Changes occur in resting state network of motor system during 4 weeks of motor skill learning

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ABSTRACT

We tested whether the resting state functional connectivity of the motor system changed during 4 weeks of motor skill learning using functional magnetic resonance imaging (fMRI). Ten healthy volunteers learned to produce a sequential finger movement by daily practice of the task over a 4 week period. Changes in the resting state motor network were examined before training (Week 0), two weeks after the onset of training (Week 2), and immediately at the end of the training (Week 4). The resting state motor system was analyzed using group independent component analysis (ICA). Statistical Parametric Mapping (SPM) second-level analysis was conducted on independent z-maps generated by the group ICA. Three regions, namely right postcentral gyrus, and bilateral supramarginal gyri were found to be sensitive to the training duration. Specifically, the strength of resting state functional connectivity in the right postcentral gyrus and right supramarginal gyrus increased from Week 0 to Week 2, during which the behavioral performance improved significantly, and decreased from Week 2 to Week 4, during which there was no more significant improvement in behavioral performance. The strength of resting state functional connectivity in left supramarginal gyrus increased throughout the training. These results confirm changes in the resting state network during slow-learning stage of motor skill learning, and support the premise that the resting state networks play a role in improving performance.

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Introduction

Motor skill learning (Doyon and Benali, 2005; Halsband and Lange, 2006; Hikosaka et al., 2002; Hotermans et al., 2006; Luft and Buitrago, 2005; Sanes, 2003; Willingham, 1998) contains an early rapid phase in which considerable improvement in performance is achieved in a single training session of a few minutes, an intermediate phase of consolidation of several hours, and a later slow-learning stage in which greater improvement in performance is achieved over relatively long duration, e.g., several weeks (Karni et al., 1998; Ungerleider et al., 2002). In the neuroimaging literature, several studies have investigated the slow-

learning stage of motor skill learning. Functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) studies investigating slow-learning stage of hand movement are listed in Table 1. These studies indicate that the slow-learning stage is associated with task related changes in the motor system indexed by blood oxygen level dependent (BOLD) signal measured by fMRI (Floyer-Lea and Matthews, 2005; Hlustik et al., 2004; Karni et al., 1995; Lehericy et al., 2005), regional cerebral blood flow measured by PET (Xiong et al., 2009), as well as task driven functional connectivity (Coynel et al., 2010) or effective connectivity (Ma et al., 2010).

The changes in brain activity levels in the motor system are thought to follow Hebbian principle (Klintsova and Greenough, 1999), which describes a fundamental mechanism for synaptic plasticity in which an increase in synaptic efficacy is the outcome of one cell's repeated and persistent stimulation of another cell (Hebb, 1949). However, there is no consensus on the pattern of change in the cortical regions following motor practice (Kelly and Garavan, 2005). For example, continued increase in BOLD signal in motor areas (Karni et al., 1995, 1998; Ungerleider et al., 2002) and a waxing and waning pattern (Hlustik et al., 2004; Ma et al., 2010; Xiong et al., 2009) have both been reported. In our previous study, we found that significant training-induced increases in resting state cerebral blood flow were noted in motor areas (Xiong et al., 2009). That is, while the activation-volume analysis for fMRI BOLD and

Table 1
Summary of neuroimaging studies on slow-learning stage of motor skill learning. M1 = primary motor cortex; and S1 = primary somatosensory cortex.

Publications	Training duration and trained hand	Neuroimaging modality and training task	Major findings
Karni et al. (1995)	Four weeks Left hand	fMRI Sequential finger movement task	Greater activation in right M1 when subjects conducted the learned sequence than when they conducted the unpracticed sequence.
Hlustik et al. (2004)	Three weeks Left hand	fMRI Sequential finger movement task	Gradual expansion of right M1 and right S1 areas activated by the practiced sequence.
Lehericy et al. (2005)	One month Left hand	fMRI Sequential finger movement task	Activation decreased in rostrodorsal (associative) regions of the putamen, and activation increased in more caudoventral (sensorimotor) regions of the putamen.
Floyer-Lea and Matthews (2005)	Three weeks Right hand	fMRI Force-tracking task	Activity induced by the trained task increased in left S1, M1, and right putamen.
Xiong et al. (2009)	Four weeks Left hand	PET Sequential finger movement task	Regional cerebral blood flow in right M1 increased during both task and resting states.
Ma et al. (2010)	Four weeks Left hand	fMRI Sequential finger movement task	Gradually enhanced cortico-basal ganglionic and gradually weakened cortico-cerebeller connections.
Coynel et al. (2010)	Four weeks Left hand	fMRI Sequential finger movement task	Gradually weakened functional connectivity in the associative/premotor network and gradually enhanced functional connectivity between associate/premotor network and the sensorimotor network.

PET cerebral blood flow during task showed an early increase followed by a return pre-training level by Week 4, our regional resting state cerebral blood flow analysis demonstrates that the apparent decrease during task performance was actually due to a substantial increase in baseline cerebral blood flow (Xiong et al., 2009). Similarly, an increase in the BOLD signal in the 0.08 Hz frequency band consistent with a focal, resting state increase in blood flow was noted (Duff et al., 2008; Xiong et al., 2009). We believe that traditional task-based conditional contrast analyses and imaging methods such as fMRI BOLD signals where baseline changes cannot be quantified partly contribute to the confusion. Thus, task independent measures of brain function, i.e., examining resting state networks of the brain may contain rich information on the mechanism of motor skill learning. Therefore, we sought to understand motor skill learning through investigating the resting state networks of the brain.

The study of resting state neural activity is an alternative approach to task related regional activity and likely provides additional information on the neurobiological mechanisms of specific brain systems (Auer, 2008; Fox and Raichle, 2007; Greicius, 2008; van den Heuvel and Hulshoff Pol, 2010; Van Dijk et al., 2010). In the resting state brain, there are spontaneous low frequency (Cordes et al., 2001) neuronal activations that show high temporal cohesion (correlation) among functionally related brain regions (Biswal et al., 1995). The temporal correlation during resting state is termed as resting state functional connectivity (Auer, 2008; Fox and Raichle, 2007; Greicius, 2008; van den Heuvel and Hulshoff Pol, 2010; Van Dijk et al., 2010), and the regions showing temporal correlation constitute a resting state (or intrinsic) network (Albert et al., 2009a; Cole et al., 2010; De Luca et al., 2006; Deco et al., 2011; Miall and Robertson, 2006; Raichle and Snyder, 2007; Uddin et al., 2010). The low frequency fluctuations in resting state are even present during sleep and sedation (Van Dijk et al., 2010). To date, the most commonly defined resting state networks include motor, visual, auditory, executive functioning, auditory processing, memory, and default-mode network systems (Cole et al., 2010). Resting state functional connectivity appears to be constrained by structural connectivity (van den Heuvel and Hulshoff Pol, 2010; Van Dijk et al., 2010). There is close correspondence of the brain's functional architecture during rest and task elicited activation (Smith et al., 2009). Resting state fMRI is a powerful tool for resting state network analysis (Fox and Raichle, 2007; Van Dijk et al., 2010). It possesses percentage BOLD signal change that is comparable to that found in task-related experiments (Damoiseaux et al., 2006). Importantly, the resting state fMRI studies require relatively short acquisition time (e.g. as brief as 5 min) (Van Dijk et al., 2010) and are not confounded by task performance issues. Resting state networks have been found to be consistent across participants (Damoiseaux et al., 2006; Shehzad et al., 2009), recording sessions (Damoiseaux et al., 2006; Meindl et al., 2010; Shehzad et al., 2009), and analysis methods (Fox and Raichle, 2007; van den Heuvel and Hulshoff Pol, 2010). Resting state data have been used to investigate both clinical (see Fox and Greicius, 2010; Greicius, 2008 for review) and non-clinical (e.g., Albert et al., 2009b; Biswal et al., 1995; Hampson et al., 2002; Jiang et al., 2004; Xiong et al., 1999, among many other studies) populations.

Related to the current study, several studies have reported that spontaneous activation in the resting state brain can be affected by learning. A number of studies have used resting state fMRI to index changes in the brain associated with learning. Albert et al. (2009b) found that a fronto-parietal resting state network and a cerebellar resting state network were altered after the participants practiced a visuomotor tracking task for 11 min. Lewis et al. (2009) found that the resting state functional connectivity and directed mutual interaction between trained visual cortex and frontal-parietal areas were significantly modified following several days (2 to 9 days) of training on a shape-indentification task. Daselaar et al. (2010) used a perceptuomotor task and found that the superior parietal cortex activated during the task training was more active during post-training rest duration than pre-training rest duration. In addition, it has been shown that resting state functional connectivity between the left and right supramarginal gyrus (SMG, part of inferior parietal lobule) was stronger for new word learners than for non-learners (Veroude et al., 2010). Critically, the above studies on learning and resting state connectivity suggest that the fronto-parietal regions are involved in learning. However, no study has investigated the resting state network during slow learning stage.

We have investigated local changes in resting state cerebral blood flow associated with slow learning of a sequential finger movement task (Xiong et al., 2009). To extend our previous work, we conducted this study to investigate whether there were changes in the resting state functional connectivity of the motor system during slow learning of the same motor task. We analyzed three sets of resting state fMRI data sequentially acquired in 4 weeks, during which participants regularly practiced a sequential finger movement task and improved their skills significantly (Ma et al., 2010; Xiong et al., 2009). Based on the evidence showing that resting state networks can be altered following learning (Albert et al., 2009b; Daselaar et al., 2010; Lewis et al., 2009; Veroude et al., 2010), we hypothesized that changes will be observed in the resting state network of motor system during slow-learning stage of motor skill learning.

Methods

Participants

This study was approved by the Institutional Review Board of University of Iowa, Iowa City, Iowa, and University of Texas Health Science Center, San Antonio, Texas. After providing informed consent, thirteen healthy normal volunteers participated in this study, and ten (5 male and 5 female) of them completed the experiment, and were included for final analysis. The participants who completed the experiment had a mean age of 30 years (± 8.33 years, standard deviation), ranging from 18 to 45 years. We used self-report to obtain demographic information that indicated that: (1) all the participants were right-handed; (2) none of the participants was a professional musical instrument player; and (3) none of the participants had known neurological and psychiatric disorders.

Motor sequence learning paradigm

Each participant was trained to perform a motor task in which the fingers of left hand were opposed to the thumb in specific sequences for a total of 15 min each day. The training lasted for 4 weeks (including weekend) for all participants. The participants were instructed that, during the 15-min practice session, they were to perform the sequence as accurately and quickly as possible. Each practice session was video recorded.

The details of the motor sequence learning task have been described elsewhere (Karni et al., 1995; Ma et al., 2010; Xiong et al., 2009). Briefly, during the task, participants performed one of two specific sequences without visual feedback. The order of finger movement in Sequence A is 5, 2, 4, 3, and 5, and the order of finger movement is 5, 3, 4, 2, and 5 in Sequence B (a mirror image of Sequence A). The numbers are coded as: 2-index finger, 3-middle finger, 4-ring finger, and 5-little finger. Five participants (Group A) were randomly assigned Sequence A as the training sequence, and the other five participants (Group B) were assigned Sequence B as the training sequence. There was no statistical difference in behavior performance between the two participant groups (see the Results section), therefore Group A and Group B were combined into a single group for this resting state fMRI study.

MRI data acquisition

There were three MRI scanning sessions. The first scanning session was performed just prior to the onset of training (Week 0). After 2 weeks of practice, there was a second scanning session (Week 2). The last scanning session occurred immediately after 4 weeks of practice (Week 4).

The MRI images were acquired on an Elscint Prestige 2-T whole-body MRI scanner (Elscint Prestige, Haifa, Israel). A total of 400 volumes of resting state fMRI images were acquired in a transverse plane using a T2-weighted gradient-echo echo-planar-imaging (EPI) sequence, with the following parameters: repetition time (TR) = 700 ms, echo time (TE) = 45 ms, flip angle = 70°, field of view (FOV) = 411×229 mm^2, 72×72 voxels image matrix, 3.28×3.28 mm^2 in-plane voxel resolution, 7 contiguous fMRI slices, slice thickness = 5 mm, interslice gap = 1 mm, and receive bandwidth = 12.21 Hz. The 7 contiguous slices cover the areas of primary motor cortex (M1), primary somatosensory cortex (S1), supplementary motor area (SMA), dorsal premotor cortex, posterior parietal somatosensory association area, and dorsal cingulate motor area (Xiong et al., 1999). The scan acquired during task performance always occurred after the resting state scan (240 volumes, transverse plane, T2-weighted gradient-echo EPI sequence, TR = 2 s, TE = 45 ms, flip angle = 90°, FOV = 411×229 mm^2, 72×72 voxels image matrix, 3.28×3.28 mm^2 in-plane voxel resolution, 16 contiguous fMRI slices, slice thickness = 5 mm, interslice gap = 1 mm, receive

bandwidth = 12.21 Hz). T1-weighted anatomical images were also acquired, with the following parameters: repetition time = 33 ms, echo time = 12 ms, flip angle = 60°, 16 contiguous slices, slice thickness = 5 mm, interslice gap = 1 mm, 256×256 voxels image matrix, and 1×1 mm^2 voxel resolution.

During MRI scanning, the participants were supine with their heads supported by a foam-padded, hemicylindrical head holder. Each participant's head was immobilized within a tightly fitting thermally molded plastic facial mask extending from hairline to chin. During the resting state fMRI scan, the participants were instructed to remain still, with their eyes closed.

MRI image preprocessing

For each participant and at each test point (Week 0, Week 2, or Week 4), the first 10 fMRI images were discarded to allow MRI signal to reach a steady state. Statistical Parametric Mapping (SPM8) software (http://www.fil.ion.ucl.ac.uk) and Resting state fMRI Data Analysis Toolkit (REST) V1.4 software (http://resting-fmri.sourceforge.net/) were used to preprocess the MRI data. The fMRI images were spatially realigned to the first volume to correct the bias due to head movements (using SPM8 software). Both the resting state fMRI images and the T1-image were co-registered to the task performance fMRI images. After that, the T1 image was transformed to the coordinates of the Montreal Neurological Institute (MNI) standard space using the SPM8 normalization procedure. This transformation was applied to the resting state fMRI images to convert them to MNI space. After spatial normalization, a linear drift correction (Tanabe et al., 2002) was applied to all fMRI images (using REST software). To increase the signal-to-noise-ratio, the fMRI images were spatially smoothed by an isotropic Gaussian filter with a full-width at half-maximum (FWHM) of 8 mm (using SPM8 software). A bandpass filter with cutoff frequencies of 0.01 and 0.12 Hz (Ma et al., 2007) was used to remove high-frequency noise and very low-frequency signals (using REST software). In the literature, different cutoff frequencies have been used or proposed: e.g., 0.08 Hz (Chuang et al., 2008; Kwak et al., 2011), 0.1 Hz (van den Heuvel and Hulshoff Pol, 2010; Van Dijk et al., 2010), and up to 0.15 Hz (Cole et al., 2010; Smith et al., 2008). In one of our previous studies, we used the same resting state fMRI data and found a significant increase in power spectrum in the 0.08 Hz frequency band in the right M1 area after the two week and four week training periods (Xiong et al., 2009). To avoid losing essential signals at 0.08 Hz frequency band, we chose 0.12 Hz as the cutoff frequency. All the programs were run on a platform of MATLAB 7.1 (The MathWorks, Inc., Natick, MA).

Group independent component analysis

Group ICA (Calhoun et al., 2009), an extension of the traditional ICA (McKeown et al., 1998), was used to analyze the fMRI data. Among the two broadly-used and performance-comparable group ICA alternatives (Schopf et al., 2010), i.e., Group ICA of fMRI Toolbox (GIFT) (Calhoun et al., 2001), and Probabilistic ICA or PICA (Beckmann et al., 2005), we chose GIFT software (http://icatb.sourceforge.net/). GIFT software results in the detection of consistent resting state networks across multiple sessions at least over a period of several weeks (Chen et al., 2008). Using the ICA algorithm which was proposed by Lin et al. (2010) and implemented in the GIFT software version 2.0d, we analyzed the resting state fMRI data for each test point (Week 0, Week 2, or Week 4). Prior to ICA analysis, principal component analysis (PCA) is used to reduce data. The number of ICA components was set to 20 because one of our previous studies has shown that 20 components can yield robust ICA results for motor network with a moderate computation load for the current data set (Ma et al., 2007). Spatially independent components were back-reconstructed (Calhoun et al., 2001, 2009) for all participants and all test points (Week 0, Week 2, and Week 4).

One of the challenges in ICA analysis is the selection of components of interest among several identified independent components (Calhoun et al., 2005; Lin et al., 2010). It has been shown that, the ICA algorithms proposed by Calhoun et al. (2005) and Lin et al. (2010) are able to deal with this challenge. These algorithms use some prior temporal (Calhoun et al., 2005) or spatial information (Lin et al., 2010) on the fMRI data to search the components of interest, and therefore they are referred to as "semi-blind" ICA algorithms (Calhoun et al., 2005; Lin et al., 2010). In this study, to select spatially independent components for motor system resting state network, we chose the semi-blind ICA algorithm with spatial constraint (Lin et al., 2010). Our previous study (Ma et al., 2007) using the same data set showed that the resting state network of motor system essentially contains M1, S1, and premotor cortex (including SMA). Therefore the spatial constraint map was constructed by combining the probabilistic atlases of M1, S1, and premotor cortex (including SMA), provided by the SPM Anatomy toolbox version 1.6 (Eickhoff et al., 2006, 2007, 2005). All the independent components (or maps) generated by the semi-blind ICA algorithm were visually inspected to ensure that they indeed were part of the motor system.

All independent components were converted to z maps (Ma et al., 2007; McKeown et al., 1998). Each z-score represents the fit of a specific voxel BOLD time course to the time course of the group averaged component (Assaf et al., 2010). The z maps were tested for the strength of the connectivity (i.e. signal synchronization) of each voxel to the entire spatial component using standard SPM statistical analysis package.

SPM full factorial analysis

The main effects of the z-score (averaged across Week 0, Week 2, and Week 4) and planned comparisons among the test points were analyzed using SPM8 second-level full factorial analysis (random effects), with the z maps from ICA analysis as inputs (one independent component for each participant and each test point). The full factorial module included a factor of test point (three levels: Week 0, Week 2, and Week 4). Planned comparisons between test points included Week 2 minus Week 0, Week 0 minus Week 2, Week 4 minus Week 2, Week 2 minus Week 4, Week 4 minus Week 0, and Week 0 minus Week 4. The planned comparisons were masked with significant clusters obtained from the main effects to ensure that only robust signals were considered for the planned comparisons (Van Dijk et al., 2010).

The cluster-defining threshold was $t = 3.5$, and all p values resulting from the SPM second-level analysis reported in this article are cluster p values that were corrected for multiple comparisons using random field theory and computed by SPM8 to control the family-wise error (FWE) rate to be less than 0.05 (Friston et al., 1996, 1994). Approximate anatomical labels for regions of significant clusters were determined using the SPM Anatomy toolbox version 1.6 (Eickhoff et al., 2005, 2006, 2007).

Results

Motor sequence learning paradigm

The learning curve for the trained sequence has been shown elsewhere (Ma et al., 2010; Xiong et al., 2009). Statistical analysis of the behavioral data has a between-subject factor of group (Group A versus Group B) and a within-subject factor of training duration (Week 0, Week 2, and Week 4). A two by three repeated measures analysis of variance (ANOVA) analysis based on the movement rate revealed significant difference between the training durations ($F(2,24) = 25.84$, $p < 0.00001$). Neither the difference between the two subject groups ($F(1,24) = 0.39$, $p = 0.54$) nor the interaction between the subject group and the training duration ($F(2,24) = 0.02$, $p = 0.98$) were significant.

Post hoc unpaired Student *t*-test analyses indicate that the mean movement rates (pooled across Group A and Group B) at Week 2 ($t = 5.63$, degree of freedom or DF = 18, $p < 0.001$, Bonferroni corrected) and Week 4 ($t = 7.27$, DF = 18, $p < 0.00001$, Bonferroni corrected) were significantly greater than that at Week 0. No significant difference was found between Week 2 and Week 4 ($t = 1.08$, DF = 18, $p > 0.2$).

Group independent component analysis

The GIFT software using the semi-blind ICA algorithm with spatial constraint (Lin et al., 2010) generated a single independent component for each participant and for each test point (Week 0, Week 2, or Week 4). Visual inspection on the independent components confirmed that the semi-blind ICA algorithm with spatial constraint (Lin et al., 2010) was able to distinctly detect the independent component of motor resting state network from other independent components for all participants and for all test points (Week 0, Week 2, and Week 4).

SPM full factorial analysis

The SPM random effects full-factorial analysis of the independent components found two significant clusters for the main effects of z-score (averaged across Week 0, Week 2, and Week 4). The two significant clusters, which are overlaid in color on axial slices of an MNI template brain, are shown in Fig. 1. In addition, two significant clusters (Cluster 1 and Cluster 2 respectively) were found for the planned comparison Week 2 minus Week 0; two significant clusters (Cluster 3 and Cluster 4 respectively) were found for the planned
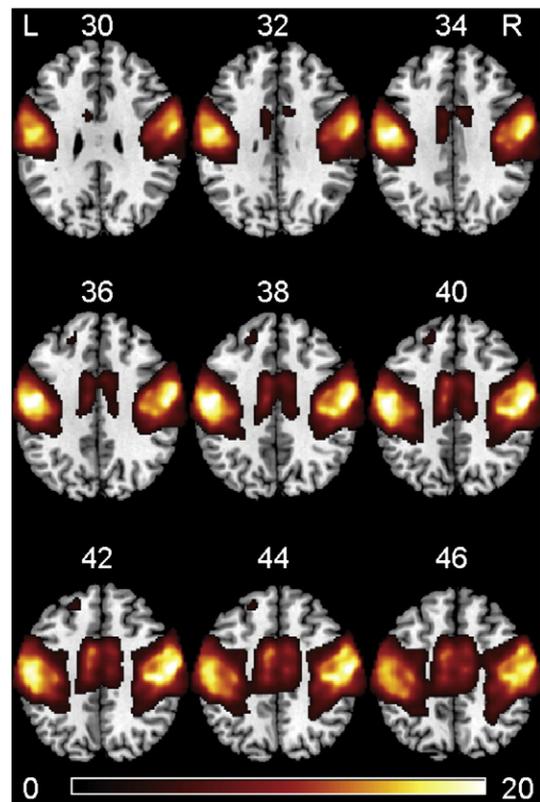

Fig. 1. Significant clusters (main effects) of resting state network of motor system found by the SPM second-level full-factorial analysis, based on the output (z maps) from ICA analysis. The significant clusters are overlaid in color on axial slices of an MNI template brain. The number above each slice indicates slice location (mm) of MNI z coordinate. Scale on color bar represents voxel t values. Left (L) side in the figure is left hemisphere of the brain, and right (R) side of figure is right hemisphere of brain.

comparison Week 2 minus Week 4; and a significant cluster (Cluster 5) was found for the planned comparison Week 4 minus Week 0. No significant cluster was found for the other planned comparisons (Week 0 minus Week 2, Week 0 minus Week 4, and Week 4 minus Week 2). The five significant clusters (Clusters 1 to 5), which are overlaid in color on axial slices of an MNI template brain, are shown in Fig. 2. For each of the seven significant clusters, the cluster-level family-wise error corrected p value, cluster volume, and the MNI coordinate and approximate anatomical location (within 3 mm radius) of the voxel with maximal t value are listed in Table 2.

The Anatomy toolbox indicated that Cluster 1 found by the planned comparison Week 2 minus Week 0 represented a portion of the right postcentral gyrus (PCG), and that Cluster 2 found by the planned comparison Week 2 minus Week 0 was in a portion of the right SMG. In addition, Cluster 3 (Week 2 minus Week 4) was in a portion of the right PCG; Cluster 4 (Week 2 minus Week 4) was in a portion of the right SMG; and Cluster 5 (Week 4 minus Week 0) was in a portion of the left SMG.

Cluster 1 and Cluster 3 overlapped with a volume of 1.120 mL, corresponding to 32% of the volume of Cluster 1 and 71% of the volume of Cluster 3. Cluster 2 and Cluster 4 overlapped (volume of 0.552 mL), corresponding to 25% of the volume of Cluster 2 and 100% of the volume of Cluster 4.

A trend analysis was used to investigate the temporal dynamics of the strength of the resting state functional connectivity in Cluster 5 that showed a significant effect for the planned comparison of Week 4 minus Week 0. The mean z-score (across all voxels within Cluster 5) was computed for each participant and for each test point (Week 0, Week 2, or Week 4). The trend analysis was conducted under an SPSS (SPSS Inc, Chicago, Illinois) one-way ANOVA in which there was a within-group factor of test points (Week 0, Week 2, and Week 4). This trend analysis indicated that the mean z-score in Cluster 5 was well fit by a linear model ($p = 0.002$), which accounted for 29% of the variance. The mean plot of the mean z-score (averaged across all participants at each test point) in Cluster 5 is depicted in Fig. 3.

Discussion

We used group ICA and SPM random effects full factorial analysis to test if there are changes in the resting state motor network associated with 4 weeks of motor skill learning. Based on the data (z maps generated by the group ICA), the SPM analysis revealed five clusters that were sensitive to the slow learning. The clusters (right PCG and bilateral SMG) were in the parietal lobe, consistent with the role of the parietal lobe in motor control (Fleming and Crosby, 1955), the findings that the parietal lobe plays an important role in later stages of motor learning (Halsband and Lange, 2006; Sakai et al., 1998), and findings that the fronto-parietal regions may be important for learning (Albert et al., 2009b; Daselaar et al., 2010; Lewis et al., 2009; Veroude et al., 2010). We also found involvement of SMG in the motor skill learning, consistent with the strong anatomical connection of SMG with ventral premotor area and M1 (Koch et al., 2010), and the role of this region in motor cognition (Hanakawa et al., 2008; Tunik et al., 2008). Motor cognition refers to the concept that cognition is embodied in action, and that the motor system contributes to mental processing (Sommerville and Decety, 2006).

We found changes associated with different periods of learning. Cluster 1 and Cluster 2, significant for Week 2 minus Week 0, were in right PCG and right SMG respectively. Cluster 3 and Cluster 4, significant for Week 2 minus Week 4, were also in right PCG and right SMG. Therefore, we conducted a further analysis to determine if the same portion of right PCG or SMG was involved in the connectivity changes. To that end, we examined volume of overlap between clusters, and found that the volume of the overlap between Cluster 1 and Cluster 3 was 71% of the volume of Cluster 3, and the volume of the overlap between Cluster 2 and Cluster 4 was 100% of the volume of Cluster 4. Based on these results, we assume that, under the current experimental conditions, the same regions of right PCG and right SMG were affected by the motor skill learning in the remaining part of this paper.

The PCG and SMG contralateral (right) to the trained hand, exhibited difference for two specific comparisons, Week 2 minus
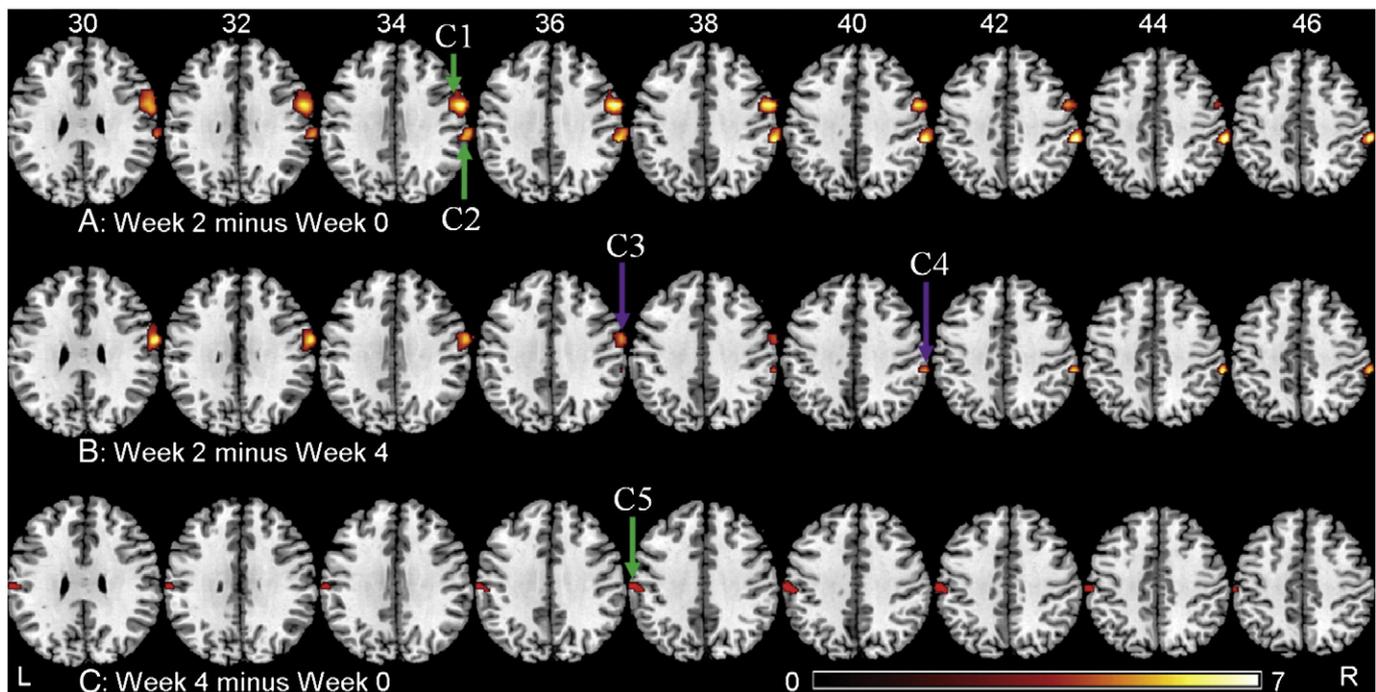

Fig. 2. Significant clusters (planned comparison among the test points) of resting state network of motor system found by the SPM second-level full-factorial analysis, based on the output (z maps) from ICA analysis. The significant clusters are overlaid in color on axial slices of an MNI template brain. The number above each slice indicates slice location (mm) of MNI z coordinate. Scale on color bar represents voxel t values. Left (L) side in the figure is left hemisphere of the brain, and right (R) side of figure is right hemisphere of brain. A: Week 2 minus Week 0 planned comparison. B: Week 2 minus Week 4 planned comparison. C: Week 4 minus Week 0 planned comparison. C1 to C5 denote Cluster 1 to Cluster 5.

Table 2

SPM full factorial second-level (random effects) analysis results. Within each significant cluster, the voxel with maximal t value and its approximate anatomical locations within 3 mm radius were listed. x, y, and z = MNI standard space coordinates (mm). Negative x = left hemisphere and positive x = right hemisphere. Smoothness of residual field (FWHM) = [10.7 10.2 14.1] mm. FWE = family-wise error corrected probability.

Contrast	Cluster label	Cluster P [FWE-corrected]	Cluster volume [mL]	Maximal voxel t value	Voxel MNI coordinate [x, y, z]	Maximal voxel t location
Week 2 minus Week 0	1	<0.001	3.536	6.77	60, 0, 36	Right postcentral gyrus
	2	<0.001	2.200	6.97	62, −32, 44	Right supramarginal gyrus
				5.43	66, −26, 34	Right supramarginal gyrus
Week 2 minus Week 4	3	0.001	1.584	6.54	64, −4, 30	Right postcentral gyrus
	4	0.038	0.552	6.08	62, −34, 44	Right supramarginal gyrus
Week 4 minus Week 0	5	0.008	1.024	4.32	−66, −20, 30	Left supramarginal gyrus
				4.21	−62, −22, 42	Left supramarginal gyrus
Main effect of z-score (across Week 0, Week 2, Week 4)	6	<0.001	83.752	23.48	56, −12, 40	Right postcentral gyrus
				22.00	−48, −14, 41	Left postcentral gyrus
				20.81	46, −20, 42	Right postcentral gyrus
				19.79	60, −6, 38	Right postcentral gyrus
				19.52	40, −20, 42	Right postcentral gyrus
				17.86	52,0, 44	Right postcentral gyrus
				15.01	−40, −34, 46	Left postcentral gyrus
				14.82	−6, 0, 44	Left middle cingulate cortex
				14.18	38, −10, 46	Right precentral gyrus
				13.26	−8, −10, 42	Left middle cingulate cortex
				11.97	8, −14, 46	Right middle cingulate cortex
	7	0.028	0.632	4.88	−18, 38, 42	Left superior frontal gyrus

Week 0 and Week 2 minus Week 4. Specifically, the strength of resting state functional connectivity in right PCG and right SMG increased (from Week 0 to Week 2) and then decreased (from Week 2 to Week 4), suggesting that the regions in the right hemisphere are supportive of the learning process in early phases of motor skill learning. This finding supports the literature that suggests the dominance of the right hemispheric parietal regions in the early phases of motor skill learning (Halsband and Lange, 2006). The right SMG is involved visuospatial attention (Gitelman et al., 1999; Kim et al., 1999; Lacquaniti et al., 1997; Loayza et al., 2011; Nobre et al., 1997). It is well known that attention is an important component of motor learning (Perchet and Garcia-Larrea, 2000; Posner et al., 1982). The dynamic changes (increased-first-then-decreased) in resting state functional connectivity in the right PCG and right SMG probably reflect the necessity of sensorimotor integration and visuospatial attention in the earlier phases of motor skill learning which became less necessary in the later phases of motor skill learning.

We also found that the left SMG exhibited a significant effect for the Week 4 minus Week 0 comparison. In addition, the trend analysis showed that the mean z-score in the left SMG was well fit by a linear model (Fig. 3). Thus, the strength of resting state functional connectivity in the left SMG systematically increased throughout the 4-week training duration. We interpret these changes as evidence that the dynamic change in the resting state functional connectivity in the left SMG
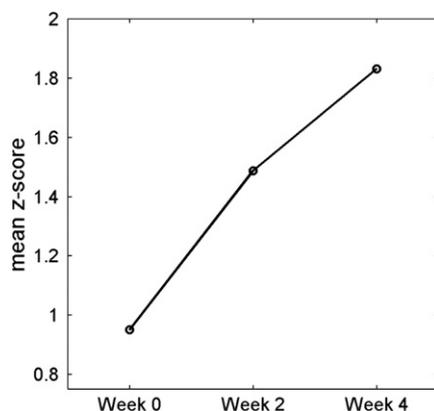
reflects long-term motor skill learning. The role of left SMG in learning is likely associated with retention of learned skills. The role of dominant-hemisphere in the later phases of motor skill learning (Halsband and Lange, 2006), and the role of the left SMG in higher motor cognition (Deiber et al., 1996; Hesse et al., 2006; Kimura, 1993; Krams et al., 1998; Rushworth et al., 2001, 1997) strongly support our interpretation of resting state changes in this region. Others have suggested that the left SMG plays a role in motor programming and attention (Deiber et al., 1996; Hesse et al., 2006; Kimura, 1993; Krams et al., 1998; Rushworth et al., 2001, 1997), including the storage of visuomotor skills (Heilman et al., 1982; Johnson-Frey et al., 2005). Therefore, we hypothesize that the systematic increase in the strength of resting state functional connectivity in the left SMG is an index of the retention of the learned motor skills.

The findings of the current study have important implications for understanding the role of the resting state networks in behavior. Currently, it is hypothesized that the resting state networks may help to keep functional systems in an active state (Miall and Robertson, 2006; Raichle et al., 2001; van den Heuvel and Hulshoff Pol, 2010), represent a dynamic prediction about expected use of the functionally correlated regions (Fox and Raichle, 2007), make critical contributions to the off-line memory consolidation (an improvement or enhancement in performance observed after a delay) (Miall and Robertson, 2006), and help to improve behavioral performance (van den Heuvel and Hulshoff Pol, 2010). The increased strength of functional connectivity in the right PCG and right SMG and the subsequent decrease from Week 2 to Week 4 accompanied by increases and then stabilization in our behavioral measure of learning, suggesting these regions serve to regulate early stages of learning and in particular the initial enhancement of behavioral performance (van den Heuvel and Hulshoff Pol, 2010).

Previous studies have implicated M1 as critical for the consolidation of motor skills (Muellbacher et al., 2002; Robertson et al., 2005) and for performance changes during the slow learning stage (Wilkinson et al., 2010). It has also been reported that SMA is critical for motor consolidation (in some conditions; Tanaka et al., 2010) but not for slow learning stage (Wilkinson et al., 2010). Strong task-related changes in regional activation in these two regions during the slow-learning stage of motor learning have consistently been reported in the literature (Hlustik et al., 2004; Karni et al., 1995; Ma et al., 2010; Xiong et al., 2009). However, unlike during task, the data from the current study showed that the resting state functional connectivity in M1 and SMA does not vary. This dissociation between task-induced and resting state

Fig. 3. Mean plot for the mean z-score in Cluster 5, portion of left supramarginal gyrus.

spontaneous activation likely reflects differences in the neurobiology underlying the task-induced activation and resting state spontaneous activation. As well, there is a clear difference in the physiology underlying task-evoked BOLD responses and spontaneous BOLD fluctuations (Fox and Raichle, 2007) that is also reflected by our data.

One limitation of this study is the partial spatial coverage (only seven contiguous axial slices), therefore other regions modulated by the motor skill training such as basal ganglia, thalamus, and cerebellum were missed. However, the limited spatial coverage is accompanying with a relatively high sampling rate (700 ms), which reduces aliasing of high frequency cardiac or respiratory activity (Fox and Raichle, 2007; Van Dijk et al., 2010). In addition, the participant sample size (ten participants were included in the final analysis) is relatively small and the observed changes in the resting state network are generally quite small, thereby reducing power. Future studies with more participants and/or controlling the effect of order (e.g., by having a group of control participants who perform a matched untrained task or not, and the resting state network is recorded at the same time as the trained group) will help provide greater insight into resting state network changes associated with learning. Furthermore, although we have excluded participants who were professional musical instrument players, we did not question the participants about their history in sports. Despite these limitations, the results observed in this study confirm that there are changes in the resting state network during slow-learning stage of motor skill learning, and support the hypothesis that the resting sate networks help to improve behavioral performance.

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Conflict of interest

None of the authors has any conflict of interest with regard to the findings presented in this manuscript, financial or otherwise.

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