Effects of 10 Hz rTMS on the Neural Efficiency of Working Memory

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Abstract

■ Working memory (WM) has been described as short-term retention of information that is no longer accessible in the environment, and the manipulation of this information for subsequent use in guiding behavior. WM is viewed as a cognitive process underlying higher-order cognitive functions. Evidence supports a critical role for PFC in mediating WM performance. Studies show psychomotor processing speed and accuracy account for considerable variance in neural efficiency (Ne). This study compared the relative effects of active and sham 10 Hz rTMS applied to dorsolateral prefrontal cortex (DLPFC) on indices of Ne in healthy participants performing a WM paradigm that models the association between WM load and task behavior [Sternberg, S. High-speed scanning in human memory. *Science, 153,* 652–654, 1966]. Previous studies identified a relationship between diminished Ne and impaired WM across a broad array of clinical disorders. In the present study, the authors predicted there would be a main effect of stimulation group (STM) on accuracy (SCR) and processing speed (RT), hence, Ne. We observed a main effect of STM for RT without an effect on SCR; even so, there was a robust effect of STM on Ne. ■

INTRODUCTION

Working memory (WM) has been described as short-term retention of information that is no longer accessible in the environment, and the manipulation of this information for subsequent use in guiding behavior (D'Esposito, Postle, & Rypma, 2000). WM is widely viewed as a cognitive process that underlies an array of higher order cognitive functions, such as reasoning (Rypma, Prabhakaran, Desmond, & Gabrieli, 2001), planning (Goel & Grafman, 1995), and problem solving (Duncan & Owen, 2000), for instance. Over the past few decades, such studies have developed a substantial body of convergent evidence that supports a critical role for prefrontal cortex (PFC) in mediating WM performance. For example, in a study aimed to identify the relationship between WM demand and task performance, Rypma, Berger, and D'Esposito (2002) found that task factors exert their effects largely during WM encoding. Subject factors' influence on task performance occurred mainly during WM retrieval. In an fMRI study (Rypma et al., 2002), subjects performed a WM task that required them to maintain from one to eight letters over a brief delay. Neural activity was measured during encoding, maintenance, and retrieval task phases. With increasing memory load, the researchers observed that RT increased and accuracy (SCR) decreased. Additionally, a decline in ventrolateral PFC (VLPFC) activation was seen during encoding, whereas dorsolateral PFC (DLPFC) activation increased during maintenance and retrieval. The authors concluded that VLPFC mediates WM storage and that DLPFC mediates memory organization processes that facilitate supra-capacity WM storage. Interestingly, high-performing subjects in toto showed less activation than low-performing subjects, suggesting that high performers utilized fewer neural resources in resolving task requirements. In comparison to low performers, such task performance could plausibly be seen as an example of greater neural efficiency (Ne). Even so, higher-scoring performers showed activation increases with increasing memory load during maintenance and retrieval in lateral PFC. Overall, low-performing subjects showed more activation than high-performing subjects, but high performers showed minimal activation increases in DLPFC with increasing memory load. The authors suggested that their results indicate that individual differences in Ne and cognitive strategy mediate individual differences in WM performance (Rypma et al., 2002). In a subsequent study comparing WM performance in younger and older adults, Rypma, Berger, Genova, Rebbechi, and D'Esposito (2005) used event-related fMRI to measure brain activity while younger and older adults performed an item-recognition task with set size varying between one and eight letters. Both groups experienced a decline in Ne indexed as RT increases and accuracy decreases with increasing memory set size. The authors also found related differences in neural activation with increasing memory set size in PFC. Analysis of individual subjects' performance relative to cortical activity

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suggested that speed and accuracy accounted for considerable variance in dorsal and ventral PFC activity during encoding and retrieval. The authors concluded that their results suggested support to a model of cognitive slowing in which processing rate is related to Ne (Rypma et al., 2005). In a similar vein, Altamura et al. (2007) used fMRI to dissociate the effects of Sternberg WM demands on DLPFC. The effect of varying loads of three, five, or eight letters on WM maintenance was determined by using two time delays (1 sec and 6 sec) between the letter set and the probe stimuli. The authors observed strongly activated DLPFC with load manipulation. Notably, regions of right DLPFC were exclusively affected by load. The authors concluded that their results suggested the possibility that top–down modulation of cognitive control during encoding or response to probe stimulus could be mediated by these areas (Altamura et al., 2007).

Increasingly, transcranial magnetic stimulation (TMS) is used as a research tool for mapping brain function and modification of neural processes during WM tasks that engage PFC. TMS has been shown to be a safe, noninvasive means of stimulating the awake and alert human cerebral cortex in carefully screened subjects (Wassermann, 1998). For instance, Koch et al. (2005) used a repetitive TMS (rTMS) approach to disambiguate the spatial distribution and reciprocal interactions of different regions of the parieto-frontal network in healthy human participants performing a spatial WM task. These researchers compared the effect of 25 Hz rTMS on neural activity within PFC and posterior parietal cortex (PPC) during the delay and decision phases of the task. Trains of rTMS at 25 Hz were applied to PPC, premotor cortex, and right DLPFC alternatively during the two phases. They found that TMS during the delay phase in both parietal cortex and DLPFC interfered with performance. When 25-Hz rTMS trains were applied during the decision phase, they observed interference in DLPFC, but not in PPC or premotor cortex. A local neural network subserving decisional processes and a second neural population functionally interconnected with PPC that was activated when spatial information was maintained temporarily in WM (Koch et al., 2005). Brandt, Ploner, Meyer, Leistner, and Villringer (1998) investigated the role of DLPFC and PPC in a visuospatial delayed-response task. Using high-frequency rTMS, the researchers interfered temporarily with cortical activity in DLPFC and PPC during the maintenance period in order to determine whether rTMS to DLPFC or PPC during maintenance affects accuracy of memory-guided saccades. Stimulation over DLPFC significantly impaired accuracy of amplitude and direction of saccades. They concluded that, within this network, DLPFC mediates the mnemonic representation and PPC with the sensory representation of spatially defined perceptual information (Brandt et al., 1998). Studies of the chronometrics of WM phase evolution have used TMS in conjunction with fMRI to induce a temporary lesion that is intended to interfere with task performance, hence, identifying a causal role for the targeted cortical region in mediating WM task performance. Such studies have shown that the effects of rTMS on cognitive performance are dependent on domain, experimental design, cortical target, stimulation frequency, timing, and duration of TMS application relative to the stage of task processing. Consequently, most studies of WM and the role of PFC have been aimed to identify whether and precisely when functional disruption of PFC would degrade WM performance. For example, Mull and Seyal (2001) aimed to determine whether transient functional disruption of DLPFC would impair performance in a WM task in which participants were shown sequences of letters and asked to decide if the letter just displayed was the same as the letter presented three trials back. Single-pulse TMS was applied over DLPFC between letter presentations. TMS to left DLPFC caused increased errors relative to controls. The authors concluded that their results supported the idea that DLPFC played a crucial role in this paradigm. Deleterious effects of TMS to LPFC on WM were also observed by Osaka et al. (2007) in a study using paired-pulse TMS. Albeit fewer in number, studies showing beneficial effects of TMS on WM have also observed a critical role for stimulation frequency and timing relative to the phase of task evolution. For example, individual power and peak frequency attributes of alpha band oscillations have been shown to predict performance on a WM task (Luber et al., 2007; Klimesch, Sauseng, & Gerloff, 2003). In a previous study, the present authors designed a combined EEG–TMS study of the interaction between WM Ne, alpha band oscillations, and 10 Hz rTMS applied to DLPFC prior to the onset of a Sternberg task (Anderson, Preston, & Silva, 2007). We predicted first that compared with sham active 10 Hz rTMS would significantly reduce psychomotor processing speed indexed as RT. Second, we predicted that improvement in RT would be associated with a 10-Hz rTMS induced increase in pretask alpha power and pretask alpha band phase synchrony. We identified a robust association between 10 Hz rTMS perturbed individual mean peak alpha frequency and alpha spectral phase synchrony on task performance.

Frequency and target-specific effects have also been observed in studies of cognitive domains other than WM: for example, enhancement of picture naming and posterior superior temporal cortex (Mottaghy, Sparing, & Topper, 2006); enhancement of episodic memory and left inferior PFC (Kohler, Paus, Buckner, & Milner, 2004); analogic reasoning and left DLPFC (Boroojerdi et al., 2001); mental rotation of 3-D objects and mesial frontal and right parietal cortex (Klimesch et al., 2003). Finally, Luber et al. (2007) showed that TMS could enhance WM. They predicted that healthy subjects' performance on a delayed match-to-sample task would be enhanced when TMS of 1, 5, or 20 Hz was applied to either left dorsolateral prefrontal or midline parietal cortex during the delay phase of the task. They found 5 Hz, but not 1 Hz or 20 Hz, stimulation to the midline parietal site during delay resulted in a significant decrease in RT without a corresponding decrease in accuracy

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(SCR). In a second experiment, 5 Hz rTMS was applied to the parietal site during the delay or during presentation of the probe. RT enhancement occurred only with stimulation during the delay phase. The authors concluded TMS could enhance WM performance under specific conditions of time, target, and stimulation frequency.

The present study was designed to determine the effects of 10 Hz rTMS directed to right or left DLPFC on psychomotor processing speed (RT), accuracy (SCR), and indices of Ne, on a WM task (Sternberg, 1966). In view of the numerous studies that showed a critical role for DLPFC in processing WM tasks, yet a minority of studies that show performance enhancement when rTMS was directed to DLPFC during evolutionary stages of a WM task, we entertained the notion that subject distraction might play a role in such an apparent discrepancy. Relevant in this regard is the study of Abler et al. (2005). In order to determine the relation between TMS-induced distraction and performance, Abler et al. asked healthy subjects to evaluate the discomfort caused by TMS during a verbal WM task. Subjects were first studied using fMRI to identify specific cortical regions engaged in task processing. Subsequently, left DLPFC, inferior frontal, parietal, and temporo-parietal cortices were identified and stimulated during the delay phase of a delayed match-to-sample task. Task performance and subjective disturbance due to side effects were monitored. Subjects' level of discomfort was correlated with their error rates: The higher the discomfort, the more errors they made. Abler et al. concluded that TMS sensory–motor side effects induced during task evolution may bias task performance and lead to misinterpretation of the results. Our predictions were also influenced by earlier work that showed DLPFC plays an important role in WM. For example, Hamidi, Tononi, and Postle (2009) used high-frequency rTMS to evaluate the role of DLPFC in memory-guided response to two different types of spatial WM tasks: one requiring a recognition decision about a probe stimulus using a YES–NO button press, another requiring recall of the stimulus location. In half the trials, randomly distributed rTMS was applied to DLPFC; in a separate session, the same stimulation was directed to the superior parietal lobule (SPL), a brain area implicated in spatial WM storage. In each condition, a 3-sec train of 10 Hz at 110% of motor threshold was delivered at the onset of the response period. DLPFC, but not SPL, rTMS affected performance; rTMS to right DLPFC decreased SCR of delayed-recall trials; rTMS to left DLPFC enhanced SCR on delayed-recognition trials. The authors concluded that their results suggested DLPFC plays an important role in memory-guided response and that the nature of such a role varies with the processes required for making a response (Hamidi et al., 2009).

The concept of Ne in human studies is largely derived from fMRI studies of the relationship between cognitive task performance and neural activation indexed by the signal magnitude of blood oxygen level-dependent BOLD utilization. An array of similar investigations lends support to the finding that as item-load increases, BOLD signal amplitude increases. Such increases have been repeatedly shown to be inversely associated with task performance. For example, Gould, Brown, Owen, ffytche, and Howard (2003) used event-related fMRI to measure PFC activity while younger and older adults performed an item-recognition task in which the memory set size varied between one and eight letters. RT increased and accuracy decreased with increasing memory set size. Variance in RT and BOLD signal in dorsal and ventral PFC accounted for most of the variance. The authors concluded that their results support a model of cognitive slowing with age in which a decline in processing speed is related to a decline in Ne (Gould et al., 2003).

In the present rTMS study, we predicted first that compared with sham active 10 Hz rTMS applied to either right or left DLPFC 10 sec prior to task onset would enhance the neural efficiency (Ne) of WM operationally indexed by the relationship between RT and SCR, whereby Ne = work/time; hence, Ne = accuracy/RT. Guided, in part, by earlier work that suggested the auditory and sensory stimulation of rTMS could degrade cognitive performance in participants who are distracted by such extraneous stimuli (Abler et al., 2005), we directed 10 Hz rTMS to either right or left DLPFC serially 10 sec prior to task onset with the intention of allowing time for resolution of the putative disruptive effects of stimulation. Second, we posited that if sensorimotor side effects of rTMS biased our results, we would see equal or better performance in the sham-stimulated group compared with the actively stimulated group.

METHODS

Experimental Design

This was a single-blind, sham-controlled study (Figure 1). In 32 healthy participants, active or sham 10 Hz rTMS was directed to either right or left DLPFC 10 sec prior to the onset of a Sternberg short-term verbal recognition memory paradigm. Five 5-sec trains of 10 Hz rTMS (for a total of 250 pulses) were applied to DLPFC ending 10 sec prior to task onset. Stimulation was followed by 48 single trials of 6- and 8-item strings of capital letters that were randomized and counterbalanced. Next, 250 additional pulses of 10 Hz rTMS were delivered to DLPFC of the same side, followed by a second set of 48 single trials of 6- and 8-item strings of capital letters. After a 15- to 20-min rest, the same sequence of events was repeated on side-2.

Outcome measures were pre- and poststimulation accuracy (SCR), RT, and Ne by stimulation group (STM).

Participants

The Investigational Review Boards for the University of Utah and Veterans Health Affairs of the Salt Lake City Health Care System approved this study. Thirty-four medically healthy, right-handed participants, ages 18–55 years,

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from the University of Utah and the Salt Lake City community were admitted to the study free of exclusionary conditions for TMS (Wassermann, 1998) and without a past or present psychiatric disorder. All participants had a negative screen for drugs of abuse on the morning of the study. Participants were instructed not to drink caffeinated beverages for 12 hours prior to testing. Participants were compensated for their time. Group assignment to stimulation (active or sham) and side first stimulated (S-1) were pseudorandomized and counterbalanced.

The Sternberg Paradigm

Task stimuli and computation of RTs and accuracy (SCR) were derived using Presentation 9.90 software (Neurobehavioral Systems, San Francisco, CA). A single trial of this task was composed of four phases: *stimulus* (a 5- or 7-item string of uppercase consonants and vowels was presented at the center of a 19-inch video monitor for 1.5 sec), *delay* (participants focused on a fixation marker appearing at the center of the computer monitor while maintaining the previous string in memory for 1.5 sec), *probe* (a single uppercase letter appeared at center screen for 3 sec), and *response* (participants were instructed to decide as quickly and accurately as possible whether the probe was present in the previous string, and to respond by pressing one of two keypad buttons; if there was a response within 3 sec, it was recorded, and the next trial began. If there was no response, the trial was marked as an error, and the next trial began). A minimum baseline SCR of 80% on the 5-item, and 70% on the more difficult 7-item task was required to continue. If necessary, participants were allowed to repeat each of the training paradigms once and were disqualified if they failed to make the minimum SCR. Training and testing phase item-strings had equal numbers of randomized and counterbalanced true positive and true negative probes.

Paradigm Training

Participants were trained and tested between 11:00 a.m. and 1:00 p.m. They were familiarized with the task and response procedures by practicing to use their right first finger to press one of two buttons (YES or NO) on a handheld keypad as comfortably quick as possible while attending to a fixation cue at the center of a 19-inch computer monitor. Baseline values of SCR and RT were derived from 20 randomized and counterbalanced 5- and 7-item single trials of the Sternberg task.

Transcranial Magnetic Stimulation

During the experiment, participants were comfortably seated in an individually adjustable chair. Participants' single-pulse TMS resting motor threshold (RMT) was determined by identification of the lowest level of TMS machine output that would induce a visible contraction of the first dorsal interosseous muscle of the dominant hand on 5 of 10 pulses delivered with a 10-sec interpulse interval. A MagStimTM Super Rapid stimulator with physically identical sham and active air-cooled figure-of-eight coils (Magstim, Whitland, Dyfed UK) was used to deliver TMS pulses directed to either left or right DLPFC. The sound generated by capacitor discharge was identical in the two coils; the sham coil did not generate a sensorimotor stimulus. A custom-designed mechanical coil holder was used to maintain contact between the midpoint of the 70-mm figure-eight coil and the location of the frontal scalp overlying right or left DLPFC. To determine the scalp correlates for targeting of DLPFC, we used the measures 10–20 EEG system. Positioning of the coil on the scalp was determined by the measured position of EEG sensors F3 (left) and F4 (right). Participants used disposable in-ear sound protection during the experiment. Side stimulated first (S-1) was randomly assigned and counterbalanced.

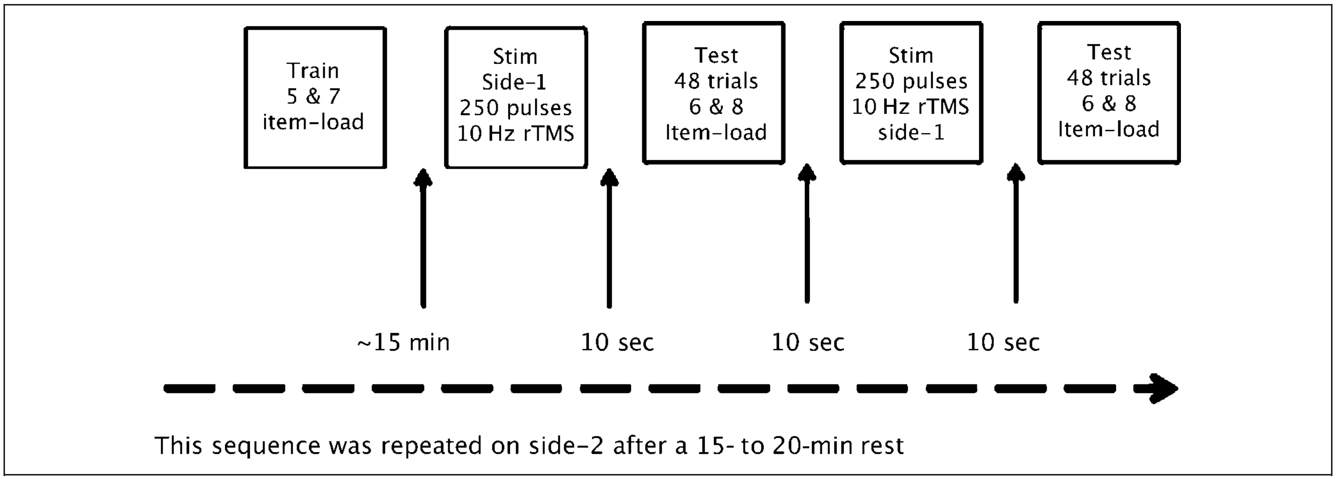

Figure 1. Experimental design.

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Subject Stimulation and Testing

A brief period of acclimation to the laboratory environment was followed by the onset of five 5-sec trains of 10 Hz rTMS with an intertrain interval of 10 sec at 100% of RMT for a total of 250 pulses of 10 Hz rTMS. Stimulation ended 10 sec prior to the onset of the first 48 single trials of the task. In order to minimize the effects of practice on performance, single trials in the testing phase were composed of more difficult 6- or 8-item uppercase letters pseudorandomly presented and counterbalanced for true positive and true negative probes.

This sequence was repeated once more on S-1. Following a 15- to 20-min rest period, the entire sequence was repeated on S-2; hence, the study totaled 192 single trials and 1000 pulses of 10 Hz rTMS.

Planned Analyses

Skewness and kurtosis in the distribution of dependent variables were identified and normalized with square root transformation. Repeated measures ANOVA with Bonferroni correction for multiple comparisons was used to identify the main effects of STM, S-1, and interactions between STM and S-1. Dependent variables were covaried with RMT and age. Pairwise comparisons were used to determine the within-subject effects of active and sham 10 Hz rTMS on SCR and RT by task load.

RESULTS

Thirty-four right-handed men and 12 women recruited from the Salt Lake City, Utah, community participated in this study. Two subjects in the actively stimulated group were unable to complete the study due to the development of moderate muscle contraction headaches. In both cases, the headaches spontaneously resolved. There were no adverse events in the sham group. All participants achieved the minimum 5- and 7-item training SCR on their first attempt.

Demographics

There was no difference in mean age between stimulation groups or by sex. Mean age by Stimulation group: active = 28.6 (*SD* = 5.68); sham = 30.88 (*SD* = 11.2); independent-samples two-tailed t test for equality of means; equal variance not assumed: $t(31) = -0.707$, $p = .478$. Mean age by Sex: male = 28.75 years; female = 29.50 years; two-tailed t test: $t(30) = -0.25, p = .80$. There was equal distribution of the sexes between groups [Pearson uncorrected chi-square test: $\chi^2(1, n = 32) = 0.139, p = .710$].

Resting Motor Threshold

The groups were evenly matched for the intensity of stimulation indexed as RMT and expressed as a percent of maximum machine output [active RMT = 67%, sham RMT = 66%; two-tailed $t(34) = 0.252$, $p = .4484$].

Results of the Repeated Measures ANOVA

There was no main effect of S-1, and no interaction between S-1 and STM. Measures of dependent variables did not covary with RMT, sex, or age. In the absence of a main effect of S-1, prestimulation and poststimulation values of dependent variables were collapsed across side for subsequent analysis. There were no prestimulation differences between groups regarding SCR, RT, or Ne. There was, however, a robust main effect of STM on poststimulation RT and Ne, but not SCR, as presented in Table 1.

In the present study, the authors directed 10 Hz rTMS to right or left DLPFC 10 sec prior to task onset, predicting there would be a main effect of STM on SCR, RT, and Ne. We observed a robust main effect of STM in the comparison of poststimulation RT and Ne, but not SCR. The mean poststimulation RT in the active group was 219 msec (±0.16) faster than the prestimulation baseline, whereas the mean poststimulation RT in the sham group was 30 msec (±0.16) slower than the mean baseline RT. Pairwise comparisons of pre- and poststimulation RT, SCR, and Ne were computed by comparing the relatively easier 5- and 7-item (prestimulation) measures with the 6- and 8-item (poststimulation) measure. Pairwise comparisons of the 5- and 7-item training RT data (Table 2) show a small but nonsignificant within-subject difference in both groups for this comparison. Specifically, pairwise comparisons in the actively treated group showed that compared with the larger 6-item and 8-item poststimulation loads, the 5-item prestimulation RT was slower when the converse would be expected. Similar results were seen when the comparison of the prestimulation 7-item RT was compared with the poststimulation 8-item RT. In the sham group, the same comparisons failed to show a difference for pre- or post-measures of RT, SCR, or Ne (Figures 2 and 3).

DISCUSSION

The present study compared the relative effects of active and sham 10 Hz rTMS directed to the right and left DLPFC on psychomotor processing speed and accuracy, indices of Ne, in healthy participants performing the Sternberg task, a short-term verbal recognition memory paradigm that has been shown to model the association between WM load and task behavior (Sternberg, 1966). Previous studies of the role of DLPFC in WM have been designed to identify the temporal and spatial dynamics of the computational role of DLPFC in a WM network. For example, Osaka et al. (2007) investigated the role of executive function in human left DLPFC in eight normal participants using low-frequency TMS after fMRI activation confirmed a role for left DLPFC. TMS was applied to left DLPFC immediately after subjects finished reading sentences from the reading span test, a measure of verbal WM. They found

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Table 1. Effects of 10 Hz rTMS on the Neural Efficiency of Working Memory

Descriptive Statistics				
	Active		*Sham*	
	Mean	*SD*	*Mean*	*SD*
Pre-10 Hz rTMS SCR[a]	0.920	0.07	0.970	0.03
Post-10 Hz rTMS SCR[a]	0.870	0.06	0.860	0.05
Pre-10 Hz rTMS RT[b]	1.117	0.08	1.010	0.10
Post-10 Hz rTMS RT[b]	0.874	0.05	1.014	0.11
Pre-10 Hz rTMS NE[c]	0.832	0.17	0.969	0.21
Post-10 Hz rTMS NE[c]	0.995	0.13	0.866	0.20
Mean % Change NE[c]	1.200	0.30	0.900	0.10

Repeated Measures ANOVA		
	F (df = 1, 30)	*Sig.*
Pre-10 Hz rTMS SCR[a]	0.019	.892
Post-10 Hz rTMS SCR[a]	0.012	.915
Pre-10 Hz rTMS RT[b]	3.170	.086
Post-10 Hz rTMS RT[b]	7.380	.011
Pre-10 Hz rTMS NE[c]	1.628	.212
Post-10 Hz rTMS NE[c]	5.344	.028
Mean % Change NE[c]	14.253	.001

[a] Accuracy.

[b] Reaction time.

[c] Neural efficiency.

a significant deterioration of performance in this WM task, hence, supporting a crucial role for DLPFC in WM. Koch et al. (2005) used an rTMS approach to investigate the temporal and spatial dynamics of the parieto-frontal network in normal subjects performing a spatial WM task. They aimed to compare neural activity in the relevant areas during the delay and decision phases of the task. Trains of rTMS at 25 Hz were directed to PPC and right DLPFC during the two phases. Premotor cortex was used as a spatial control. They observed that TMS interfered with performance during the delay phase in the posterior parietal and DLPFC sites. There was no effect for the control site. When rTMS trains were applied during the retrieval phase, interference was observed only in DLPFC. The authors concluded that their study identified an example of parallel processing in the parieto-frontal network of spatial WM during the delay phase. The results of Koch et al. represent additional evidence of the critical role of DLPFC during both the delay and the retrieval phases of a WM task. Mottaghy, Gangitano, Krause, and Pascual-Leone (2003) observed significant interference with WM RT after 180 msec of left PFC stimulation. Results in a similar vein were observed by other researchers (Postle et al., 2006; Mull & Seyal, 2001; Mottaghy et al., 2000).

The present study was designed, in part, to identify a putative role for DLPFC in the Ne of a WM task. Accuracy (SCR) declined to a similar extent in both groups, likely due to the effects of memory load, hence supporting the conclusion of previous studies that also found no effect of TMS on WM task accuracy (Luber et al., 2007, 2008; Desmond, Chen, & Shieh, 2005). In turn, such findings suggest that the effect of 10 Hz rTMS on RT when directed to DLPFC 10 sec prior to task onset mediates the enhancement of Ne. Additionally, these data suggest that the retrieval phase of this WM task may be the temporal boundary of the observed effects.

Results of the present study are in line with Rypma et al. (2006), who set out to identify the neural bases of interindividual differences in cognitive performance. They had participants perform a simple speed of processing task during fMRI scanning. In certain prefrontal cortical regions (PFC), faster performers used fewer neural resources than slower performers, whereas in other PFC and parietal regions, they used more. These results were interpreted to suggest that a critical determinant of interindividual differences in cognitive performance was the efficiency of interactions between brain regions. In order to perform well, slower individuals may utilize more prefrontal resources than faster individuals (Rypma et al., 2006).

Taking into account the lack of difference between groups in baseline RT (Table 1), together with a robust RT enhancement with active stimulation, and considering that participants in both groups had equal practice experience over the course of experiment, one might plausibly argue that our data support the conclusion that the poststimulation difference in task performance between groups is best explained as a difference between active and sham stimulation (Table 3). Even so, we recognize valid challenges to these conclusions. Our results were

Table 2. Pairwise Comparisons: Effects of 10 Hz rTMS Pre- and Post-10 Hz rTMS

	t	*p (Two-Tailed)*
Active		
Pre vs. Post SCR	2.362	.0340
Pre vs. Post RT	4.417	.0010
Pre vs. Post Efficiency	−4.993	.0002
Sham		
Pre vs. Post SCR	3.113	.008
Pre vs. Post RT	−1.264	.228
Pre vs. Post Efficiency	0.986	.342

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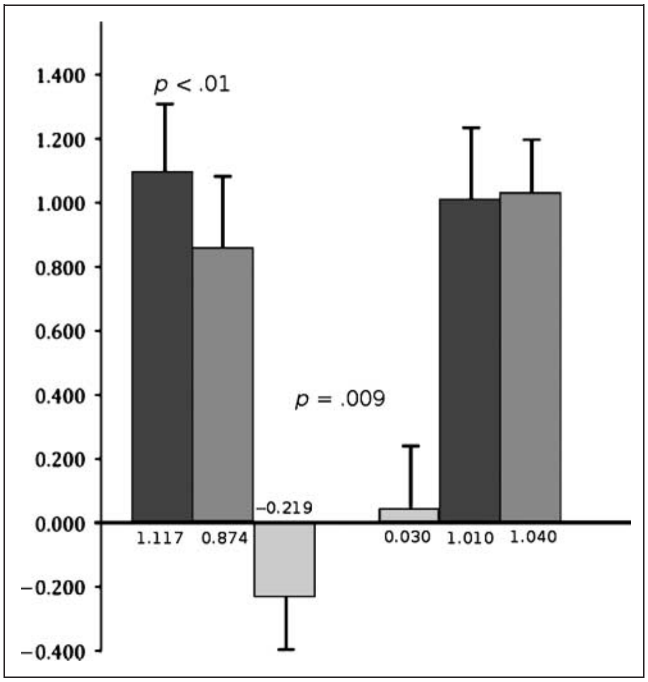

Figure 2. Comparative effects of active and sham 10 Hz rTMS on working memory reaction time. Left-side sequence: Pre-10 Hz rTMS RT*; Post-10 Hz rTMS RT; RT difference. Right-side sequence: RT difference; Pre-10 Hz rTMS RT*; Post-10 Hz rTMS RT. Compared with sham, the group treated with active 10 Hz rTMS applied to DLPFC 10 sec before onset experienced a 219-msec enhancement of RT.

specific to SCR, RT, and Ne; even so it is possible that the effects were due to a priming effect of rTMS on psychomotor functions that are also mediated through prefrontal networks (Rounis, Yarrow, & Rothwell, 2007; Vogt et al., 2007). Although we would suggest that it is unlikely the observed effects are strictly due to learning, inasmuch as both the sham and active rTMS groups had equal opportunity to practice, we recognize there may have been an interaction between 10 Hz rTMS and the learning of a response strategy that results in faster but not more accurate responses. An additional challenge to our conclusions is related to the capacity limits of short-term memory (Marois & Ivanoff, 2005; Cowan, 2001). To overcome such limitations, study subjects may devise strategies, such as chunking to successfully perform at supra-capacity limits, which can affect neural activity in a complex way, leading to potential complications in the interpretation of results. In view of the high-capacity nature of the task we used in this study, it is possible that chunking or other mnemonic strategies may have been used to manage supra-capacity aspects of task performance.

The underlying neurobiological mechanisms subserving the effects of TMS on WM Ne are unclear. In a previous exploratory study, the present authors found that 10 Hz rTMS applied to DLPFC in healthy humans resulted in a significantly enhanced measure of individual mean peak alpha frequency, and enhanced within band 10–12 Hz phase synchrony (Anderson et al., 2007). These results are in line with Klimesch et al. (2003), who showed that mean peak alpha spectral frequency (IAF) is related to memory performance. Klimesch et al. showed that compared with attentional demands, memory performance exerted the strongest effect on IAF. The difference in IAF between good and bad memory performers peaked when subjects retrieved information from memory. During retrieval, the IAF of good performers was 1.25 Hz higher than that of bad performers.

Brignani, Manganotti, Rossini, and Miniussi (2008) found that low-frequency TMS over primary motor cortex induced a synchronization of the background oscillatory activity in the stimulated region, hence suggesting that TMS effects may involve short-term modification of the neural circuitry sustaining motor behavior (Brignani et al., 2008; Leiberg, Lutzenberger, & Kaiser, 2006; Klimesch, 1997). Emergent evidence suggests that a diminished capacity to synchronize distributed neural assemblies mediating WM may be a critical and enduring underlying mechanism of impaired WM in a broad array of seemingly disparate neuropsychiatric disorders such as schizophrenia (Ford, Krystal, & Mathalon, 2007; Andreasen et al., 1999; Friston, 1999), depression (Linkenkaer-Hansen et al., 2005), Alzheimer's disease (Yener, Güntekin, Oniz, & Basar, 2007; Osipova, Ahveninen, Jensen, Ylikoski, & Pekkonen, 2005), and autism (Uhlhaas & Singer, 2007). Despite such recognition, there is no treatment for impaired memory in any such disorder. TMS has been shown to mediate events at the neural synapse (Fuggetta, Pavone, Fiaschi, & Manganotti, 2008). In light of previous work, this suggests that such effects may be related to 10 Hz rTMS induced phase-state perturbation (Anderson et al., 2007); if so, it may also suggest a role for TMS as a clinical tool for

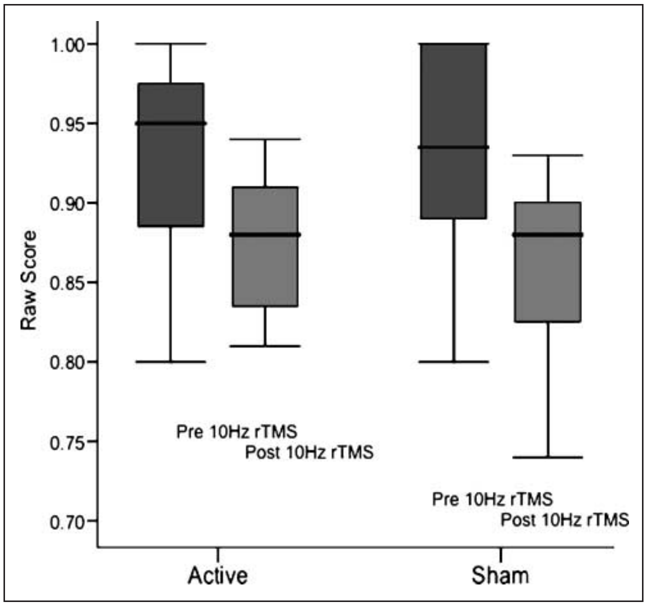

Figure 3. Lack of effect of 10 Hz rTMS on accuracy within or between subjects. The difference in accuracy within and between groups pre- and poststimulation was not significant.

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Table 3. Pairwise Comparisons of Reaction Time × Memory Load for Each Group

			Mean		
Group	*RT (I)*	*RT (J)*	*Difference (I−J)*	*SEM*	*Sig.*
Active	5-item	6-item	0.278	0.07	.0060
		8-item	0.252	0.07	.0170
	7-item	6-item	0.167	0.03	.0001
		8-item	0.141	0.03	.0005
Sham	5-item	6-item	−0.046	0.03	1.0000
		8-item	−0.101	0.04	.1930
	7-item	6-item	0.098	0.04	.1450
		8-item	0.052	0.05	1.0000

In the actively stimulated group, the 5-item prestimulation RT is slower than the 6- and 8-item RT. The same relationship is true for comparison of the 7- with the 8-item RT; in the sham group, the 6- and 8-item RTs are slower than the 5-item RT, as would be expected.

neural circuit repair or enhancement (Plewnia et al., 2008; Sauseng & Klimesch, 2008). In a study with 24 subjects, Hamidi et al. (2009) used high-frequency rTMS to evaluate the role of DLPFC in memory-guided response to two different types of spatial WM tasks: one requiring a recognition decision about a probe stimulus (operationalized with a yes/no button press), and another requiring direct recall of the memory stimulus by moving a cursor to the remembered location. In half the trials, randomly distributed, rTMS was applied to DLPFC, and in a separate session, to the SPL, a brain area implicated in spatial WM storage. A 10-Hz (3 sec, 110% of motor threshold) train of rTMS was delivered at the onset of the response period. They found that only rTMS applied to DLPFC significantly affected performance. When 10 Hz rTMS was directed to right DLPFC, accuracy declined on delayed-recall trials. When 10 Hz rTMS was directed to left DLPFC, accuracy on the delayed-recognition trials was enhanced. These findings support DLPFC's role in memory-guided response and suggest that the nature of this role varies depending on the processes required for making a response. Koch et al. (2005) used an rTMS approach to investigate the temporal dynamics and reciprocal interactions of different regions of the parieto-frontal network in normal subjects performing a spatial WM task. They aimed to compare neural activity in these regions in the delay and decision phases of the task. Trains of rTMS at 25 Hz were delivered over PPC, premotor cortex (SFG), and DLPFC of the right hemisphere alternatively during the two phases. They observed TMS interference during the delay phase for PPC and DLPFC sites of stimulation, with no effect on the control site. When rTMS trains were applied during the retrieval phase, task interference was limited to DLPFC. The authors concluded their study supported the existence of a parallel processing network that was active during the delay phase of the task. They concluded that in DLPFC, two task-specific networks coexisted: a local neural network subserving the decisional processes, and a second neural population functionally connected to PPC that was activated when spatial-specific information maintained in memory was made available for use.

Luber et al. (2007) designed a delayed match-to-sample task in which rTMS at 1, 5, or 20 Hz was applied to either left DLPFC or midline parietal cortex during the delay phase of the task. Only 5 Hz stimulation to the parietal site resulted in a significant decrease in RT with no effect on SCR. In a second experiment, 5 Hz rTMS was directed to the parietal site during either the maintenance or retrieval phase of the recognition probe. RT enhancement occurred in the retention phase but not the probe phase. They concluded their results suggest that 5 Hz rTMS may improve WM performance when stimulation of a specific frequency was timed to a specific phase of task performance.

Earlier work to show that TMS may enhance prefrontal oscillatory synchrony in spectral bands subserving WM information processing (Anderson et al., 2007), as noted above, lends support to the idea of developing a neural circuit-based model for the treatment of memory impairment using noninvasive brain stimulation (NIBS) methods such as TMS. Presently, evidence to support an NIBS-based approach is supported by work to show improved clinical status in depression (O'Reardon et al., 2007), hallucinations in schizophrenia (Aleman, Sommer, & Kahn, 2007; Hoffman et al., 2005), and posttraumatic stress disorder (Osuch et al., 2009; Grisaru, Amir, Cohen, & Kaplan, 1998).

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