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Neurofeedback fMRI-mediated learning and consolidation of regional brain activation during motor imagery

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Abstract

We report the long-term effect of real-time functional MRI (rtfMRI) training on voluntary regulation of the level of activation from a hand motor area. During the performance of a motor imagery task of a right hand, blood-oxygenation-level-dependent (BOLD) signal originating from a primary motor area was presented back to the subject in real-time. Demographically matched individuals also received the same procedure without valid feedback information. Followed by the initial rtfMRI sessions, both groups underwent two-week long, daily-practice of the task. Off-line data analysis revealed that the individuals in the experimental group were able to increase the level of BOLD signal from the regulatory target to a greater degree compared to the control group. Furthermore, the learned level of activation was maintained after the two-week period, with the recruitment of additional neural circuitries such as the hippocampus and the limbo-thalamo-cortical pathway. The activation obtained from the control group, in the absence of proper feedback, was indifferent across the training conditions. The level of BOLD activity from the target regulatory region was positively correlated with a self evaluative score within the experimental group, while the majority of control subjects had difficulty adopting a strategy to attain the desired level of functional regulation. Our results suggest that rtfMRI helped individuals learn how to increase region-specific cortical activity associated with a motor imagery task, and the level of increased activation in motor areas was consolidated after the two-week self-practice period, with the involvement of neural circuitries implicated in motor skill learning.

Introduction

In addition to its utility in cognitive and neuroscientific research, functional neuroimaging has created new opportunities in various clinical applications. These include the evaluation of the efficacy of neuro-pharmacological treatment [Bryant and Jackson, 1998; Steward et al., 2005; Wise and Tracey, 2006] and neurosurgical planning for the treatment of brain tumors or epilepsy [Yoo et al., 2004; Medina et al., 2007]. Another interesting and important research topic of functional neuroimaging is to empower an individual to gain a degree of voluntary control of region-specific brain function by providing real-time status of the brain activity [Yoo et al., 2002, Weiskopf et al., 2004].

This notion of real-time feedback of brain activity is not new. For example, real-time relay of the magnitude or spectrum of a specific signal bandwidth of electroencephalography (EEG) has enabled the voluntary regulation of a level of attention [Delorme and Makeig, 2003; Egner and Gruzelier, 2004]. The learned regulation of cortical activity was even applied to control computer devices [McFarland and Wolpaw, 2003]. Although its clinical

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utility is still an active area of investigation, EEG-based self-training and the learning of neurophysiological processes/behavior have already been applied to the management of attention deficiency and hyperactivity disorder (ADHD) [Lubar et al., 1995; Fernandez et al., 2003] and to the treatment of phobic anxiety as well as seizure-related disorders [Walley et al., 1994; Swingle, 1998; Kotchoubey et al., 1999]. These EEG-mediated approaches, however, lack the spatial specificity required to characterize regional brain activity since detected EEG signals reflect the activation of a widespread network of cortical/subcortical function. Topographic EEG source mapping or MEG (magneto-encephalography) [Wang et al., 2001; Chauveau et al., 2004] still are deficient of the spatial resolution necessary to resolve localized brain activities. Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) are alternative neuroimaging modalities, but both require the injection of radioactive contrast material, which make their routine application less desirable.

Among the different imaging modalities, functional MRI (fMRI) has surfaced as one of the major tools to provide a basis for the self-regulation of cortical function. In addition to its excellent spatial resolution and its non-invasive nature, real-time (rtfMRI) or near real-time processing of fMRI data [Cox et al., 1995; Yoo et al., 1999] has provided a means for individuals to receive information relating to the state of their own brain activity [Posse et al., 2003; Weiskopf et al., 2003]. For example, fMRI was applied for the regulation of pain-related activity in rostral-ventral/dorsal parts of the anterior cingulate cortex [deCharms et al., 2005]. Posse et al. [2003] studied the feasibility of inducing human emotion by measuring the MR signal changes associated with amygdala activation. fMRI-mediated regulation of activity from the auditory areas was also demonstrated through a selective auditory attention task [Yoo et al., 2006]. Recently, regulation of the activity in the anterior insula cortex has also been reported [Caria et al., 2007].

The utility of fMRI-based feedback has been demonstrated for the regulation of cortical activity in the somatomotor areas [Yoo et al., 2002], whereby the immediate feedback of activation in the somatomotor areas after hand-clenching tasks helped individuals expand the size of cortical activation. However, in case of motor imagery (*i.e.* mental rehearsal of the execution of motor activity without actual motor output), the proprioceptive information from motor execution is absent. The absence of the feedback information, necessary for the fine motion control and subsequent learning (*i.e.* motor skill learning), renders the motor imagery task challenging [deCharms et al., 2004]. deCharms and colleagues [2004] have shown that rtfMRI helped the individuals learn and retain (immediately after the trial sessions) the strategy to execute hand motor task to enhance cortical activity from the motor cortex.

Motivated by this work, we applied rtfMRI-based feedback technique to modulate the cortical activity from the motor cortex during the imagery task. The main design feature that distinguishes the current work from the work by deCharms et al. [2004] is that we probed the effect of a two-week long, daily self-practice of the motor imagery task after the initial rtfMRI session. We postulated that rtfMRI-based training would help subjects achieve a greater degree of regulation, as measured by the BOLD signal magnitude, in the primary motor areas when compared to a demographically-matched control group. We also postulated that the learned task elements and associated cortical activity will be consolidated after the two-week period, as being manifested by the differential pattern of activation across the brain volume in the experimental group compared to the control subject group.

Method

Study Overview

The study was conducted in accordance with the ethical standards set forth by the institutional review board of Brigham and Women's Hospital, Harvard Medical School. A total of 24 healthy volunteers without a history of neurological disorders, and also free of axis I psychiatric disorders, participated in the study. The participants were divided into two groups - an experimental group undergoing rtfMRI and a control comparison group. All participants' demographic features were matched in terms of gender, education, age, and handedness (right-handed according to the Edinburgh Handedness inventory [Oldfield, 1971]). Using Digit Forward and Backward, a Letter Number Sequencing test in the Wechsler Adult Intelligence Scale (WAIS-R: The Psychological Corporation, San Antonio, TX), we also attempted to match the participants' cognitive/intellectual ability. Reduction of the inhomogeneity in both level of education and cognitive ability was necessary since the rtfMRI training involved an element of learning. Due to a technical problem during a scan, data from one participant (from the control group) and a matched experimental subject were not included in the study. Detailed subject information (n=11 in each group) is listed in Table I.

An overall schematic of the study is shown in Fig.1A. All the participants were blinded to the nature of their trials (real or sham), and were instructed that they were undergoing real rtfMRI trial sessions. A set of standardized task instructions using a procedural checklist was used in order to maintain uniformity of the procedures. Anatomical MRI was performed prior to the rtfMRI trials to automatically segment and label the brain regions by co-registering the anatomical image space to the reference EPI data according to normalized brain coordinates. Each participating subject underwent multiple scan sessions, which consisted of three 'pre-trial', seven 'rtfMRI-trial', and three 'post-trial' fMRI sessions. The pre-trial fMRI sessions were used to delineate the activated primary somatomotor areas to be evaluated during the subsequent rtfMRI sessions as well as to examine the level of cortical activation prior to rtfMRI. During the rtfMRI sessions, the participants observed their own BOLD signal originating from the region-of-interest (ROI) in the primary motor area (more detailed description of the ROI will be presented in the following section). For the comparison group, the same experimental procedure was administered except that the 'sham' feedback contents were displayed to the subjects (more detailed description on creating the content is presented in the following 'Study Protocol' section). After the first day of scanning, the participants in both the experimental and comparison groups perform the motor task paradigm once per day for two weeks using a Personal Digital Assistant (PDA) device. After the two weeks of daily practice, the subjects were called in again to undergo the last three sets of fMRI sessions using the trained task-strategy (noted as 'post-training' sessions).

MR Imaging Parameters and Real-time fMRI Platform

The study was conducted in a 3 Tesla clinical scanner (Signa VH, GE Medical Systems, Waukesha, WI) using a standard birdcage head coil for RF detection. All fMRI data was acquired using a gradient-echo echo planar imaging (EPI) sequence (TR/TE=1000/40 msec, flip angle = 80°, 24 × 24 cm^2 field-of-view, 64×64 in-plane matrix) to detect blood oxygenation level dependent (BOLD) signal changes associated with neural activities. Thirteen axial-oblique slices with a thickness of 5 mm (1 mm slice gap) were acquired to image the whole brain volume, including the superior part of the cerebellum. T_1-weighted images (Spin Echo sequence, TR/TE=100/3.5 msec, 256 × 128 in plane matrix, 6mm slice thickness) covering the same brain volume were acquired to assist in the identification of ROIs and the normalization of functional data. After the fMRI session, high-resolution

structural anatomical information of each subject was obtained using a 3D-SPGR (Spoiled Gradient-Recalled) sequence (sagittal orientation, TE/TR=6/35 msec, FA=75°, slice thickness=1.25 mm, 256×256 in-plane matrix) to provide anatomical information for off-line data processing.

Feedback of region-specific cortical activity was implemented with rtfMRI using the automated method to monitor the BOLD MR signals from multiple cortical areas. Although the detailed method of its implementation is shown elsewhere [Lee et al., 2007], a brief workflow of the processing is presented. The acquired EPI volume data was transferred to a local computer via FTP (File Transfer Protocol) immediately after each TR period, and was made available for real-time access and evaluation. The rtfMRI platform also included an on-line motion-correction capability for the EPI data. An automated segmentation and indexing of brain anatomy based on the neuroanatomical template [Tzourio-Mazoyer et al., 2002] were used to assist the expedited definition of the ROI. Subsequently, localized BOLD signals were measured and displayed from the user-selected areas with a short time delay (on the order of 1–2 s) upon data acquisition.

Task Paradigm

Trial-based task design was used in all scan sessions (Fig. 1B) except for the rtfMRI trial sessions (Fig. 1C). A total of 70 volume images were acquired per session (scan time was 1 minute 10 seconds), and the first 10 sets of volumetric data were excluded from further data processing to allow for T_1 signal equilibration. We previously reported that a 1-minute long fMRI session, combined with trial-based task design, was sufficient enough to generate an adequate BOLD signal response during the motor imagery task [Yoo et al., 2007]. Similarly in a present study, motor imagery task was employed whereby the subjects were instructed to *imagine* squeezing their right fist when the prerecorded sound instructed them to ‘go’ (occurred at 20s) and to continue until they were instructed to ‘stop’ (occurred at 25s), as presented via an MRI-compatible headset (Silent Scan, Avotec Inc., Stuart, FL). In order to provide a ‘resting’ condition without interruption of confounding thoughts and diversions, the individual was instructed to passively listen to the scanner noise. To ensure that subjects were performing only an imagery task and not actual motor execution, the subjects’ hand motion was monitored using an optical probe (GE Medical Systems). Subjects were also instructed to avoid deliberate changes in their general arousal state other than the given imagery task [DeCharms et al., 2004]. To do so, subjects were instructed to remain calm (without excitement, frustration, or disappointment) regardless of the outcome of the training procedure.

Study Protocol

All subjects practiced the task 2–3 times prior to the scanning session to reduce variant activation patterns, especially during the early stage of task performance [McGonigle et al., 2000]. Three sets of pre-trial fMRI sessions, with a gap of approximately 15-seconds between sessions, were administered to (1) identify the ROI to be monitored for the rtfMRI, and to (2) estimate the baseline level of the BOLD signal from the target regulatory area. A voxel-wise correlation coefficient was calculated with respect to the canonical hemodynamic function based on the given task timing (obtained from SPM2; www.fil.ion.ucl.ac.uk/spm/spm2.html), and a resulting correlation coefficient map was thresholded at > 0.414 (corresponding to $p<10^{-3}$). Then, the *union* of activation across the three pre-trial sessions within the left precentral gyrus contra-lateral to the task was identified as a single contiguous cluster. The BOLD signal measured from pixels within the cluster was then averaged and converted to feedback signal measures (in terms of BOLD signal contrast) in the subsequent rtfMRI sessions.

Seven rtfMRI sessions (each 1 min 11 sec long; first 10 sec being the 'dummy scan') were administered in which the subjects were shown their own BOLD signal activities, originating from the ROI as a line graph, via MR compatible goggles (600×800 resolution, Resonance Technology, CA). An example of the display interface is shown in Fig. 1C. The rest condition, the first 15s and the last 16s of the scan, was administered to establish/confirm the resting baseline level of BOLD signal. During the trial duration (70 sec), the minimum target modulatory level was marked at the level of a 1.5% increase from the baseline signal, which we determined based on the lower limit of normal variation in BOLD contrast from our previous observation of a motor imagery task [Yoo et al., 2007]. The Fig. 1C illustrates the target value of ±2% (just an example for the illustrative purpose).

For the experimental group, based on the information that participants observe through the goggles, participants were instructed to perform the hand imagery task while aiming to increase the magnitude of BOLD signal from the target ROI beyond the minimum target modulatory level. If the subjects attained the target level of BOLD activation, they were asked to maintain the state of activation for a minimum of 5 seconds above the target level. The participants were allowed to disengage and re-engage the task during the trial period. For the control comparison group, the same experimental procedure was applied, except that the BOLD signal originating from non-activated white matter regions in a medial frontal gyrus was sampled during the (previous) reference session and was scrambled in a temporal sequence (therefore, uncorrelated with the task and session) to create 'sham' contents, which were then displayed to the subjects. If the participants believed that they learned to regulate their targeted brain function, they were allowed to discontinue the trial sessions.

The same procedural instructions were provided for both groups, including the consistent time gaps between scan trials (1 minute). Once the experiment was initiated, no further intervention/advice was provided to the subject regarding how to perform the task. Upon the completion of the rtfMRI trial, three fMRI sessions were conducted (noted as 'post-trial') without the feedback. This time, the participants were instructed to perform the motor imagery task using the same strategy (based on the rtfMRI session) that he or she believed to achieve the task goal. At the end of the each trial session, self-evaluation of each subject's performance was obtained (on a scale from 1 through 10; 1 being unable to perform, 10 being best performance in achieving the goal).

Two-Week Self-Practice and Post-Training fMRI Session

The main goal of our study was to examine whether the learned degree of cortical regulation can be maintained through daily practice of the task. To do so, we developed a software to allow participants to remember the task strategy and to practice the task regularly. A PDA device (HP iPAQ rz1710), with capability to remind (as an alarm; send sound alert until the subject turns off the alarm) the participants of the timing of the daily practice, was programmed to pace the self-practice once a day. Upon running the software, four sets of practice runs, each taking the first 30 sec of trial-based task praradigm (shown in Fig.1B), were given. Participants were allowed to add pauses between each run. On the 14^{th} day (two-weeks later), a second set of three fMRI sessions was performed. We put forth an effort to image the same brain volume that was scanned in the first scan session by using anatomical landmarks (nasion and superior part of the skin where the ears meet the skin).

Off-Line ROI Analysis

After the completion of study, the activation from each ROI was analyzed to probe the effects of the rtfMRI trials and the subsequent self-practice using Matlab-based computation scripts. To do so, data acquired from each task condition were grouped and coregistered, and the site of activation was selected from the voxels within the left precentral gyrus that passed

the condition of $p<10^{-3}$ from a voxel-wise correlation coefficient map. The time course of the BOLD signal was subsequently obtained from the four planar pixels around a pixel with the maximum correlation coefficient observed from the pre-trial session *(i.e.* a center voxel and four voxels neighboring in a planar section). The use of fixed location/volume for analysis across the three different conditions (pre-trial, post-trial, and post-training) was necessary to provide unified measurement conditions across the subjects (note that number of pixels chosen for measuring feedback information was different for each subject). The measured signals then were averaged in the time-domain, and the amount of generated BOLD contrast was defined as the difference between (1) the baseline signal level and (2) the mean value of the maximum signal magnitude including the two adjacent time points during the task-related period (*i.e.* during the 10s window after the task). The baseline signal was represented as the mean value of the first 10 (from the rest period before the trial) and the last 20 temporal points (from the rest period after the trial). From this, the percentage BOLD signal increase from the baseline signal level (noted as '% BOLD') was calculated.

Off-Line Group-Processing of fMRI

The effect of the rtfMRI and self-practice across the brain volume was examined using SPM2. After applying slice timing correction to account for the trial-based design, all sets of fMRI data from day-1 (containing pre-trial and post-trial data) were grouped and realigned with respect to the first image volume. The data obtained from the post-training sessions were also motion-corrected with respect to the first image volume within the session. After motion correction, the images were normalized to Montreal Neurological Institute (MNI) coordinates and concurrently smoothed with an isotropic Gaussian kernel (8 mm full-width at half-maximum). Condition and subject effects were estimated using a general linear model [Friston et al., 1995]. Individual contrast images were first produced by comparing the task-dependent activation for each subject separately (therefore controlling within-subject variance). These contrast images were then entered into a second-level group analysis using a random-effects model [Friston et al., 1999], which compared the activation of three different trial conditions between the two groups. A paired *t*-test was conducted to compare the two groups (n=11 for each group) with a threshold of $p<0.01$ (Z-score>2.32, a cluster of >14 voxels). The anatomical location of activation loci was identified with Brodmann's area (BA) nomenclature using coordinate translation software (Talairach Daemon, ver 2.0; http://ric.uthscsa.edu/projects/talairachdaemon.html).

Results

Evaluation of the rtfMRI Sessions

We did not detect any motion of fingers or hands from all subjects throughout the course of the study. Most participants in the experimental group (n=10 out of 11) were able to achieve the desired performance goal within seven rtfMRI trial sessions (*i.e.* continuously exceeding the target level by 1.5% or more for a minimum duration of 5s). Five of the subjects satisfied the condition at the 4^{th} rtfMRI trial while three subjects achieved the target level at the 5^{th} trial. One subject reached the target regulatory level at the 7^{th} trial. In the control group where the task was performed without proper feedback information, all 11 individuals did not elect to stop the trials early, and completed all seven rtfMRI sessions. Only four individuals were able to attain the required task goal few times during the sessions. In order to evaluate the magnitude of session-specific BOLD contrast achieved during the rtfMRI sessions, the time course of BOLD signal that generated the feedback information was retrieved from each individual and session. Then, the 5-sec time interval(s) satisfying the regulatory goal was searched during each trial session, and the averaged BOLD signal level within the interval represented the performance measures for the given trial session. Since the experimental group was allowed to discontinue the rtfMRI if the individual determined

that there was no need for further trial, there were an unequal number of scan sessions across the subject base. Thus, the data from the last four trial sessions were sampled from each subject to represent the group trend (again, at least four rtfMRI sessions were needed across the subjects). As is evident from Fig. 2, the experimental group reached the level of activity from the ROI above the target level (1.5% contrast) at the 4^{th} rtfMRI sessions while the control subjects did not show any improvement over time.

Retrospective ROI Analysis

A plot of group-averaged BOLD contrast signals from the three conditions (pre-trial, post-trial, and post-training) is shown in Figure 3A. The group-averaged time course of activation is shown in Figure 3B. Note that the BOLD contrast, measured from the smaller number of pixels (5 pixels), shows a slightly higher percentage of BOLD signal compared to those that were measured from the rtfMRI session (shown in Figure 2). This is due to reduced partial volume effects. The experimental group showed a greater increase in BOLD signal after the rtfMRI session compared to the pre-trial sessions (paired *t*-test, one-sided; $p=8.04\times10^{-5}$). The enhanced magnitude of BOLD contrast after the rtfMRI sessions was maintained after the two-week practice period ($p=0.02$). However, no further improvement was detected compared to the post-trial session (paired *t*-test, two-sided; $p=0.17$). In the control group, neither the rtfMRI session nor the practice had any influence on increasing BOLD contrast.

Group Analysis: Establishment of Baseline Condition Prior to Trials

In order to confirm the establishment of equal activation levels during the motor imagery task prior to rtfMRI, we examined the presence of any differences in activation during the pre-trial sessions between the two groups. Group analysis (based on a paired *t*-test) showed that there was no group difference in brain activities during pre-trial sessions. The lowering of the threshold to $p<0.05$ (from $p<0.01$) did not alter our observation.

Group Analysis: the Effect of rtfMRI-mediated Trial

The differences in group activation patterns associated with rtfMRI are shown in Table 2. The primary motor area (M1) in the left precentral gyrus showed an increased level of activation compared to the control group. The postcentral gyrus (BA3) showed an increased level of BOLD activity from the experimental group. It is notable that the right parahippocampal gyrus (BA28) showed a greater degree of activation compared to the matched control group. On the other hand, the right medial frontal gyrus (BA6; a part of supplemental motor area-SMA), along with the parietal lobule (BA40), showed greater BOLD activation in the control group than in the experimental group. A greater level of activation from the occipital lobe (precuneus) was also evident from the control group.

Group Analysis: the Effect of PDA-based Self-Practice

The effect of PDA-based two-week self-practice was examined between the two groups. As shown in Table 3, a greater extent of cortical areas other than primary motor area (compared to the post-rtfMRI session; Table 2) showed a difference between two groups. It is notable that the left precentral gyrus (contralateral M1) from the experimental group showed a greater BOLD signal compared to the control group after the practice, with increased statistical significance compared to the results obtained from the post-trial session (peak Z-score increased to 2.89 from 2.65). The anterior cingulate gyrus (BA24), the right parahippocampal gyrus, the right superior temporal gyrus, and the frontal gyrus (inferior frontal: BA47 and dorso-lateral frontal gyrus: BA46/8) also showed increased levels of activation in the experimental group. It was interesting to find that areas such as the bilateral thalamus (medial pulvinar), the putamen, and the insular cortex showed greater BOLD signal in the experimental than the control group. When we examined the inverse of the

group effect (*i.e.* {control > experimental}) the inferior parietal lobule (BA40) and the superior temporal gyrus (BA22) were detected.

Group Analysis: Activation Map of Effects-of-interest

In addition to tabulated results from the group analysis, group activation map summarizing the main findings within the experimental group are shown in Figure 4 (n=11; p<0.01; random effect analysis). The rtfMRI training itself did not elicit marked increase in activation in the motor area (Fig. 4A; activation detected in the parietal lobule only); however, 2-week practice resulted in the increased level of activation in left precentral gyrus (SM1) including premotor areas (Fig. 4B). Between groups, the task-associated BOLD contrast was indifferent prior to the rtfMRI session (paired t-test, two-sided; p=0.11). However, participants that had just undergone rtfMRI-trials showed an enhanced level of BOLD signal contrast compared to the control group (paired t-test, one-sided; p=0.03). These differential effects were maintained after the two-week self-practice (paired t-test, one-sided; p=0.01).

Subjective Ratings and Correlation with ROI Activity

Participants' self evaluations of their performance during the fMRI sessions are summarized in Figure 5A. During the motor imagery task prior to the rtfMRI sessions, there was no difference in subjective ratings between the two groups (p>0.1, paired t-test). From between session comparisons, the experimental group reported that their performance improved after the rtfMRI trial (paired t-test, one-sided; p=0.001). This perception of improved performance was maintained after the self-practice (paired t-test, one-sided; p=0.003). The control comparison group, on the other hand, did not express any improvement from the evaluation after either the rtfMRI trial or the practice period (paired-t, one-sided, all p>0.09). Most (n=9) of the participants in the control group expressed that the information presented to them during the scans was not helpful, and their task was based on blind-guessing. The changes in self-evaluation of task performance, based on the feedback information, were further correlated with the activation from the targeted motor areas (as measured by the BOLD contrast), and a tight correlation (p<0.05) between the two was identified for both post-trial and post-training sessions (Fig. 5B&C). On the other hand, no meaningful correlation between the cortical activation and self evaluative score was found from the members in the control group.

Discussion

Using functional neuroimaging techniques, regional brain activities can be characterized *in vivo* and can be made available as a basis for the self-regulation/modulation of brain function. We have demonstrated that rtfMRI helped individuals better guide their cortical activity in somatomotor areas compared to the matched control group during the performance of a motor imagery task, confirming the results from the previous work by de Charms et al. [2004]. These individuals were able to consolidate the learned degree of activation after a time-lapse of two weeks through self-practice, as paced by the use of a PDA-device. The control group did not receive any benefit from either the rtfMRI trials or the self-practice. The differential effect of the rtfMRI was also observed based on subjective evaluation as the majority of control subjects had difficulty in adopting a strategy to attain the desired level of functional modulation in their target modulatory ROIs.

Based on the correlation between subjective ratings and BOLD activity from the M1 (Fig. 5B), the participants in the experimental group were able to associate and correctly evaluate their own brain activity based on the feedback information from the rtfMRI. Since the given motor imagery task is *not* an impossible task to perform, we found that four individuals in

the control group managed to reach the target regulatory level in a sufficient duration of time. However, their self-evaluation, based on the randomized pseudo-feedback, was disassociated from their actual performance. This indicates that control subjects, in the absence of feedback, were indeed deceived and blinded to the task outcome while the rtfMRI-guided feedback provided the basis for learning the difficult motor imagery task.

From the analysis of the effects of the two-week practice period after the initial rtfMRI trials, we confirmed that the learned level of increased BOLD signal was maintained after the self-practice sessions. It indicates that the effects of rtfMRI were consolidated in the target ROI (*i.e.* M1 contralateral to the task). Meanwhile, both the ROI analysis (Fig.3) and the subjective evaluation score (Fig.5) showed the two-week practice period did not result in any further increase in either the level of BOLD signal or the perception of task performance. The seemingly plateaued level of activation that we have seen in this study is in accordance with other behavioral/neuroimaging studies whereby newly acquired motor skill, once rapidly consolidated ('fast learning'), tapers off in terms of both performance and functional representation in the long term [Karni et al., 1998;Muellbacher et al., 2002;Krakauer and Shadmehr 2006]. However the current study does not provide enough data to examine this 'learning curve' effect and calls for the examination of the longitudinal studies extending to longer terms beyond the tested two-week practice period. In addition, the detailed utility of the PDA-driven self-practice after the rtfMRI, which was embedded in our study protocol, was not able to be isolated, and warrants further investigation.

Off-line data analysis revealed that effects of rtfMRI-mediated neural activation, as compared to the control participants, were shown in the left precentral gyrus (PrCG; BA4) as well as the bilateral postcentral gyrus (PoCG; BA3), suggesting the successful regulatory effects on the primary target-of-interest. We could not completely rule out the possibility of the presence of active sensory stimulation via isometric muscle movement since the EMG activity was not measured in this study. However, the absence of apparent finger movement (there were no physical restraints to the hand) suggests that the observed involvement of PoCG may indeed have been implicated in motor learning [Krakauer and Shadmehr, 2006].

One of the intriguing findings from the retrospective group fMRI processing was the elevated level of activation identified from the right parahippocampal gyrus among the experimental group. The parahippocampus has been known to be mediated in the process of conditional motor learning, which requires the formation of an association between stimuli and motor responses [Brasted et al., 2005], or in general learning and memory procedures [Aguirre et al., 1998]. In this regards, we conjecture that the experimental group started to engage the hippocampal gyrus to learn the motor imagery task after the rtfMRI trials, whereas the control group did not receive any useful information to learn from. The relative increased level of activation in the parahippocampal gyrus was still observed after the self-practice period, which is suggestive of an incomplete or even on-going consolidation of a newly learned process (and thus the remaining role of the hippocampal gyrus).

We found that there were much wider areas of cortical activation that showed an enhanced level of activation compared to the control group upon the completion of the self-practice. These areas include the anterior cingulate gyrus (BA24), the frontal gyri (inferior frontal: BA47), and the dorsolateral frontal gyrus (BA46/8). The bilateral thalamus (medial pulvinar) and the putamen/caudate complex also showed increased activation with the involvement of the insular cortex. The medial pulvinar is known to have widespread connections with the cingulate, posterior parietal, and prefrontal cortical areas [Jueptner et al., 1997[a]], whereas the putamen and caudate are implicated in motor learning [Jueptner et al., 1997[b]]. Therefore, the involvement of these additional neural substrates detected during

the post-practice session may support the engagement of the limbo-thalamo-cortical pathway associated with the consolidation of motor learning [Kew et al., 1993].

Apart from the neural substrates that showed the increased signal contrast from the experimental group, the right medial frontal gyrus (BA6; a part of SMA) along with the parietal lobule (BA40) and the occipital lobe (Precuneus) showed greater BOLD activation in the control comparison group (Table 2). The parietal lobule, especially, remained with greater BOLD signal from the control group after the two-week practice period (Table 3). Although we could not isolate the definite cause of this relative increase in BOLD signal among the control subjects, we conjecture that a visual imagery of hand movement, often reported by the individual from the control group, might have contributed to the findings. Medial frontal gyrus and parietal areas including the Precuneus have been commonly involved in visual imagery and the subsequent association with perception of objects [Grezes et al., 2002].

The ability to learn and consolidate specific task strategies and associated cortical function, as mediated by rtfMRI, may provide crucial early evidence that rtfMRI-based training can be used for planning rehabilitation strategies and monitoring the functional recovery/ reorganization after CNS damage. The ultimate goal of neuro-rehabilitation is to induce functional reorganization at the affected cortical areas through the induction neural plasticity. However, conventional rehabilitation efforts have been directed toward the modification of motor activity and physical training, demanding a new adjunctive paradigm accounting for other than physical rehabilitation was sought after. Recently, You and colleagues [2005] have shown such a possibility whereby virtual-reality assisted feedback of body-movement helped to improve the locomotor ability of patients who did not respond to conventional physical therapy. Although the detailed mechanisms associated with training-dependent functional recovery are not clearly understood, rtfMRI mediated engagement of region-specific cortical areas may induce effective synaptic potentiation or even facilitate the re-establishment of functional connectivity through region-specific regulation of cortical activity.

Future applications of rtfMRI-training may include self-initiated monitoring/improvement of mental states to external cues and stimulation (such as emotional responses in patients with depression or craving-inducing stimulation for the individuals with substance abuse). Since rtfMRI has been employed to reinforce the induction of mood states by feedback of amygdala activation [Posse et al., 2003], it is reasonable to believe that neuro-psychiatric conditions associated with (but not limited to) the pathology of the amygdala-hippocampus circuitry could be treated using an rtfMRI approach.

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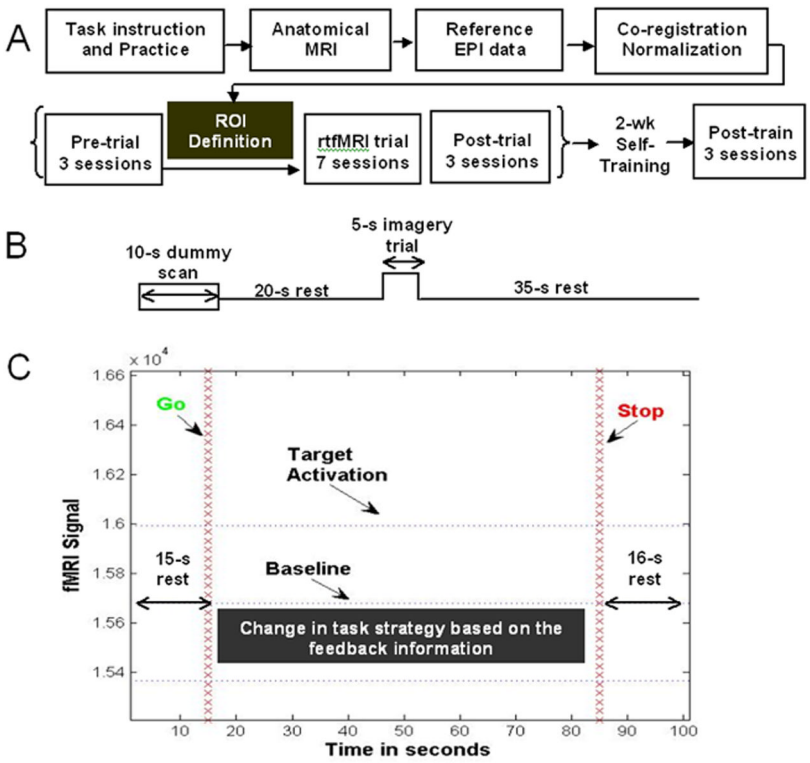

Figure 1.

(A) Flow chart of the overall experimental procedure, (B) trial-based task paradigm used in the pre-trial, post-trial, and post-training sessions, (C) an example of the visual interface used in the rtfMRI training, shown with the instruction set for the participants (excluded first 10s dummy scan). The y-axis indicates arbitrary units in the measured MR signal.

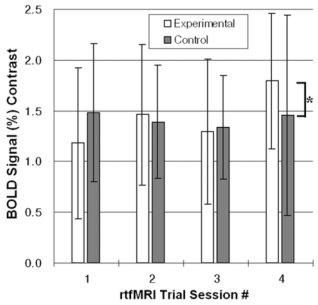

Figure 2.

The group trend of learned level of BOLD signal contrast (as a percentage compared to baseline) during the rtfMRI trials (sampled last four trial sessions) with standard deviation as error bars. The data was obtained from the actual rtfMRI sessions from each individual. The 4^{th} trial session showed a significantly elevated level of BOLD activity (* p=0.02, paired-t test, one-sided) from the experimental group whereas the control group did not show any difference. Note that data from the last four sessions were included since the participants in the experimental group elected to not continue once the task goal was achieved.

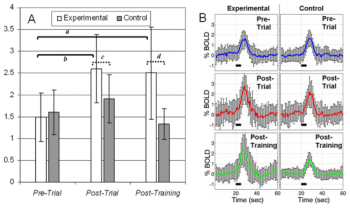

Figure 3.

(A) BOLD signal contrast averaged among the 11 participants before the rtfMRI trials, after the rtfMRI trials, and after two-weeks of practicing for experimental (white) and control subjects (gray). All signals are measured from the ROI (5-pixel) in the primary motor area. Only the experimental group experienced an increased level of improvement after the rtfMRI trial (a: p=0.0004; paired t-test) and throughout the training session (b: p=0.0001; paired t-test). A dotted bracket indicates that there are marked differences among the two groups after the rtfMRI trial and two-week self-practice period (c& d; p<0.0001; paired t-test). (B) The averaged time course of the obtained BOLD signal normalized to the baseline line signal level (as a percentage). A black bar indicates the timing of the task trial.

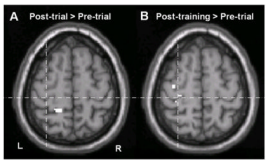

Figure 4.

Group-activation map (*n*=11; p>0.01) in the axial slice in the hand motor area (z=60; MNI space) obtained among the experimental group. (A) Postcentral gyrus was involved in the {Post-trial > Pre-trial} condition. However, (B) the activation was detected in the left precentral gyrus (SM1) and pre-motor areas in {Post-training > Pre-trial} condition. The dotted cross hair was inserted to show the relative position of activation patterns.

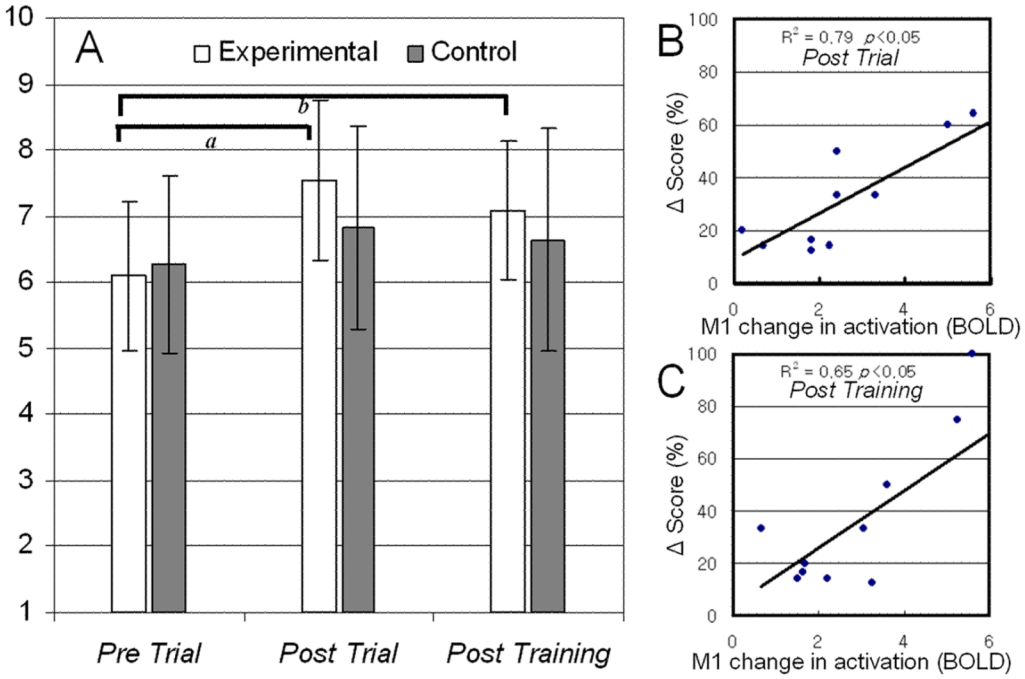

Figure 5.

(A) Subjective score of the self-evaluation of performance before rtfMRI trials, after the rtfMRI trials, and after two-weeks of practice for experimental (white) and control subjects (gray). Only the experimental group experienced an increased level of improvement after the rtfMRI trial (*a: p*=0.004; paired *t*-test) and throughout the training session (*b: p*=0.001; paired *t*-test), (**B&C**) significant correlation ($p<0.05$, linear regression with fitting) was observed between the percentage change in subjective scores and the BOLD contrast measured from the M1 contralateral to the task (same ROI used in the Fig. 3).

Table 1

Demographic characteristics and performance accuracy for participants in the experimental and control groups. There was no group difference.

	Experimental (*n*=11)			Control (*n*=11)					
	Mean	***std.***	**Range**	**Mean**	***std.***	**Range**	***t*-value**	***p*-value**	***stat***
Age (years)	24.2	±5.0	19–35	24.9	±4.8	19–35	1.23	0.25	n.s.
Handedness[*]	79	±24.6	50–100	86.7	±13.1	53–100	0.84	0.42	n.s.
Education (years)	15.1	±2.1	12–19	15.2	±2.2	12–18	0.11	0.91	n.s.
Digit forward[**]	13.5	±2.3	10–16	13.2	±2.5	10–16	−0.61	0.55	n.s.
Digit backward[**]	10.6	±2.0	7–14	9.8	±2.1	7–13	−1.22	0.24	n.s.
Letter Number Sequencing[**]	14.9	±1.9	11–18	13.8	±2.2	11–17	−1.26	0.23	n.s.

[*] Edinburg Handedness Inventory (Positive % means right handedness)

[**] From Wechsler Adult Intelligence Scale (WAIS-R)

Table 2

Group difference in activation after the rtfMRI trials (noted as 'Post-trial', thresholded at *p<0.01 with cluster more than 14*). L-left, R-right.

	Region (Brodmann's Area)	Cluster Size (voxels)	x	y	z	peak Z score
POST-TRIAL	***{Experimental GROUP > Control GROUP}***					
	Precentral gyrus (BA4) – L	15	−40	−21	51	2.65
	Postcentral gyrus (BA3)- L	99	−24	−24	32	3.26
	Postcentral gyrus (BA3)- R	70	34	−32	38	3.51
	Middle temporal gyrus (BA19) -R	44	36	−70	14	3.39
	Parahippocampal gyrus (BA28) -R	32	18	−44	2	3.07
	{ Control GROUP > Experimental GROUP}					
	Medial frontal gyrus (BA6) – R	51	8	−12	52	3.4
	Inferior parietal lobule (BA40)- R	19	28	−54	38	2.52
	Occipital lobe					
	Cuneus (BA19) -L	211	−10	−96	20	3.2
	Precuneus (BA19) - R	22	32	−88	24	2.56
	Precuneus (BA19) - L	43	−20	−78	42	2.74

Table 3

Group difference in activation after the 2-week self training period (noted as 'Post-training', thresholded at *p<0.01 with cluster more than 14*). L-left, R-right, B-bilateral.

	Region (Brodmann's Area)	Cluster Size (voxels)	x	y	z	peak Z score
POST-TRAINING	***{Experimental GROUP > Control GROUP}***					
	Precentral gyrus (BA4) – L	15	−36	−23	55	2.89
	Anterior cingulate gyrus (BA24)	1320	10	32	22	4.34
			−10	14	44	3.9
	Superior temporal gyrus (BA22)-R	79	32	−52	14	3.52
	Inferior frontal gyrus (BA47)-R	395	40	30	−10	3.5
	Insula					
	anterior –R	255	42	8	−4	3.32
	anterior- L	63	−46	8	−6	3.31
	posterior-R	107	42	−16	6	3.26
	posterior-L	50	−28	−22	12	2.52
	Thalamus- B	154	0	−26	8	3.28
	Putamen/caudate-B	1507	12	4	6	2.92
			−12	10	2	3.02
	Parahippocampal gyrus (BA28) –R	39	18	−42	5	2.83
	Middle frontal gyrus (BA46) –R	27	42	40	20	2.8
	Middle frontal gyrus (BA8) –L	26	−24	14	44	2.62
	{ Control GROUP > Experimental GROUP}					
	Inferior parietal lobule (BA40)- L	45	−40	−38	34	2.86
	Superior temporal gyrus (BA22)-L	28	−60	−44	6	2.51