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Exploring the contributions of premotor and parietal cortex to spatial compatibility using image-guided TMS

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Functional brain imaging studies have demonstrated increased activity in dorsal premotor and posterior parietal cortex when performing spatial stimulus–response compatibility tasks (SRC). We tested the specific role of these regions in stimulus–response mapping using single-pulse transcranial magnetic stimulation (TMS). Subjects were scanned using functional magnetic resonance imaging (fMRI) prior to the TMS session during performance of a task in which spatial compatibility was manipulated. For each subject, the area of increased signal within the regions of interest was registered onto their own high-resolution T1-weighted anatomic scan. TMS was applied to these areas for each subject using a frameless stereotaxic system. Task accuracy and reaction time (RT) were measured during blocks of compatible or incompatible trials and during blocks of real TMS or sham stimulation. On each trial, a single TMS pulse was delivered at 50, 100, 150, or 200 ms after the onset of the stimulus in the left or right visual field. TMS over the left premotor cortex produced various facilitatory effects, depending on the timing of the stimulation. At short intervals, TMS appeared to prime the left dorsal premotor cortex to select a right-hand response more quickly, regardless of stimulus–response compatibility. The strongest effect of stimulation, however, occurred at the 200-ms interval, when TMS facilitated left-hand responses during the incompatible condition. Facilitation of attention to the contralateral visual hemifield was observed during stimulation over the parietal locations. We conclude that the left premotor cortex is one of the cortical regions responsible for overriding automatic stimulus–response associations.

Keywords: Compatibility; Transcranial magnetic stimulation; Choice reaction time; Facilitation; Dual-route model; Response selection

Introduction

The ability to deliver adaptive motor responses to surrounding sensory stimuli is a fundamental aspect of intelligent behavior. In the study of human performance, a phenomenon called stimulus–response (S–R) compatibility has inspired research for over half a century. Given a set of stimuli and a set of permissible responses, some S–R pairs are more efficient than others (Fitts, 1952). Spatial S–R compatibility (SRC) occurs when the overlap of some spatial dimensions of stimuli and responses determines faster and more accurate responses (Fitts and Seeger, 1953). For instance, when subjects are instructed to respond with the left hand to left lateralized stimuli and with the right hand to right lateralized stimuli (compatible condition), subjects are faster than when instructed to respond with the left hand to right lateralized stimuli and with the right hand to left lateralized stimuli (incompatible condition). The difference in reaction times (RT) between compatible and incompatible conditions is about 40–80 ms and is called the compatibility effect (Proctor and Reeve, 1990).

A general consensus in the cognitive literature is that two response selection processes are available during spatial S–R compatibility tasks (Kornblum et al., 1990). A direct, automatic response selection process is the expression of long-term, overlearned S–R mappings (i.e., right-hand response to a right-sided stimulus), whereas an indirect (or intentional) task-dependent process is based on short-term S–R mappings defined by task instructions (Hommel and Prinz, 1997). In compatible response conditions, both long-term and short-term S–R mappings are in agreement, whereas in incompatible response conditions, short-term S–R mappings (i.e., left-hand responses to right-sided stimuli) are in opposition to long-term ones (i.e., right-hand responses to right-sided stimuli).

When compatible and incompatible responses are mixed in the same block of trials, such that subjects are instructed on a trial-to-trial basis whether to respond compatibly or incompatibly, compatible responses are slowed so that the compatibility effect disappears or is considerably reduced (Hommel and Prinz, 1997). A widely

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accepted explanation for this phenomenon is that, when compatible and incompatible trials are mixed, the automatic, direct response selection process based on long-term S–R transformations would determine a large number of errors for incompatible trials and thus is actively suppressed. Hence, only short-term, task-dependent S–R transformations are available for response selection.

In a series of imaging studies, we have described the functional anatomy of the compatibility effect (Iacoboni et al., 1996, 1997, 1998). Dorsal premotor and superior parietal areas are associated with greater blood flow changes during incompatible responses than compatible ones, with the greatest blood flow changes occurring in the left hemisphere (see also Dassonville et al., 2001; Schumacher and D'Esposito, 2002). We investigate here the interplay of cognitive processes that might occur in the cortical regions we have previously described. To do so, we used transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI). The combined use of TMS and fMRI is a powerful approach to the study of the neural processes instantiating cognitive mechanisms in the human brain (Paus and Wolforth, 1998; Rushworth et al., 1997). The use of fMRI allows the visualization of activated cortical areas in an individual subject. The use of TMS with frameless stereotaxy allows the targeting of the areas activated in that given individual at precise time points during the fast sensory–motor transformations occurring in spatial S–R compatibility tasks.

To test the role of dorsal premotor and superior parietal areas in the cognitive mechanisms of S–R transformations, we applied TMS over dorsal premotor and posterior parietal areas previously shown by fMRI to be activated in individual subjects. Capitalizing on the exquisite temporal resolution of single-pulse TMS, we applied TMS over dorsal premotor and superior parietal areas at different time points from stimulus presentation, in order to map the temporal unfolding of direct, long-term and indirect, short-term S–R transformations.

Materials and methods

Subjects

A total of 26 neurologically normal right-handed subjects gave informed consent to participate in this study, which was approved by the UCLA Medical-IRB. Screening questionnaires were used to exclude volunteers who had a neurological, psychiatric, or serious medical history, who took medications or stimulants, or in whom TMS is contraindicated (Wassermann, 1998). A neurological examination was also conducted on each volunteer to assure the absence of neurological impairment. The data from two of the subjects were excluded: one fell asleep repeatedly during the task and the other tended to respond too early, that is, before the onset of the visual stimulus (approximately 40% of trials). The remaining 24 subjects included 16 women and 8 men with a mean age of 24.3 years (range: 19–45). Four subjects returned for a second TMS session, resulting in a total of 28 sets of behavioral data obtained during TMS. All subjects were naive to the purpose of the experiment.

General procedures and study design

Each subject attended one fMRI session and at least one TMS session. fMRI scans obtained while subjects performed the S–R compatibility task were analyzed to locate subject-specific regions of interest within the posterior parietal and dorsal premotor cortex (Dassonville et al., 2001; Iacoboni et al., 1996, 1997, 1998; Schumacher and D'Esposito, 2002). In some subjects, sites could be identified in all four regions of interest. These regions were later targeted for stimulation in a separate TMS session while subjects performed the S–R compatibility task.

The design of the TMS study involved within-subject manipulation of real versus sham TMS, stimulus–response compatibility, visual field, and the time between onset of the visual stimulus and delivery of the TMS pulse (SOA). Separate blocks of compatible and incompatible stimulus–response pairings were crossed with separate blocks of real and sham TMS. Visual field and SOA varied within blocks within each subject. Each block also contained baseline trials in which no pulse was delivered. The sham stimulation blocks were included to control for the nonspecific effects of TMS (e.g., air- and bone-conducted auditory stimulation, static sensation of coil on head).

The procedures for most sessions involved real TMS over more than one location and sham stimulation over only one of these locations. The selection of the sham location was counterbalanced across subjects. However, we do not report here the data from real TMS at locations that could not be matched within each subject with data from sham stimulation at the same location. This approach was chosen to match as closely as possible the general experimental conditions for the real and sham stimulation.

fMRI session

Functional scans were acquired while subjects performed four 32-s blocks of task alternating with 32-s blocks of rest. Two (n = 19) or four (n = 7) functional runs were acquired for each subject. Within each scanning run, the S–R compatibility factor was blocked so that two task blocks in a row were performed under compatible instructions and two were performed under incompatible instructions. The order of instructions was counterbalanced across runs and across subjects.

Each block of trials contained 16 trials. Visual stimuli were presented under computer control through magnet-compatible goggles or on a projection screen. Stimuli were presented in white on a black background. A fixation cross appeared 1 s before the onset of the first lateralized stimulus and remained present in the center of the screen throughout the block of trials. A small outline of a square was presented in the left (eight trials) or right (eight trials) visual field for 50 ms every 2 s. Subjects responded using the left or right index finger. They were instructed to place their index fingers on each of two response buttons to maintain their gaze on the fixation cross throughout the task block and to respond by pressing the appropriate button as quickly as possible after the onset of a square in the left or right visual field. They were instructed to press the button on the same side as the stimulus (compatible) in half of the blocks and on the opposite side to the stimulus (incompatible) in the other half of the blocks. Fast but error-free performance was emphasized. Response times and accuracy were recorded in the scanner using a magnet-compatible response box for the first six subjects. Due to technical difficulties, data were collected outside the scanner for the remaining subjects prior to performing the task inside the scanner. For each subject, a t test comparing the reaction times from compatible and incompatible trials was conducted (after removing trials with incorrect responses) to ensure the presence of a behavioral S–R compatibility effect. The median reaction times for each condition during the fMRI session were analyzed using a repeated-measures ANOVA with two factors: S–R compatibility and visual field.

Images were acquired using a GE 3.0-T MRI scanner with an upgrade for echo-planar imaging (EPI) (Advanced NMR Systems, Inc.). A 2D spin-echo image (TR = 4000 ms; TE = 40 ms, 256 × 256 matrix, 4 mm thick, 1-mm spacing) was acquired in the sagittal plane to allow prescription of the slices to be obtained in the remaining sequences and to ensure the absence of structural abnormalities in the brain. Two or four functional EPI scans [gradient-echo, TR = 4000 ms, TE = 70 ms (3 subjects) or TE = 25 ms (21 subjects), 64 × 64 matrix, 26 slices, 4 mm thick, 1-mm spacing] were acquired for a duration of 5 min and 4 s each covering the whole brain. The data from the first 16 s were excluded to allow the signal to stabilize. A high-resolution structural T2-weighted echo-planar image (spin-echo, TR = 4000 ms, TE 54 ms, 128 × 128 matrix, 26 slices, 4 mm thick, 1-mm spacing) was acquired coplanar with the functional images. A high-resolution structural T1-weighted image of the entire head was also acquired in each subject to allow for stereotaxic localizing of the stimulation targets. This was a 1-NEX 3D SPGR image acquired with parameters TR = 24 ms, TE = 4 ms, field-of-view: 250 × 250 × 150 mm, and 1.5-cm-thick slices.

A rigid-body linear registration algorithm (Woods et al., 1998) was used first to align the functional scans for each subject with the T2-weighted EPI structural image and then to align the T2-weighted EPI structural image with the T1-weighted whole-head structural image. Finally, the T2-aligned functional scans were realigned with the T1-weighted whole head image by combining the transformation matrices of the previously described image registration processes (Woods et al., 1998). Functional data were then spatially smoothed using an in-plane, Gaussian filter for a final image resolution of 8.7 × 8.7 × 8.6 mm.

Three statistical contrasts were performed for each subject. These contrasts were performed on a voxel-by-voxel basis for each subject by constructing a full ANOVA model to partial out the variance associated with each of four factors: Run, Activity, Condition, and Block. Run refers to the functional scanning run and had two to four levels, depending on the number of scans acquired from a particular subject. Activity refers to the alternating task and rest blocks. Condition refers to the instruction to perform compatible or incompatible mapping, and Block refers to the repetition of each condition (two blocks of each). The dependent variable was the sum of the signal intensity across each block (Iacoboni et al., 1999). The first contrast, Compatible Map, contrasted task minus rest for the compatible condition only (collapsing across Run and Block). The second contrast, Incompatible Map, contrasted task minus rest for the incompatible condition only (collapsing across Run and Block). The third contrast, Direct Comparison, contrasted the incompatible task minus the compatible task (collapsing across Run and Block).

Each of the three contrast maps was examined to identify the voxel containing the greatest signal intensity within our regions of interest in the posterior parietal cortex and the dorsal premotor cortex bilaterally. In order to identify peaks in as many of the four regions as possible for each subject, no statistical thresholding was used for this procedure. Priority was given to peaks identified in the Incompatible Map. If no peak could be identified within a region of interest, then a peak in that region was selected from the Direct Comparison map, if and only if it was also present in the Compatible Map (n = 7 cases).

TMS session

TMS pulses were delivered through a small figure-8 coil (2.5-cm coil diameter) enclosed in a rectangular plastic case and attached to a high-speed MES-10 stimulator (Cadwell Laboratories, Inc.).

Motor-evoked potentials (MEPs) were recorded from the first dorsal interosseus (FDI) muscle of each hand using Ag/AgCl surface electrodes. Signal was amplified and bandpass-filtered at 0.3–3000 Hz (Grass Instruments, Astro-Med, Inc.), digitized at 1000 Hz (NI-DAQ board, National Instruments), and recorded for offline analysis in 100-ms epochs triggered by the TMS pulse (Labview, National Instruments). Recordings were obtained during the thresholding procedure (see below) and also throughout the entire TMS session to permit identification of any trials in which stimulation over the posterior parietal or dorsal premotor cortex might produce an MEP that could interfere with manual responses.

The intensity of stimulation was calibrated for each subject to 110% of the resting motor threshold for the FDI muscle of the right hand. The coil was oriented to produce an induced current in the anterior-medial direction, perpendicular to the central sulcus (Brasil-Neto et al., 1992) over the location of the hand representation in the primary motor cortex. Motor threshold was determined at the beginning of the session following conventional criteria, that is, the minimum stimulator output that produced a motor-evoked response of at least 50 μV in 5 out of 10 trials (Rossini et al., 1994).

Stimulation sites were targeted using the BrainSight Frameless system for frameless stereotaxy (Rogue Research Inc., Montreal, Canada). Subjects sat in a chair adjusted to their height and with their head in a chin rest to minimize head movements. Landmarks on the subject's head were coregistered with landmarks on the structural MRI to allow tracking of the position of the TMS coil with respect to the underlying cortex. The coordinates of activity in the subject's regions of interest obtained from the functional fMRI session were marked on the structural MRI. For stimulation of each region, the figure-8 coil was first held flat and tangential to the scalp, minimizing the distance between the coil and the cortex. The coil was then guided so that an imaginary line drawn from the point of intersection of the two coils and perpendicular to the plane of the coil casing would intersect the targeted coordinates. During sham stimulation blocks, the coil was positioned so that the casing made contact with the subject's head at the same point as for real TMS, producing a steady tactile sensation. However, the coil was oriented at 90° to the normal stimulating position, with the long edge of the plastic casing touching the head so that when a pulse was delivered through the coil, its highly focal area of effectiveness was aimed into the air. Thus, the sham stimulation controlled for nonspecific effects of the lateralized auditory stimulus during the pulse (Lisanby et al., 2001).

The behavioral task was similar to that used during functional imaging, with some minor differences related to the timing of the trials. The presentation of visual and magnetic stimuli and the recording of responses were controlled using Superlab Pro software (Cedrus Corporation). Visual stimuli were presented on a computer screen positioned at eye level at a distance of 57 cm from the subject's head. A white fixation cross (width and height 1.5 angular degrees) appeared in the center of the screen at the beginning of each block of trials and remained present throughout the block. A small white outline of a square (width and height 1.5 angular degrees) was presented in the left or right visual field at an eccentricity of 12 angular degrees for 50 ms every 5 s. At least 5 s elapsed between each trial to reduce the possibility of interference between successive TMS pulses. Subjects responded using the left and right buttons of a response box designed to record response times with an accuracy of 4 ms (Cedrus Corporation). Subjects were instructed to place their left and right index fingers on the corresponding left and right response buttons to maintain their gaze on the fixation cross and to respond by pressing the appropriate button in response to the onset of a square in the left or right visual field. They were instructed to respond as quickly as possible but without making mistakes.

The task was presented in 4-min blocks of 50 trials. S–R compatibility (SRC) was manipulated across blocks in a counterbalanced order across subjects. Each subject received blocks of TMS over one or more sites, with the order of sites (and of the sham stimulation blocks) counterbalanced across subjects. Two factors were manipulated within each block: the time elapsed between onset of the visual stimulus and onset of the TMS (or sham) pulse (SOA), and visual field. The SOAs used were 50, 100, 150, and 200 ms. SOA and visual field were fully crossed to produce the same number of trials for each possible combination, presented in a random order. For 10 trials of each block (randomly intermixed), no pulse was presented. These no-TMS trials served as a baseline control condition. Response accuracy and reaction time were recorded for later analysis.

Trials were coded as correct-response trials or error trials. Error trials included incorrect responses and late (>800 ms) or no responses. The error data were analyzed using the Wilcoxon signed ranks test to compare the compatible and incompatible conditions. On a handful of trials, subjects responded to the visual stimulus before the TMS pulse. These data as well as the error trials were excluded from the analysis of reaction times.

The data from the TMS sessions were analyzed in two steps. First, we evaluated the nonspecific effects of a TMS pulse on reaction times by calculating each subject's median RT for the baseline (no stimulation) trials and the stimulation trials (at all SOAs) for all four locations. These data were entered into a two-way ANOVA with factors location (left parietal, right parietal, left premotor, right premotor) and stimulation (no vs. yes). The same analysis was conducted on the data from the sham stimulation blocks. Second, we evaluated the specific effects of TMS as compared with sham stimulation at each location. For these analyses, we entered the median RT for each subject in each condition, excluding the baseline (no TMS) trials. A five-way ANOVA was performed with factors: stimulation (TMS vs. sham), location, S–R compatibility, SOA, and visual field. Significant interactions of stimulation with location were followed up with lower level ANOVAs and direct t tests. Statistical significance for the t tests was set at $P = 0.05$ with Bonferroni correction for multiple comparisons. The main effect of S–R compatibility was taken to demonstrate induction of a spatial stimulus–response compatibility effect in this experimental protocol.

Results

fMRI session

Few errors were made, as expected given the emphasis on accuracy in the task instructions. The average percent total errors was 1.6% (median 1.6%). More errors were made in the incompatible trials (average 2.6%; median 3.1%) than the compatible trials (average 0.6%; median zero; $P = 0.001$).

The reaction time data from the six subjects tested inside the scanner showed significant compatibility effects ($P < 0.0003$), comparable to those obtained in the remaining subjects which were acquired before entering the scanner. Therefore, the results presented here are based on the pooled data acquired from all subjects. A two-way ANOVA on the reaction time data showed the expected main effect of compatibility (compatible faster than incompatible, $P = 0.0001$). It also revealed an interaction between compatibility and visual field ($P = 0.03$), such that subjects responded faster to a stimulus in the right visual field (182 ms) than in the left visual field (198 ms) in the compatible condition but not in the incompatible condition (right: 251 ms; left: 248 ms).

TMS thresholding

All subjects tolerated the stimulation procedures well and did not complain of any side effects. The average resting motor threshold was 77.2% of stimulator output (SD 13.8).

Errors during TMS

Few errors were made in the TMS session. The average percent total errors was 3.1% (median 1.9%). More errors were made during blocks of trials that included real TMS and incompatible stimulus–response mapping (average 4.1%) than in the other three blocks of trials (TMS-compatible: 2.4%, $P = 0.007$; sham-compatible: 2.9%, $P = 0.06$; sham-incompatible: 3.0%, $P = 04$; uncorrected). The breakdown of error rates by group is shown in Table 1.

Nonspecific effects of stimulation on reaction times

The overall effect of TMS was to slow reaction times (mean 290 ms, SD 34) when compared with the baseline trials (mean 275 ms, SD 37), regardless of site of stimulation [$F(1, 24) = 20.3$, $P < 0.0001$]. Interestingly, the same effect was observed in the sham stimulation blocks (stimulation trials: mean = 298 ms, SD 41; baseline trials: mean = 272 ms, SD 42). Again, only the main effect of stimulation was significant [$F(1,24) = 17.8$, $P = 0.0003$]. Thus, nonspecific factors involved in stimulation appear to play an important role in producing the RT increases observed in response to TMS.

Direct comparison of reaction times during real TMS versus sham stimulation

The true measure of the specific effects of TMS on functionally distinct cortical regions was in the direct comparison between real TMS and sham stimulation. The protocol was effective in

Table 1
Mean error rates (%) for each block of trials

	TMS-Comp	Sham-Comp	TMS-Incom	Sham-Incom
Left parietal	1.4	1.4	2.9	2.5
Right parietal	1.6	2.5	4.1	2.5
Left premotor	4.6	5.0	4.6	3.3
Right premotor	2.1	2.9	5.4	3.9

Comp, compatible blocks; Incom, incompatible blocks.

producing a spatial S–R compatibility effect. The main effect of S–R compatibility was highly significant, showing longer reaction times during spatially incompatible (mean 322, SD 53) compared with compatible (mean 271 ms, SD 43) mapping conditions [$F(1,24) = 124$, $P < 0.0001$].

A five-way interaction was found between stimulation, location, S–R compatibility, SOA, and visual field [$F(9,72) = 2.5$, $P = 0.02$]. The four-way interaction of stimulation, compatibility, SOA, and visual field was tested for each location separately and was found to be significant only for the group who received left premotor stimulation [$F(3,15) = 6.4$, $P = 0.005$]. The general trend for the left premotor group was toward faster reaction times in the TMS condition relative to the sham condition [main effect of stimulation: $F(1,5) = 5.3$, $P = 0.07$]. The results of the t tests for individual conditions in the left premotor group are shown in Table 2. The reaction time differences for the real TMS versus sham stimulation conditions are plotted in Fig. 1 for each combination of compatibility, SOA, and visual field. When real TMS was delivered over the left premotor cortex at a late stage in the response preparation process, it hastened the execution of left-hand responses to right visual field stimuli ($P = 0.03$, corrected). There was also a tendency for real TMS to speed all right-hand responses when stimulation was given early after the onset of the visual stimulus. However, this tendency did not reach our criterion for statistical significance when Bonferroni correction was applied ($P = 0.16$, corrected).

The five-way ANOVA also revealed a three-way interaction between stimulation, location, and visual field [$F(3, 24) = 3.4$, $P = 0.04$]. The two-way interaction of stimulation and visual field was significant for the left parietal ($P = 0.04$) and right parietal ($P = 0.03$) locations (see Fig. 2). When the left parietal group received right visual field stimuli, there was a slight trend toward faster reaction times during real TMS relative to sham stimulation, although this effect did not reach significance after Bonferroni correction ($P = 0.16$, corrected). The effect of stimulation was not significant for left visual field stimuli ($P = 0.99$, corrected). In contrast, for the right parietal group, TMS tended to produce slower reaction times to right visual field stimuli ($P = 0.06$, corrected). The effect of stimulation was not significant for left visual field stimuli ($P = 0.52$, corrected).

Discussion

The present study combined fMRI and TMS to investigate the neural processes underlying spatial S–R transformations. Three main results were observed: first, late TMS led to faster incompatible responses to right visual field targets over the left premotor cortex. This is the most robust empirical result observed in this study and the one most relevant to the dual route model of response selection for spatial S–R transformations (Hommel and Prinz, 1997; Kornblum et al., 1990). Second, TMS over parietal sites affected attention to the two visual fields. Third, early TMS over the left premotor cortex showed a trend toward speeding up right-hand responses, regardless of the type of S–R transformation required. This result is reliable only if uncorrected for multiple comparisons and will have to be confirmed. We think, however, that it is worth some discussion, in that it may provide some additional information useful for a better understanding of the mechanisms at play during S–R transformations.

Table 2
Uncorrected p values for direct contrast between real TMS and sham stimulation over the left premotor location

	50 ms	100 ms	150 ms	200 ms
C-left	0.13	0.30	0.14	0.12
C-right	0.01	0.02	0.11	0.91
I-left	0.02	0.01	0.33	0.77
I-right	0.14	0.25	0.50	0.002[a]

[a] Significant after Bonferroni correction. C, indicates compatible S–R mapping; I, incompatible S–R mapping; left, left visual field presentation; right, right visual field presentation.

Facilitation of incompatible responses by left premotor TMS

TMS over left premotor cortex led to faster left-hand responses to a right visual field stimulus. This effect cannot be explained by inhibition of right-hand responses, or we should have seen slower right-hand responses in response to left-visual field targets. We interpret the facilitation of incompatible left-hand responses within the dual-route model of S–R mapping. Fig. 3 represents graphically the hypothetical rate of increased activation of long-term and short-term S–R mappings. Long-term S–R mapping have steeper slopes of activations than short-term ones. The long-term S–R mapping rapidly reaches threshold for response during compatible trials. During incompatible trials, early activation of long-term S–R compatible mappings would show decay, such that short-term S–R incompatible mappings with their slower rate of activation can actually reach threshold for motor response earlier than long-term compatible S–R mappings.

How might facilitation of incompatible responses occur? TMS might inhibit long-term S–R mapping, such that the short-term S–R incompatible mapping does not have to compete with the automatic response mapping during incompatible responses. A study of motor-evoked potentials revealed that stimulus location primes activity in the primary motor cortex contralateral to the spatially compatible response hand and may also inhibit activity in the ipsilateral motor cortex (Sturmer et al., 2000). This effect is observed mainly for MEPs evoked from the left hemisphere. By this reasoning, the role of the left premotor cortex at late stages of response selection might be to enhance activity in left primary motor cortex while actively inhibiting activity in the right primary motor cortex. If TMS were to disrupt this function, the right motor cortex would be released from inhibition, allowing earlier buildup of activation in response to the short-term S–R mapping.

Our data, however, are not entirely consistent with this interpretation, in that they do not show increased RT for compatible blocks. If TMS disrupts the function of left premotor cortex, it should also reduce its enhancing effect on the left primary motor cortex. This would result in slowed RT during compatible blocks, which we did not observe. Moreover, it has long been known that inhibiting long-term S–R mappings experimentally by mixing compatible and incompatible trials results in slower compatible responses but does not affect RT for incompatible trials (Hommel and Prinz, 1997).

A second means by which the observed effect might be obtained is through facilitation of short-term S–R mapping. Stimulation of the left premotor cortex might increase the rate of activation of short-term S–R mapping, resulting in shorter reaction times (Fig. 3; dotted line). That the effect was observed for TMS over left premotor cortex is consistent with a wealth of data from

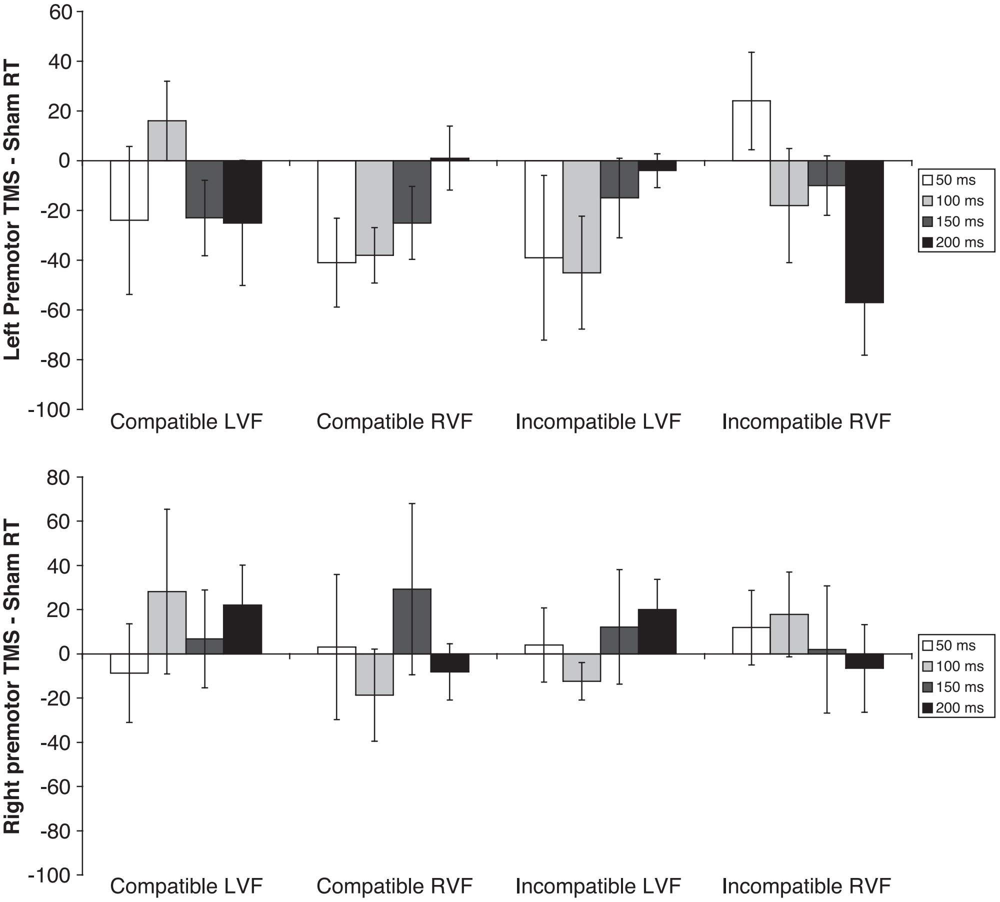

Fig. 1. Difference between reaction times obtained during real TMS and sham stimulation over left premotor cortex (top panel) and right premotor cortex (bottom panel). For the left premotor cortex, the facilitation of reaction time (RT) during incompatible (left hand) responses to right visual field stimuli was significant after Bonferroni correction (P = 0.03). For the right premotor cortex, no interactions involving stimulation were significant. Error bars represent standard error.

single cell recording studies and lesions studies in the monkey (Passingham, 1993). Those studies showed that the dorsal premotor cortex is a critical region for associating sensory stimuli and motor responses, particularly in response to context-specific, short-term mappings. Moreover, some previous neuroimaging studies revealed the left dorsal premotor cortex to be more associated than the right one with increased activity during incompatible S–R mappings.(Iacoboni et al., 1996, 1997, 1998; but see also Dassonville et al., 2001).

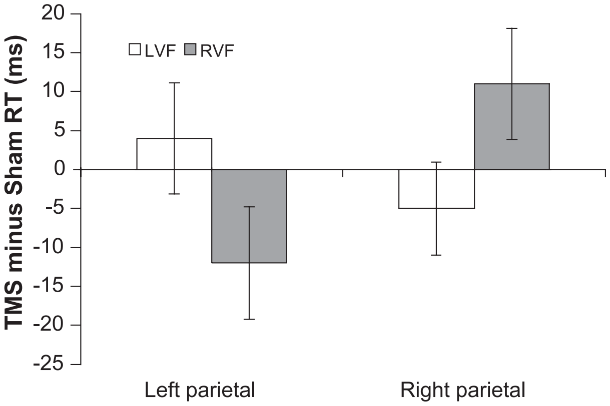

Fig. 2. Effect of TMS (as compared with sham stimulation) over the parietal cortex on choice reaction times to stimuli presented in the left or right visual field. Opposite effects were observed in the response to right visual field stimuli for TMS over the left and right parietal cortex.

This model alone, however, is insufficient to account for one unexpected element of our results, namely, that right-hand responses were not also facilitated by TMS over the left premotor cortex. A further specification is required: that the observed effect results from the interaction of facilitated short-term incompatible mapping with enhanced processing of visual stimuli in the contralateral hemifield. Single cell studies have indeed shown stimulus-dependent and response-dependent activity in dorsal premotor neurons during spatial compatibility tasks in nonhuman primates (Crammond and Kalaska, 1994). Thus, the facilitatory effect observed here may result from additive effects on speed of stimulus encoding in the visual hemifield contralateral to the stimulated premotor cortex and on efficacy of short-term S–R mappings.

In the present study, TMS had facilitative effects on reaction time. Previous studies, however, have demonstrated disruptive effects of TMS over left premotor cortex on manual choice reaction time. Using a choice reaction time task, Schluter et al. (1998, 1999) found increased reaction times for both hands when TMS was delivered between 100 and 180 ms after visual stimulus onset over the left premotor cortex and increased reaction times

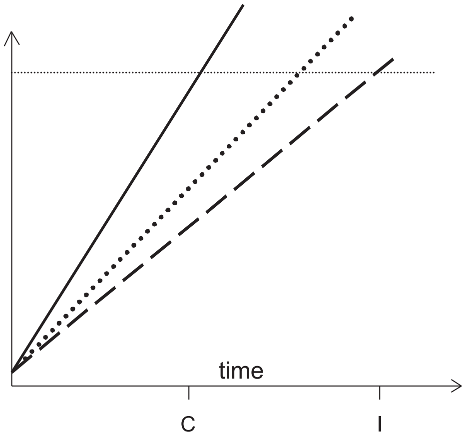

Fig. 3. Schematic depiction of the effect of TMS on S–R mapping within the context of the dual-route model. The x-axis represents time, and the y-axis represents the intensity of response-related activity supplied by each mapping. The dotted horizontal line represents the threshold for emitting a response. Solid line: long-term (automatic/direct) response route; dashed line: short-term (context-controlled/indirect) response route. C indicates the time at which activity fed by long-term mapping reaches threshold. This corresponds to the normal reaction time under compatible conditions. I indicates the time at which activity fed by the short-term mapping reaches threshold. Under incompatible conditions, the long-term route must be suppressed in order to prevent an early, incorrect response and allow time for the short-term route to reach threshold. Dotted line: hypothetical facilitation of the short-term route by stimulation of the left premotor cortex. This effect was observed for the response to right visual field stimuli only, suggesting a need for further modification of this model.

for the left hand when TMS was delivered over right premotor cortex.

We have compared our study with the previous studies by Schluter et al. (1998, 1999) in considering different explanations for the contrasting effects of TMS. The use of different choice reaction time tasks (nonspatial arbitrary S–R mapping vs. S–R mapping defined by spatial compatibility) appears unlikely to provide an adequate account of the difference in results. In the previous studies, the effects on reaction time were calculated by comparing TMS trials with no-TMS baseline trials. Nonspecific effects of stimulation were tested by comparing these results with the results obtained using TMS over a functionally "silent" cortical location, rather than with a sham stimulation condition as we used here. Nevertheless, we were able to perform a reasonably direct comparison of our data with the data obtained in the previous studies by selecting out the data from the compatible trials as if they were data obtained from any choice reaction time task and then comparing reaction times for TMS trials with reaction times for no-TMS trials. We found that TMS over left premotor cortex at 200 ms increased reaction times for the left hand only ($P = 0.001$, uncorrected), whereas TMS at 200 ms over right premotor cortex increased reaction times for the right hand only ($P = 0.002$, uncorrected). There was no evidence that TMS over premotor cortex disrupted performance with the contralateral hand. Moreover, since increased reaction times were observed for both hands in the sham stimulation condition relative to no-stimulation trials, the absence of disruption of the RTs for the contralateral hand during real TMS implies a facilitative effect. We conclude from this comparison that we are far from a full understanding of the factors that interact to determine whether stimulation of a particular brain region will have a facilitative or inhibitory effect on behavior.

Other studies have also found facilitative effects of TMS on reaction times. In a recent preliminary report on TMS over the supplementary motor area (Osswald et al., 2003), train of pulses over the supplementary motor area resulted in faster reaction times during a condition in which subjects had to reverse the S–R mapping rules of an overlearned manual response task. Similarly, a study of saccadic reaction times showed that TMS over the prefrontal cortex results in an increase in the number of express saccades (Muri et al., 1999). The authors made a reasonable argument that the prefrontal cortex exerted an inhibitory effect on the superior colliculi, which effect was disrupted by TMS, thereby releasing express saccades from inhibition. An alternative explanation is that stimulation of this region had a direct facilitative effect on the cortex, which shortened saccadic reaction times. This latter explanation is consistent with the generally facilitative effect of TMS observed in the present study.

Although subjects gained experience with the spatial–compatibility task over the course of the study, it seems unlikely that task practice could be responsible for the effects observed here. A recent study of S–R mapping showed that the effects of TMS over frontoparietal regions on reaction time were influenced by learning (Osswald et al., 2003). However, that study involved arbitrary mapping of finger responses onto a set of abstract visual stimuli, whereas the S–R mapping rules used in the present study were based on dimensional overlap (spatial location) between the stimulus and response. Indeed, dimensional overlap is a hallmark of stimulus–response compatibility tasks. Psychophysical studies indicate that the behavioral effect of stimulus–response compatibility does not change over time, even with several hundreds of trials (Dutta and Proctor, 1992; Proctor and Dutta, 1993). Moreover, our previous neuroimaging work showed that the cerebral blood flow changes related to extensive practice effects do not interact with the blood flow changes related to spatial compatibility (Iacoboni et al., 1996). On these grounds, we conclude that practice effects are unlikely to be a confounding factor in this study. The TMS effects described here relate to the role of premotor cortex in a stimulus–response compatibility task. A description of the functional contribution of the dorsal premotor cortex during arbitrary stimulus–response mapping awaits further research.

Attention effects produced by parietal TMS

The second effect we observed was associated with the two parietal sites. When compared to sham, TMS over the parietal sites determined faster RT for contralateral stimuli, and slower RT for ipsilateral ones, regardless of S–R mapping rules. This effect was stronger for stimulation of the left hemisphere and did not interact with the time of stimulation.

We interpret this finding within the context of the recent literature on the neural systems underlying spatial attention. The importance of the posterior parietal cortex in controlling spatial attention has been amply demonstrated in early neuropsychological and neuroimaging studies (see Mesulam, 1981; Nobre, 2001; Yantis and Serences, 2003, for reviews). A recent critical review of the literature suggests that attention is controlled by a top-down system for directing attention to a particular location, subserved by a dorsal frontoparietal network, and a bottom-up system for reorienting attention to unattended stimuli, subserved by a ventral frontoparietal network (Corbetta and Shulman, 2002). The top-down system is specialized for directing attention to the contralateral visual field, whereas the bottom-up system is strongly lateralized to the right hemisphere. The top-down system, which is activated when attention is directed to a particular spatial location, shows great overlap with the regions implicated in spatial working memory (Corbetta et al., 2002).

In the present study, TMS reduced reaction times to contralateral stimuli relative to ipsilateral stimuli. This is consistent with the hypothesis that stimulation modulated activity in the top-down attentional network. Initially, the onset of the visual stimulus would have drawn attention to the corresponding visual field, presumably implicating both systems. The top-down system would remain active, representing the location of the stimulus throughout the trial while the correct response is mapped onto the stimulus according to the current mapping rule. The relative increase in RT to stimuli in the ipsilateral hemifield may be explained by interhemispheric competition models of spatial attention (Kinsbourne, 1987), according to which enhanced attention to one side of space determines reduced attention to the other.

Interestingly, our data reveal the greatest effects of TMS for right visual field stimuli. TMS over the right parietal cortex might have inhibited left parietal activity, resulting in reduced attention to the right visual field. In contrast, TMS over the left parietal cortex predominantly enhanced attention to the right visual field without reliably impairing attention to the left visual field. An explanation for this difference may lie in the leftward bias of spatial attention observed in neurologically normal subjects, termed “pseudoneglect” (Bowers and Heilman, 1980). Stimulating the left parietal cortex may simply bring the two hemispheres into balance, thereby enhancing responses to the right visual field without impairing responses to the left visual field.

Facilitation of right-hand responses by left premotor TMS

The third effect we observed was an early facilitation over the left premotor cortex for right-hand responses, regardless of S–R mapping rule. This early facilitation is in line with an earlier study using TMS (Leocani et al., 2000), in which corticospinal excitability was tracked at multiple points in time between cue and response in a choice reaction time task. The authors found preferential activation of the left primary motor cortex early on in the time before response-related activity starts to build. The early facilitation observed in the present study was specific to stimulation of the left premotor cortex, consistent with this interpretation.

It appears that TMS over left premotor cortex early after cue onset facilitates the execution of responses made with the right hand. This facilitation does not change the accuracy of responses but might take the form of improving the efficiency of the pathways involved in executing a command to move the right index finger. Thus, it becomes effective only after the appropriate stimulus–response mapping has been completed.

Nonspecific effects of stimulation

Other options for controlling for the nonspecific effects of stimulation include real TMS over a behaviorally “silent” location, such as the midline parietal region (Schluter et al., 1998, 1999), or producing an auditory click by discharging the TMS coil into the air without making contact with the subject’s head. In the present study, however, the strong interfering effect of sham stimulation relative to the baseline (no stimulation) trials points to the importance of controlling for the general effects of lateralized tactile and auditory stimulation when testing for the specific effects of TMS.

The comparatively strong nonspecific interference effects observed here are likely due to the relevance of spatial position in this particular S–R compatibility task. Subjects knew that the side of the stimulation click did not determine the hand with which they were supposed to respond, yet they were sensitized to the possible interfering effects of lateralized stimuli since spatial compatibility was the rule that governed the appropriate response. Moreover, unlike in previous studies of TMS effects on manual responses, we completely lateralized the responses, associating each hand with a different response, rather than using two different response options performed by the same hand. In other words, there was high “set-level” compatibility (Kornblum et al., 1990) between the irrelevant lateralized auditory stimulus and the cued response. It seems reasonable to hypothesize, therefore, that the presence of lateralized stimulation pulses induced a shift to a more cautious response strategy, perhaps increasing the threshold for responding.

Recall that the typical compatibility effect of 40–80 ms that has been reported in the cognitive psychology literature is obtained under conditions of blocked compatible versus incompatible trials. In blocked tasks, compatible reaction times arise from the faster activation of long-term S–R mappings, whereas incompatible reaction times are slower (and error rates higher) due to competition. Note, however, that our blocked trials may take on some of the characteristics of mixed trials when subjects cannot predict from one trial to the next whether the lateralized auditory click will be compatible or incompatible with the visual field in which the imperative stimulus will be presented. This predicts a smaller overall compatibility effect, just as reported in the literature for blocks of mixed compatibility trials. We tested this prediction by calculating the difference in compatible and incompatible reaction times during the fMRI session (in which TMS never occurred) and during the randomly presented baseline (no stimulation) trials from the TMS session. These were 60 and 12 ms, respectively, consistent with our interpretation that the presence of lateralized irrelevant auditory stimuli during task performance influenced subjects’ criteria for responding.

Conclusion

Our data add to the growing evidence for the occurrence of facilitating effects of TMS on cortical function. Facilitation of manual or saccadic reaction times has been demonstrated in several earlier studies during single-pulse (Muri et al., 1999; Topper et al., 1998), dual-pulse (Wipfli et al., 2001), or high-frequency (Cappa et al., 2002; Mottaghy et al., 1999; Osswald et al., 2003; Topper et al., 1998; Wassermann et al., 1999) stimulation. We found three different kinds of TMS-induced facilitation in this study: an early motor facilitation in left premotor cortex for right-hand responses, an attentional facilitation over the two parietal sites, and a late ‘cognitive’ facilitation of short-term S–R mappings. Thus, it seems that TMS-induced facilitation may be observed across a variety of functional domains. The variations in stimulation and experimental parameters that determine whether TMS will be inhibitory or facilitatory are still unclear and an answer to this question lies outside the scope of this paper. The present study quite clearly emphasizes the importance of nonspecific factors in modulating behavioral responses to stimulation. The most original contributions of our study are substantially two: first, the left dorsal premotor cortex is a cortical area relevant to short-term S–R mappings; and second, short-term S–R mappings seem to have a relatively slow time course, given that TMS was effective on them only at a 'late' time point of stimulation.

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