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**Research Report**

# Evaluating frontal and parietal contributions to spatial working memory with repetitive transcranial magnetic stimulation

Massihullah Hamidi\*, Giulio Tononi, Bradley R. Postle

University of Wisconsin-Madison, USA

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**ABSTRACT**

Functional neuroimaging studies have produced contradictory data about the extent to which specific regions of the frontal and the posterior parietal cortices contribute to the retention of information in spatial working memory. We used high frequency repetitive transcranial magnetic stimulation (rTMS) to assess the necessity for the short-term retention of spatial information of brain areas identified by previous functional imaging studies: dorsolateral prefrontal cortex (dlPFC), frontal eye fields (FEF), superior parietal lobule (SPL) and intraparietal sulcus (IPS). 10 Hz rTMS spanned the 3-s delay period of a spatial delayed-recognition task. The postcentral gyrus (PCG) was included to control for any regionally non-specific effects of rTMS. The only regionally-specific effect was a significant decrease in reaction time when rTMS was applied to SPL. Additionally, rTMS lowered accuracy to a greater extent when applied to left than to right hemisphere, and was more disruptive when applied contralaterally vs. ipsilaterally to the visual field in which the memory probe was presented. Although seemingly paradoxical, the finding of rTMS-induced improvement in task performance has a precedent, and is consistent with the idea that regions associated with spatial sensory-motor processing make necessary contributions to the short-term retention of this information. Possible factors underlying rTMS-induced behavioral facilitation are considered.

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**1. Introduction**

Performance of spatial working memory tasks is associated with robust, sustained activity in many regions, including the dlPFC (Leung et al., 2002, Corbetta et al., 2002, D'esposito and Postle, 1999), FEF (Curtis and D'esposito, 2006, Postle, 2006a, Corbetta et al., 2002, Postle and Hamidi, 2007), SPL (Curtis, 2006), and IPS (Curtis, 2006, Postle, 2006a, Schluppeck et al.,

2006). However, there is controversy about the functions supported by each of these areas, particularly the dlPFC (Leung et al., 2002, Passingham and Rowe, 2002, Lebedev et al., 2004, Postle, 2005, Watanabe, 1996). Some ascribe a storage function to this frontal region (Courtney et al., 1998, Leung et al., 2002), whereas others emphasize roles in such control mechanisms as attentional selection (Passingham and Rowe, 2002, Lebedev et al., 2004), controlling interference

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\* Corresponding author. 1202 West Johnson Street, Madison, WI 53706, USA. Fax: +1 608 262 4029.

E-mail address: [mhamidi@wisc.edu](mailto:mhamidi@wisc.edu) (M. Hamidi).

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; dlPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; SPL, superior parietal lobule; IPS, intraparietal sulcus; fMRI, functional magnetic resonance imaging; PCG, postcentral gyrus; ITI, intertrial interval; RT, reaction time; IAF, individual resting alpha frequency

(Knight et al., 1999, Postle, 2005), preparing a response (Jiang and Kanwisher, 2003, Schumacher et al., 2003) and anticipating a reward (Watanabe, 1996). To date, neuroimaging techniques such as functional magnetic resonance imaging (fMRI) have failed to resolve conclusively this controversy, in part because they only provide correlational evidence about brain-behavior relationships (Logothetis and Pfeuffer, 2004, Fellows et al., 2005). Using rTMS to temporarily alter neural processing, however, offers one means of testing hypotheses of necessity (Pascual-Leone et al., 1999, Walsh and Rushworth, 1999).

In this study we applied rTMS during the entire delay period of a spatial delayed-recognition task to evaluate the necessity of the areas summarized above in the short-term retention (storage) of information. Based on previous studies by our group and others, we assumed that, for critical regions, rTMS would have the effect of inducing a “virtual lesion,” and thus produce decrements in performance (e.g., Postle et al., 2006, Sack and Linden, 2003, Feredoes et al., 2007). Because previous studies have shown that 10 Hz rTMS has functionally-relevant effects (Feredoes et al., 2007, Kennerley et al., 2004), we also used a stimulation frequency of 10 Hz. Due to practical and safety considerations limiting how long a rTMS experimental session can last, our study was divided into two experiments with two groups of subjects. Both experiments involved the same experimental procedures, with the exception that different areas were targeted with rTMS. In Experiment 1, the dlPFC and SPL were targeted, with the area representing the leg in the primary somatosensory cortex of the postcentral gyrus (PCG) serving as a control area. In Experiment 2, the FEF and IPS were targeted. Because a different group of subjects participated in Experiment 2, the PCG was once again targeted to serve as a control. Finally, our counterbalanced study design allowed us the opportunity to assess the whether there exist differential effects of rTMS with respect to hemisphere of stimulation or visual field of stimulus presentation.

## 2. Results

Presented here is a summary of the significant results from the two experiments. Full details of the results (e.g., full reporting of ANOVAs) are available in the Supplementary Materials. We computed accuracy in terms of mean percentage correct and the signal detection measures of  $d'$  and criterion. Because the results were the same for both indices of performance, signal detection measures, too, are only presented in the Supplementary Materials.

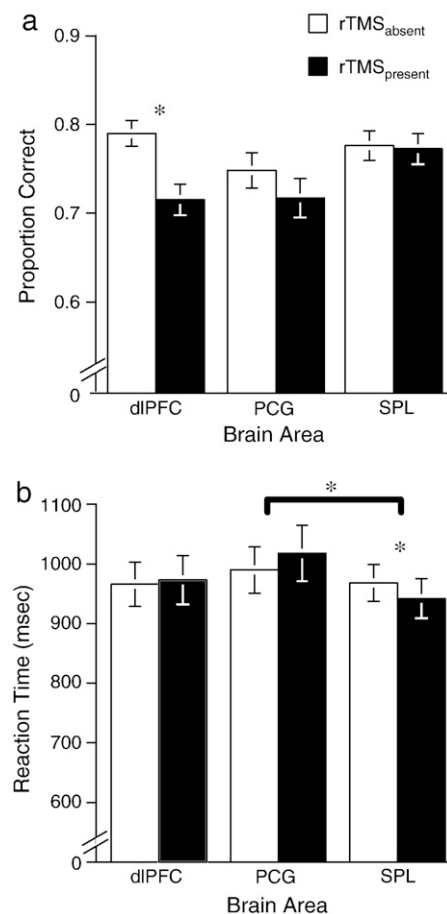
ANOVAs included 3 levels of the factor Brain Area (frontal region, parietal region, PCG), 2 levels of rTMS (present, absent), 2 levels of hemisphere of stimulation (left, right), and 2 levels of visual hemifield of probe presentation (ipsilateral, contralateral to hemisphere targeted). When significant interactions suggested region-specific effects, we evaluated evidence for these by calculating the rTMS effects for each region (e.g.,  $rTMS_{\text{absent}} - rTMS_{\text{present}}$  for dlPFC) and comparing these region-specific effects versus the analogous effect for PCG with t-tests. The same procedure was followed for hemi-

sphere-of-stimulation and visual-hemifield-of-presentation analyses.

### 2.1. Experiment 1

#### 2.1.1. Accuracy

Experiment 1 revealed that rTMS had a general effect of decreasing accuracy (main effect of rTMS [ $F(1,28)=8.73$ ;  $p<0.01$ ]; Fig 1a), more so when applied to the left than the right hemisphere (Hemisphere  $\times$  rTMS interaction [ $F(1,28)=9.84$ ;  $p<0.01$ ]). There was also a Brain Area  $\times$  rTMS interaction [ $F(2,56)=4.34$ ;  $p<0.05$ ], reflecting the fact that rTMS had its largest effect on dlPFC, a smaller effect on PCG, and a still smaller effect on SPL. However, follow-up tests indicated that the rTMS effect of neither dlPFC nor SPL was significantly different from that of the (control area) PCG [dlPFC:  $t(29)=-1.52$ ; n.s., SPL:  $t(29)=0.87$ ; n.s.]. There was also a Brain Area  $\times$  Visual Hemifield interaction [ $F(2,56)=4.34$ ;  $p<0.05$ ], and a marginal Visual Hemifield  $\times$  rTMS  $\times$  Hemisphere of stimulation interaction [ $F(1,28)=3.89$ ;  $p=0.06$ ]. The latter was driven by the fact that accuracy was decreased for contralateral stimuli only when rTMS was applied to the left hemisphere [ $t(29)=-5.22$ ;  $p<0.0001$ ; Supplementary Fig. S1].



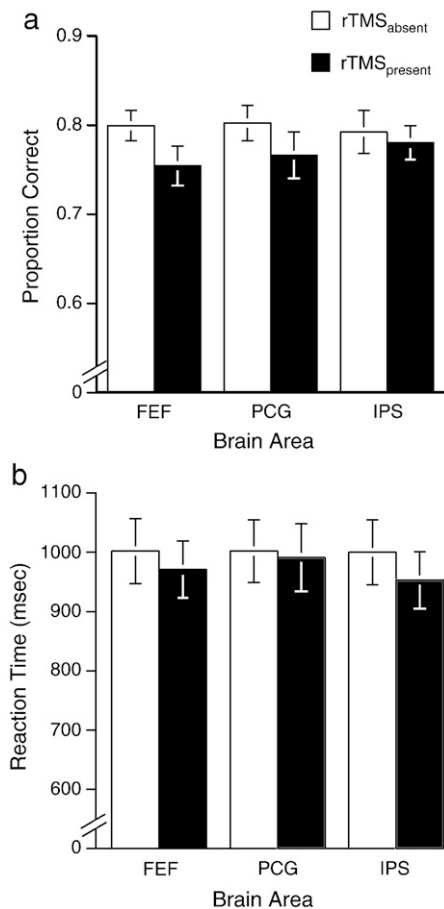
**Fig. 1 – Experiment 1: performance by brain area. Accuracy, in proportion correct, (a) and RT (b) in Experiment 1, collapsed over hemisphere and visual hemifield. Error bars indicate standard errors. \* $p<0.05$ .**

### 2.1.2. Reaction time

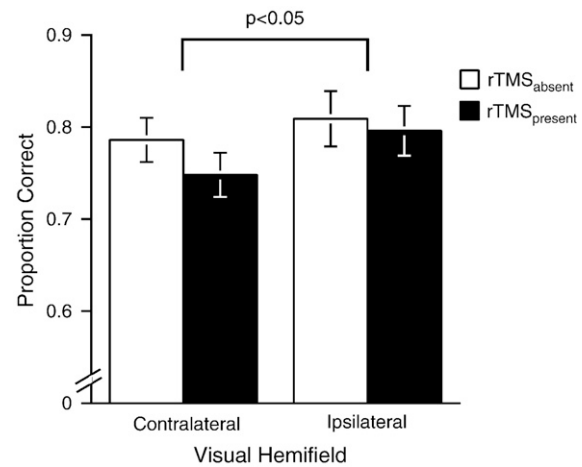
With reaction time (RT) there was no main effect of rTMS [ $F(1,28)=0.05$ ; n.s.], however, there was a region-specific effect (Brain Area  $\times$  rTMS interaction [ $F(2,56)=4.78$ ;  $p<0.05$ ]; Fig 1b), with rTMS of the SPL producing faster responses (compared to rTMS effect on PCG:  $t(29)=-2.30$ ;  $p<0.05$ ). Within SPL, the pairwise comparison of RT in the rTMS<sub>absent</sub> versus the rTMS<sub>present</sub> condition was significant [ $t(29)=-2.29$ ;  $p<0.05$ ]. The only relevant effect involving visual hemifield of probe presentation was that, relative to ipsilateral stimuli, response to trials in which stimuli appeared contralaterally was faster with left hemisphere rTMS and slower with right hemisphere rTMS [ $t(28)=3.12$ ;  $p<0.005$ ].

## 2.2. Experiment 2

The results of Experiment 2 revealed that rTMS had an overall effect of decreasing accuracy [ $t(23)=2.82$ ;  $p<0.01$ ] and RT [ $t(23)=2.68$ ;  $p<0.05$ ; Fig 2]. It also had the general effect of lowering accuracy when probe stimuli appeared contralateral to the hemisphere to which rTMS was applied [ $t(23)=2.49$ ;  $p<0.05$ ; Fig 3]. There were neither region-specific (all



**Fig. 2 – Experiment 2: performance by brain area. Accuracy, in proportion correct, (a) and RT (b) in Experiment 2, collapsed over hemisphere and visual hemifield. Error bars indicate standard errors.**



**Fig. 3 – Experiment 2: rTMS effect on visual hemifield. Accuracy, collapsed over brain area and hemisphere. Error bars indicate standard errors.**

$F_s<1.41$ ) nor hemisphere-specific (all  $F_s<0.29$ ) effects on either accuracy or RT.

## 3. Discussion

### 3.1. Effects of rTMS on accuracy

In both experiments, rTMS produced a general decrease in accuracy over all the brain areas we tested, with no difference between experimental and control areas. Although the absence of any region-specific effects was not expected, there were nonetheless selective effects of rTMS on accuracy, with Experiment 1 producing a hemisphere-specific effect and Experiment 2 producing a visual hemifield-specific effect (both of which are discussed further below). Of primary theoretical interest, however, were the effects of rTMS on RT.

### 3.2. Parietal cortex is sensitive to delay-period rTMS — a role in storage

Our principal goal in this study was to use rTMS to assess whether any specific brain area plays a necessary role in the storage of items in spatial working memory. We will start with the SPL. The role of the parietal lobes in spatial processing is well established, as is evidence for sustained activity in SPL and IPS during spatial working memory tasks (Schluppeck et al., 2006, Postle, 2006a). Furthermore, with damage to the parietal lobe, in addition to the expected neglect syndrome, there is evidence that patients have difficulty with working memory tasks even when stimuli are restricted to the intact visual hemifield (Ferber and Danckert, 2006). In the present study, we found that rTMS of the SPL resulted in a significant decrease in RT. Non-significant trends in this direction were also seen with rTMS of FEF and IPS. Abstracted from the specific pattern of the data, the fact that performance on a task requiring the short-term retention of spatial information was sensitive to rTMS of SPL is consistent with a role for this region in the short-term retention of spatial

information (Postle and Hamidi, 2007, Postle, 2006b). It is nevertheless the case, however, that our a priori prediction was that delay-period rTMS would produce a *decrement* in performance. It is noteworthy, in this regard, that another study has also found that delay-period rTMS to SPL, but not PFC, can speed RT in a delayed-recognition task (Luber et al., 2007). This phenomenon also generalized beyond working memory with another study describing improvement in a task of spatial perception with rTMS of SPL (Klimesch et al., 2003). Why do these studies and the current study produce facilitation, whereas other studies employing rTMS to the SPL have produced disruption of behavior (Postle et al., 2006, Feredoes et al., 2006, Terao and Ugawa, 2006)?

### 3.3. Facilitation with rTMS

That the improvement in RT with rTMS of SPL was not accompanied by a corresponding decline in accuracy rules out the possibility that the effect resulted from a simple speed-accuracy tradeoff. There are at least two other possible explanations that might account for the speeding of RT with rTMS. One is that improved performance with rTMS may be the result of a shift in resources available in cognitive processing. If two areas have reciprocally inhibitory influence on each other, goes the reasoning, the disruption of one area can result in hyperactivity of the second area (Théoret et al., 2003). The second possible explanation is that rTMS, when delivered at the right frequency, interacts with a region's endogenous activity in a manner that improves performance (Klimesch et al., 2003). Amplitude and phase dynamics of oscillations in the  $\alpha$ -band (8–13 Hz) of the EEG correlate with performance on a variety of cognitive tasks, including tests of attention and working memory (Palva and Palva, 2007). Because the amplitude of parietal lobe delay-period  $\alpha$ -band activity increases monotonically with memory load (Jensen et al., 2002, Busch and Herrmann, 2003), rTMS interactions with oscillations in the  $\alpha$  band might underlie the improved performance observed here and in previous studies (Luber et al., 2007, Klimesch et al., 2003). Consistent with this explanation, Klimesch et al. (2003) delivered parietal rTMS at various frequencies and found that performance on a mental rotation task improved only when rTMS was delivered at a frequency slightly above the peak individual resting  $\alpha$  frequency (IAF) of each subject. The fact that our stimulation frequency of 10 Hz is approximately equal to the mean IAF in young adults fits with this idea. More directly relevant to the present results, Luber et al. (2007) used this logic to apply rTMS at 1, 5, and 20 Hz to the dlPFC and parietal cortex during the delay period of a working memory task. They found that application of rTMS speeded RT only when applied to the parietal cortex at 5 Hz, which they suggested was effective because it is a subharmonic of the average IAF. Of course it is possible that rTMS may lead to facilitation through many other mechanisms, including effects on other frequency bands (Brignani et al., 2008; Fuggetta et al., 2008) or downstream effects in brain areas distal to the point of stimulation (Valero-Cabré et al., 2005, Ferrarelli et al., 2004). Without measurement of the neurophysiological effects of SPL rTMS, it is not possible to determine the mechanism behind the facilitation observed in this study.

### 3.4. Failure to find evidence of a role for dlPFC in storage

Although compared to the rTMS<sub>absent</sub> condition we did observe a decrease in accuracy with rTMS applied to the dlPFC, a similar decrease was also present when targeting the PCG control area. Therefore, we cannot rule out the possibility that the effect of dlPFC rTMS on accuracy resulted from regionally non-specific effects of rTMS. That the change in accuracy or RT with application of rTMS did not differ between dlPFC and PCG suggests that the dlPFC may not have a necessary role in the short-term retention of spatial information. Although one must always be cautious when interpreting null results, several factors support this interpretation. First, the sample size of 30 subjects in Experiment 1 does not support a low-sensitivity argument. Second, the present null result for the dlPFC replicates analogous results from previous studies that have targeted the dlPFC and SPL with rTMS (Luber et al., 2007, Postle et al., 2006, Feredoes et al., 2007). One study employed two versions of a verbal working memory task, one requiring subjects to simply retain a list of letters in the order presented, the other requiring them to reorder the list into alphabetical order during the delay period (Postle et al., 2006). In that study, accuracy decreased with rTMS of dlPFC only when subjects were required to manipulate the items in memory. rTMS of SPL, in contrast, impaired performance in both task conditions. Finally, the present null results are also consistent with evidence that patients with frontal lobe lesions show intact performance on tasks requiring the short-term retention of information (D'Esposito and Postle, 1999).

### 3.5. Effects on hemisphere of stimulation

Previous experiments have provided evidence of hemispheric asymmetry during tasks of working memory (D'Esposito et al., 1998, Hester et al., 2007, Muri et al., 2000). The overall pattern of these findings is such that with spatial working memory right hemisphere activity dominates, whereas with verbal and other non-spatial working memory tasks the left hemisphere dominates. Although we did not find evidence of region-specific hemispheric asymmetry in the effects of rTMS, we did find, in Experiment 1, a general effect of rTMS decreasing accuracy to a greater extent when targeting the left versus the right hemisphere. This finding runs counter to the idea that the right hemisphere dominates storage of spatial information.

### 3.6. Relationship with visual hemifield of stimulus presentation

Spatial perception is organized in a cross-hemispheric manner according to visual hemifield. Similarly, there is evidence that spatial working memory is organized in a retinotopic manner (Hagler and Sereno, 2006, Kastner et al., 2007). In the present study we observed a relationship between change in performance with rTMS and the visual hemifield in which the probe stimulus appeared. Experiment 2 produced a lateralized visual-field specific effect on accuracy in that subjects had lower performance on trials in which probe stimuli appeared in the visual hemifield contralateral to the brain hemisphere

targeted. It is noteworthy that Experiment 2 targeted the FEF and IPS, both areas involved in oculomotor control. To our knowledge, such an effect of contralateral delay-period rTMS has not been described before, although there is previous evidence of parietal rTMS disrupting perception of targets in the visual hemifield contralateral to the hemisphere of stimulation (Valero-Cabré et al., 2006). There were also visual-field specific effects in Experiment 1, although those results were more complex. Nonetheless, the fact that in both experiments there is a significant difference in the effect of rTMS based only on the part of the visual field in which the probe stimulus appears supports the idea that spatial working memory is organized retinotopically.

### 3.7. Relation to other TMS studies

Previous rTMS studies of spatial working memory have used a variety of TMS and behavioral procedures, which complicates comparison with our findings. For example, many studies have used sham TMS as a control (as opposed to rTMS of a cortical control area) and therefore blocked trials by TMS condition, both differences that may influence the outcome of a study. Furthermore, there have been several studies that have used either a behavioral task (e.g., n-back) or a TMS stimulation procedure (e.g., “preconditioning” designed to suppress cortical activity for tens of minutes) that do not allow for isolation of any single component process of working memory (e.g., encoding vs. storage vs. response selection). Here we focus only on studies that restricted rTMS to the delay period. Two early studies of spatial delayed response described selective impairment of accuracy with TMS delivered to the PFC but not parietal cortex (Brandt et al., 1998, Muri et al., 2000). The seeming disparity with the present results may be attributable to procedural factors. These two studies used a delayed-response procedure, which affords anticipatory motor preparation during the delay period (e.g., Takeda and Funahashi, 2002). The delayed-response procedure also produces relatively greater activation of PFC, whereas the delayed-recognition procedure (which we used in the present study) produces relatively greater activity of the SPL (Curtis et al., 2004). More recently, Koch et al. (2005) found a slowing of RT with rTMS (at 25 Hz for the first 300 ms of a 3.3 s delay period) to either dlPFC or SPL in a task that required memory for the sequential order of spatially defined stimuli. Interpreted from the perspective of our findings, the effect of rTMS to dlPFC reported by Koch et al. may be attributable to the role of this region in the processing of the sequential order of target stimuli (e.g., Knutson et al., 2004).

### 3.8. General conclusions

We found evidence for SPL playing a necessary role in retention of spatial information in working memory, whereas we did not find such evidence for dlPFC. This is in accordance previous fMRI studies that have found spatial-specific SPL activity, but have not found evidence for domain-specific sustained delay-period activity in dlPFC (reviewed in Postle, 2006b). It is also consistent with previous proposals that spatial working memory behaviors may rely heavily on mechanisms of spatial perception, spatial attention, and

motor preparation, which in turn are dependant on dorsal-stream regions posterior to the PFC (e.g., Postle, 2006b).

The nature of the region-specific rTMS effect, an improvement of performance, is inconsistent with a disruption account of rTMS. Although analogous effects have been described before with cognitive tasks, the mechanism behind it is not known. Direct investigation of hypothesized interactions between rTMS and endogenous neuronal oscillations (Luber et al., 2007, Klimesch et al., 2003) may prove to be fruitful in understanding when rTMS will have disruptive versus facilitatory effects on performance.

## 4. Experimental procedures

### 4.1. Subjects

54 young adults (28 male, mean age=22.7 [S.D.=4.4]) were recruited from the University of Wisconsin community. 30 (16 male) participated in Experiment 1, 24 (12 male) in Experiment 2. Subjects did not have any psychiatric or neurological conditions, as determined by a psychiatrist or clinical psychologist who administered a structured psychiatric diagnostic interview (MINI, Sheehan et al., 1998) and mood assessment (HAM-D, Hamilton, 1960). All subjects were compensated monetarily.

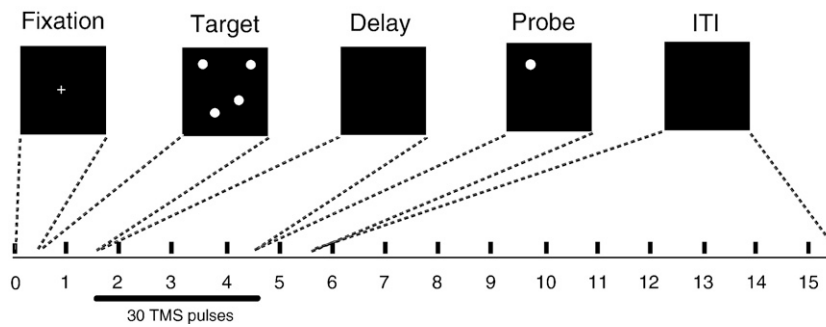
### 4.2. Behavioral task

In both experiments the delayed-recognition task began with a 500-ms presentation of a central fixation cross, followed by a 1-s presentation of a target set: four white circles of 1.4° of visual angle, each located at a random location within a different quadrant of the screen. This was followed by a 3-s delay, after which a probe circle identical to the targets was presented for 1 s. The probe appeared in each of the four quadrants with  $p=.25$ , and at one of the target locations with  $p=.5$ . If the probe was non-matching, the distance from the nearest target circle location varied between 3.33 and 4.74° of visual angle. Subjects were instructed to make a yes/no response with a hand-held button box (right thumb/left thumb) as to whether the location of the probe circle matched that of any of the four target circles (Fig. 4). Each trial was followed by a 10-s intertrial interval (ITI) consisting of a blank, dark screen.

The behavioral task was administered in 4 runs of 12 trials each per target brain area with trials blocked by brain area. The experimental factor of principle theoretical interest was rTMS, which was present or absent for an equal number of trials in each block, and randomized orthogonal to the factor of probe validity. This yielded 48 trials per brain area targeted, 24 with rTMS, 24 without. Of these, in 12 trials probe stimuli were presented ipsilateral to stimulation, 12 contralateral to stimulation.

### 4.3. Anatomical MRI

Whole-brain images were acquired with a 3 T scanner (GE Signa VH/I). High resolution T1-weighted images (256 sagittal slices, 0.5 mm×0.5 mm×0.8 mm) were obtained for all participants. This scan was used to reconstruct a 3-dimensional image of each subject's head, which was used to target rTMS. Because the principal function of the imaging data for this study was to



**Fig. 4 – Schematic of the spatial delayed-recognition task in this study. rTMS (10 Hz, 110% motor threshold, corrected) was delivered throughout the entire 3-s delay period. Task procedures were the same in both Experiment 1 and Experiment 2.**

provide a guide for the targeting of rTMS, the analyses were performed at the single-subject level, on the unsmoothed, native-space data. Transforming a subject's data into a "normalized" atlas space would not be appropriate with this approach for the simple reason that rTMS can only be applied to a subject's brain in its "native" configuration. For a similar approach, see Herwig et al. (2003).

For seven subjects in Experiment 1, prior to the TMS session, functional scans were acquired while they performed the delayed-recognition task. For these subjects targets were chosen based on the presence of delay-period fMRI activity during the task. Because the results between fMRI-guided and anatomy-guided rTMS did not differ<sup>1</sup>, we combined the data here for analysis. fMRI data acquisition and analysis procedures are detailed in the Supplementary Materials.

#### 4.4. rTMS session

##### 4.4.1. rTMS procedures

For the rTMS session the subject was seated comfortably and his/her head was localized in space via an infrared-based frameless stereotaxy system (eXimia Navigated Brain Stimulation (NBS), Nexstim, Helsinki, Finland). The TMS coil was also fitted with infrared-reflecting beacons, thereby permitting us to accurately target specific regions of the brain.

Prior to the start of the behavioral task, resting motor threshold was determined for each subject as measured by an electromyograph (Bagnoli Handheld EMG System, Delsys, Boston, MA). For the first 12 subjects of Experiment 1, stimulation for all brain regions targeted during the experimental task occurred at 110% of motor threshold. For the remainder of the subjects, we modified the stimulation intensity by starting at 110% of motor threshold, but accounting for scalp-to-cortex distance for each brain area targeted (Stokes et al., 2005). The correction generally resulted in a minor change in stimulation intensity and there were no significant differences in rTMS effect between the two groups<sup>2</sup>.

<sup>1</sup> The 3-way ANOVA (Brain Area × rTMS × Targeting technique) was not significant for either accuracy [ $F(2,56)=0.78$ ; n.s.] or RT [ $F(2,56)=1.37$ ; n.s.].

<sup>2</sup> The mean change in stimulation intensity was -4.18% of the maximum stimulator output. The 3-way ANOVA (Brain Area × rTMS × Stimulation Intensity Calculation technique) was not significant for either accuracy [ $F(2,56)=2.16$ ; n.s.] or RT [ $F(2,56)=1.92$ ; n.s.].

In both experiments, during rTMS<sub>present</sub> trials a 3-s train of 10 Hz rTMS (30 pulses) began with the offset of the target set. Because it is possible that rTMS-induced scalp sensations and muscle contractions can affect performance, prior to the start of the experiment, all subjects experienced 10 Hz stimulation. Care was taken to ensure that subjects were fully comfortable with rTMS at each brain area targeted. TMS was delivered with a Magstim Standard Rapid magnetic stimulator fit with a 70 mm figure 8 stimulating coil (Magstim Co., Whitland, U.K.).

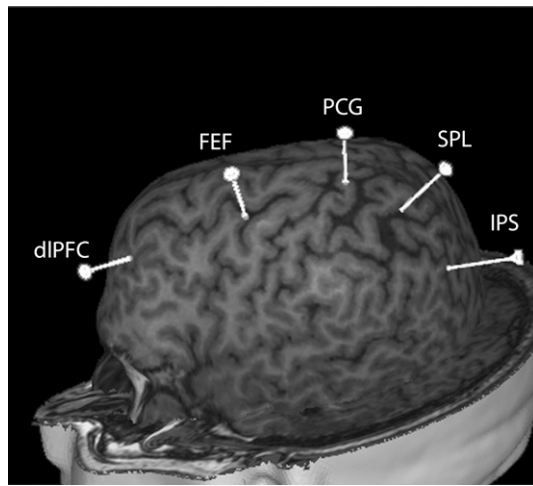
##### 4.4.2. rTMS controls

We used two levels of control in this study. The first level consisted of the half of the trials in each block during which rTMS was not applied. This allowed us to establish an estimate of the "baseline" performance for each subject by the following logic. Although our procedure was intended to target only the delay period, it is possible that the effects of rTMS may last beyond the duration of stimulation. Were this to happen, our estimate of the effect of delay-period rTMS could be contaminated by "spillover" effects on processes other than storage (e.g., encoding, response selection, etc.). Our randomized interleaving of rTMS<sub>present</sub> and rTMS<sub>absent</sub> trials controlled for this possibility by ensuring that any long-lasting effects of rTMS would also affect the latter trial types, and this hypothetical "spillover" effect would thereby be removed upon computing the difference between performance on rTMS<sub>absent</sub> and rTMS<sub>present</sub> trials<sup>3</sup>.

The second level of control was the inclusion of a brain area that was not expected to have a direct involvement in working memory—the area representing the leg in the primary somatosensory cortex of the PCG.

We used this approach rather than such alternatives as sham stimulation or stimulation over the vertex, for several reasons. First, although some sham coils attempt to simulate some of the side effects of TMS (such as the noise produced), the sensations they produce are not indistinguishable from

<sup>3</sup> A possibility that this procedure would not account for would be if the hypothetical "spillover" were differentially time-limited in different brain areas (e.g., spillover may affect encoding in rTMS<sub>absent</sub> trials in brain area X, but not brain area Y). To address this comparison of rTMS<sub>present</sub> trials across brain areas was also performed. The results, which were qualitatively similar to those reported here, are presented in the Supplementary Materials.



**Fig. 5 – Targets of rTMS.** For 23 subjects in Experiment 1 and all the subjects in Experiment 2, targets of rTMS were chosen based on individual brain anatomy, as illustrated on one subject's MRI scan by the white markers. The orientation of the marker indicates the orientation of the TMS-related magnetic field at that region. In Experiment 1, the dIPFC and SPL were experimental targets and the PCG was used as a control. In Experiment 2, the FEF and IPS were experimental targets and PCG, once again used as a control area.

real stimulation (Robertson et al., 2003). Thus, having a control brain area would allow us to account for all the non-specific superficial effects of rTMS such as scalp sensations and noise. Second, rTMS of a control area will reveal any regionally non-specific effects on performance that induction of current in the cortex might have. This is not necessarily true for rTMS of the vertex, for which cortical stimulation may be minimal.

#### 4.4.3. Target selection

Five brain areas (dIPFC, FEF, PCG, SPL and IPS) were targeted by rTMS across two experiments. Subjects were randomly assigned to receive rTMS of the left hemisphere or the right hemisphere, with the exception of the 7 subjects for whom rTMS was guided by fMRI (see below).

Because of safety concerns, the study was split into two experiments. In Experiment 1 the dIPFC, SPL, and PCG were targeted. In Experiment 2, the FEF, IPS and PCG were targeted (Fig. 5). Of the 30 subjects participating in Experiment 1, 18 received rTMS to the left hemisphere, 12 of the right. For 7 subjects (5 left hemisphere), rTMS was guided by individual brain activity as measured by fMRI. Areas of activation within dIPFC and SPL were chosen as targets of rTMS. For PCG, an area was chosen that did not include any significantly active voxels. rTMS targeting for the remaining 23 subjects was based on anatomy. The dIPFC target was identified as the middle frontal gyrus on the ventral bank of the superior frontal sulcus at the level of the sulcus frontalis medius (approximately at  $\pm 40, +45, +28$  atlas coordinates, Talairach

and Tournoux, 1988)<sup>4</sup>, a region corresponding to the border of Brodmann areas 9 and 46 (Petrides, 2000, Oliveri et al., 2001). The PCG target was chosen as an area immediately posterior to the central sulcus, close to the midline. SPL targets were chosen dorsal and medial to the intraparietal sulcus and posterior to the postcentral sulcus (corresponding to Brodmann area 7).

Of the 24 subjects who participated in Experiment 2, 12 had rTMS applied to the right hemisphere, 12 to the left. All targets were chosen based on anatomy. The FEF stimulation site was chosen as the rostroventral portion of the intersection of the superior frontal and precentral sulci. The PCG target was chosen in the same manner as described above. The IPS target was located at the medial bank of the IPS, at the level of the parieto-occipital fissure.

In both experiments the order of brain area stimulated was counterbalanced across the subjects.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.brainres.2008.07.008](https://doi.org/10.1016/j.brainres.2008.07.008).

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<sup>4</sup> For 7 subjects, because of excessive facial muscle contractions when targeting the ventral bank of the superior frontal sulcus, we stimulated the dorsal bank. Comparison of subjects with dorsal bank stimulation versus those with ventral bank stimulation revealed no differences in rTMS effect on accuracy [ $t(28)=1.35$ ; n.s.] or RT [ $t(28)=1.24$ ; n.s.].

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