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Functionally Specific Reorganization in Human Premotor Cortex

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SUMMARY

After unilateral stroke, the dorsal premotor cortex (PMd) in the intact hemisphere is often more active during movement of an affected limb. Whether this contributes to motor recovery is unclear. Functional magnetic resonance imaging (fMRI) was used to investigate short-term reorganization in right PMd after transcranial magnetic stimulation (TMS) disrupted the dominant left PMd, which is specialized for action selection. Even when 1 Hz left PMd TMS had no effect on behavior, there was a compensatory increase in activity in right PMd and connected medial premotor areas. This activity was specific to task periods of action selection as opposed to action execution. Compensatory activation changes were both functionally specific and anatomically specific: the same pattern was not seen after TMS of left sensorimotor cortex. Subsequent TMS of the reorganized right PMd did disrupt performance. Thus, this pattern of functional reorganization has a causal role in preserving behavior after neuronal challenge.

INTRODUCTION

Following unilateral brain damage, for example after stroke, retained and recovered use of the affected limb is frequently associated with increased activation of dorsal premotor cortex (PMd) in the intact hemisphere (Gerloff et al., 2006; Johansen-Berg et al., 2002; Seitz et al., 1998; Staudt et al., 2002). The functional importance of such changes, however, can be difficult to interpret. Increased activation in the intact hemisphere is prominent in patients with poor motor recovery (Ward et al., 2006). It may therefore simply reflect the removal of transcallosal inhibition from the damaged hemisphere (Shimizu et al., 2002). Nevertheless, TMS-induced disruption of newly emergent activity in the intact PMd impairs recovered movement of the stroke-affected hand (Lotze et al., 2006), particularly in poorly recovered patients (Johansen-Berg et al., 2002), suggesting that such activity is functionally relevant.

An alternative way to investigate the functional importance of new PMd activity is to assess its functional specificity. If we were to examine subjects in whom only a small part of the motor system was compromised, we might predict that induced compensatory changes would be specific to those functions that are normally mediated by the compromised area. Normally, PMd is important for action selection and the left PMd (lPMd) plays the dominant role (Amiez et al., 2006; Cavina-Pratesi et al., 2006; Deiber et al., 1993; Grol et al., 2006; Passingham et al., 1998; Toni et al., 2002). Therefore, if neural activity in lPMd were to be perturbed, we might expect compensatory changes to occur in the right PMd and perhaps some other premotor areas. Such changes, however, might only be expected during action selection, the process for which lPMd is normally specialized.

Rather than studying patients, the present study used repetitive TMS to induce mild and transient disruption to a focal cortical area and fMRI to image resulting compensatory changes elsewhere in the brain. The combined TMS/fMRI approach enabled experimental control over the focality, onset, and duration of neural interference, unconfounded by variations in lesion size or location, symptom severity, or diaschisis. Further, it provided information about the immediate impact of neural disruption on activity in connected brain regions. Healthy individuals acted as their own controls, thus providing more closely matched baseline data than might be possible with patients.

To investigate the issue of functional reorganization, we combined an action selection task with low-frequency offline TMS. Experiment 1 tested whether fifteen minutes of 1 Hz TMS of lPMd would affect *subsequent* performance on an action selection task, or alter corticospinal excitability, as assessed by a single-pulse TMS test. Corticospinal excitability was suppressed. Performance was also disrupted immediately (<4 min) after TMS, but there was no such deficit during later testing (>4 min). The short-lived behavioral deficit suggested that a process of adaptive compensation might have intervened. Experiment 2

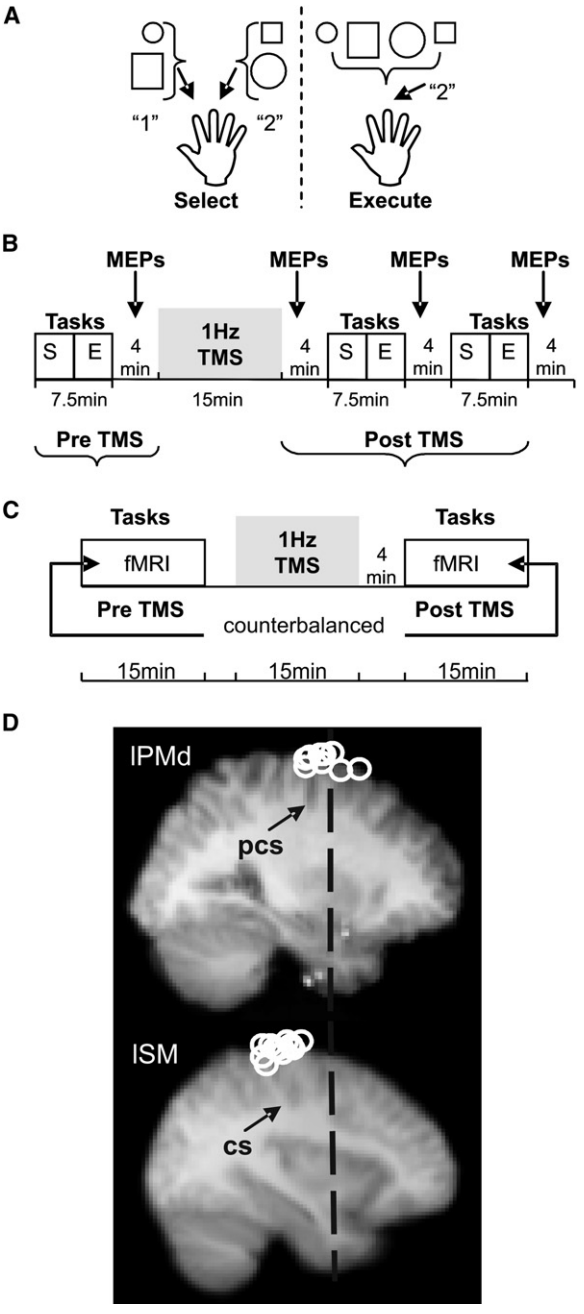

Figure 1. Experimental Design

(A) Behavioral tasks. In both tasks, a shape was presented on each trial. In the experimental select task, subjects pressed button 1 (index finger) in response to a large square or a small circle and button 2 (middle finger) in response to a large circle or a small square. In the control execute task, subjects pressed the same button with the same finger in response to every shape.

(B) TMS/MEP design. In Experiment 1, subjects performed one block each of the select (S) and execute (E) tasks, after which the baseline motor-evoked potential (MEP) amplitude was measured. This was followed by 1 Hz TMS of lPMd (15 min). MEPs were remeasured (1) immediately post-TMS, (2) after 7.5 min, and (3) after 15 min. In each interval between MEP measurements, subjects performed one block of each task. Block order was counterbalanced across subjects. Task performance was measured pre- and post-TMS.

(C) TMS/fMRI design. Subjects underwent two fMRI sessions, one of which was preceded by 15 min of 1 Hz TMS to lPMd (Experiment 2) or a control site in left sensorimotor (lSM) cortex (Experiment 3). The order of scan sessions was counterbalanced across subjects. During each fMRI session, subjects performed alternating blocks of the select and execute tasks interleaved with rest blocks in which they passively viewed the stimuli. There was a 4 min interval between the end of 1 Hz TMS and the start of the post-TMS fMRI scan.

(D) Cortical stimulation sites. Each circle represents the MNI coordinates for an individual subject at which TMS was applied to left PMd (lPMd) (n = 9), or left sensorimotor cortex (lSM) (n = 11). It is clear that lPMd sites cluster above the superior branch of the precentral sulcus (pcs), while lSM sites cluster above the central sulcus (cs). Sections represent the group average saggital plane (PMd, x = −26; SM, x = −35). Dashed line denotes y = 0. Coordinate range for lPMd: −37 < x < −21, −14 < y < 15, 68 < z < 79; and lSM: −53 < x < −22, −31 < y < −12, 63 < z < 75.

therefore used fMRI to test the hypothesis that TMS-induced disruption of lPMd would induce a compensatory increase in activation of the right PMd and other premotor areas, which would be specific to the process of action selection. Because our results confirmed this hypothesis, in Experiment 3 we stimulated left sensorimotor cortex (SM) to establish the anatomical specificity of the pattern of compensatory change. Finally, in Experiment 4, we showed that this pattern of reorganization *causally* mediates preserved performance. Prior to 1 Hz TMS of lPMd, stimulation of the right PMd had no effect on action selection performance. However, after 1 Hz TMS induced compensatory reorganization, stimulation of the right PMd caused a behavioral deficit.

RESULTS

Experiment 1

Effect of lPMd TMS on Action Selection Performance

Experiment 1a examined the effect of offline 1 Hz TMS of lPMd on the subsequent performance of two behavioral tasks (Figure 1A). The "select" task emphasized the selection of action: subjects had to select a different button press response on each trial, according to the identity of a visual cue. A small circle or large square instructed an index finger response, while a large circle or small square instructed a middle finger response. The fact that neither size nor shape instructed responses in a simple way meant that actions had to be selected with care, even after practice. By contrast, the "execute" task de-emphasized action selection: subjects made the same finger movement on every trial regardless of which visual cue was presented. The execute task enabled us to effectively distinguish selection-related from movement-related activity and thus test the functional specificity of our TMS effects. In several previous studies, it has been shown that PMd, especially lPMd, is more active during the select than the execute task, and that TMS of lPMd has an effect on the select task but little impact on the execute task

(Johansen-Berg et al., 2002; Koch et al., 2006; Passingham et al., 1998; Schluter et al., 1998, 1999; Mochizuki et al., 2005).

We compared subjects' performance on both tasks before and after 15 min of 1 Hz TMS was applied offline (while no task was being performed) to lPMd (Figures 1B and 1D). There was no measurable change in select task performance after 1 Hz TMS. A repeated measures ANOVA of reaction times (RTs) with two levels of task (select, execute) and four levels of TMS (pre-TMS and post-TMS tests 1, 2, and 3) revealed a main effect of task, with longer RTs on the select than the execute task ($F(1,6) = 84.335$, $p < 0.001$). There was, however, no main effect or interaction of TMS ($p > 0.1$). A similar error analysis also showed no effect of TMS. However, since task periods were interleaved with periods of motor-evoked potential (MEP) recording (Figure 1B), behavioral testing only began ca. 4 min after TMS. To test whether there might be a behavioral deficit *immediately* after TMS, we performed another experiment (1b), in which subjects performed the select task for ca. 4 min immediately before and after 1 Hz TMS. RTs were significantly delayed after TMS in all subjects ($t(6) = -4.809$, $p = 0.003$; Figure 2A). Importantly, this shows that 1 Hz TMS disrupted the *function* of action selection, detectable as a behavioral deficit in the immediate poststimulation period (<4 min). However, there was no such deficit when testing occurred later (>4 min after TMS). This suggests that, at least for a task of this complexity and TMS of this intensity, the functional disruption caused by lPMd TMS recovers quickly, implicating a process of adaptive compensation.

Effect of lPMd TMS on Corticospinal Excitability

In Experiment 1a, the effect of 1 Hz lPMd TMS on corticospinal excitability was assessed using a technique devised by Gerschlager et al. (2001) (see also Rizzo et al., 2004). Single TMS pulses were applied to left primary motor cortex (lM1), and MEPs were measured before and after 1 Hz offline TMS (15 min) of lPMd. MEP measurements were interleaved with the behavioral measurements described above in the same group of subjects (Figure 1B).

Although a one-way repeated-measures ANOVA with four levels of TMS (pre-TMS, post-TMS 1, 2, 3) was not significant ($F(3,21) = 1.215$, $p = 0.329$), planned contrasts showed that MEP amplitude was significantly reduced immediately after TMS compared to the pre-TMS baseline ($F(1,7) = 6.166$, $p = 0.042$; Figure 2B). MEP amplitude at post-TMS intervals 2 and 3 (7.5 and 15 min after 1 Hz TMS) was also lower than the pre-TMS baseline, but the difference was smaller and not significant ($p > 0.4$). We ran two control experiments. Experiment 1c ruled out the possibility that the change in MEP amplitude was an artifact of an inflated pre-TMS baseline caused by muscle use during task performance. We repeated the experiment without task blocks in a new group of subjects. There was a main effect of TMS ($F(3,12) = 9.744$, $p = 0.002$). Planned contrasts showed that MEPs were suppressed immediately after TMS ($p = 0.006$) and at the second ($p = 0.035$) and third post-TMS intervals ($p = 0.055$), ruling out that

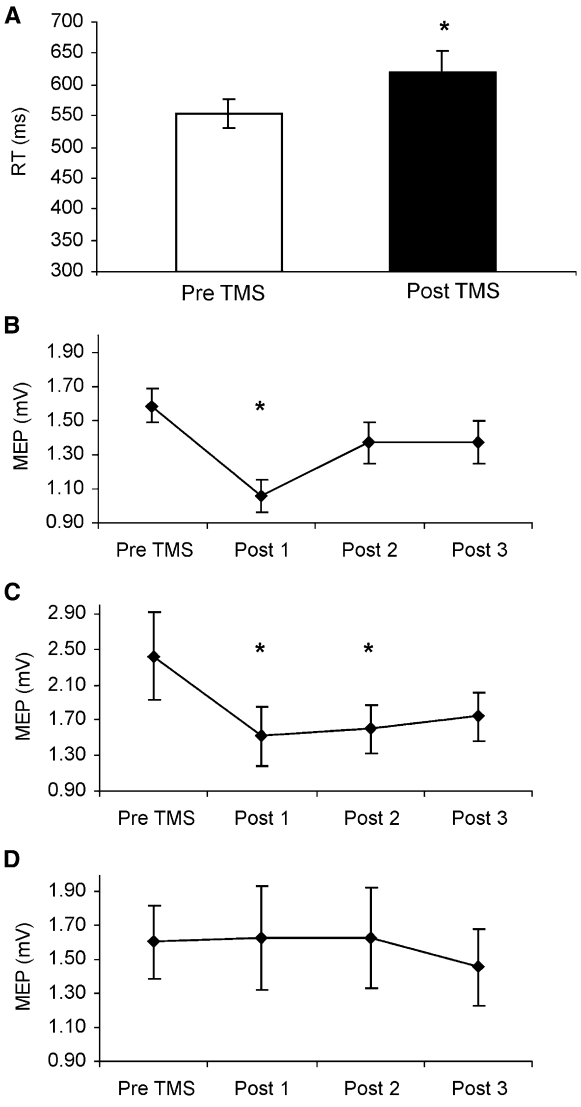

Figure 2. Effect of 1 Hz lPMd TMS on Behavior and Corticospinal Excitability

(A) Select task RTs were delayed immediately (<4 min) after 1 Hz lPMd TMS.

(B) MEPs were measured before and after 1 Hz TMS, interleaved with blocks of the select and execute tasks. The peak-to-peak amplitude (mV) of MEPs from left M1 was suppressed after 1 Hz TMS of lPMd.

(C) A control experiment without task blocks replicated the effect.

(D) A control experiment applied 1 Hz TMS to left sensorimotor cortex and had no effect on MEPs. (*$p < 0.05$, error bars = 1 SEM).

critique (Figure 2C). Control Experiment 1d again replicated Gerschlager et al. (2001) by showing that MEP suppression was a specific effect of stimulation at that anatomical site, lPMd, and not merely an effect mediated by current spread to lM1. We applied the same TMS protocol without a task to left sensorimotor (lSM) cortex. There was no effect on MEPs ($F(3,12) = 0.449$, $p = 0.723$; Figure 2D). To confirm that the effect of TMS at each anatomical site differed significantly, we normalized the MEPs for analysis

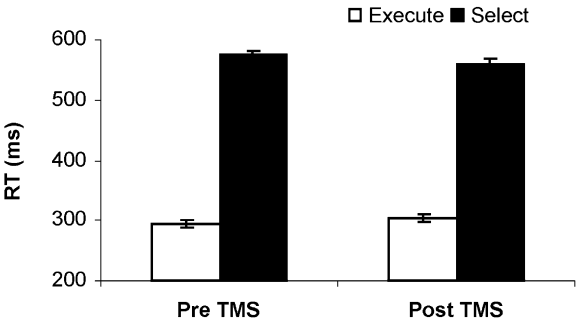

Figure 3. 1 Hz TMS of lPMd Had No Effect on Select Task Performance

Graph shows mean reaction time (RT) data for the execute and select tasks from the two fMRI sessions (pre- and post-TMS) of Experiment 2. RTs were longer on the select task. There was no effect of 1 Hz TMS of lPMd on task performance during this period (>4 min after 1 Hz TMS). Error bars = 1 SEM.

(% change from baseline). There was a main effect of TMS site ($F(1,8) = 9.713$, $p = 0.014$) and MEPs at the first post-TMS interval also differed significantly ($t(8) = -3.035$, $p = 0.016$).

In combination, experiments 1a–1d confirm that our 1 Hz lPMd TMS protocol both disrupted the function of action selection, and exerted an anatomically specific, suppressive effect on left motor corticospinal excitability. The absence of a behavioral deficit beyond the immediate poststimulation period (>4 min) suggests that compensatory changes elsewhere in the brain may mediate behavioral recovery after 1 Hz TMS. Experiment 2 used fMRI to identify where compensatory changes were occurring.

Experiment 2

Action Selection Network Prior to TMS

In Experiment 2, subjects performed the select and execute tasks interleaved with rest periods while fMRI was used to measure changes in the blood oxygenation level-dependent (BOLD) signal. Two fMRI data sets were acquired: one before (pre-TMS) and one after (post-TMS) 1 Hz offline TMS (15 min) was applied to lPMd. To control for potential order or learning confounds, the order of the pre-TMS and post-TMS scans was counterbalanced across subjects, so that half the subjects participated in the post-TMS session prior to the pre-TMS session (Figure 1C).

In the post-TMS fMRI session, 4 min elapsed between the end of TMS and the start of image acquisition. Based on experiments 1a and 1b, we therefore expected that any behavioral deficit induced by the TMS would have recovered by the time of scanning. Consistent with this, an analysis of behavioral RT confirmed that TMS did not disrupt performance of the select task (Figure 3). Although there was a main effect of task ($p < 0.001$) and a significant TMS * task interaction ($F(1,9) = 6.28$, $p = 0.034$), there was no evidence for a slowing of RT in the select task: if anything subjects were slightly but nonsignificantly faster

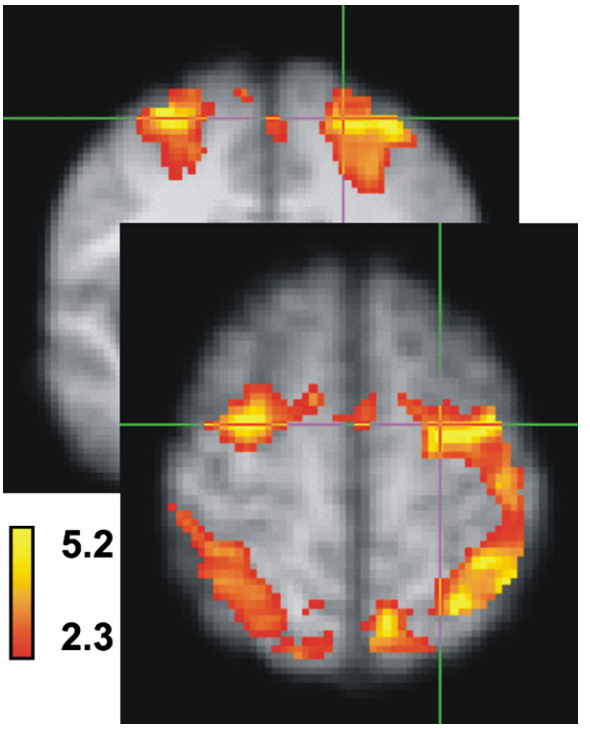

Figure 4. Action Selection Network Prior to 1 Hz TMS

During select as opposed to execute task performance (select > execute), subjects activated a bilateral premotor-parietal network. There was a trend toward stronger and more spatially extended activity in left PMd (crosshairs) than right PMd.

after TMS ($p > 0.18$). The TMS * task interaction was driven by the fact that after TMS there was also a tendency to perform the execute task more slowly, but the simple main effect was only marginally significant ($F(1,9) = 3.945$, $p = 0.078$). Block-by-block analyses found no evidence of learning within or across the two scan sessions (see Figure S1 in the Supplemental Data available with this article online), nor was there any evidence of a behavioral deficit in the first blocks of the post-TMS session.

In the pre-TMS session, subjects activated the expected left hemisphere dominant premotor-parietal network more during performance of the select than the execute task (Figure 4; Table S1). There was bilateral activation along the intraparietal sulcus (IPS) and in PMd and additional activity in the cerebellum and the supplementary motor area (SMA). Consistent with previous reports, activity was more spatially extended in the left hemisphere (Figure 4), although the trend toward higher activity in left than right PMd did not reach significance (Figure S2). Several authors have shown that the network of areas revealed by this and similar contrasts mediates action selection (Amiez et al., 2006; Cavina-Pratesi et al., 2006; Deiber et al., 1993; Grol et al., 2006; Rushworth et al., 1998; Toni et al., 2001), and so we refer it from here onward as the action selection network.

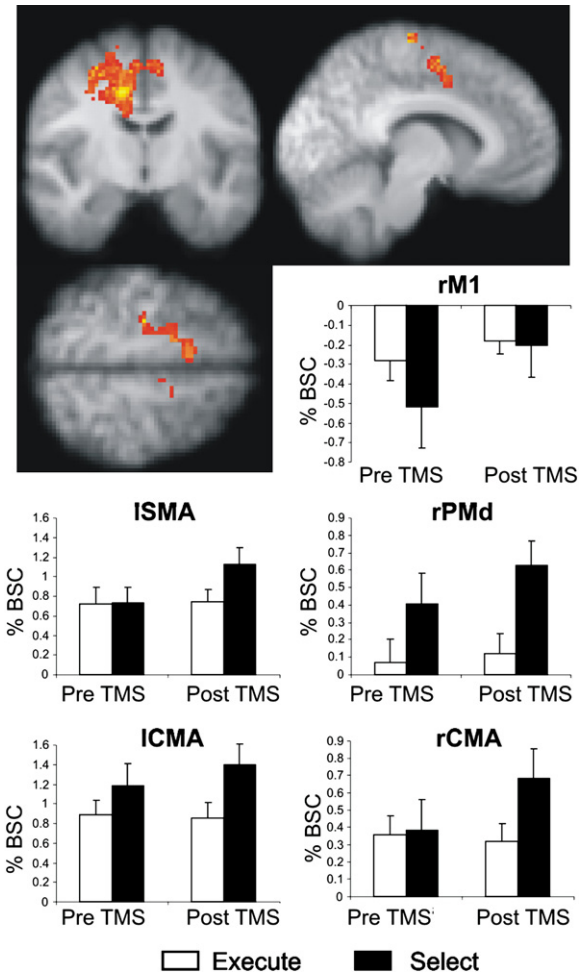

Figure 5. Compensatory Activation Increases in the Action Selection Network after lPMd TMS

A whole-brain random-effects analysis showed that lPMd TMS induced increased activation that was most prominent in rPMd and the rCMA. Additional changes were seen in rM1, the lSMA, and the lCMA. For each of these regions, the graphs show mean percent BOLD signal change (%BSC) values for each task (select/execute) and TMS condition (pre-/post-TMS). Note that the TMS-induced activation increases are specific to the process of action selection. White bars = execute; black bars = select. Error bars = 1 SEM.

Effect of lPMd TMS on the Action Selection Network

An analysis of the interaction between task (select > execute) and TMS (post-TMS > pre-TMS) allowed us to look for an effect of lPMd TMS on activity in the action selection network. As predicted, lPMd TMS was followed by a task-specific increase in activation of the right PMd (rPMd). Significant activation change was also prominent in the right cingulate motor area (rCMA) and, though of smaller extent, there was also significantly increased activation in the left supplementary motor area (lSMA) and left CMA (lCMA) (Figure 5; Table S2). Since the activation change in right primary motor cortex (rM1) was a decrease in deactivation, which is difficult to interpret, we do not discuss it further. A parallel analysis using the same factor of TMS and an execute > rest task comparison did not identify any activation changes specific to the execute condition.

To clarify the nature of the activation increases, spherical region of interest (ROI) masks were centered on the peaks of each of the five activation clusters and mean percent BOLD signal change values in these ROIs were calculated. In case there were changes in activation over time, both pre-TMS and post-TMS fMRI periods were divided into three 5 min time blocks for analysis. To confirm that the activation increases were task specific, signal change values for the select and execute tasks were contrasted across conditions using repeated measures ANOVA (site * TMS * task * time). Each of the four main effects was significant (all $p < 0.026$). There was also a significant interaction of TMS * task ($F(1,10) = 15.055$, $p = 0.003$), indicating that the effects of TMS were task dependent. The critical task was the select task; two separate follow-up ANOVAs (site * TMS * time) showed an effect of TMS on signal change in the select ($F(1,10) = 18.361$, $p = 0.002$) but not in the execute task ($F(1,10) = 0.173$, $p = 0.686$). This analysis thus confirmed the functional specificity of the TMS effect. Following lPMd TMS, there was increased activation of four regions in the action selection network (rPMd, lSMA, rCMA, lCMA, and a decrease in deactivation in rM1), which was specific to periods when subjects were performing the task emphasizing action selection, rather than repetitive execution of the same movement. The lack of any significant interactions involving TMS and time suggested that the impact of TMS on the five areas of activation change did not change significantly over the three 5 min time blocks.

Neither a whole-brain nor an ROI analysis revealed evidence for task-related activation changes in the area underneath the PMd TMS coil. There was also no evidence of TMS-induced deactivation elsewhere in the brain. While task-related activation changes in the stimulated cortex might reasonably be expected, the TMS/fMRI literature is consistent in reporting no such changes after subthreshold TMS (e.g., Rounis, et al. [2006]). The question of why this is the case, and the implications it raises for interpreting TMS effects, requires further investigation (see Supplemental Data for further discussion of this issue).

In addition to the factorial analysis described above, we also used a psychophysiological interaction (PPI) analysis (Friston et al., 1997) to identify areas of the action selection network in which the correlation with lPMd activity changed as a function of both Task and TMS. In other words, the analysis identified areas in which the BOLD signal was predicted by the interaction between activity in lPMd, the select > execute task contrast, and the pre-TMS versus post-TMS contrasts. It should be noted that a PPI analysis and a factorial analysis are differentially sensitive. Whereas the factorial analysis detects a mean change in task-specific activity after TMS, the PPI analysis identifies areas that show a change in correlation with the TMS-induced activity change in lPMd. Hence, areas of increased activity after TMS need not be identified by the

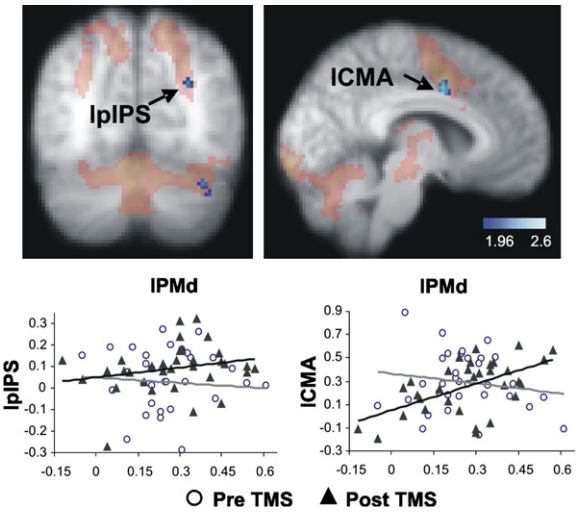

Figure 6. Areas in the Action Selection Network Showing Altered Patterns of Correlated Activity with lPMd after 1 Hz TMS

After TMS, there was a change in correlation between activity in the stimulated region (lPMd) and activity in other areas of the left hemisphere action selection network. For illustrative purposes, the areas of activation change (blue clusters, Z > 1.96) are superimposed on the network activated during select task performance (red, select > rest). The graphs show representative changes in correlation between activity in lPMd and activity in the lpIPS and lCMA. Although areas of changed correlation were identified using a random effects analysis, for illustrative purposes each data point represents the mean % BOLD signal change for one 5 min block for a single subject. Open circles and thin regression line represent pre-TMS data, closed triangles and thick regression line represent post-TMS data.

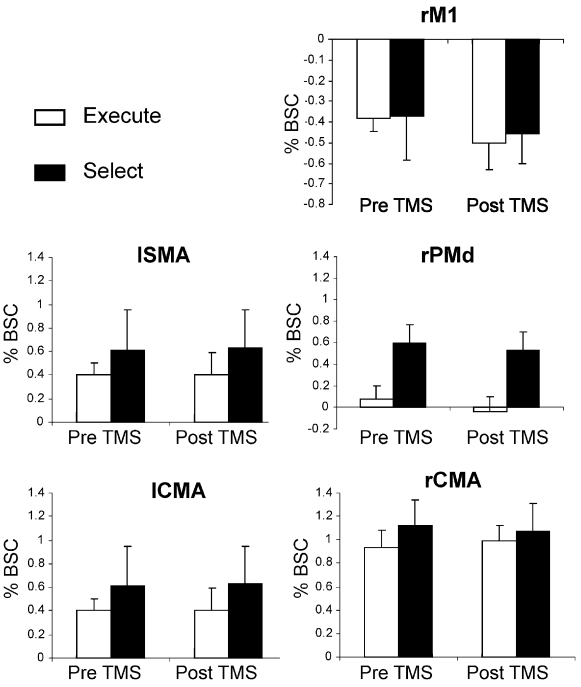

Figure 7. Compensatory Activation Increases Are Anatomically Specific

In Experiment 3, a whole-brain random effects analysis showed that TMS of lSM had no effect on activity in the action selection network. To confirm the absence of a subthreshold pattern of activation change, ROIs were centered on the regions in which activity was modulated by lPMd TMS in Experiment 2. Mean percent BOLD signal change (%BSC) values for each task (select/execute) and TMS condition (pre/post-TMS) confirm the absence of any selection-specific activation change. Error bars = 1 SEM.

PPI analysis, so long as the time course of activity in that region does not change its correlation with lPMd. We restricted the PPI analysis to a liberal mask of the action selection network, defined as all voxels activated during the select task (pre-TMS select > rest contrast), using an activation threshold uncorrected for multiple comparisons (Z > 1.96) and a cluster extent threshold of 10 voxels. The PPI analysis identified a number of clusters, all in the left hemisphere, that changed their correlation with lPMd activity after TMS, specifically: sensorimotor cortex, posterior IPS, SMA, and CMA (Figure 6; Table S3).

These changes in correlation mean that for every change in lPMd activity during the select task, these areas within the left hemisphere action selection network showed a proportionally greater change in activity after TMS than before. Such a pattern is consistent with either increased responsiveness of these areas to input from lPMd or a possible compensatory change in these regions if the lPMd activity is no longer effective in bringing about action selection.

Experiment 3

Effect of Left Sensorimotor TMS on the Action Selection Network

Experiment 3 investigated whether the pattern of task-specific activation increases in Experiment 2 was a specific consequence of lPMd TMS, a general consequence of disruption of the left hemisphere motor system, or an artifactual consequence of some other aspect of the TMS procedure. Subjects performed the same select, execute, and rest blocks, but TMS was applied to the left SM cortex (Figure 1D) rather than to lPMd. All procedures were identical to Experiment 2.

Left SM TMS had no effect on performance of either task (p > 0.2). As in Experiment 2, subjects activated the same left hemisphere dominant premotor-parietal network during action selection (Figure S2). The same region of interest analysis that had been used in Experiment 2 was used again in Experiment 3 to search for any task-specific TMS-induced changes (Figure 7). Unlike after lPMd TMS, there was no evidence of any task-specific change in activity after left SM TMS in rPMd, rM1, the lSMA, or the CMAs. To confirm that the effects of lPMd and lSM TMS differed significantly, we compared the mean percent BOLD signal change in these ROIs across the two experiments (ANOVA, experiment [2 versus 3] * task * TMS [pre-, post-] * ROI). The three-way interaction of experiment, TMS, and task was significant ($F(1,20) = 6.910$, $p = 0.016$). This confirmed that the observed pattern of functionally-specific reorganization was also an

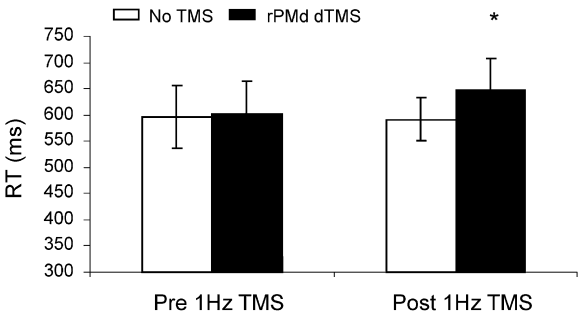

Figure 8. Causal Role of the Reorganized Right PMd in Preserving Action-Selection Behavior

In the pre-TMS session, dTMS of the rPMd (black bars) did not change select task RTs from baseline (no TMS = white bars). However, after 1 Hz TMS reorganized activity in the rPMd, dTMS caused a behavioral deficit. Error bars = 1 SEM.

anatomically-specific consequence of neural disruption in lPMd. A whole-brain analysis confirmed the absence of any lSM TMS-induced task-specific activation changes anywhere else in the action selection network.

Experiment 4

Role of rPMd in Preserving Action Selection Performance

To test if the compensatory increase in rPMd activity had a *causal* role in preserving behavior after 1 Hz TMS, we tested the effect of rPMd TMS. Subjects performed the select task for 4 min before and after 1 Hz TMS of lPMd. Since Experiment 1b showed that performance was impaired in the first 4 min after TMS (Figure 2A), the post-TMS session did not begin until 4 min after the end of the 1 Hz train (just as in Experiment 2). In the pre- and post-TMS sessions, double-pulse TMS (dTMS) was applied to rPMd at 100 and 140 ms after the onset of the shape stimulus—times at which PMd TMS has been shown to disrupt action selection (Schluter et al., 1998; Johansen-Berg et al., 2002). ANOVA revealed a significant interaction between TMS (no TMS, rPMd TMS) and session (pre-/post-1 Hz TMS) ($F(1,5) = 8.485$, $p = 0.033$; Figure 8). Prior to 1 Hz TMS, dTMS applied to rPMd had no effect on select task RTs ($t(5) = -4.14$, $p = 0.696$), confirming that the rPMd is not normally critical for the selection of actions to be performed with the ipsilateral hand. However, after 1 Hz TMS, dTMS of rPMd significantly delayed RTs in every subject ($t(5) = -2.624$, $p = 0.047$). Thus, the reorganized rPMd makes a causal contribution to intact action selection performance after 1 Hz TMS.

DISCUSSION

We set out to investigate two issues: (1) do compensatory changes occur in the motor system after TMS-induced disruption of PMd? (2) Are compensatory changes specific to the specialized functions of the disrupted area? Left PMd was targeted using a TMS protocol that transiently disrupted action selection performance and corticospinal excitability (Figure 2).

Since the interference effects were short-lived, we reasoned that a compensatory mechanism may have contributed to action selection. fMRI was used to map activation in the action selection network before and after lPMd TMS. A factorial analysis showed that preserved performance correlated with increased activation of regions in the action selection network, most prominently in the right hemisphere—in rPMd and the rCMA. Additional changes occurred in two left midline areas, the lSMA and lCMA areas, and there was a change in relative deactivation in rM1 (Figure 5). The increased activation of right PMd is particularly notable because several studies have confirmed that right PMd, compared to the left PMd, normally plays the subdominant role during action selection with the ipsilateral right hand (Johansen-Berg et al., 2002; Passingham et al., 1998; Rushworth et al., 2003). The PPI analysis showed that correlations between activity in lPMd and other areas of the action selection network were changed by TMS. Since the only difference between the two fMRI sessions was that one was preceded by lPMd TMS, the analysis thus showed that reorganizational changes were a direct causal consequence of lPMd TMS. Such changes occurred within the left hemisphere and on the medial wall: in sensorimotor cortex, M1, SMA, CMA, and in anterior and posterior regions of the IPS (Figure 6). The combined factorial and PPI analyses thus identified lPMd TMS-induced changes in the network configuration mediating action selection.

Importantly, the TMS-induced changes were both functionally and anatomically specific. There was no effect of lPMd TMS on the network mediating movement execution. This is consistent with the significantly greater activation of PMd and the greater RT deficits caused by PMd TMS in tasks that emphasize action selection by requiring subjects to select a different action on each trial, compared with action execution tasks, in which subjects repeat the same movement on every trial (Amiez et al., 2006; Johansen-Berg et al., 2002; Mochizuki et al., 2005; Passingham et al., 1998; Rushworth et al., 2003; Schluter et al., 2001). TMS of a primary sensorimotor control site (SM) did not lead to adaptive changes in the action selection network (Figure 7), consistent with the lack of evidence from the same fMRI and TMS experiments for a dedicated role for SM cortex in action selection. Our study shows that activation changes that occur when the motor system is challenged may be adaptive because they mediate those specific functional processes normally associated with the disrupted region.

Compensatory Changes after PMd TMS Are Functionally Specific

Several previous studies have combined TMS with neuroimaging in the absence of any behavioral manipulation. It is established that TMS of one brain area, such as PMd, can be followed by activation changes in connected areas (Bestmann et al., 2004, 2005; Chouinard et al., 2003; Paus

et al., 1997). More recently, a few studies have begun to investigate activation changes that result when TMS is used to modify behavioral performance. Pleger et al. (2006) showed that TMS of primary somatosensory cortex induces an activation increase in the same region and a correlated improvement in somatosensory discrimination performance. Lee et al. (2003) showed that TMS of primary motor cortex induced changes in the stimulated region and in connected premotor regions while subjects performed a simple motor task, similar to the execute control task used in the present study. Rounis et al. (2006) reported that dorsolateral prefrontal cortex TMS changes attentional orienting and induces activation changes in prefrontal and parietal cortex. The present study confirms the utility of the combined TMS/fMRI approach pioneered by these authors, but it also provides important additional information about this experimental approach.

First, our study addresses the functional specificity of TMS-induced changes: activation changes in premotor and parietal areas occurred only during periods of the select task and not during execute task periods. In other words, the activation changes occurred during performance of the task that would be expected, under normal circumstances, to be most reliant on the lPMd that had been disrupted by TMS (Amiez et al., 2006; Cavina-Pratesi et al., 2006; Deiber et al., 1993; Passingham et al., 1998; Rushworth et al., 2003; Toni et al., 2002).

Second, it is important to note that the change in task-related activation in the post-TMS fMRI session was not accompanied by any change in indices of task performance. Although 1 Hz TMS has been shown to disrupt motor performance (Chouinard et al., 2005) and Experiment 1b confirmed that 1 Hz TMS disrupted the action selection functions of the lPMd, the deficit was short-lived. The absence of a behavioral change during the post-TMS fMRI session of Experiment 2 (>4 min after 1 Hz TMS) enabled us to isolate a neural process of adaptive compensation that was not confounded by performance-related effects.

Finally, it should be noted that the functional specificity of TMS-induced changes in the right PMd suggests they are not just a trivial consequence of the removal of transcallosal inhibitory inputs from the stimulated lPMd. Further, selection-specific activation increases in right PMd occurred without any concomitant decrease in lPMd activation. This argues against interpreting the activation changes in terms of a simple change in the balance of interhemispheric competition (Shimizu et al., 2002; Sprague, 1966).

Compensatory Changes Are Specific to the Anatomical Region of Interference

To establish the specificity of the compensatory effects, we also looked for regions of activation change after stimulation of a control site in left primary sensorimotor cortex. SM TMS neither suppressed MEPs (Figure 2C) nor induced reorganization in the action selection network, confirming the anatomical specificity of the lPMd TMS effects.

Previous studies have shown that online TMS of left SM impairs aspects of motor performance, but unlike PMd TMS, such effects are not specific to action selection per se (Johansen-Berg et al., 2002; Passingham et al., 1998; Schluter et al., 1999). It is therefore not surprising that we did not see activation changes in the action selection network after SM TMS. Nevertheless, this does not preclude a role for SM cortex in the adaptive response to lPMd TMS, as suggested by the PPI analysis of Experiment 2.

In contrast to PMd TMS, TMS of SM cortex disrupts performance on tasks that require coordinated movements of several digits, such as grasping (Chouinard et al., 2005; Nowak et al., 2005). Hence, while SM TMS did not affect activation in the action selection network, we would predict that SM TMS combined with a grasping task would produce an analogous pattern of compensatory changes in the cortical network that normally mediates grasping (Binkofski et al., 1999a, 1999b).

Causal Role of Reorganized Right PMd in Preserving Behavior

The pattern of functionally and anatomically specific neural reorganization that we have characterized correlated with intact action selection performance in the period >4 min after 1 Hz TMS. If there is a causal link between this neural reorganization and preserved behavior, then it follows that disruption of the reorganized activity should lead to a behavioral deficit (for a related argument, see Strens et al. [2003]). We tested for a causal link in Experiment 4 which, consistent with previous work, showed that the right PMd does not normally make a critical contribution to the selection of actions to be executed with the ipsilateral hand (Schluter et al., 1998; Johansen-Berg et al., 2002). However, *after* 1 Hz TMS disrupted the action selection functions of the left PMd, reorganized activity in the right PMd *then* became critical for action selection performance (Figure 8). This demonstrates that the pattern of neural reorganization mediates behavior after TMS: if you perturb the activity of the reorganized right PMd, preserved performance breaks down. Thus, this pattern of neural reorganization is an adaptive response to neuronal challenge.

Compensatory Changes in the Motor System in Patients

Naturally occurring lesions do not neatly respect anatomicrofunctional boundaries. If after a large lesion several functional processes are impaired, it can be difficult to ascertain with precision whether newly emerging areas of activity mediate specific recovered functions. Our results suggest that when neural interference compromises the specialized functions of a particular brain region (in this case lPMd and action selection), compensation first entails the exploitation of connected areas in the existing network that normally implements those functions. Thus, at least in the initial stages of adaptive compensation, recruitment of the right PMd is likely restricted to those functions for which it is already specialized.

Interference in the present experiment was anatomically restricted to lPMd, and compensatory changes occurred in right PMd. The right PMd is part of the action selection network, and has a role in selecting actions based on learned associations with arbitrary stimuli. However, compensatory activation increases also occurred in other premotor association areas, notably the right CMA. Although the CMA, like the SMA, may not normally play a central role in selecting actions based on arbitrary visual cues, it nevertheless contributes to action selection performance (Kennerley et al., 2006; Procyk et al., 2000; Tanji, 2001).

Evidence suggests that the PMd may be particularly well positioned to mediate recovery of a range of motor functions. For example, two patient studies using combined TMS/fMRI demonstrated that recovered manual performance on either simple or choice reaction tasks was mediated by increased activation of the contralesional PMd (Johansen-Berg et al., 2002; Lotze et al., 2006). One anatomical basis for those findings may be bilateral projections to the spinal cord. This may enable PMd to exert some influence on movements made by either hand. A caveat is that such projections terminate in ventromedial spinal areas, less concerned with distal limb movements (Kuypers and Brinkman, 1970), and reliance on this route may explain why some of those patients were unable to make individuated finger movements. A likely alternative route by which PMd could exert control over ipsilateral finger movements is via interhemispheric connections with contralateral M1. Such connections are known to exist in other primates (Boussaoud et al., 2005; Marconi et al., 2003), and in a recent study using diffusion-weighted MRI, we have found evidence for similar connections in the human brain (E.D. Boorman, J.O'S., C. Sebastian, M.F.S.R., and H.J.-B., unpublished data). Functional connections have been demonstrated using dual-site TMS: TMS-induced activation changes in PMd have a causal impact on contralateral M1 at short latencies (Baumer et al., 2006; Mochizuki et al., 2004; J.O'S., C. Sebastian, E.D. Boorman, H.J.-B., and M.F.S.R., unpublished data). Even in the healthy state, PMd has a bilateral role in action selection, and this is especially true of the dominant lPMd. This baseline bilaterality may also be an important factor mediating functional recovery from unilateral injury. Finally, the PMd is an area of the motor system that is especially important for learning novel visuomotor mappings (Deiber et al., 1993; Petrides, 1985; Scott et al., 2000). This may mean that the PMd is particularly well placed to mediate learning of new motor strategies after brain damage results in the normal routes to action being compromised.

Conclusions

In the initial stages of adaptive compensation for neuronal interference, the adult brain exploits pre-established patterns of functional specialization. When a key node in an information-processing circuit is impaired, healthy cortical networks can flexibly reconfigure processing in a way that is rapid, functionally-specific, and preserves behavior.

EXPERIMENTAL PROCEDURES

Subjects

Fifty-three subjects (28 males) participated in this study (seven in Experiment 1a, eight in 1b, five in 1c, five in 1d, eleven in Experiment 2, eleven in Experiment 3, six in Experiment 4; ages 21–37). All subjects were right-handed, reported an absence of psychiatric or neurological disease in both their personal and family histories, and gave written, informed consent. The study was carried out under permission from the Central Oxford Research Ethics Committee (COREC 05-Q1606-96).

Behavioral Tasks

In all experiments, subjects performed the same tasks: select or execute (Figure 1A). On each trial, one of four visual shape stimuli was presented (large/small circle/square). In the select task, subjects responded by pressing one of two buttons with the index or middle finger of the right hand depending on a learned rule; a large square or small circle instructed an index finger response (button 1); a large circle or small square instructed a middle finger response (button 2). The stimulus-response mappings were counterbalanced across subjects. The four stimuli differed in both shape and size, so accurate performance required care, even after practice. In the execute task, subjects pressed the same button with their index finger in response to every shape. In Experiment 1a (Figure 1B), subjects alternated between performing blocks of both tasks. Each block had 60 trials, and block order was counterbalanced across subjects. In Experiment 1b, subjects performed the select task for ca. 4 min. Trials were response-terminated and separated by a variable inter-trial interval (1–1.5 s). The task was controlled by Pascal software.

Experiment 1: Effect of 1 Hz lPMd TMS on Behavior and Corticospinal Excitability

The aim of Experiment 1a was to establish whether the 1 Hz lPMd TMS protocol would affect (1) task performance or (2) corticospinal excitability. A previously used method, involving single-pulse TMS of M1 (Gerschlager et al., 2001; Rizzo et al., 2004), was used to assess changes in corticospinal excitability. One block of data was acquired before the application of 1 Hz lPMd TMS, and three blocks were acquired afterwards. In each block, MEPs were recorded from the first dorsal interosseous (FDI) muscle of the right hand during TMS of left M1. Single TMS pulses were applied at that intensity sufficient to evoke an MEP of ~1 mV mean amplitude from the relaxed FDI on ten consecutive trials. The 1 Hz TMS train was applied to lPMD at 90% of active motor threshold (AMT): the intensity sufficient to evoke a 200 μV MEP on five out of ten trials during a 10% of maximal FDI contraction (Rossini et al., 1994). To control for the possibility that muscle use during task blocks had led to an artificially inflated baseline MEP, we repeated the experiment (1c) with the task blocks removed. In a second control experiment (1d), we applied the identical procedure to a sensorimotor cortex control site.

FDI MEPs were recorded with Ag-AgCl electrodes using a tendon-belly montage. Electromyographic (EMG) responses were amplified, filtered, and sampled using a CED 1902 amplifier, a CED 1401 analog-to-digital converter, and a Pentium 4 computer running Signal (version 2.14) software (Cambridge Electronic Design Ltd.). The sampling rate was 10 kHz (Experiment 1a) or 5 kHz (1c, 1d), and signals were band-pass filtered between 10 and 10,000 Hz (1a) or 10 and 1000 Hz (1c, 1d).

A biphasic Magstim Super Rapid machine (Magstim Company) was used to deliver 1 Hz TMS through a 70 mm figure-of-eight coil. The coil was held tangential to the skull, oriented 45° to the midsaggital axis, inducing lateromedial current flow. The coil was replaced after 7.5 min to avoid overheating. Coil changeover took approximately 30s. MEPs were measured using a monophasic Magstim 200.

In Experiment 1a, behavioral and MEP data collection was interleaved both before and after 1 Hz lPMd TMS (Figure 1B). In brief, subjects first performed alternating blocks of both tasks. Single-pulse TMS was then applied to left M1 to yield the baseline MEP measurement. Subjects then received 15 min of 1 Hz lPMd TMS at 90% AMT. MEP

size was remeasured at three time points: immediately after 1 Hz PMd TMS and after approximately 7 and 15 min. Subjects performed blocks of both tasks during the periods between MEP recordings.

Experiment 2: Effect of 1 Hz lPMd TMS on the Action Selection Network

The day before scanning each subject practised the task and the AMT was established. Practice was refreshed briefly prior to the first fMRI scan. Subjects underwent two fMRI sessions (15 min each) on the same day, one of which was preceded by 1 Hz lPMd TMS (15 min, 90% AMT). Scan order was counterbalanced so that half the subjects participated in the post-TMS session prior to the pre-TMS session (Figure 1C). A 45 min interval occurred between scan sessions.

In the post-TMS session, the time required for scanner setup meant that ca. 4 min had elapsed between the end of 1 Hz TMS and the onset of fMRI data acquisition. During the interval, subjects were asked to interact with the experimenters as little as possible. They were moved to the immediately adjacent MRI scanner room and were only required to actively take the last few steps into the room and get onto the scanner bed.

In addition to select and execute task blocks, there were also baseline rest blocks in which subjects passively viewed the same stimuli. Prior to block onset, an instruction cue (1 s) signaled block type (select/execute/rest). Shapes were also color-coded to remind subjects of the current block type (select = red, execute = green, rest = blue). Subjects performed 36 task blocks per fMRI session. Blocks were presented in a pseudorandom and counterbalanced order, cycling in threes, such that four blocks of each type were performed every 5 min. Each block contained 17 trials. On each trial, the stimulus was presented for 700 ms, followed by a 700 ms response window. Subjects were instructed to respond as quickly and accurately as possible. The task was controlled by Presentation software (Psychology Software Tools, Inc.) running under Windows XP. Visual stimuli were back-projected onto a screen and viewed through a mirror.

Experiment 3: Effect of 1 Hz lSM TMS on the Action Selection Network

Identical procedures were followed from Experiment 2, except that TMS was delivered to left SM.

Experiment 4: Causal Role of the Reorganized Right PMd in Preserving Behavior

Subjects performed two blocks of the select task (4 min), one before and after 1 Hz lPMd TMS. Since Experiment 1b showed that performance was impaired within the first 4 min after stimulation, the post-TMS session did not begin until 4 min after the end of the 1 Hz train. Note that the timing is the same as in fMRI Experiment 2. Each block had 90 pseudorandomized trials: 60 no-TMS trials and 30 TMS trials. On TMS trials, dTMS was applied to right PMd (at 100 and 140 ms after the onset of the shape stimulus—times at which PMd TMS has been shown to disrupt action selection: Schluter et al., 1998; Johansen-Berg et al., 2002). Median RTs were analyzed to test for a change in the effect of rPMd stimulation before and after 1 Hz TMS of lPMd.

Localization of lPMd and lSM TMS Sites

TMS was applied to the left motor cortex hot spot, defined as the optimal scalp position at which the lowest intensity TMS evoked a just-noticeable twitch from the relaxed right FDI. The sites for 1 Hz TMS were localized relative to the hot spot scalp coordinates: 2 cm anterior and 1 cm medial for lPMd; 1 cm posterior for the lSM control site (Figure 1D). Previous studies have shown that TMS at these respective sites leads to graded dissociable effects on both brain activity and RT in action selection and execution tasks (Chouinard et al., 2003; Johansen-Berg et al., 2002; Koch et al., 2006; Lee and van Donkelaar, 2006; Mochizuki et al., 2004, 2005; Passingham et al., 1998; Schluter et al., 1999).

The two TMS sites were verified anatomically using Brainsight frameless stereotaxy (Rogue Research). Each subject's head was first coregistered with their anatomical MRI in native space, and a trajectory was plotted from each scalp location at which TMS was applied onto the cortical surface using Brainsight software. Individual subjects' structural MRI scans were then normalized to the MNI 152-mean brain T1 template. lPMd TMS was applied just anterior to the dorsal branch of the precentral sulcus (mean MNI coordinates, x = −25.7 [SE ± 1.7], y = −3.83 [±3.04], z = 73.5 [±1.3]), corresponding well with published coordinates and sulcal landmarks (Amiez et al., 2006). lSM TMS was applied over the posterior lip of the motor hand hook in the central sulcus (mean MNI coordinates, x = −35.1 [± 2.6], y = −27.3 [± 1.9], z = 70.7 [±1.2]), which also concurs with previous studies (Chouinard et al., 2003; Johansen-Berg et al., 2002). To confirm that 1 Hz TMS at 90% AMT did not evoke muscle twitches, subjects received 30 s of TMS at each site. No MEPs were evoked from the relaxed right FDI at that stimulation intensity (intensities in % of stimulator output, Experiment 1, 39%–56%, mean = 49.4; Experiment 2, 27%–57%, mean = 41.5; Experiment 3: 34%–54%, mean = 41.9).

MRI Data Acquisition

BOLD fMRI images and T1-weighted anatomical images were acquired on a 3T Siemens MR scanner with a maximum gradient strength of 40 $mT \cdot m^{-1}$. BOLD fMRI data were acquired by using echo planar imaging (EPI) (25 × 5mm thick axial slices positioned from the top of the brain, with a base resolution of 64 mm, matrix size 192 × 192, field of view 192 × 192 mm^2, giving a voxel size of 3 × 3 × 5 mm, repetition time = 1.5 s, 620 volumes, echo time =30 ms, and flip angle = 73°). A T1-weighted anatomical image was acquired for each subject by using a FLASH sequence (repetition time = 3 ms, echo time = 4.71 ms, and flip angle =80°, giving a voxel size of 1 × 1 × 1 mm).

fMRI Analysis

fMRI data were analyzed using tools from the FMRIB Software Library (www.fmrib.ox.ac.uk/fsl). At the first level (within-subjects), preprocessing involved several stages. The first four EPI volumes were deleted owing to tissue relaxation artifacts. Motion was corrected using MCFLIRT (Jenkinson and Smith, 2001). The program produced six motion-correction parameters that were used as regressors in the design matrix. Nonbrain structures were removed using BET (Smith, 2002). The data were spatially smoothed using a 5 mm Gaussian kernel of full-width at half maximum. Each dataset was normalized by a single scaling factor ("grand mean scaling"), whereby each volume in a 4D dataset is normalized by the same value, to allow for cross-subject statistics to be valid. High-pass temporal filtering with a 90 s cut-off was used to remove low-frequency drifts. MELODIC (Beckmann and Smith, 2004) was used out to identify and remove artifacts related to head motion and to an intermittent fault in the radio-frequency head coil. The resulting denoised time series data were analyzed using a general linear model (GLM) approach. Registration to standard space was carried out using FLIRT (Jenkinson and Smith, 2001). Statistical analysis was carried out in FEAT v.5.63 using FILM with local autocorrelation correction (Woolrich et al., 2001). The hemodynamic response function was modeled as a γ function, a normalization of the probability density function of the γ distribution with zero phase, standard deviation of 3 s, and a mean lag of 6 s.

Head motion was modeled by six regressors of no interest that were orthogonalized with respect to the rest of the design. The explanatory variables (EVs) and motion covariates were modeled with their temporal derivates. In addition to motion parameters, there were seven EVs in the first level model. Block instruction cues were modeled as transient events of no interest (1.5s = 1TR). Since the MEP data (Experiment 1b) suggested that the effects of 1 Hz TMS might be maximal immediately poststimulation and decay during the session, the time-series data for both fMRI sessions were divided into three 5 min blocks for analysis. This yielded six main EVs for each fMRI session, one per task (select/execute) and block ($1^{st}/2^{nd}/3^{rd}$). Each EV specified the onset and duration of task periods during each block (four periods of each task in each 5 min block, each task period lasting 27 s). FEAT was used to fit this model to the data, to generate parameter estimates for

each of the six main EVs against rest, and to contrast these parameter estimates against one another (e.g., select > execute in 1st block).

To generate statistical activation maps for each of the within-session EVs and to test for an effect of TMS across sessions, random effects analyses were applied to the whole-brain group data for each experiment and session using FLAME. Group Z (Gaussianized T) statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster extent significance threshold of $p = 0.05$. To clarify the nature of the activation changes induced by TMS, a series of spherical regions of interest (radius 0.9 cm) were centered on the peaks of activation clusters identified by the whole-brain analysis. Since the clusters were interconnected, ROI dimensions were chosen to avoid overlap and "double counting" of adjacent clusters. The ROIs were within the "effective spatial resolution" of TMS because we have previously shown dissociable behavioral effects of lPMd and lSM TMS on action selection at scalp sites 2 cm apart. Mean percent BOLD signal-change values (versus rest) in these clusters were calculated for each of the six main EVs in our model (i.e., select/execute in 1st/2nd/3rd 5 min blocks). These parameter estimates were then contrasted across conditions using repeated measures ANOVA. An additional sphere was generated to capture any potential subthreshold activation changes that might occur in the region underneath the TMS coil. The sphere was positioned using Brainsight coordinates from the cortical surface and centering the sphere one radius distance inward from that point along a trajectory perpendicular to the angle of orientation of the coil. MNI coordinates for lPMd were centered at x −18, y −4, z 64, and were confirmed to capture lPMd activity for the contrast of select > execute in both the Pre- and Post-TMS fMRI sessions. The search for TMS-induced deactivations elsewhere in the brain was constrained to those regions captured by a mask of either movement task (i.e., select/execute > rest).

Finally, a PPI approach was used to test for changes in the correlations between activity in lPMd and activity in other motor areas (Friston et al., 1997). The mean time course across all voxels within the lPMd ROI was found for each session and de-meaned. The first-level design matrix for the PPI analysis included two EVs which were the interaction between the lPMd time course for that subject and the select > rest regressor (EV1) or the execute > rest regressor (EV2). Our contrast of interest was EV1 > EV2, which identified voxels showing a greater correlation with lPMd activity during the select than the execute task. A random effects higher-level analysis identified voxels captured by this contrast in which activity differed in the post- versus pre-TMS session. This higher-level analysis was restricted to all voxels activated during the select task (defined by select > rest pre-TMS), using an activation threshold uncorrected for multiple comparisons ($Z > 1.96$) and a cluster extent threshold of ten voxels. Spherical ROIs were centered on peaks of clusters identified thus. Mean % BOLD signal change in these ROIs was calculated for the select > rest contrast for each 5 min block. These values were plotted against the equivalent values for the lPMd ROI, and regression lines were fitted to the pre- and post-TMS data to allow for visualization of the PPI effects.

Supplemental Data

The Supplemental Data for this article can be found online at http://www.neuron.org/cgi/content/full/54/3/479/DC1/.

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REFERENCES

Amiez, C., Kostopoulos, P., Champod, A.S., and Petrides, M. (2006). Local morphology predicts functional organization of the dorsal premotor region in the human brain. J. Neurosci. *26*, 2724–2731.

Baumer, T., Bock, F., Koch, G., Lange, R., Rothwell, J.C., Siebner, H.R., and Munchau, A. (2006). Magnetic stimulation of human premotor or motor cortex produces interhemispheric facilitation through distinct pathways. J. Physiol. *572*, 857–868.

Beckmann, C.F., and Smith, S.M. (2004). Probabilistic independent component analysis for functional magnetic resonance imaging. IEEE Trans. Med. Imaging *23*, 137–152.

Bestmann, S., Baudewig, J., Siebner, H.R., Rothwell, J.C., and Frahm, J. (2004). Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. Eur. J. Neurosci. *19*, 1950–1962.

Bestmann, S., Baudewig, J., Siebner, H.R., Rothwell, J.C., and Frahm, J. (2005). BOLD MRI responses to repetitive TMS over human dorsal premotor cortex. Neuroimage *28*, 22–29.

Binkofski, F., Buccino, G., Posse, S., Seitz, R.J., Rizzolatti, G., and Freund, H. (1999a). A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. Eur. J. Neurosci. *11*, 3276–3286.

Binkofski, F., Buccino, G., Stephan, K.M., Rizzolatti, G., Seitz, R.J., and Freund, H.J. (1999b). A parieto-premotor network for object manipulation: evidence from neuroimaging. Exp. Brain Res. *128*, 210–213.

Boussaoud, D., Tanne-Gariepy, J., Wannier, T., and Rouiller, E.M. (2005). Callosal connections of dorsal versus ventral premotor areas in the macaque monkey: a multiple retrograde tracing study. BMC Neurosci. *6*, 67.

Cavina-Pratesi, C., Valyear, K.F., Culham, J.C., Kohler, S., Obhi, S.S., Marzi, C.A., and Goodale, M.A. (2006). Dissociating arbitrary stimulus-response mapping from movement planning during preparatory period: evidence from event-related functional magnetic resonance imaging. J. Neurosci. *26*, 2704–2713.

Chouinard, P.A., Van Der Werf, Y.D., Leonard, G., and Paus, T. (2003). Modulating neural networks with transcranial magnetic stimulation applied over the dorsal premotor and primary motor cortices. J. Neurophysiol. *90*, 1071–1083.

Chouinard, P.A., Leonard, G., and Paus, T. (2005). Role of the primary motor and dorsal premotor cortices in the anticipation of forces during object lifting. J. Neurosci. *25*, 2277–2284.

Deiber, M.P., Pollak, P., Passingham, R., Landais, P., Gervason, C., Cinotti, L., Friston, K., Frackowiak, R., Mauguiere, F., and Benabid, A.L. (1993). Thalamic stimulation and suppression of parkinsonian tremor. Evidence of a cerebellar deactivation using positron emission tomography. Brain *116*, 267–279.

Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., and Dolan, R.J. (1997). Psychophysiological and modulatory interactions in neuroimaging. Neuroimage *6*, 218–229.

Gerloff, C., Bushara, K., Sailer, A., Wassermann, E.M., Chen, R., Matsuoka, T., Waldvogel, D., Wittenberg, G.F., Ishii, K., Cohen, L.G., and Hallett, M. (2006). Multimodal imaging of brain reorganization in motor areas of the contralesional hemisphere of well recovered patients after capsular stroke. Brain *129*, 791–808.

Gerschlager, W., Siebner, H.R., and Rothwell, J.C. (2001). Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. Neurology *57*, 449–455.

Grol, M.J., de Lange, F.P., Verstraten, F.A., Passingham, R.E., and Toni, I. (2006). Cerebral changes during performance of overlearned arbitrary visuomotor associations. J. Neurosci. *26*, 117–125.

Jenkinson, M., and Smith, S. (2001). A global optimisation method for robust affine registration of brain images. Med. Image Anal. *5*, 143–156.

Johansen-Berg, H., Rushworth, M.F.S., Bogdanovic, M.D., Kischka, U., Wimalaratna, S., and Matthews, P.M. (2002). The role of ipsilateral premotor cortex in hand movement after stroke. Proc. Natl. Acad. Sci. USA *99*, 14518–14523.

Kennerley, S.W., Walton, M.E., Behrens, T.E., Buckley, M.J., and Rushworth, M.F. (2006). Optimal decision making and the anterior cingulate cortex. Nat. Neurosci. *9*, 940–947.

Koch, G., Franca, M., Del Olmo, M.F., Cheeran, B., Milton, R., Alvarez Sauco, M., and Rothwell, J.C. (2006). Time course of functional connectivity between dorsal premotor and contralateral motor cortex during movement selection. J. Neurosci. *26*, 7452–7459.

Kuypers, H.G., and Brinkman, J. (1970). Precentral projections to different parts of the spinal intermediate zone in therhesus monkey. Brain Res. *24*, 29–48.

Lee, J.H., and van Donkelaar, P. (2006). The human dorsal premotor cortex generates on-line error corrections during sensorimotor adaptation. J. Neurosci. *26*, 3330–3334.

Lee, L., Siebner, H.R., Rowe, J.B., Rizzo, V., Rothwell, J.C., Frackowiak, R.S., and Friston, K.J. (2003). Acute remapping within the motor system induced by low-frequency repetitive transcranial magnetic stimulation. J. Neurosci. *23*, 5308–5318.

Lotze, M., Markert, J., Sauseng, P., Hoppe, J., Plewnia, C., and Gerloff, C. (2006). The role of multiple contralesional motor areas for complex hand movements after internal capsular lesion. J. Neurosci. *26*, 6096–6102.

Marconi, B., Genovesio, A., Giannetti, S., Molinari, M., and Caminiti, R. (2003). Callosal connections of dorso-lateral premotor cortex. Eur. J. Neurosci. *18*, 775–788.

Mochizuki, H., Huang, Y.Z., and Rothwell, J.C. (2004). Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. J. Physiol. *561*, 331–338.

Mochizuki, H., Franca, M., Huang, Y.Z., and Rothwell, J.C. (2005). The role of dorsal premotor area in reaction task: comparing the "virtual lesion" effect of paired pulse or theta burst transcranial magnetic stimulation. Exp. Brain Res. *167*, 414–421.

Nowak, D.A., Voss, M., Huang, Y.Z., Wolpert, D.M., and Rothwell, J.C. (2005). High-frequency repetitive transcranial magnetic stimulation over the hand area of the primary motor cortex disturbs predictive grip force scaling. Eur. J. Neurosci. *22*, 2392–2396.

Passingham, R.E., Toni, I., Schluter, N., and Rushworth, M.F. (1998). How do visual instructions influence the motor system? Novartis Found. Symp. *218*, 129–141.

Paus, T., Jech, R., Thompson, C.J., Comeau, R., Peters, T., and Evans, A.C. (1997). Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. J. Neurosci. *17*, 3178–3184.

Petrides, M. (1985). Deficits in nonspatial conditional associative learning after periarcuate lesions in the monkey. Behav. Brain Res. *16*, 95–101.

Pleger, B., Blankenburg, F., Bestmann, S., Ruff, C.C., Wiech, K., Stephan, K.E., Friston, K.J., and Dolan, R.J. (2006). Repetitive transcranial magnetic stimulation-induced changes is sensorimotor coupling parallel improvements of somatosensation in humans. J. Neurosci. *26*, 1945–1952.

Procyk, E., Tanaka, Y.L., and Joseph, J.P. (2000). Anterior cingulate activity during routine and non-routine sequential behaviors in macaques. Nat. Neurosci. *3*, 502–508.

Rizzo, V., Siebner, H.R., Modugno, N., Pesenti, A., Munchau, A., Gerschlager, W., Webb, R.M., and Rothwell, J.C. (2004). Shaping the excitability of human motor cortex with premotor rTMS. J. Physiol. *554*, 483–495.

Rossini, P.M., Barker, A.T., Berardelli, A., Caramia, M.D., Caruso, G., Cracco, R.Q., Dimitrijevic, M.R., Hallett, M., Katayama, Y., Lucking, C.H., et al. (1994). Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr. Clin. Neurophysiol. *91*, 79–92.

Rounis, E., Stephan, K.E., Lee, L., Siebner, H.R., Pesenti, A., Friston, K.J., Rothwell, J.C., and Frackowiak, R.S. (2006). Acute changes in frontoparietal activity after repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex in a cued reaction time task. J. Neurosci. *26*, 9629–9638.

Rushworth, M.F., Nixon, P.D., Wade, D.T., Renowden, S., and Passingham, R.E. (1998). The left hemisphere and the selection of learned actions. Neuropsychologia *36*, 11–24.

Rushworth, M.F.S., Johansen-Berg, H., Gobel, S.M., and Devlin, J.T. (2003). The left parietal and premotor cortices: motor attention and selection. Neuroimage *20* (Suppl. 1), S89–S100.

Schluter, N.D., Rushworth, M.F.S., Passingham, R.E., and Mills, K.R. (1998). Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements. A study using transcranial magnetic stimulation. Brain *121*, 785–799.

Schluter, N.D., Rushworth, M.F.S., Mills, K.R., and Passingham, R.E. (1999). Signal-, set-, and movement-related activity in the human premotor cortex. Neuropsychologia *37*, 233–243.

Schluter, N.D., Krams, M., Rushworth, M.F.S., and Passingham, R.E. (2001). Cerebral dominance for action in the human brain: the selection of actions. Neuropsychologia *39*, 105–113.

Scott, S.K., Holmes, A., Friston, K.J., and Wise, R.J. (2000). A thalamo-prefrontal system for representation in executive response choice. Neuroreport *11*, 1523–1527.

Seitz, R.J., Hoflich, P., Binkofski, F., Tellmann, L., Herzog, H., and Freund, H.J. (1998). Role of the premotor cortex in recovery from middle cerebral artery infarction. Arch. Neurol. *55*, 1081–1088.

Shimizu, T., Hosaki, A., Hino, T., Sato, M., Komori, T., Hirai, S., and Rossini, P.M. (2002). Motor cortical disinhibition in the unaffected hemisphere after unilateral cortical stroke. Brain *125*, 1896–1907.

Smith, S.M. (2002). Fast robust automated brain extraction. Hum. Brain Mapp. *17*, 143–155.

Sprague, J.M. (1966). Interaction of cortex and superior colliculus in mediation of visually guided behavior in the cat. Science *153*, 1544–1547.

Staudt, M., Grodd, W., Gerloff, C., Erb, M., Stitz, J., and Krageloh-Mann, I. (2002). Two types of ipsilateral reorganization in congenital hemiparesis: a TMS and fMRI study. Brain *125*, 2222–2237.

Strens, L.H., Fogelson, N., Shanahan, P., Rothwell, J.C., and Brown, P. (2003). The ipsilateral human motor cortex can functionally compensate for acute contralateral motor cortex dysfunction. Curr. Biol. *13*, 1201–1205.

Tanji, J. (2001). Sequential organization of multiple movements: involvement of cortical motor areas. Annu. Rev. Neurosci. *24*, 631–651.

Toni, I., Ramnani, N., Josephs, O., Ashburner, J., and Passingham, R.E. (2001). Learning arbitrary visuomotor associations: temporal dynamic of brain activity. Neuroimage *14*, 1048–1057.

Toni, I., Shah, N.J., Fink, G.R., Thoenissen, D., Passingham, R.E., and Zilles, K. (2002). Multiple movement representations in the human brain: an event-related fMRI study. J. Cogn. Neurosci. *14*, 769–784.

Ward, N.S., Newton, J.M., Swayne, O.B., Lee, L., Thompson, A.J., Greenwood, R.J., Rothwell, J.C., and Frackowiak, R.S. (2006). Motor system activation after subcortical stroke depends on corticospinal system integrity. Brain *129*, 809–819.

Woolrich, M.W., Ripley, B.D., Brady, M., and Smith, S.M. (2001). Temporal autocorrelation in univariate linear modeling of FMRI data. Neuroimage *14*, 1370–1386.