood flow in both task and resting states. *Neuroimage* 45:75-82.
- Xu F, Uh J, Brier MR, Hart J, Jr., Yezhuvath US, Gu H, Yang Y, Lu H (2011) The influence of carbon dioxide on brain activity and metabolism in conscious humans. *J Cereb Blood Flow Metab* 31:58-67.
- Xu G, Antuono PG, Jones J, Xu Y, Wu G, Ward D, Li SJ (2007) Perfusion fMRI

- detects deficits in regional CBF during memory-encoding tasks in MCI subjects. *Neurology* 69:1650-1656.
- Yang H, Long XY, Yang Y, Yan H, Zhu CZ, Zhou XP, Zang YF, Gong QY (2007) Amplitude of low frequency fluctuation within visual areas revealed by resting-state functional MRI. *Neuroimage* 36:144-152.
- Yoshida M, Satoh T, Nakamura KC, Kaneko T, Hata Y (2009) Cortical activity regulates corticothalamic synapses in dorsal lateral geniculate nucleus of rats. *Neurosci Res* 64:118-127.
- Zatorre RJ, Chen JL, Penhune VB (2007) When the brain plays music: auditory-motor interactions in music perception and production. *Nat Rev Neurosci* 8:547-558.
- Zeithamova D, Schlichting ML, Preston AR (2012) The hippocampus and inferential reasoning: building memories to navigate future decisions. *Front Hum Neurosci* 6:70.
- Zhang S, Ide JS, Li CS (2012) Resting-state functional connectivity of the medial superior frontal cortex. *Cereb Cortex* 22:99-111.