Learned regulation of spatially localized brain activation using real-time fMRI

R. Christopher deCharms,[a,*] Kalina Christoff,[b] Gary H. Glover,[c,d] John M. Pauly,[d] Susan Whitfield,[a] and John D.E. Gabrieli[a]

[a] Department of Psychology, Stanford University, Stanford, CA 94305, USA
[b] MRC Cognition and Brain Sciences Unit, Cambridge, UK
[c] Department of Radiology, Stanford University, Stanford, CA 94305, USA
[d] Department of Electrical Engineering, Stanford University, Stanford, CA 94305, USA

It is not currently known whether subjects can learn to voluntarily control activation in localized regions of their own brain using neuroimaging. Here, we show that subjects were able to learn enhanced voluntary control over task-specific activation in a chosen target region, the somatomotor cortex. During an imagined manual action task, subjects were provided with continuous direction regarding their cognitive processes. Subjects received feedback information about their current level of activation in a target region of interest (ROI) derived using real-time functional magnetic resonance imaging (rtfMRI), and they received automatically-adjusted instructions for the level of activation to achieve. Information was provided both as continously upated graphs and using a simple virtual reality interface that provided an image analog of the level of activation. Through training, subjects achieved an enhancement in their control over brain activation that was anatomically specific to the target ROI, the somatomotor cortex. The enhancement took place when rtfMRI-based training was provided, but not in a control group that received similar training without rtfMRI information, showing that the effect was not due to conventional, practice-based neural plasticity alone. Following training, using cognitive processes alone subjects could volitionally induce fMRI activation in the somatomotor cortex that was comparable in magnitude to the activation observed during actual movement. The trained subjects increased fMRI activation without muscle tensing, and were able to continue to control brain activation even when real-time fMRI information was no longer provided. These results show that rtfMRI information can be used to direct cognitive processes, and that subjects are able to learn volitionally regulate activation in an anatomically-targeted brain region, surpassing the task-driven activation present before training.

* Corresponding author. Department of Psychology, Stanford University, 448 Jordan Hall, Stanford, CA 94305. Fax: +1-415-727-4099.
E-mail address: decharms@psych.stanford.edu (R.C. deCharms).
Available online on ScienceDirect (www.sciencedirect.com.)

Introduction

Neuroimaging methods allow observation of the patterns of activation in localized brain regions during cognitive tasks (Jezzard et al., 2001; Raichle and Posner, 1994). The level of brain activation produced by particular tasks can be modulated in the short term by cognitive processes such as attention (Brefczynski and DeYoe, 1999; deCharms and Zador, 2000; Culham et al., 2001), and in the long term by mechanisms of learning and plasticity (Karni et al., 1995; Poldrack, 2000; Sanes and Donoghue, 2000). This suggests the possibility that given appropriate training, subjects may be able to learn to voluntarily control brain activation in spatially localized regions that are associated with specific functions. However, the degree of control that subjects might learn to exert has not previously been thoroughly explored, as appropriate techniques have only become available with the advent of neuroimaging. It has been documented over many years that subjects can be trained to regulate autonomic functions and less spatially localized measures of brain activation such as EEG activity or EEG spectrum (Lubar and Deering, 1981; Nowlis and Kamiya, 1970). Studies of physiological regulation using 'biofeedback' have been limited by available techniques to autonomic and comparatively global physiological measures such as heart rate, skin temperature, skin conductance, EMG, and EEG that reflect comparatively global physiological processes, and thus these methods have been used extensively in training of relaxation and the level of global attention or arousal (Schwartz, 1995). Using neuroimaging, it is possible for the first time to investigate the control that can be exerted over specific, localized neurophysiological and cognitive processes located anywhere within the brain.

We use the term 'neurodirected behavior' to designate the process of controlling stimuli, task parameters, or subjects behavior based upon localized brain activation. This work represents the first full study in a group of subjects trained to alter brain activation using information derived from rtfMRI (Cox et al., 1995; Gembris et al., 2000; Lee et al., 1998; Posse et al., 2001; Voyvodic, 1999). Several previous feasibility studies have demonstrated the potential for the use of methods of this type. In one prior report, subjects performed movement trials, and fMRI data were analyzed offline,

and approximately 20 s after the completion of each trial the computed results were presented to the subjects to demonstrate that subjects may be able to learn to select appropriate movements to activate a target brain area (Yoo and Jolesz, 2002). An additional study measured single-trial rtfMRI responses in the amygdala and presented this information to subjects while they performed a self-induced sadness task (Posse et al., 2003). That study demonstrated the feasibility of presenting real-time fMRI information to subjects being scanned, but it did not attempt to explore any activation changes that might be specifically induced by real-time fMRI training, since the fMRI information and the cognitive task of self-induced sadness were always presented together. That report also did not explore whether real-time fMRI information could be used in training subjects to volitionally control brain activation beyond the brain activation initially produced by performing the cognitive task employed. Most recently, an additional study presented technology for allowing fMRI data to be analyzed in real time with results presented to the subject. This study demonstrated the viability of the technology in a single subject undergoing training (Weiskopf et al., 2002, 2003). We anticipate vigorous future work in this area.

Performance information plays a critical role in guiding many types of learning that have been investigated in humans (Herzog and Fahle, 1997; Kawashima et al., 2000), animals (Brainard and Doupe, 2000; Ito, 2000; Lisberger, 1988), and computer algorithms (Rumelhart et al., 1986; Grossberg, 1987, #152). During typical skill learning, proprioceptive or other perceptual feedback information is available to guide the learning of the subject. These forms of feedback, however, have not been available to guide learning for cognitive actions that do not have outward physical manifestations, such as imagined actions or mental imagery. Real-time fMRI may be beneficial for guiding the learning of control over specific brain activation and cognitive processes. fMRI could, in principle, provide feedback information for the training of mental processes that lack physical manifestation, or for the conditioning of the level of brain activation in localized regions. If subjects can be trained to control the level of activation in localized brain regions, this has implications for the extent to which top–down processes can regulate activation during the performance of tasks.

The present study employed a task of imagined manual actions because this type of task lacks a source of overt perceptual feedback and offers a well-characterized locus of brain activation in somatomotor cortex. Overt hand movement behaviors lead to clear, robust, and well-understood activations. The strong activation observed during overt movement can serve as a benchmark for comparison with activations observed during imagined manual action both before and after rtfMRI-directed training. Early PET studies of imagined actions or motor imagery reported activations in higher-order motor areas, such as supplementary motor cortex, lateral premotor cortex, and cerebellum, for both imagined and actual actions (e.g., Roland et al., 1980). Imagined actions, however, were reported to fail to activate primary somatomotor regions. Some fMRI studies have reported activation of primary somatomotor cortex for imagined actions, perhaps benefiting from greater measurement sesnsitivity, but the activation reported is typically less than a third as great as that measured for actual movement (Porro et al., 1996) or is seen in only a subset of subjects (Stephan et al., 1995). Therefore, it is possible that subjects may be able to learn to increase the level of activation during imagined movement to more closely match the robust activation observed during overt movement.

Here, subjects performed an imagined hand movement task, where no form of proprioceptive or performance feedback could normally be made available. Subjects were provided with nearly immediate feedback information about the level of activation in the somatomotor cortex, derived in real time from fMRI. The activations that subjects achieved during imagined hand movement before training were compared with the activations that they achieved after training, and also compared with the strong activations produced during actual movement. Finally, the increase in activation seen using this form of training was compared with changes observe in a control group of subjects that underwent repeated training on the same task but with sham fMRI information, to control for any effects of plasticity due to repeated practice alone.

Methods

Familiarization pretraining

Experimental procedures are outlined in Fig. 1. Before beginning scanning, subjects spent an hour performing real and imagined tasks involving exercise or mental rehearsal of exercises of the dominant right hand. These included real and imagined finger tapping, flexion–extension, pronation–supination, abduction–adduction, and opposition of digits. It was explained to subjects that during scanning, they would be instructed to imagine hand movements while attempting to optimize their strategy to increase activation in a brain area involved in this cognitive process, and that they would receive ongoing information about the level of activation that they were producing in this brain area.

Imaging procedures

fMRI scanning was conducted using a 3.0T GE Signa scanner at the Lucas Center for Magnetic Resonance Spectroscopy and Imaging at Stanford University. Saggital T1 localizer scans were collected, and 16 axial, high-resolution T1-weighted anatomical scans were collected for anatomical localization (256×256 voxels, 0.86 mm in-plane resolution, 7 mm thick). fMRI data were then collected coplanar with these anatomical sections. fMRI used a spiral T2* pulse sequence (TR 1 s, TE 30 ms, flip angle 70) (Glover, 1999). Sixteen axial slices (64×64 voxels, 3.43 mm^2 in-plane resolution, 7 mm thick) were prescribed parallel to the anterior–posterior commissures (defined using sagittal T1 localizer scans) and collected using a volume head coil. Subject head movement was minimized with a bite bar. The functional activation signals measured here are changes in measured T2*-weighted intensity, and are presented as percentage of signal change from the session average (blood oxygen level-dependent signal, or BOLD activation).

Real-time data analysis

Real-time data analysis was performed using custom software that performed k-space to image space spiral reconstruction, and subsequent processing of time-series image data. This analysis included continuous measurement of the average level of activation in spatially defined regions of interest within a single plane of section, followed by bandpass temporal filtering of this data (0.1–120 s pass band) to produce a continuous scrolling chart of the time course of activation in the ROI during the preceding 100-s period. This ROI analysis was also performed for a large background
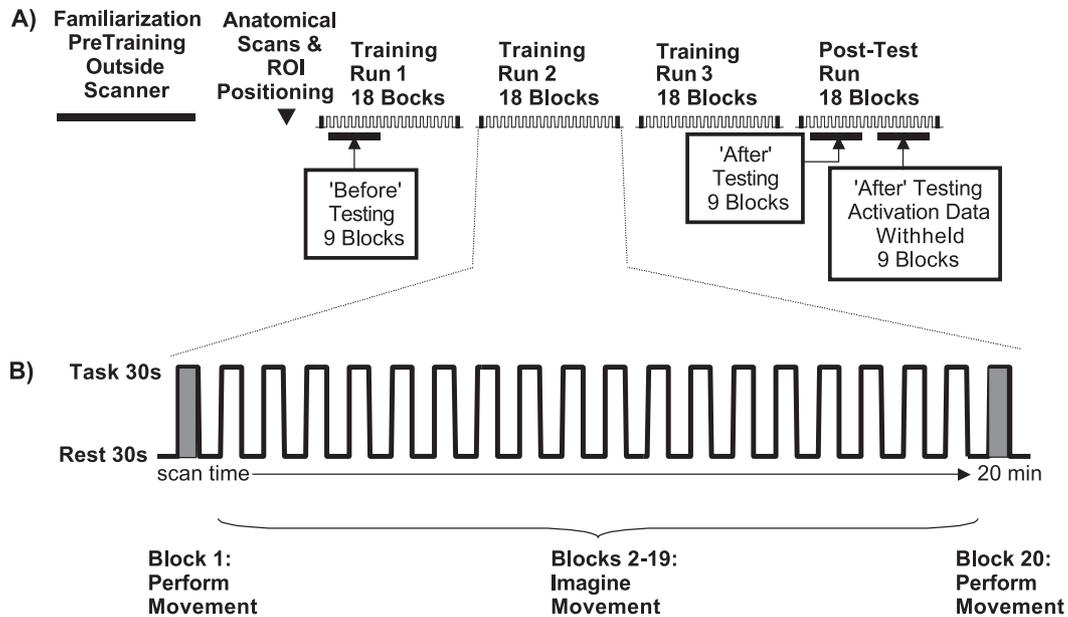
Fig. 1. Outline of training, testing, and scanning procedures. (A) Subjects received preliminary familiarization with the task outside the scanner, followed by three training runs and one post-test run inside the scanner. The first nine mental rehearsal blocks attempted by the subject (the first half of the first training session) served as the pretraining data set, and the first and second nine blocks of the post-test run, performed in the presence and absence of real-time fMRI information, served as two post-training data sets. (B) Each 20.5-min run consisted of 18 mental rehearsal blocks and two blocks of overt movement (the first and last block of each session), which provide comparison data.

region of interest. The difference between the average activation in the target ROI and the background ROI was also computed and presented as a scrolling chart. In addition, analyses were made to compare the level of activation during task periods vs. the immediately preceding rest periods, each shifted in time by 5 s to reflect hemodynamic delay. Continuously updated real-time difference maps were computed as the average percentage of signal difference for task vs. rest blocks measured for each voxel, and these images were used blocks to guide ROI selection. An index was computed that was the average activation within the ROI for each task block minus the activation during the immediately preceded background block shifted by 5 s, and these data were continuously updated and presented. In addition, event-related averages of the average level of activation at each time point through all 60 s within a block were continuously computed and presented. All of this information could be made available to both the experimentalist and the subject, although in practice, subjects were instructed to view the scrolling chart of activation in the ROI, the background ROI, and the difference. In additon, subjects viewed a simple virtual reality interface that represented the level of brain activation using a corresponding dynamic virtual object. This was provided because some subjects preferred viewing an amusing visual image in addtion to information presented as a graph. As an example, a 2D video image of an Olympic weight lifter was presented in a graphical window. As brain activation increased, the weight lifter raised a weight from the ground to over his head; as activation decreased, the weight lifter put the weight back down again.

We use 'real-time' fMRI to mean imaging where all data analysis proceeds sufficiently rapidly to keep pace with data acquisition. It should be noted that rtfMRI signals have a number of inherent delays. The processing of data requires about 2 s, and the biologically inherent hemodynamic response delay requires about 2 s to arise and about 4–6 s to reach its peak value after neural activation, as was explained to subjects. These signals also contain significant noise arising both from imaging hardware and from physiological sources, so the statistical reliability of data inherently increases through time. The software used here is able to fully reconstruct spiral fMRI data and perform all computations to produce activation maps, scrolling activation chart plots, event-related averages, and trial averages while keeping pace with new data acquisition, lagging the collection of original data by 1–2 s. Data collected here were 16 slices × 64 × 64 voxels/TR, and lag times were <2 s. Speed and reliability statistics presented were recomputed in post hoc analysis.

ROI definition

Regions of interest were defined physiologically by creating a real-time map of the area activated by repeated vigorous tapping of the contralateral, dominant hand index finger. Subjects alternated 30-s blocks of index finger tapping with 30-s blocks of rest, and maps of the voxel-wise percentage of signal difference between these two conditions were generated and superimposed upon high-resolution T1 anatomical images. ROIs were selected as rectangular zones centered on the area of activation on the margins of the central sulcus, which was visualized anatomically. The selected regions of interest were deliberately large, 10 × 10 voxels/35 × 35 mm in a single plane of section, to minimize any potential effects of subject movement. The background ROI used in real-time training was selected to assess average activation over the majority of the selected plane of section in which the target ROI was chosen. Detailed placement of a background ROI encompassing a particular set of anatomical structures or involving gray–white matter segmentation was not feasible during a real-time experiment, and the use of a large ROI covering the plane of section including the target ROI proved adequate. Post hoc tests indicated

that ROI placement was accurate, and typically reproduced across training sessions within subjects to within less than 1–2 voxels of error (mean error 0.6 ± 0.15 voxels). The mean location across subjects in Talairach Tournoux coordinates for the center of the selected ROIs ($x = -38.6$ L, $y = -16.16$ P, $z = 46$ S), corresponding to precentral sulcus, Brodmann area 4, and the mean ROI also including Brodmann area 3 (Moore et al., 2000; Talairach and Tournoux, 1988). Individual-subject ROI center locations were 3.0–9.8 mm in 3D position from the group mean.

Subject training

Once ROIs had been selected, subjects were engaged in three training sessions of performing an imagined manual action task, as outlined in Fig. 1. Subjects were instructed that during the task blocks they were to imagine moving their dominant (right) hand so as to increase the level of activation that they observed in the ROI, as they were instructed in the pretraining session. Subjects were presented with a continuously updated time-course plot of the preceding ROI activation in an ROI placed to include somatomotor cortex, as well as a large background ROI taken from the same slice, and a measure of the difference between the two. Time course plots were used because they were found to be more readily interpreted by subjects than other measures, such as continuously updated two-dimensional activation map images. Subjects were also instructed that to the extent possible they were to focus their attention specifically on imagining hand movements, and to avoid deliberate changes in their global arousal that might lead to changes in activation in broad areas of the brain, which might be indicated by changes in activation of the large background ROI that they also observed.

Each training session encompassed 20 blocks that were each made up of a 30-s rest period followed by a 30-s task period. During the first and last block of each session, subjects performed actual repetitive tapping movements of the index finger of the contralateral hand as instructed by behavioral software; these data were later used as positive control measures for benchmarking. During all other blocks, subjects were instructed to refrain from any movement and maintain all muscles in a relaxed posture while imagining movement of the dominant hand. Lack of overt movement during the imagined movement task was verified by observation of the subjects, by post-scanning interview, and by EMG that was measured during the task inside the scanner using surface electrodes placed on the extensor carpi radialis longus muscle, or the extensor digitorum muscle in 2 subjects.

Before each block, each subject was presented with a target level of activation that the subject was instructed to attempt to achieve during that block. Following the block, a task activation measure of the observed average activation in the ROI during the task block minus the preceding background block, each shifted by 5 s to reflect hemodynamic delay, was computed and presented to subjects. Subjects were informed whether they had succeeded in achieving the target level of activation during the block. The target level of ROI activation that the subject was directed to achieve on the next block was then computed based on a method of adaptively tracking the required task difficulty to match the subject's preceding ROI activation performance, adopted from standard psychophysical methodology (Leek et al., 1992). The target performance level was adjusted based on current performance using 3 up 1 down tracking methodology. If subjects achieved the target level or

greater on average during the task block for three blocks in a row then the threshold was raised (task made harder); if they failed to achieve the threshold for one block the threshold was lowered (task made easier). In post-processing, this same task activation measure was averaged within subjects for each block of 18 imagined-action blocks, and then averaged across subjects. Nine normal right-handed subjects participated (age range 19–36 years). Six were in the experimental group, three were in the sham control group. One of the nine participants was from the experimental team (this was not one of the examples shown in the figures).

To determine whether observed effects were due to subjects learning to volitionally control brain activation by using real-time fMRI information, control subjects were trained using an identical training paradigm, but with sham fMRI information. For sham training, subjects performed an identical training sequence, and performed this sequence inside the scanner while receiving information that appeared very similar. However, without their knowledge, they were being presented with sham brain activation information that was not correlated with the task being performed, and had no relation to their behavior. This information was real fMRI data collected from the same subject, but from a background ROI and at an earlier time in the same recording session. It therefore served as an essentially random signal, but with similar fluctuations and other signal characteristics to the information that was seen by the subjects who were receiving actual rtfMRI information.

Offline data analysis

Offline data analysis and verification was performed using Brain Voyager and SPM99 and confirmed activations observed during training. Analysis was hypothesis-driven, rather than exploratory, and therefore focused on activations in the ROI that was individually selected for each subject and used in training. Time-series image data were motion corrected, and statistical parametric maps were computed for statistical significance of activation assessed by a t test (t value) comparing activation for each voxel during the task blocks to background blocks, shifted by 5 s for hemodynamic delay, corrected for multiple comparisons using the Bonferroni method, and a threshold $t = 10$. Hypothesis-driven ROI analysis were repeated using the same ROIs that had been employed during subject training inside the scanner.

Results

Through the course of training, subjects were able to enhance the level of fMRI activation driven by imagined action, and this enhancement was spatially selective to the somatomotor ROI that was the target of training. This enhancement could be seen at the single-subject and group levels. Before training, there was a small but significant activation anterior to the central sulcus during imagined action, shown for an example subject (Fig. 2A). Following training, imagined action led to a significantly larger activation within the target ROI, in both presumed motor and somatosensory zones anterior and posterior to the central sulcus (Fig. 2B). The enhancement of activation following training is sufficiently robust to be apparent without block averaging or smoothing in single-subject, single-trial data (Figs. 3A and B). The activation in the somatomotor cortical region was the largest activation in each of the six subjects studied after training. Additional, smaller modulations
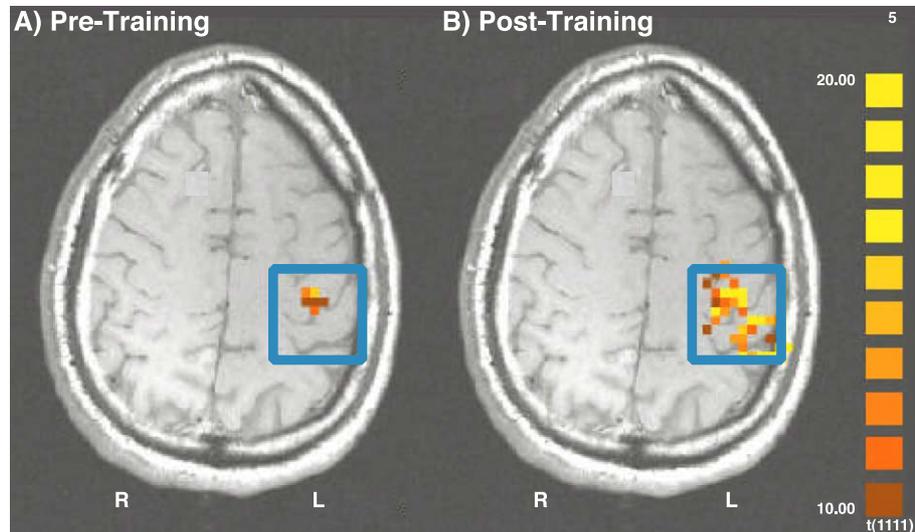
Fig. 2. Somatomotor activation before and after training. (A) BOLD activation during a right-hand imagined-action task before and (B) after training. Statistically significant activation pattern is superimposed upon a T1-weighted anatomical image with the right side of each image corresponding to the left hemisphere (radiological convention). The blue box designates the selected region of interest. The scale on the far right designates the statistical significance by *t* test (*t* value) comparing activation for each voxel during the task blocks to background blocks, shifted by 5 s for hemodynamic delay, corrected for multiple comparisons using the Bonferroni method, with threshold $t \geq 10$; both images to same scale.

associated with performing this complex task were observed in ipsilateral cerebellum, occipital, and frontal regions and varied among subjects.

Concurrently measured EMG (Fig. 3E) showed no indication of muscle contraction during mental rehearsal (Fig. 3B), suggesting that this increase in activation was not due to actual movements or muscle tensing. There was no increase in average magnitude of the RMS EMG signal between the initial training task periods (0.12 mV) and the final training task periods (0.053 mV), and in fact a moderate decrease was observed. Nor was there any increase in RMS EMG signal between background periods in the final session (0.055 mV) and the mental imagery task periods (0.053 mV). However, a strong EMG signal was evident during a control period of overt movement (Fig. 3E), which had an RMS EMG of 0.36 mV.

Group statistics were performed on activation measured from the individually selected ROIs, and showed that training enhanced the observed ROI activation significantly. Group event-related averages of the time course of activation in the region of interest aligned to each task start were computed for all study participants and showed a clear increase from before training (Fig. 3C) to after training (Fig. 3D). A task activation measure (ROI activation during task−rest) was derived from each block for each subject and averaged across subjects. There was a clear monotonic increase in task-driven activation over successive training periods [Fig. 4A, $F(2,10) = 5.87$, $P < 0.02$, repeated-measures ANOVA].

The effect was regionally selective, rather than reflecting general arousal or other widespread effects. In post hoc analysis, activation in the target ROI was compared with whole brain data for consistency. There was no increase observed when measuring the entire brain (Fig. 4B). The increase measured in the ROI was significantly greater than for the whole brain [$F(2,10) = 52$, $P < 0.0001$, two-way repeated-measures ANOVA on interaction]. In addition, a comparison was made with an ROI placed in a comparable position to the target ROI but ipsilateral to the task being performed. In this case, there was a slight but not statistically
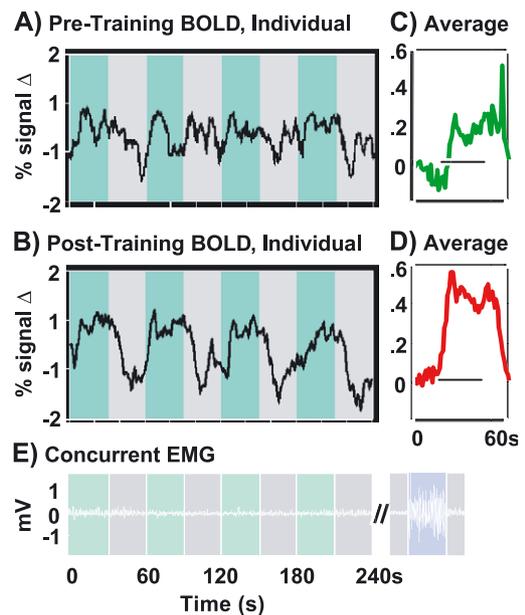

Fig. 3. Temporal progression of activation during imagined action task before and after training. (A) Average value within the ROI for a single subject at successive measurement points (TRs), expressed as percentage change from the mean for the entire period before training and (B) after training. No spatial or temporal averaging or filtering was used. Group event-related average time course of activation driven by the task before training (C) and after training (D) using data from the before testing and after testing periods indicated in Fig. 1. The period of the increase activation block is indicated by the horizontal line, 30 s. The percentage of signal change in the ROI for each time point is averaged across blocks, then averaged across all subjects. Magnitude of signals reflect volume averaging over the ROI; the signal change in strongly activated voxels reached 3−5%. (E) EMG data measured concurrently with data in (B), followed by EMG data from an immediately following period of finger tapping, shown in blue.
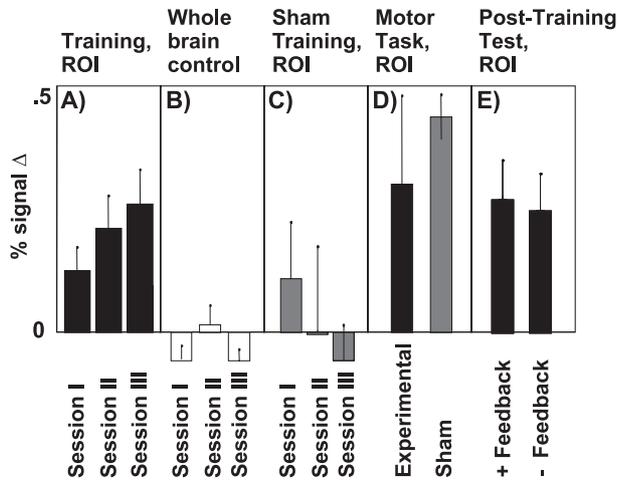
Fig. 4. Group statistics of increase in task-driven activation in target ROI with training. (A) Average percentage of signal change in the ROI during the task period relative to the background period during each of three successive training sessions. (B) Activation measures from the entire brain for the same three periods. The activation measure was computed for all voxels inside the skull on 16 sections spanning cortex to brainstem. (C) Average percentage of signal change in the ROI for the sham training control group. (D) Task-driven activation during performance of overt motor task by the experimental group (left) and the control group (right). (E) Average activation in the ROI for the experimental group during a post-test session with real-time fMRI information available (left) or withheld (right). Error bars indicate standard error across subjects. No spatial smoothing or normalization was used, ROI data was bandpass-filtered from 120 s^{-1} (double the repeat length) to 0.1 s^{-1}.

significant increase in activation in the ipsilateral background ROI [$F(2,10) = 1.5$, $P > 0.25$, repeated-measures ANOVA], possibly reflective of partial activation of contralateral somatomotor cortex induced by functional connectivity.

An important issue was whether the enhancement in ROI activation was dependent on voluntary control over brain activation learned by subjects as a result of training using rtfMRI, or whether these effects would have occurred as a natural consequence of plasticity due to other aspects of repeating the task. In a subject-blind control experiment, a second group of subjects underwent an identical period of conventional behavioral practice, also taking place within the scanner under identical conditions, but without valid rtfMRI information. These participants were given sham information that did not correspond to their fMRI activation. This control could suffer from the possibility that subjects might be confused by sham fMRI information. When questioned following training, subjects did not indicate that they were aware that the information presented had not been valid. The sham-feedback control subjects started out with a similar level of activation in the target somatomotor ROI, but did not show an increase in activation following practice (Fig. 4C). The increase in the experimental group was significantly greater than that for the sham control group [$F(2,18) = 5.0$, $P < 0.02$, two-way repeated-measures ANOVA]. Thus, the observed learning required rtfMRI-based feedback training and was not due to other aspects of repeated practice.

The magnitude of ROI activation that subjects were able to produce during imagined hand movement observed following training was compared with the activation measured in the same subjects during overt movement of the hand contralateral to the

recorded ROI (Fig. 4D). Following the limited period of training used in this study, the activation that subjects were able to produce due to imagined movement had more than doubled (Fig. 4A, right bar), and had nearly reached the activation seen for overt movement (the difference between the two was 13%, and was not statistically significant $P > 0.1$). In the sham training group after training, the activation produced by imagined movement (Fig. 4C, right bar) was much lower than that observed during overt movement (Fig. 4D, striped bar, $P < 0.005$). The fact that the sham control group showed strong activation during overt movement serves as a positive control, confirming that fMRI measurements were sound, and that the ROI selected was properly placed to detect activation driven by behaviors involving the contralateral hand. These findings show that training effects were sufficiently robust that after training subjects could produce a similar level of activation during imagined manual action compared with real movement.

A final test examined whether the subject's ability to voluntarily control activation in a localized brain area, once learned, would be sustained in the absence of further rtfMRI information. During a post-training test session conducted inside the scanner, the same subjects previously trained using rtfMRI information (same group as shown in Fig. 4A) were again instructed to perform the same imagined movement task while rtfMRI information was presented to them, repeating and verifying the initial finding, and then they were instructed to perform the imagined movement task while fMRI information was withheld. Once they had been trained using rtfMRI information, subjects could activate the ROI either with or without real-time fMRI information (Fig. 4E, both conditions in 4E were greater than before training in 4A, left bar, $P < 0.05$). This suggests that once they have learned to control a specific brain region during a task using rtfMRI, subjects can continue to use this learned ability without further direction. It is likely that this learned ability would be sustained outside of the scanner, although this could not be directly tested.

Discussion

These experiments demonstrate that given appropriate direction, practice, and rtfMRI information, subjects can learn to substantially enhance activation in an anatomically targeted brain region during the performance of a specific task. Learning studies have previously used subject's observed motor performance as a source of feedback to guide improvement, while here, information from neuroimaging was used to guide learning of increased brain activation during repeated training using an imagined task where external feedback regarding motor behavior was not possible. Following learning, subjects were able to activate the somatomotor cortex during imagined action to an extent similar to the robust activation observed during an overt motor action.

The observed increase in activation through training presumably arose as subjects learned to modify attention, strategy, or other cognitive processes based upon the information that they received to achieve greater activation of the targeted brain region, and then may have further improved as subjects continued to practice these behaviors. This study extends the literature examining somatomotor cortical activation for imagined, visually observed, and learned actions (Fadiga et al., 1999; Fourneret et al., 2002; Pascual-Leone et al., 1995; van den Bos and Jeannerod, 2002), which has shown absent or substantially reduced activation in primary cortex for

imagined relative to actual movements (Deiber et al., 1998; Jeannerod, 1995; Nilsson et al., 2000; Porro et al., 1996; Roland et al., 1980). Why might one expect enhanced activation in somatomotor cortex in the absence of overt movement? While primary motor neurons within motor cortex directly effect movements, the majority of the total neuronal population in somatomotor cortex do not serve this role. Somotomotor cortex can increase its activation in the absence of overt movement or muscle tensing. We observed a small activation in somatomotor cortex during imagined actions before training, and a significantly greater activation following real-time fMRI-based training.

The majority of functional neuroimaging experiments have involved measurement of the activation of brain regions brought about by the presentation of stimuli, or by top–down processes such as attention, mental imagery, or motor tasks (Jezzard et al., 2001; Raichle and Posner, 1994). However, it has not previously been determined whether through training using real-time neuroimaging, subjects can learn to exert additional, volitional control during task performance. Our study, which was able to employ real-time neuroimaging, has shown that subjects can use cognitive strategies to control a target brain region in real time.

This study introduces the new behavioral method of neurodirected behavior, and thereby raises a number of important questions for future research. It will be valuable to determine the extent of voluntary control over different brain regions that subjects can achieve, as well as to understand the types of strategies that they employ to engage particular brain regions. This study used training with a region of interest that included both gray and white matter and included presumed primary somatosensory and motor cortex and their immediately surrounding areas. Future studies may examine the spatial specificity of control that is achievable. By focusing on what strategies subjects employ to activate individual brain areas, the neurodirection methodology may prove useful in delineating the functional roles of different brain regions. Also, it will be valuable to determine the neural and vascular mechanisms underlying voluntary regulation of measured brain activation. This study used a method analogous to operant (or instrumental) conditioning (Skinner, 1938). It is also possible to explore modes of conditioning based upon neurodirected behavior that are analogous to classical conditioning paradigms (Pavlov, 1927).

It will be interesting for future studies to compare the efficacy of different training methods that lead to increased brain activation in detail. The sham feedback control used in this study was designed to address the question of whether subjects can use information derived from neuroimaging regarding activation in a target brain region to learn to control that brain activation. This initial study did not attempt to compare training with rtfMRI feedback to extended training with no feedback, leaving this substantial additional undertaking for future research. Traditional behavioral plasticity paradigms typically involve repeated training over many more sessions than were provided here (Merzenich and deCharms, 1996), and the most relevant comparison will be between traditional long-term training with no behavioral feedback and training employing neuroimaging information carried out over a similarly long time period. It will be important to compare in parallel the time course of increases in brain activation observed using multiple training methods, each conducted inside of a scanner so that the physical settings are identical and so that parallel measurements in brain activation may be observed, requiring substantial scan resources.

In addition to the effects on the activation of brain regions, future research may also delineate the potential impact of increased activation on perception or behavior. In this study, the subjects performed an imagined action task, so performance measures could not be made. The current data cannot therefore address potential changes in behavior that may accompany changes in brain activation.

The activation of brain regions subserving particular behavioral or physiological functions may lead to enhancement of those functions, either in normal subjects or in patient populations. As the methods available to measure localized brain activation continue to progress, the use of neurodirection to influence behavior or to regulate specific brain processes may have a number of areas of applications such as behavioral training, and as a novel means of targeted, noninvasive intervention in central nervous system disease.

References

Brainard, M.S., Doupe, A.J., 2000. Auditory feedback in learning and maintenance of vocal behaviour. Nat. Rev., Neurosci. 1, 31–40.

Brefczynski, J.A., DeYoe, E.A., 1999. A physiological correlate of the 'spotlight' of visual attention. Nat. Neurosci. 2, 370–374.

Cox, R.W., Jesmanowicz, A., Hyde, J.S., 1995. Real-time functional magnetic resonance imaging. Magn. Reson. Med. 33, 230–236.

Culham, J.C., Cavanagh, P., Kanwisher, N.G., 2001. Attention response functions: characterizing brain areas using fMRI activation during parametric variations of attentional load. Neuron 32, 737–745.

deCharms, R.C., Zador, A., 2000. Neural representation and the cortical code. Annu. Rev. Neurosci. 23, 613–647.

Deiber, M.P., 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.

Fadiga, L., Buccino, G., Craighero, L., Fogassi, L., Gallese, V., Pavesi, G., 1999. Corticospinal excitability is specifically modulated by motor imagery: a magnetic stimulation study. Neuropsychologia 37, 147–158.

Fourneret, P., Paillard, J., Lamarre, Y., Cole, J., Jeannerod, M., 2002. Lack of conscious recognition of one's own actions in a haptically deafferented patient. NeuroReport 13, 541–547.

Gembris, D., Taylor, J.G., Schor, S., Frings, W., Suter, D., Posse, S., 2000. Functional magnetic resonance imaging in real time (FIRE): sliding-window correlation analysis and reference-vector optimization. Magn. Reson. Med. 43, 259–268.

Glover, G.H., 1999. Simple analytic spiral K-space algorithm. Magn. Reson. Med. 42, 412–415.

Herzog, M.H., Fahle, M., 1997. The role of feedback in learning a vernier discrimination task. Vis. Res. 37, 2133–2141.

Ito, M., 2000. Mechanisms of motor learning in the cerebellum. Brain Res. 886, 237–245.

Jeannerod, M., 1995. Mental imagery in the motor context. Neuropsychologia 33, 1419–1432.

Jezzard, P., Matthews, P.M., Smith, S.M., 2001. Functional MRI: An Introduction to Methods. Oxford Univ. Press, Oxford.

Karni, A., Meyer, G., Jezzard, P., Adams, M.M., Turner, R., Ungerleider, L.G., 1995. Functional MRI evidence for adult motor cortex plasticity during motor skill learning. Nature 377, 155–158.

Kawashima, R., Tajima, N., Yoshida, H., Okita, K., Sasaki, T., Schormann, T., Ogawa, A., Fukuda, H., Zilles, K., 2000. The effect of verbal feedback on motor learning—A PET study. Positron emission tomography. NeuroImage 12, 698–706.

Lee, C.C., Jack Jr., C.R., Rossman, P.J., Riederer, S.J., 1998. Real-time reconstruction and high-speed processing in functional MR imaging. Am. J. Neuroradiol. 19, 1297–1300.

Leek, M.R., Hanna, T.E., Marshall, L., 1992. Estimation of psychometric functions from adaptive tracking procedures. Percept. Psychophys. 51, 247–256.

Lisberger, S.G., 1988. The neural basis for learning of simple motor skills. Science 242, 728–735.

Lubar, J.F., Deering, W.M., 1981. Behavioral Approaches to Neurology. Academic Press, New York.

Merzenich, M.M., deCharms, R.C., 1996. Experience, change, and plasticity. In: Llinas, R., Churchland, P. (Eds.), The Mind–Brain Continuum. MIT Press, Boston.

Moore, C.I., Stern, C.E., Corkin, S., Fischl, B., Gray, A.C., Rosen, B.R., Dale, A.M., 2000. Segregation of somatosensory activation in the human rolandic cortex using fMRI. J. Neurophysiol. 84, 558–569.

Nilsson, L.G., Nyberg, L., Klingberg, T., Aberg, C., Persson, J., Roland, P.E., 2000. Activity in motor areas while remembering action events. NeuroReport 11, 2199–2201.

Nowlis, D.P., Kamiya, J., 1970. The control of electroencephalographic alpha rhythms through auditory feedback and the associated mental activity. Psychophysiology 6, 476–484.

Pascual-Leone, A., Nguyet, D., Cohen, L.G., Brasil-Neto, J.P., Cammarota, A., Hallett, M., 1995. Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. J. Neurophysiol. 74, 1037–1045.

Pavlov, I.P., 1927. Conditioned Reflexes. Dover, New York.

Poldrack, R.A., 2000. Imaging brain plasticity: conceptual and methodological issues—A theoretical review. NeuroImage 12, 1–13.

Porro, C.A., Francescato, M.P., Cettolo, V., Diamond, M.E., Baraldi, P., Zuiani, C., Bazzocchi, M., di Prampero, P.E., 1996. Primary motor and sensory cortex activation during motor performance and motor imagery: a functional magnetic resonance imaging study. J. Neurosci. 16, 7688–7698.

Posse, S., Binkofski, F., Schneider, F., Gembris, D., Frings, W., Habel, U., Salloum, J.B., Mathiak, K., Wiese, S., Kiselev, V., et al., 2001. A new approach to measure single-event related brain activity using real-time fMRI: feasibility of sensory, motor, and higher cognitive tasks. Hum. Brain Mapp. 12, 25–41.

Posse, S., Fitzgerald, D., Gao, K., Habel, U., Rosenberg, D., Moore, G.J., Schneider, F., 2003. Real-time fMRI of temporolimbic regions detects amygdala activation during single-trial self-induced sadness. NeuroImage 18, 760–768.

Raichle, M.E., Posner, M.I., 1994. Images of Mind. Scientific American Library, New York, NY. Scientific American Library: Distributed by W.H.

Roland, P.E., Larsen, B., Lassen, N.A., Skinhoj, E., 1980. Supplementary motor area and other cortical areas in organization of voluntary movements in man. J. Neurophysiol. 43, 118–136.

Rumelhart, D.E., Hinton, G.E., Williams, R.J., 1986. Learning representations by back-propagating errors. Nature 323, 533–536.

Sanes, J.N., Donoghue, J.P., 2000. Plasticity and primary motor cortex. Annu. Rev. Neurosci. 23, 393–415.

Schwartz, M.S., 1995. Biofeedback—A Practitioner's Guide. Guilford Press, New York, NY.

Skinner, B.F., 1938. The Behavior of organisms. An Experimental Analysis. Appleton-Century-Crofts, New York.

Stephan, K.M., Fink, G.R., Passingham, R.E., Silbersweig, D., Ceballos-Baumann, A.O., Frith, C.D., Frackowiak, R.S., 1995. Functional anatomy of the mental representation of upper extremity movements in healthy subjects. J. Neurophysiol. 73, 373–386.

Talairach, J., Tournoux, P., 1988. Co-planar Stereotaxis Atlas of the Human Brain. Thieme, Stuttgart.

van den Bos, E., Jeannerod, M., 2002. Sense of body and sense of action both contribute to self-recognition. Cognition 85, 177–187.

Voyvodic, J.T., 1999. Real-time fMRI paradigm control, physiology, and behavior combined with near real-time statistical analysis. NeuroImage 10, 91–106.

Weiskopf, N., Veit, R., Erb, M., Mathiak, K., Grodd, W., Goebel, R., Birbaumer, N., 2002. Feedback of cortical activity using real-time functional magnetic resonance imaging (fMRI). Paper Presented at Human Brain Mapping (Sendai, Japan).

Weiskopf, N., Veit, R., Erb, M., Mathiak, K., Grodd, W., Goebel, R., Birbaumer, N., 2003. Physiological self-regulation of regional brain activity using real-time functional magnetic resonance imaging (fMRI): methodology and exemplary data. NeuroImage 19, 577–586.

Yoo, S.S., Jolesz, F.A., 2002. Functional MRI for neurofeedback: feasibility study on a hand motor task. NeuroReport 13, 1377–1381.