

FEATURE ARTICLE

TMS Over Human Frontal Eye Fields Disrupts Trans-saccadic Memory of Multiple Objects

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We recently showed that transcranial magnetic stimulation (TMS) over the right parietal eye fields disrupts memory of object features and locations across saccades. We applied TMS over the frontal eye fields (FEF) as subjects compared the feature details of visual targets presented either within a single eye fixation (*Fixation Task*) or across a saccade (*Saccade Task*). TMS pulses were randomly delivered at one of 3 time intervals around the time of the saccade, or at equivalent times in the *Fixation Task*. A No-TMS control confirmed that subjects could normally retain ~3 visual features. TMS in the *Fixation Task* had no effect compared with No-TMS, but differences among TMS times were found during right FEF stimulation. TMS over either the right or left FEF disrupted memory performance in the *Saccade Task* when stimulation coincided most closely with the saccade. The capacity to compare pre- and postsaccadic features was reduced to 1–2 objects, as expected if the spatial aspect of memory was disrupted. These findings suggest that the FEF plays a role in the spatial processing involved in trans-saccadic memory of visual features. We propose that this process employs saccade-related feedback signals similar to those observed in spatial updating.

Keywords: frontal eye fields, saccades, transcranial magnetic stimulation, trans-saccadic memory, visual working memory

Introduction

Humans typically make 3–5 rapid eye movements, called saccades, per second (Rayner 1998). Because visual processing is partially suppressed during a saccade (Matin 1974) our view of the world is limited to discrete moments between saccades when our eyes are stationary. To perceive a unified visual world, visual information acquired during these discrete eye fixations must be retained across saccades, a process referred to as trans-saccadic memory (Irwin 1991, 1996). It has been previously shown that the capacity of trans-saccadic memory is limited to only 3–4 items (Irwin 1992; Irwin and Andrews 1996; Irwin and Gordon 1998; Prime et al. 2007)—similar to visual working memory (Luck and Vogel 1997; Vogel, Woodman, and Luck 2001). However, trans-saccadic memory is more complex than visual working memory. Trans-saccadic memory takes into account changes in gaze by updating object and spatial information with every saccade (Hayhoe et al. 1991; Prime et al. 2006). Presently, little is known about the neural mechanisms that contribute to the putative processes that maintain and update objects and their locations across saccades.

Functional imaging studies have found that activity in the posterior parietal cortex is tightly correlated with the number of items maintained in visual working memory before reaching its capacity limit of about 4 items (Todd and Marois 2004; Vogel

and Machizawa 2004; Xu and Chun 2006). In a recent study, we showed that trans-saccadic memory of multiple feature objects was disrupted when transcranial magnetic stimulation (TMS) was applied to the right, but not the left, parietal eye field (PEF), an area analogous to the monkey lateral intraparietal cortex (Prime et al. 2008). Our results confirmed that parietal TMS interferes with memory for even one object feature (Harris et al. 2008). Moreover, in our previous study, parietal TMS produced additional reductions in memory of multiple objects, especially when it coincided with a saccade. The PEF is part of a cortical network involved in saccadic eye movements (for review see Pierrot-Deseilligny and Muri 1997), spatial working memory (Jonides et al. 1993; Smith et al. 1995), and visual attention (Saalmann et al. 2007), and is involved in the spatial updating of movement goals across saccades—a process called spatial remapping (Duhamel et al. 1992; Colby and Goldberg 1999; Medendorp et al. 2003; Merriam et al. 2003). Based on our TMS data, we argued that the PEF also plays a role in updating the remembered locations of object features across saccades, perhaps through recurrent interconnections with the “ventral stream” of visual analysis (Prime et al. 2008).

Another cortical structure involved in saccade production and remapping is the frontal eye field (FEF). The FEF is part of the same complex cortical network that governs saccadic eye movements (Leichnetz and Goldberg 1988; Milea et al. 2007; Pierrot-Deseilligny et al. 2004). And like the PEF, some FEF neurons also show spatial remapping in response to saccadic eye movements (Sommer and Wurtz 2006; Umeno and Goldberg 1997, 2001). Also, the PEF and FEF in both the human and monkey brain share a role in a variety of visuospatial processes related to trans-saccadic memory such as spatial working memory (Jonides et al. 1993; Smith et al. 1995; Courtney et al. 1998; Gaymard et al. 1999; Curtis and D’Esposito 2006), visual search (Schall and Hanes 1993; O’Shea et al. 2006; Anderson et al. 2007), and visual attention (Corbetta et al. 1998; Beauchamp et al. 2001; Juan et al. 2004; Petersen et al. 1994; Shomstein et al. 2006; Saalmann et al. 2007). Finally, the FEF is known to influence processing in visual area V4, a “ventral stream” area involved in feature analysis (Moore and Armstrong 2003). These properties suggest that the FEF could also play a role in trans-saccadic memory.

However, the FEF and PEF appear to serve different functions within this frontoparietal network mediating oculomotor control (Connolly et al. 2002; Grosbras et al. 2005), spatial memory (Postle 2005; Curtis 2006), and attention (Wardak et al. 2006; Buschman and Miller 2007). The PEF acts as a general salience map of object locations that integrates sensory and motor information for a variety of cognitive and behavioral tasks (Andersen and Buneo 2002; Goldberg et al. 2006; Gottlieb 2007), whereas the salience map of the FEF is more specifically tied

with latter stages of oculomotor processing downstream from the PEF (Pierrot-Deseilligny et al. 1995). Moreover, TMS of the human PEF and FEF during concurrent functional magnetic resonance imaging has offered evidence that the PEF and FEF exert different top-down control over early visual processing in the visual cortex (Ruff et al. 2008). As mentioned earlier, we showed that the right PEF plays a crucial role in trans-saccadic memory using TMS (Prime et al. 2008). The goal of the present study was to use TMS to investigate the possible contribution of the FEFs to trans-saccadic memory and compare the results here with our PEF results.

Previous TMS studies have shown that magnetic stimulation of the human FEF can disrupt spatial working memory (Campana et al. 2007; O'Shea et al. 2007), visual search performance (Muggleton et al. 2003; O'Shea et al. 2004), and covert spatial attention (Grosbras and Paus 2002; Smith et al. 2005; Neggers et al. 2007). TMS-induced changes to task performance in these studies offer evidence that the stimulated brain region plays a role in the task (Pascual-Leone et al. 1999, 2000). However, to our knowledge, no study to date has demonstrated a specific role of the FEF in trans-saccadic memory.

In the present study, we used TMS to deliver a magnetic pulse to our subjects' FEF as they performed the same trans-saccadic memory task from our previous PEF study (Prime et al. 2008). In our task, subjects memorized the location and feature details of multiple objects and compared one of them to probe at the same location presented after a memory interval that either contained a saccade (*Saccade Task*) or did not (*Fixation Task*). We hypothesized that applying TMS to the FEF will also disrupt trans-saccadic memory of multiple feature objects, as we found earlier with the right PEF. Moreover, we contrasted our new FEF findings with our previous PEF findings, specifically asking: does the FEF show the same asymmetry between the left and right cortices? Does TMS to the FEF produce the same baseline deficits to feature memory and/or deficits to retention of multiple objects? And finally, do the effects of TMS to FEF show the same saccade-timing sensitivity as the PEF? The results show that, like the PEF, TMS to the FEF also disrupts trans-saccadic memory, but the 2 structures showed different patterns of disruption that may reveal differences in their contribution to trans-saccadic memory.

Methods

Subjects

Six subjects (4 males and 2 females; age range was 20–34 years and mean age was 26.3) participated in this study after providing written informed consent. All participants were in good health and had normal or corrected-to-normal visual acuity, and according to a self-report, without any known contraindications to TMS. All experimental procedures received ethical approval by York Human Participants Review Subcommittee.

Apparatus

Subjects sat in a dark room with their head immobilized by a personalized dental impression bar. A customized computer network system of 3 microprocessor personal computers was used for both stimulus presentation and data recording. The experimental device was the same for all conditions and consisted of a video projector that back-projected visual stimuli onto a 1.9- × 1.4-m display screen, spanning 124.5° visual angle horizontally by 108.9° visual angle vertically. Subjects sat 50 cm in front of the screen. The screen was unlit (black) with a luminance level of 0.015 cd/m². Eye position was monitored in

4 subjects using the EyeLink 2 eye-tracking system (SR Research, Mississauga, Ontario, Canada). To access the FEF with the TMS coil, the eye-tracker was removed from its headband and bolted to the apparatus that held the bite-bar leaving the top of the subject's head exposed. The two-dimensional (2-D) coordinates of eye movements were recorded at a sampling rate of 500 Hz and stored on hard disk for off-line analysis. Saccades continuously were detected using a velocity criterion of 36° per second and eye position criterion of 1.5° visual angle around the fixation-cross. In both the *Saccade* and *Fixation Tasks*, eye position was monitored in real time by custom-written software that only accepted trials for a predetermined "tolerance" window of performance for both eye fixations and movements. In particular, for a trial to be successful, subjects were required to maintain eye fixations within a 1.5° window around the fixation-cross and, in the case of the *Saccade Task*, begin the saccade within one second following the onset of the second fixation-cross and then end the saccade at the correct, specified fixation location. Trials were automatically aborted if eye fixation was not maintained within the tolerance window of 1.5° centered on the fixation-cross and if subjects did not begin their saccade within one second of the presentation of the saccade-target in the *Saccade Task* (the presentation of the second fixation-cross). Auditory tones provided feedback for whether the trial was successful or aborted.

Localization of Brain Sites and TMS Protocol

Stimulation sites were determined individually in each subject using frameless stereotaxy. Before testing in the behavioral sessions, a T_1 -weighted MR brain scan was obtained from each subject. To localize FEF, we selected stereotaxic coordinates (left FEF: $x = -32$; $y = -2$; $z = 46$; right FEF: $x = 32$; $y = -2$; $z = 47$) based on a previous review of several brain imaging studies identifying activation foci for FEF (Paus 1996). These coordinates correspond well with other TMS studies targeting this region in humans (Terao et al. 1998; Ro et al. 1999; O'Shea et al. 2006; Silvanto et al. 2006; Campana et al. 2007; O'Shea et al. 2007; Juan et al. 2008) and allow for a comparison between our stimulation sites and other TMS and functional magnetic resonance imaging (fMRI) studies. These anatomical coordinates corresponding to left and right FEF were then converted from standardized stereotaxic space (Talairach and Tournoux 1988) into each subject's native coordinate space (Paus 1999), and the corresponding region was labeled on the MRI (Fig. 1). To coregister the TMS coil and scalp topography in real 3-D space with cortical regions identified in the MRI of the subject's head, we used an ultrasound-based TMS-MRI coregistration system and Brain Voyager QX software (Brain Voyager TMS Neuronavigator; Brain Innovation, Maastricht, The Netherlands).

This system consists of several miniature ultrasound senders, which are attached to the subject's head and TMS coil. Local spatial coordinate systems are then created by linking the relative raw spatial position of the ultrasound senders to a set of fixed additional landmarks on the subject's head (nasion and the 2 incisurae intertragicae) via a digitizing pen. After this stage, the system provides topographic information of the head ultrasound senders relative to a subject-based coordinate frame. Similarly, the TMS coil also hosts a set of ultrasound senders whose relative spatial positions are linked to fixed landmarks specified on the coil to calculate another local coordinate system. Once the local spatial coordinate system is defined for the subject's head and the TMS coil in real 3-D space, these coordinate systems are coregistered with the coordinate system of the MR space. TMS coil placement was guided by on-line TMS-MRI coregistration.

Three additional control conditions were conducted to yield estimated of nonspecific effects of TMS. First, performance was assessed following stimulation of Cz (vertex) according to the 10–20 EEG (electroencephalogram) coordinate system. Specifically, the vertex was localized by placing the coil over the very apex of the subject's head—the junction halfway between the preauricular points and halfway between the nasion and inion. Second, 2 sham conditions were included, one over the right FEF and the other over the left FEF, in which the coil was held close to the subject's skull, but angled away so that no current was induced in the brain for both right and left FEF. Stimulation conditions were performed on separate days to minimize fatigue and TMS exposure for each session. Consecutive testing sessions were separated by at least 24 h. Site of stimulation (left FEF,

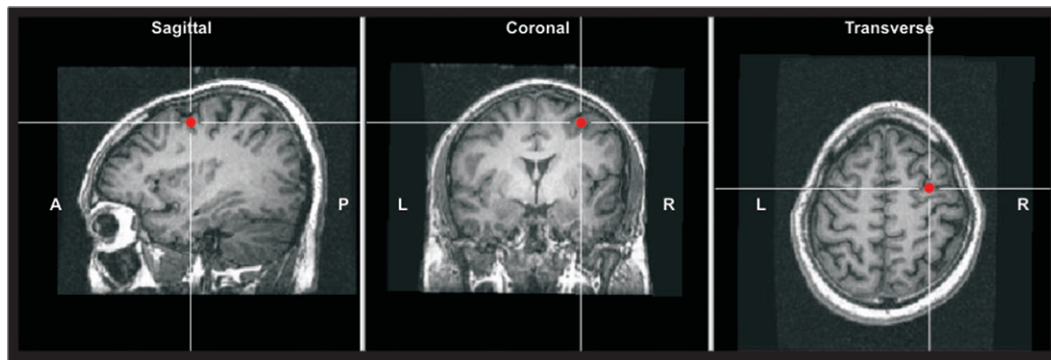


Figure 1. Location of right FEF TMS site for one representative subject. The anatomical site of stimulation for right FEF (shown here) is indicated by the line intersection in the sagittal (rightmost panel), coronal (middle panel), and transverse (leftmost panel) sections of T_1 -weighted MRI. The coil was placed tangential to the skull with the handle pointing backward parallel to the midline. Left and right FEF sites were identified based on a previous review of the several brain imaging studies of the activation foci for FEF (Paus 1996) that reported the average anatomical Talairach coordinates: left FEF ($x = -32$; $y = -2$; $z = 46$) and right FEF ($x = 32$; $y = -2$; $z = 47$).

right FEF, and vertex) and sham conditions (left FEF sham and right FEF sham) order were counterbalanced across subjects over 2 experimental sessions. Last, a “No-TMS” baseline condition was included where subjects received no stimulation as they performed the task.

Single-pulse TMS was delivered using a MagStim 200 magnetic stimulator and a 70-mm figure-of-8 coil (MagStim, Whitland, UK). The locus of TMS stimulation has a spatial resolution of approximately 0.5–1 cm (Brasil-Neto et al. 1992; Wilson et al. 1993) with an estimated penetration depth of roughly 2 cm (Epstein et al. 1990; Rudiak and Marg 1994), reflecting stimulation of the underlying cortex near the grey-white junction (Epstein et al. 1990). Custom software triggered the magnetic stimulator at 100, 200, or 300 ms after the onset of the saccade-go signal for the stimulation and sham conditions only (see *experimental paradigm* below). As a result of the normal latency distribution of saccades, in the *Saccade Task* this placed the timing of the TMS pulse either approximately 100 ms before, about the same time, or about 100 ms after the initiation of the saccade. These 3 discrete stimulation times are the same as those used in our previous study so our results here would be comparable with our previous PEF TMS results (Prime et al. 2008). It was observed in that study that the TMS-induced effects on the right PEF occurred at these times, especially in the *Saccade Task*. By having different stimulation times, we can determine the timing of the contribution of the cortical areas of interest for this experimental trans-saccadic memory task (“causal chronometry”).

The intensity of magnetic stimulation was fixed to 60% of the stimulator output, the same as a number of previous TMS studies of the FEF (Muggleton et al. 2003; O’Shea et al. 2004; Campana et al. 2007; Juan et al. 2008). It has been argued that using the motor threshold is not an appropriate method to gauge TMS thresholds in nonmotor areas of the brain (Stewart et al. 2001; Boroojerdi et al. 2002) and methods that attempt to adjust intensity to correct for scalp-to-brain target distance (e.g., Stokes et al. 2005) do not take into account the possibility that different brain areas may have different susceptibilities to a given stimulation intensity depending on such factors as task-related activation (Robertson et al. 2003). Nonetheless, we still recorded the mean resting motor threshold of our subjects to allow for comparisons with other TMS studies over the FEF; thus, our stimulation intensity was 115% relative to our subjects’ mean resting motor threshold ($SD = \pm 2.9\%$; range = 107–125%). All stimulation parameters were in accordance with the safety guidelines for magnetic stimulation (Wassermann 1998). Earplugs were provided to dampen the noise associated with the discharge from the TMS coil. None of the subjects reported any undesirable side effects as a result of the stimulation.

Experimental Procedure

The experimental procedure is similar as the one previously described in Prime et al. (2008), but instead of applying TMS to the PEF we stimulated the FEF to investigate if this brain area is also included among the putative neural mechanisms underlying trans-saccadic memory. This experimental procedure is illustrated in Figure 2. As

before, the experiment was designed to test subjects in 2 memory tasks: the *Saccade Task* for trans-saccadic memory and as a comparison the *Fixation Task* for simple visual working memory. Recall that in the *Saccade Task* subjects were required to compare the orientation of a postsaccadic probe relative to the orientation of a presaccadic target at the same location usually among similar looking presaccadic distracters. When distracters were included in the target-display, subjects did not know which presaccadic item was the target and which items were distracters, thus, were required to remember the details of as many of the presaccadic items of the target-display as possible. *Saccade Task* performance was compared with performance in the *Fixation Task* where subjects maintained fixation throughout the trial.

During *Saccade Task* trials (Fig. 2A), subjects fixated a cross (subtended 1.5°) randomly presented at one of 29 possible spatial locations within a display area spanning $18^\circ \times 18^\circ$. Upon fixation, subjects were briefly presented (100 ms) with a target-display. In the 2 subjects that did not have their eye movements monitored, the interstimulus interval between the fixation-cross and the target-display was 1 s. The target-display consisted of either a solitary target or a target accompanied by a random number of distracters, ranging from 1 to 5, or 7. In other words, the total set-size of the target-display ranged from 1 to 6, or 8 items (target + distracters). Spatial locations for all items in the target-display (i.e. target and distracters) were randomly generated within the display area. None of the target-display items spatially overlapped with the fixation-cross.

All targets and distracters were gabor-like patches (2° in diameter) of alternating black and white bars. The gratings’ mean luminance was 17 cd/m^2 and the spatial frequency was 2 cycles per degree of visual angle. The orientation of the target and each distracter in the target-display was selected randomly from 6 possible orientations— 35° , 45° , or 55° clockwise or counterclockwise from vertical.

A mask—a white uniform field (i.e., 33.61 cd/m^2) covering the entire screen—briefly flashed for 150 ms to reduce the possibility of visual persistence immediately following the target-display. Following the mask, the fixation-cross reappeared in a new randomly determined spatial location within the display area. Subjects then made a saccadic eye movement to this new location of the fixation-cross. The delivery of the TMS pulse was time-locked to the onset of the saccade-go signal (i.e., the reappearance of the fixation-cross). The TMS pulse was delivered after the onset of the saccade-go signal at one of 3 possible time intervals (100, 200, or 300 ms). These time intervals, including the no stimulation condition, were randomly interleaved within each block of trials for each site of stimulation (left FEF TMS, right FEF TMS, and vertex) and sham conditions (left FEF sham and right FEF sham).

Once subjects refixated the fixation-cross and after a brief 200 ms delay (after refixation was detected by the experimental computer), a probe was flashed for 100 ms in the same location as the presaccadic target followed by a second mask. The rationale behind the brief delay before presenting the probe was based on previous findings that show that subjects can mislocalize stimuli presented around the time of the

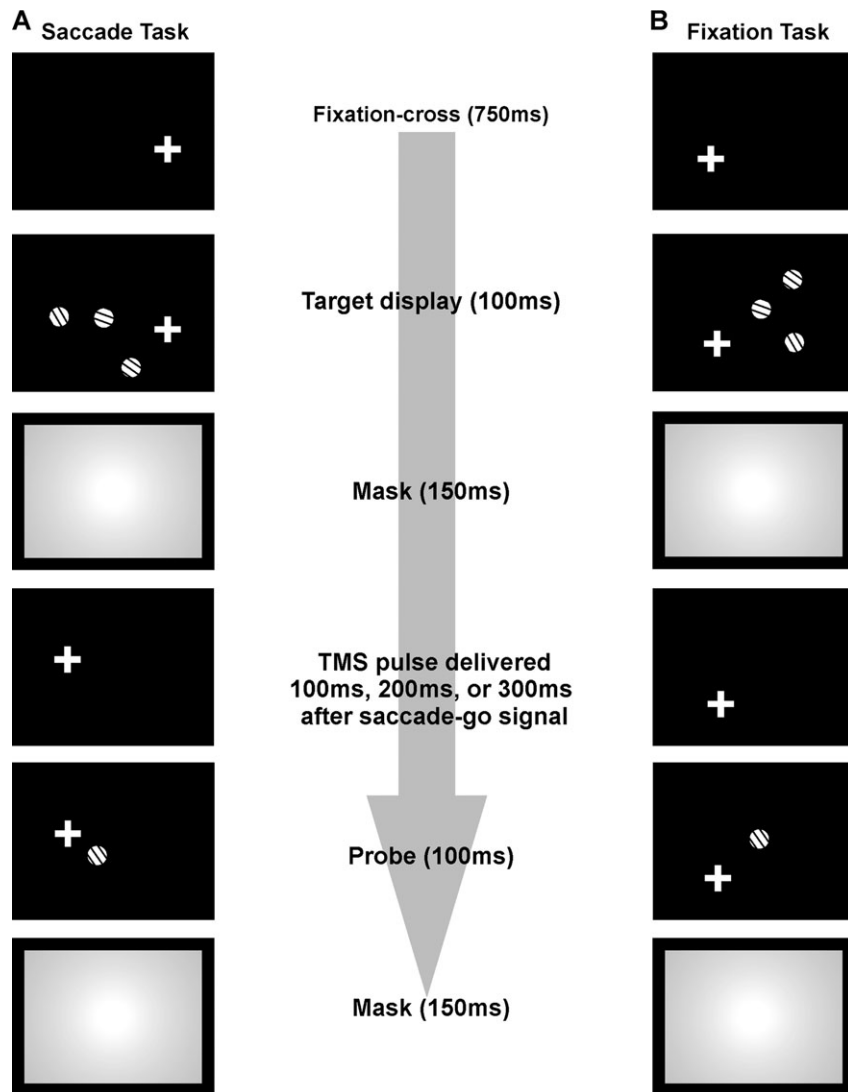


Figure 2. General experimental paradigm of TMS study. (A) In the *Saccade Task* subjects fixated on the fixation-cross while the target display was briefly presented containing either a lone target or a target accompanied by a random number of distracters (i.e., total set-size of target + distracters was 1 to 6, or 8). Following the mask, subjects moved their eyes to the new location of fixation-cross. In TMS trials, TMS pulses were time-locked to the onset of the second fixation-cross. Pulses were delivered either 100, 200, or 300 ms after the second fixation-cross was presented. After the saccade a probe was presented (100 ms) at the same location as the target. Subjects were required to indicate how the probe's orientation differed relative to the target's orientation. (B) The *Fixation Task* was the same as the *Saccade Task* except that subjects were required to maintain eye fixation through target display and probe presentations. The fixation-cross remained fixed in the same position throughout the trial. Again, TMS pulses were delivered at one of the 3 time intervals relative to the onset of the second fixation-cross in TMS trials. This figure is slightly adapted from our previous TMS study of the parietal cortex (Prime et al. 2008).

saccade, including stimuli presented immediately after saccade onset (Honda 1991, 1999; Schlag and Schlag-Rey 1995; Miller 1996; Lappe et al. 2000; Park et al. 2001), or the perception of the feature details of a postsaccadic stimulus presented too soon after a saccade can be influenced by the feature detail of a similar presaccadic stimulus (Wittenberg et al. 2008). In the 2 subjects that did not have their eye movements monitored, the interstimulus interval between the onset of the second fixation-cross and the probe was 500 ms. The probe resembled the target except that the probe's line orientation differed by a predetermined amount, either 9.9° clockwise or counterclockwise from the originally displayed target's orientation. This probe-target difference corresponded to the average discrimination threshold for 80% of correct responses across subjects when comparing the orientation of only 2 targets separated by a saccade, as shown in our previous study (Prime et al. 2007).

Subjects then judged whether the probe's lines were clockwise or counterclockwise to the target's lines by a 2 alternative forced-choice task. Subjects' used their dominant right hand to report the orientation

of the target by pressing the left mouse button with the index finger for counterclockwise target orientations and the right mouse button with the middle finger for clockwise target orientations. Subjects were instructed to make their best estimate if uncertain about the orientation of the target.

We also included a *Fixation Task* (Fig. 2B) that was identical to the *Saccade Task* aside from the fixation-cross not changing location after the target-display's presentation. In this way, subjects maintained eye fixation throughout the trial. As a result, targets and probes are presented within a single fixation. TMS pulses were delivered at the same intervals of time as in the *Saccade Task*. To ensure the stimulus onset asynchrony (SOA) of the target-display and the probe were the same between the 2 tasks, saccade time and latencies for *Saccade* trials only were recorded in real time and used to deliver the subsequent SOA for *Fixation* trials. For this reason, the blocks were designed so *Saccade* trials always preceded an equal number of *Fixation* trials. A total of 2100 trials were performed over multiple sessions (2 blocks of 420 trials for each TMS stimulation site and each control condition).

Results

Baseline Performance: No-TMS Condition

Figure 3 shows the mean percentage correct responses of the No-TMS trials across all subjects for both the *Saccade* and *Fixation* tasks as a function of set-size. These data replicated our earlier results (Prime et al. 2007). Specifically, subjects' accuracy in the *Saccade Task* was the same as in the *Fixation Task*, as revealed by a 2-way ANOVA (task \times set-size) for repeated measures that yielded no significant difference for task ($F_{1,5} = 1.02$; $P = 0.36$) but a significant difference was found for set-size ($F_{6,30} = 8.01$; $P < 0.01$). The interaction was not

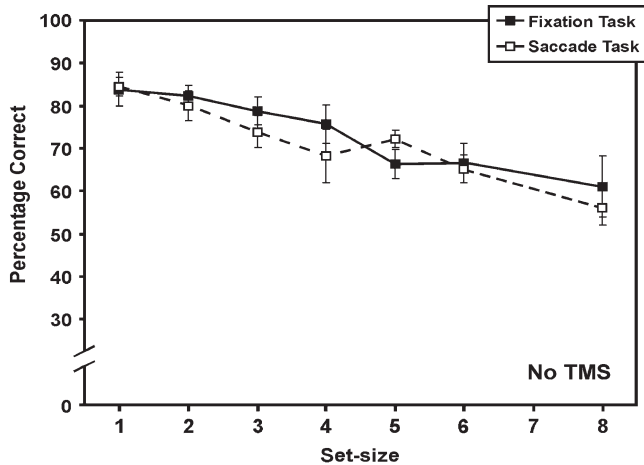


Figure 3. Results of the baseline No-TMS trials. This figure shows the mean percentage correct responses across all subjects ($n = 6$) in both the *Saccade* and *Fixation* tasks for different set-sizes. *Fixation Task* performance is represented by the solid curve with the closed squares. *Saccade Task* performance is represented by the dashed curve with the open squares. Performance in these tasks was found statistically the same. These data replicated our previous findings (Prime et al. 2007). Error bars represent standard error.

significant ($F_{6,30} = 1.17$; $P = 0.35$). A statistical estimate of the numerical capacity of this memory system is provided below; here this No-TMS data will be used as a baseline in which to compare the TMS conditions in the subsequent analyses.

Left and Right FEF TMS

Figure 4 shows the main results of mean percentage correct responses across all subjects when stimulation was applied to either the left or right FEF in both *Saccade* and *Fixation* tasks for the 3 different TMS time intervals. Results of left FEF TMS are shown in Figure 4A and right FEF TMS shown in Figure 4B. Top panels show performance from the *Fixation Task* and bottom panels show performance from the *Saccade Task*. The mean latency (\pm SD) for saccades in the left and right FEF TMS conditions were 224.8 (± 60.5 ms) and 257.1 ms (± 46.3 ms), respectively, indicating that saccade onset usually occurred sometime between the 200-ms TMS pulse and the 300-ms TMS pulse, whereas the 100-ms pulse occurred before saccade onset. Each colored data curve in Figure 4 represents a different TMS time interval. The baseline data from the No-TMS condition shown in Figure 3 were replotted here as the black curves for comparison.

Starting with the *Fixation Task* (Fig. 4, top panels), left FEF TMS data curves showed similar trends as the No-TMS curves (Fig. 4A). This was confirmed by separate repeated measure ANOVAs comparing the baseline No-TMS condition to each different TMS time interval in the *Fixation Task*. No significant differences were found comparing the baseline No-TMS to 100-ms TMS interval ($F_{1,5} = 0.85$; $P = 0.4$), 200-ms TMS interval ($F_{1,5} = 1.47$; $P = 0.28$), and 300-ms TMS interval ($F_{1,5} = 0.61$; $P = 0.47$). Similarly, for the right FEF (Fig. 4B) TMS at 200 ms did not yield any differences compared with baseline ($F_{1,5} = 0.67$; $P = 0.45$) in the *Fixation task*. And even though some points of the 100- and 300-ms curves were lower than the baseline curve, we found no statistical differences compared with

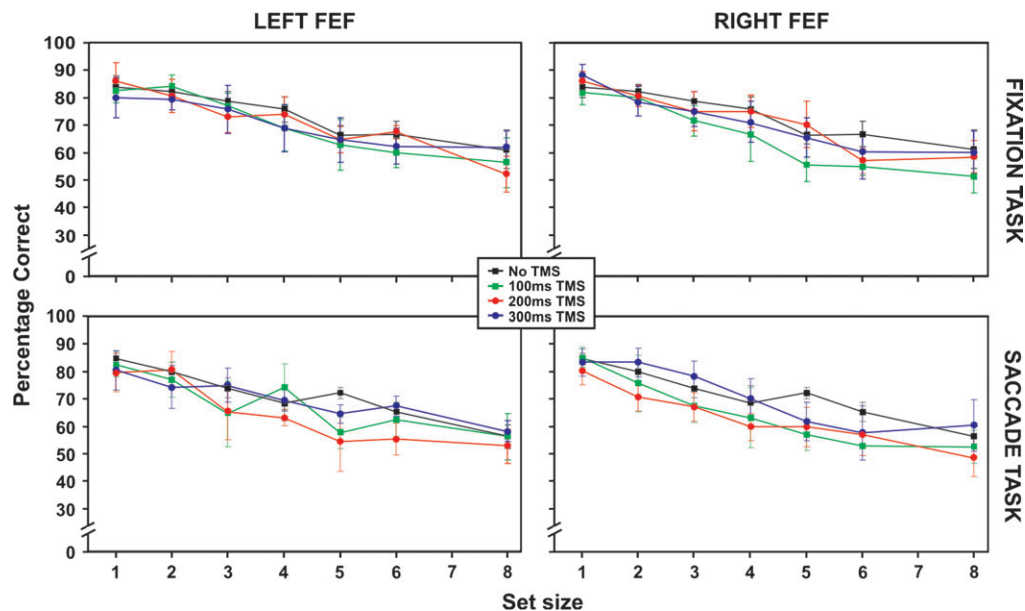


Figure 4. Main FEF TMS results. Left FEF TMS (A) and right FEF TMS (B) conditions for both the *Fixation Task* (top panels) and *Saccade Task* (bottom panels). These data are shown as mean percentage correct responses across all subjects ($n = 6$) against different set-sizes. Each colored data curve represents the different TMS time intervals in the TMS trials. The green curve represents the TMS data when TMS was delivered at the 100-ms time interval. Similarly, the red curve represents the 200-ms time interval and the blue curve represents the 300-ms time interval. As a comparison, we replotted the baseline No-TMS data curves from Figure 3 for each task (black curves). Error bars represent standard error.

baseline performance ($F_{1,5} = 3.32$; $P = 0.12$ and $F_{1,5} = 0.48$; $P = 0.51$, respectively).

Errors were observed more consistently in the *Saccade Task* (Fig. 4, bottom panels), with significant results for one of the time intervals for the left FEF and 2 of the time intervals for the right FEF. Left FEF TMS (Fig. 4A) elicited more errors at the 200-ms interval compared with baseline ($F_{1,5} = 6.73$; $P = 0.04$). No difference was found between the left FEF TMS and No-TMS conditions for the 100 and 300-ms TMS time intervals ($F_{1,5} = 0.87$; $P = 0.39$ and $F_{1,5} = 1.24$; $P = 0.32$, respectively). For the right FEF (Fig. 4B), TMS-induced errors relative to baseline were found in both the 100- and 200-ms intervals ($F_{1,5} = 7.09$; $P = 0.04$ and $F_{1,5} = 14.39$; $P < 0.01$, respectively), but no difference was found between the 300-ms interval and baseline ($F_{1,5} = 0.08$; $P = 0.78$). Thus overall we observed 2 trends similar to our previous observations with the PEF: greater effects for the *Saccade task*, and greater effects for the right hemisphere, but in this case there was less asymmetry in the *Saccade Task*.

We also analyzed the mean correct responses with respect to the timing of the TMS pulse relative to saccade onset in the *Saccade Task* for both the left and right FEF conditions. Mean correct responses were calculated for relative TMS timings that was divided into 50-ms-size bins relative to the onset of the saccade: that is, -500 to -450 ms, -450 to -400 ms, -400 to -350 ms, -350 to -300 ms, -300 to -250 ms, -250 to -200 ms, -200 to -150 ms, -150 to -100 ms, -100 to -50 ms, -50 to 0 ms, 0 to +50 ms, +50 to +100, and +100 to +150, where negative timings represent the TMS pulses delivered before the saccade and positive timings represent the TMS pulses delivered after the saccade. In the left FEF condition, mean correct responses were the lowest when the TMS pulse was delivered just before the onset of the saccade (-100 to -50 ms, $M = 49.23\%$, $SE = \pm 0.06\%$ and -50 to 0 ms, $M = 51.99\%$, $SE = \pm 0.04\%$) and immediately after saccade onset (0 to +50 ms, $M = 56.15\%$, $SE = \pm 0.02\%$). Mean correct responses increased as TMS timings increased further from saccade onset in both directions: for example, -200 to -150 ms, $M = 64.17\%$, $SE = \pm 0.04\%$ and +50 to +100 ms, $M = 69.17\%$, $SE = \pm 0.05\%$. These differences among these different TMS timing relative to saccade onset in the left FEF TMS was significant: $F_{13,42} = 2.28$; $P < 0.01$. Similar results were found in the right FEF condition except the greatest reduction in correct responses occurred earlier before the saccade at -200 to -150 ms ($M = 51.0\%$, $SE = \pm 0.03\%$), -150 to -100 ms ($M = 56.68\%$, $SE = \pm 0.03\%$), -100 to -50 ms ($M = 54.01\%$, $SE = \pm 0.09\%$), and -50 to 0 ms ($M = 59.73\%$, $SE = \pm 0.04\%$). Mean correct responses increased as TMS timings increased from saccade onset in both directions: for example, -250 to -200 ms ($M = 62.2\%$, $SE = \pm 0.04\%$) and 0 to 50 ms ($M = 66.32\%$, $SE = \pm 0.06\%$). These differences among these different TMS timing relative to saccade onset in the right FEF TMS was significant: $F_{13,42} = 2.92$; $P < 0.01$.

In our previous TMS study (Prime et al. 2008) we found that differences between the data curves in the TMS conditions relative to baseline were partially due to a downward shift in their intercepts, designated by the percentage correct at the set-size of 1 item. We also sought to determine if the same shift in intercept applies to the data in the present study. Separately for the left and right FEF in the *Saccade Task* where we found TMS effects, we compared percentage correct responses among the different TMS conditions and baseline No-TMS condition when the set-size was 1 item in both tasks. No differences were found in the *Saccade Task* during the right FEF TMS ($F_{3,20} = 0.14$; $P = 0.93$). Similarly, the left FEF TMS in the *Saccade Task* did not

yield any differences among the TMS time conditions and the No-TMS condition at 1 set-size ($F_{3,20} = 0.11$; $P = 0.95$). Though we did not find any shifts among the data curve intercepts relative to their respective baseline curve as in our previous study, there also was a complex effect on the rate at which performance dropped off for higher set-sizes. However, to be consistent with our previous study's analysis of the data, we still take into account the data curves' actual intercept at one item set-size when we fit models to the data (Fig. 6).

We also sought to determine whether the TMS effects were related to the visual hemifield the target was presented in or the direction of the saccade. We found no interaction between TMS site (left FEF vs. right FEF) and visual field (left hemifield vs. right hemifield) in either the *Fixation Task* ($F_{1,5} = 0.43$; $P = 0.55$) or the *Saccade Task* ($F_{1,5} = 0.12$; $P = 0.74$). Similarly, we found no interaction between TMS site (left FEF vs. right FEF) and saccade direction (left saccades vs. right saccades) in the *Saccade Task* ($F_{1,5} = 2.21$; $P = 0.19$).

Control Site and Sham Conditions

To rule out any nonspecific TMS-induced effect, control conditions were included—a vertex TMS condition and 2 sham conditions, one left FEF sham and the other right FEF sham. For these conditions, the same repeated measures ANOVAs were conducted as done earlier with the right and left FEF TMS conditions. None of TMS intervals in the vertex TMS condition yielded any significant differences relative to baseline No-TMS. Specifically, in the *Fixation Task* mean percentage correct was the same as baseline for TMS intervals at 100 ms ($F_{1,5} = 0.06$; $P = 0.82$), 200 ms ($F_{1,5} = 0.14$; $P = 0.72$), and 300 ms ($F_{1,5} = 0.3$, $P = 0.87$). Similarly, vertex TMS mean percentage correct in the *Saccade Task* was the same as baseline for TMS intervals at 100 ms ($F_{1,5} = 0.26$; $P = 0.63$), 200 ms ($F_{1,5} = 0.89$; $P = 0.39$), and 300 ms ($F_{1,5} = 0.003$; $P = 0.95$).

For each sham condition the data from the different TMS time intervals were pooled together, because no magnetic stimulation was actually delivered and comparisons between the TMS time intervals within each sham condition in both tasks confirmed that there were no statistical differences: different TMS time intervals in left sham condition and *Fixation Task* ($F_{2,15} = 0.76$; $P = 0.48$), in left sham condition and *Saccade Task* ($F_{2,15} = 1.11$; $P = 0.35$), in right sham condition and *Fixation Task* ($F_{2,15} = 0.99$; $P = 0.39$), and in right sham condition and *Saccade Task* ($F_{2,15} = 0.63$; $P = 0.54$). Other than simplifying the data analysis, the benefit of collapsing across TMS intervals would be to increase statistical power when comparing the sham conditions to baseline. Even so, left sham condition was found the same as baseline in both the *Fixation Task* ($F_{1,5} = 0.57$; $P = 0.48$) and the *Saccade Task* ($F_{1,5} = 0.02$; $P = 0.89$). Likewise, right sham data were the same as baseline in the *Fixation Task* ($F_{1,5} = 0.46$; $P = 0.53$) and the *Saccade Task* ($F_{1,5} = 1.81$; $P = 0.24$). In sum, no differences were found between the baseline condition—that is, No-TMS—and the control conditions. These results suggest that the effect of TMS on task performance by increasing subjects' errors in the present study was specific to the FEF.

Magnitude of the TMS Effect

The bar graphs in Figure 5 show the magnitude of the TMS-induced effect on the subjects' accuracy after calculating the mean change-correct, the differences of mean percentage

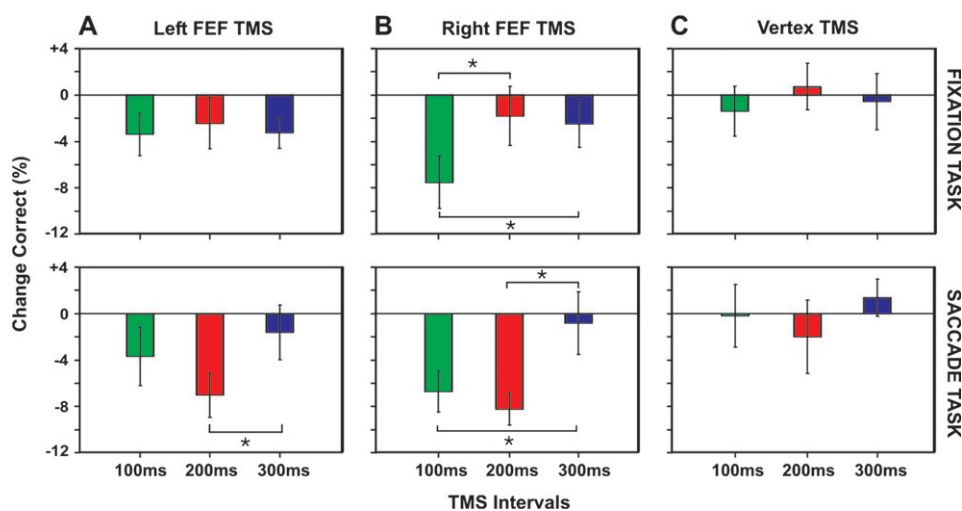


Figure 5. Magnitude of TMS effect. To determine the magnitude of the TMS effect we subtracted the TMS data curves of Figure 4 from their respective baseline No-TMS data from Fig3. The change in mean percentage correct is shown for the left FEF (A), the right FEF TMS (B), and the control site TMS aimed at the subjects' vertex (C). The top panels represent the change in the *Fixation Task* and the bottom panels represent the change in the *Saccade Task*. Positive numbers reflect a greater percentage correct and negative numbers reflect a lesser percentage correct compared with baseline. The line at zero represents no change from baseline. Consistent with Figure 4, left FEF TMS only increased errors in the *Saccade Task* at the 200-ms time interval. Performance in the *Fixation Task* was only disrupted in the right FEF TMS condition when TMS was delivered at the 100-ms time interval relative to other time intervals. The most errors were found in the *Saccade Task* during right FEF TMS where accuracy declined at the 100- and 200-ms TMS time intervals. No disruption was found for the vertex TMS and neither the right sham nor left sham (not shown).

correct responses between the No-TMS condition and left FEF TMS (Fig. 5A), right FEF TMS (Fig. 5B), and the vertex TMS (Fig. 5C). To simplify the analyses, the data was plotted according to TMS time intervals after collapsing set-size. These bar graphs are informative in that they show the change in percentage correct for each TMS condition relative to baseline condition and relative to the different TMS time intervals. Here, we can compare the mean change-correct among the different TMS intervals within each condition.

Comparisons of mean change-correct among the TMS time intervals in the *Fixation Task* during left FEF TMS (Fig. 5A) yielded no significant differences ($F_{2,18} = 0.18$; $P = 0.83$). However, differences were found in the *Saccade Task* ($F_{2,18} = 3.93$; $P = 0.04$). Post hoc Tukey tests show that accuracy for the 200-ms interval was significantly lower compared with 300 ms ($P = 0.03$), but no differences were found between 100 and 200 ms ($P = 0.5$) and 100 and 300 ms ($P = 0.25$). During right FEF TMS (Fig. 5B), mean change-correct among the different TMS time intervals were also found significant in the *Fixation Task* ($F_{2,18} = 4.37$; $P = 0.03$) and the *Saccade Task* ($F_{2,18} = 4.53$; $P = 0.02$). In the *Fixation Task*, post hoc tests show a significant difference between 100 ms and both the 200 ms ($P = 0.03$) and the 300 ms ($P = 0.05$), but no difference between 200 and 300 ms ($P = 0.95$). Post hoc tests in the *Saccade Task* yielded significant differences between 100 and 300 ms ($P = 0.05$) and 200 and 300 ms ($P = 0.02$). No difference was found between 100 and 200 ms ($P = 0.84$). Figure 5C shows the mean change-correct for the control site, the vertex TMS. No differences were found among the TMS intervals in the vertex TMS condition for both the *Fixation Task* ($F_{2,18} = 0.39$; $P = 0.68$) and the *Saccade Task* ($F_{2,18} = 0.29$; $P = 0.75$). Taken altogether, these mean change-correct results are consistent with our earlier analyses.

Estimating the Memory Capacity of Baseline and FEF Performance

As in our previous studies (Prime et al. 2007, 2008), we estimated subjects' memory capacity for the No TMS condition

from Figure 3 and the TMS conditions where we found TMS had an effect from Figure 4 (i.e., in the *Saccade Task* during left FEF TMS at 200 ms and during right FEF TMS at 100 and 200 ms) including the right FEF TMS in the *Fixation Task* at 100 ms where we found greater errors relative to other TMS intervals. To estimate the memory capacity in these conditions, we compared their data curves to the same predictive model from our previously cited studies. This model generates simple predictive curves of what the data would look like under different hypothetical memory capacities. This is not intended to be a formal model of visual working memory (see example Bays and Husain 2008), but rather to address a simple question in a way that allows quantitative comparison between conditions: how many visual objects can humans remember across saccades compared with simple fixation, with and without TMS? In formulating our simple model, we assumed that remembered items would be randomly selected from the target display and took into account subjects guessing when the set-size of the target display exceeded their memory capacity. As in our previous TMS study (Prime et al. 2008), the model took into account the different y -intercept positions (i.e., set-size of one item) of the data curves in the baseline and FEF TMS conditions so that the maximum predicted proportion of correct responses were free to vary according to their true performance at one item set-size. Thus, the model consisted of the expected proportion of correct responses (z), the obtained proportion of correct responses when the set-size of target display is one item (a), capacity of trans-saccadic memory (y), and number of items presented in the target display (x). This is expressed as:

$$z = \begin{cases} \frac{y \cdot a}{x} + \frac{x - y}{2x}, & \text{if } x \geq y \\ a, & \text{if } x < y \end{cases}$$

The model predicts different theoretical curves to show the expected proportion of correct responses (z) for each potential memory capacity (y) plotted as a function of set-size (x), plotted

in the same way as the data curves from Figure 4. These curves are characterized by a plateau in performance at a up until the memory capacity is reached, followed by a nonlinear drop-off in performance when the set-size exceeds the memory capacity. In order to quantitatively compare these predictive curves to the data curves in the current study, the actual a values obtained from each subject were used to plot the predictive curves (i.e., the percent correct for one object \times 0.01). To estimate our subjects' memory capacity, we calculated the mean squared residual (MSR) errors for each subject between their actual data and the curves of the predictive model at every specific set-size. The best fit between the predictive curve and the data was determined by the least MSR.

The bar graphs of Figure 6A and B shows the average MSR errors for the *Fixation Task* and *Saccade Task*, respectively. For brevity Figure 6 only shows MSR errors of the No-TMS conditions and FEF TMS conditions where TMS-induced greater errors. Lower bars signify a better fit. The No-TMS condition in the *Fixation Task* (Fig. 6A top panel) best fits the model predicting a capacity of 3 items. Similarly, the No TMS condition in the *Saccade Task* appeared to have a capacity of 3 items (Fig. 6B top left panel). A Mann-Whitney test comparing the MSR errors distributions between these 2 tasks yielded no statistical difference ($P = 0.84$). In general, these results replicate previous findings and are consistent with several studies showing that trans-saccadic memory and visual working memory have the same capacity of at least 3 objects (Irwin 1992; Irwin and Andrews 1996; Luck and Vogel 1997; Irwin and Gordon 1998; Vogel et al. 2001; Prime et al. 2007, 2008).

In general, TMS appeared to reduce this memory capacity. The 100-ms right FEF TMS condition in the *Fixation Task* yielded MSR errors that best fit the predictive curve for a memory capacity of only 1 item (Fig. 6A bottom panel). A comparison between MSR errors of the 100-ms right FEF TMS condition and baseline No-TMS in the *Fixation Task* was found significant ($P < 0.01$). The estimated memory capacity of the left FEF TMS condition at the 200-ms TMS time in the *Saccade*

Task declined to 2 items (Fig. 6B bottom-left panel). The Mann-Whitney test did not yield a significant difference between these MSR errors of the 200 ms left FEF TMS condition to those of the baseline No-TMS condition in the *Saccade Task* ($P = 0.18$). MSR errors of both 100- and 200-ms right FEF TMS in the *Saccade Task* at 100-ms TMS (Fig. 6B top-right panel and bottom-right panel, respectively) best fit the predictive curve for a memory capacity of only 1 item. Separate comparisons of these 2 right FEF TMS conditions of 100 and 200 ms with that of the baseline No-TMS in the *Saccade Task* were found significant (both $P < 0.01$). In summary, the TMS effects found in the left and right FEF TMS conditions showed a general reduction in the numerical capacity of object memory, but our predictive model suggests that the right FEF TMS showed a larger reduction to only one object.

Effects of TMS on Saccade Metrics and Latency

To ensure that the *Saccade Task* results were not simply due to TMS disrupting saccade metrics, saccade accuracy, and latency of the left and right FEF TMS conditions were compared with those of the baseline No-TMS condition. Some studies have shown evidence that TMS stimulation of the frontal cortex can affect saccade latency, but not amplitude, of endogenous saccades (Muri et al. 1991; Ro et al. 1997; Olk et al. 2006) and memory-guided saccades (Wipfli et al. 2001). However, these findings remain controversial—in particular, visually guided saccades, like the saccades done in this study, have been found to be unaffected by TMS (Muri et al. 1991; Wessel and Kompf 1991; Ro et al. 1997). Here, we show that the changes in *Saccade Task* performance cannot be attributed to changes in saccade metrics. We compared the baseline No-TMS condition to each FEF TMS condition with respect to mean saccade error, mean ellipse area, and saccade latency.

Mean saccade error was calculated as the average distance between the saccade-target (i.e., second fixation-cross) and the postsaccadic eye position after the primary saccade (i.e., saccade end-point). No statistical differences of mean

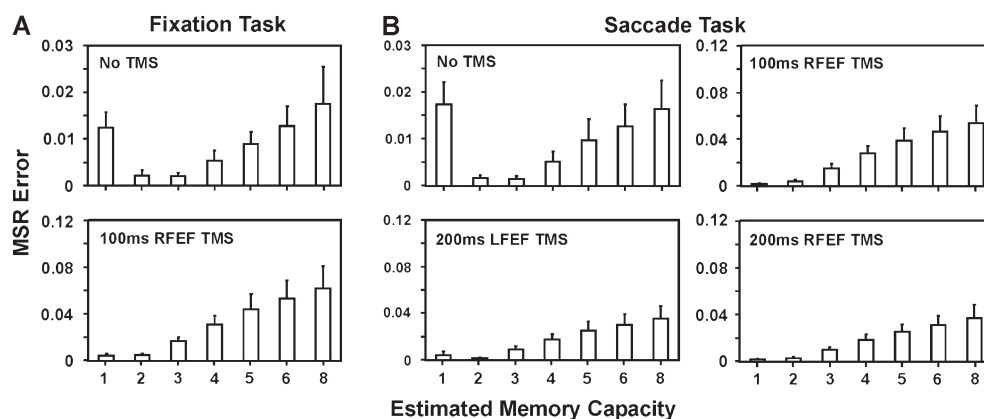


Figure 6. Estimating memory capacity during FEF stimulation. We used a simple predictive model from our previous study (Prime et al. 2007) for estimating the numerical memory capacity of trans-saccadic memory and simple working memory. To determine which predictive curve from our predictive model estimating a specific memory capacity best fit our data curves, we calculated the mean square residual errors (MSR errors) between the predictive curves and these data curves from Figure 4. Bar graphs represent the average MSR errors across all subjects after calculating the MSR errors for each subject individually. The least average MSR error indicates the best fit to a theoretical memory capacity according to our predictive model. For brevity we only show MSR errors for the FEF TMS conditions where we found significant effects. (A) MSR errors of the baseline No-TMS condition (top panel) and 100-ms right FEF TMS (bottom panel) in the *Fixation Task*. The average MSR errors of the No-TMS condition best fit our predictive model estimating a memory capacity of 3 items, replicating our previous results (Prime et al. 2007). MSR errors of the 100-ms right FEF TMS show a reduced capacity estimate to 1 item. (B) MSR errors of the baseline No-TMS condition (top left panel), 200-ms left FEF TMS (bottom left panel), 100-ms right FEF TMS (top right panel), and 200-ms right FEF TMS (bottom right panel) in the *Saccade Task*. MSR errors of the No-TMS best fit our predictive model estimating 3 items capacity. Again, this replicated our previous results. During 200-ms left FEF TMS in the *Saccade Task*, memory capacity was reduced to 2 items. Memory capacity in both the 100- and 200-ms right FEF TMS conditions was reduced to 1 item.

saccade error were found between the baseline No-TMS condition and both FEF TMS conditions: No-TMS versus left FEF TMS ($t_{(14)} = -0.3$; $P = 0.96$) and No-TMS vs. right FEF TMS ($t_{(14)} = -0.46$; $P = 0.65$). Similarly, the mean ellipse area of the saccade end-points in the baseline No-TMS condition was the same as left and right FEF TMS conditions: $t_{(14)} = 1.02$; $P = 0.32$ and $t_{(14)} = 0.58$; $P = 0.57$, respectively. Finally, no differences were found for average saccade latency among the different conditions: No-TMS vs. left FEF ($t_{(14)} = -1.14$; $P = 0.27$) and No-TMS vs. right FEF ($t_{(14)} = -1.62$; $P = 0.13$). Taken together, these results show that the TMS-induced effect found in the FEF TMS conditions cannot be attributed to TMS-induced changes to the subjects' saccades, consistent with other TMS studies (Muri et al. 1991; Wessel and Kompf 1991; Ro et al. 1997), but instead were due to disruptions of the putative cognitive processes mediated by stimulating the FEF.

Discussion

In the present study, TMS was used to determine whether the FEF plays a role in trans-saccadic memory of multiple object features. The main findings show that TMS disrupted performance in the *Saccade Task* when stimulation was applied to either the right or left FEF, but not because it changed the subjects' saccade metrics. These observed TMS effects were dependent on the timing of the TMS pulse. Specifically, TMS disruption in the *Saccade Task* was found at 100 and 200 ms in the right FEF TMS condition but only at 200 ms in the left FEF TMS condition. Our analyses of the TMS timing relative to saccade onset revealed that the largest TMS effect was found when the TMS pulse was delivered immediately before saccade onset and, in the case of the left FEF condition, immediately after saccade onset. *Fixation Task* performance was not disrupted during left FEF stimulation; however, differences among TMS time intervals in the *Fixation Task* were found when TMS was applied to the right FEF. In the baseline condition without TMS, subjects were able to retain about 3 items in both the *Saccade* and *Fixation* tasks, replicating previous results (Prime et al. 2007, 2008). However, this capacity seemed to be generally reduced in conditions where we observed a TMS effect. Taken together, our results suggest that the FEF plays a functional role in maintaining visual details in trans-saccadic memory.

Significant TMS Effects in the Saccade Task

Our *Saccade Task* involved 2 aspects—subjects had to remember the orientations of multiple objects and spatially update the locations of these objects to take into account the saccade. We found that TMS during the *Saccade Task* elicited a consistent performance deficit when the magnetic pulse was delivered at 200 ms in both the left and right FEF conditions, coinciding most closely with the time of the saccade. We suggest these TMS-induced disruptions may be due to TMS injecting “neural noise” into the saccade signals that arise when subjects are about to make a saccade. How would neural noise in the saccade signal interfere with *Saccade Task* performance? The *Saccade Task* was designed so that subjects would have to remember the feature *and* location details of multiple objects across the saccade to compare the postsaccadic probe with the correct presaccadic target, the target sharing the same spatial location as the probe. To perform the *Saccade Task* accurately, objects stored in trans-saccadic memory must be spatially

updated across the saccade. Thus, compared with the *Fixation Task*, trans-saccadic memory must use oculomotor signals about the saccade vector to take the change of gaze into account. We have previously proposed that trans-saccadic memory may “borrow” spatial remapping mechanisms, like those found in the FEF (Umeno and Goldberg 1997, 2001; Sommer and Wurtz 2006), for updating the spatial locations of visual stimuli stored in memory across saccades (Prime et al. 2006, 2008). The TMS-induced deficit in the *Saccade Task* around the time of the saccade offers support for this hypothesis.

Right FEF More Susceptible to TMS in the Saccade Task

Our results show that stimulation of either the left or right FEF disrupted *Saccade Task* performance. However, this deficit was broader in the right FEF condition—left FEF was disrupted at only at the 200-ms TMS time, whereas the right FEF was disrupted at 100 and 200 ms. These findings were consistent with our analysis of TMS timings relative to saccade onset showing that the TMS effect in the right FEF condition was broader and occurred earlier than in the left FEF condition. This broader TMS effect during right FEF stimulation appear consistent with previous findings that show the frontal and parietal cortices of the right hemisphere have a privileged role in spatial memory (Jonides et al. 1993; Smith et al. 1995; Asselen et al. 2006; c.f., Ruchkin et al. 1997) including a variety of other visuospatial tasks (Honda et al. 1998; Karnath et al. 2004; Weidner and Fink 2007). Indeed, the right FEF has been argued to be specialized for visuospatial processes (Muggleton et al. 2003; O'Shea et al. 2004).

On the other hand, the deficit in *Saccade Task* performance in the left FEF TMS condition found only at the 200-ms TMS time may also be consistent with recent TMS studies that show magnetically stimulating the left FEF disrupts spatial priming (Campana et al. 2007; O'Shea et al. 2007) and interferes with attentional orienting (Smith et al. 2005). We add to these findings by showing that the left FEF also plays a role in maintaining visual information across saccades.

TMS Effect is Time Dependent

The findings that the TMS-induced disruptions depended on the timing of the TMS pulse might suggest a possible “mental chronometry” of both memory systems (i.e., trans-saccadic memory and visual working memory) where different cortical areas are active at different cognitive stages (e.g., Bledowski et al. 2006). We have already discussed the larger TMS-induced errors in the *Saccade Task* when the magnetic pulse was delivered over the right or left FEF at 200 ms, the stimulation time that was closest to time of the subjects' saccade confirmed by our analyses of TMS timing relative to saccade onset. We proposed that these larger errors at 200 ms in the *Saccade Task* may reflect TMS disruption of the spatial remapping mechanisms found in the FEF that are active around the time of a saccade (Umeno and Goldberg 1997, 2001; Sommer and Wurtz 2006), and possibly used in trans-saccadic memory to spatially update objects in our *Saccade Task*. We also found that TMS over the right FEF in the *Fixation Task* yielded more errors when delivered at 100 ms relative to the other TMS time intervals (i.e., 200 and 300 ms). These greater errors in *Fixation Task* performance during right FEF TMS could suggest that the mental chronometry of working memory without saccades (*Fixation Task*) and trans-saccadic mem ory

(*Saccade Task*) roughly overlap in the right FEF. However, we do not wish to make strong conclusions about the *Fixation Task* because we failed to find a significant TMS effect compared with the baseline No TMS condition.

TMS Effect not Attributed to Changes in Saccade Metrics

The results here show that the FEF TMS effect in the *Saccade Task* cannot be attributed to TMS affecting our subjects' saccadic eye movements. Some recent TMS studies of FEF have also induced changes to putative cognitive processes without affecting eye movement (Grosbras and Paus 2002; Muggleton et al. 2003; O'Shea et al. 2004, 2007; Campana et al. 2007). Other studies have shown that TMS over the FEF can increase the latency of endogenous saccades (Muri et al. 1991; Ro et al. 1997; Olk et al. 2006) and memory-guided saccades (Wipfli et al. 2001) when applied at a precise time interval before the saccade. However, the evidence that TMS over the FEF affects saccade latency remains controversial. First, TMS impairment of endogenous saccades is susceptible to between-subject variability (Muri et al. 1991; Ro et al. 2002). Second, the TMS effect on saccade latency has been shown to be inconsistent when TMS is applied to identical sites on the opposite hemisphere (Leff et al. 2001). Finally, TMS of the FEF does not appear to affect visually guided saccades (Muri et al. 1991; Wessel and Kompf 1991; Ro et al. 1997; Terao et al. 1998), like the saccades used in our task. Thus, these findings suggest that the TMS effect on saccade latency may be task-dependent, specific to saccades with a top-down or memory component, which does not apply to the visually guided saccades subjects made in our task.

Comparing Results from Current FEF TMS Results with Previous PEF TMS Study

Because the PEF and FEF are heavily interconnected (Stanton et al. 1995) and because TMS may produce both local and network effects (Paus et al. 1997; Ruff et al. 2008) it is not surprising that our current results show some similarities to our previous results with the PEF (Prime et al. 2008). However, we did find 3 key differences that might be instructive to understanding the differential roles of these structures in trans-saccadic memory: unlike the PEF results we found no baseline deficit at one item; the TMS effect in the PEF study was limited to the right hemisphere while the TMS effect here was found in both hemispheres during the *Saccade Task* only; and, using the same TMS timings yielded slightly different timing effects of the TMS pulse. We elaborate on each of these differences between the current FEF results and the previous PEF study below.

First, in our previous study we found that TMS over the PEF reduced memory capacity for even one feature. In contrast, we observed little or no effect of TMS over the FEF on memory of one feature. This may suggest that the PEF has a more direct role in feature analysis (or at least more direct connections with areas that carry out feature analysis). In contrast, TMS over both structures reduced memory capacity for multiple targets (which in our task required spatial knowledge), especially in the presence of a saccade. This suggests that—consistent with neurophysiological findings (Wurtz 2008)—both of these areas participate in the mapping and remapping of spatial locations and communicate this information to areas of the brain involved in feature memory.

Second, TMS-induced disruptions of the *Fixation Task*, testing working memory without saccades, occurred when

magnetically stimulating the PEF of the right hemisphere. In the present study, we found errors were greater when stimulating the right FEF at the 100-ms time interval relative to other TMS time intervals (i.e., 200 and 300 ms), but this increase in TMS-induced errors only approached statistical significance compared with the baseline No TMS condition. On the other hand, whereas trans-saccadic memory was only disrupted during right PEF stimulation, here we were able to disrupt trans-saccadic memory during stimulation of both the left and right FEF. Note again that the *Saccade Task* is associated with updating dependent on saccade efference copies. This might mean that the cortical asymmetry of TMS effects here is most closely linked to visual working memory per se (e.g., Jonides et al. 1993; Smith et al. 1995), whereas there is less asymmetry to the effects on the saccade efference signals used for updating, which are more fully processed at the level of the FEF (Sommer and Wurtz 2008).

Finally, the results from both studies show slightly different timing effects of the TMS pulse. Right PEF TMS disruption in the *Saccade Task* was found at all 3 TMS times (i.e., 100, 200, and 300 ms) but largest at 200 ms. Here, the TMS effect in the left FEF condition here was limited to only the 200-ms TMS time in the *Saccade Task*, and the right FEF condition yielded an equal deficit at 100 and 200 ms. Furthermore, in our PEF study where we found that *Fixation Task* performance was disrupted at 200-ms TMS. However, the present study shows only greater errors in the *Fixation Task* when TMS was delivered over the right FEF earlier at 100 ms. This slightly earlier effect compared with PEF TMS at 100 ms when TMS was applied to the right FEF may be consistent with the “fast brain” hypothesis of the FEF (Bullier 2001), which suggests that the FEF occupies the same level of the visual processing hierarchy as the visual cortex (Nowak and Bullier 1997; Schmolesky et al. 1998) rather than the same level of the parietal cortex as generally thought (e.g., Maunsell and van Essen 1987).

Overall, these differences between the PEF and FEF results may be consistent with the view that the FEF and PEF subserve different functions in visuospatial processing and oculomotor control. Specifically, the PEF is thought to act as a general salience map of object locations that integrates sensory and motor information for a variety of cognitive and behavioral tasks (Andersen and Buneo 2002; Goldberg et al. 2006; Gottlieb 2007). On the other hand, the salience map of the FEF is more specifically tied with latter stages of oculomotor processing downstream from the PEF (Pierrot-Deseilligny et al. 1995) receiving information from both the dorsal and ventral streams of visual processing (Huerta et al. 1987; Schall et al. 1995).

Putative Mechanisms for Trans-saccadic Memory

To perform the *Saccade Task* accurately, our task for testing trans-saccadic memory, information stored in working memory must be remapped according to the saccade's metrics (Hayhoe et al. 1991; Prime et al. 2006). In our previous TMS study of the PEF, we showed that trans-saccadic memory of multiple feature objects was disrupted when TMS was applied to the right, but not the left, PEF around the time of the saccade (Prime et al. 2008). The PEF is well-known for its role in maintaining spatial constancy by updating neural representations of object locations across saccades, a process called spatial remapping (Duhamel et al. 1992; Colby and Goldberg 1999; Medendorp et al. 2003; Merriam et al. 2003). The PEF may also be involved in other functions such as numerical processing (Sawamura

et al. 2002; Nieder and Miller 2004; Hubbard et al. 2005) and attention (Shomstein et al. 2006; Saalman et al. 2007), but perturbations to these mechanisms would not explain why our TMS effects were more prominent during saccades. Therefore, we argued that 1) the TMS-induced disruptions we found when stimulating the right PEF were likely due to the magnetic stimulation adding “neural noise” to the spatial remapping process, and 2) that these remapping mechanisms are used for trans-saccadic memory of the spatial locations of multiple object features (see also Melcher and Colby 2008, for a similar account of trans-saccadic perception.)

Here, we add to our previous PEF TMS findings by showing novel results that the FEF also plays a role in trans-saccadic memory. Specifically, TMS-induced disruptions were found when stimulating both the right and left FEFs during the *Saccade Task*. Both the PEF and FEF are part of the same complex cortical network that governs saccadic eye movements (Leichnetz and Goldberg 1988; Pierrot-Deseilligny et al. 2004; Milea et al. 2007), as well as a variety of visuospatial processes such as spatial working memory (Jonides et al. 1993; Smith et al. 1995; Courtney et al. 1998; Gaymard et al. 1999; Curtis and D’Esposito 2006), visual search (Schall and Hanes 1993; O’Shea et al. 2006; Anderson et al. 2007), and visual attention (Petersen et al. 1994; Corbetta et al. 1998; Beauchamp et al. 2001; Juan et al. 2004; Shomstein et al. 2006; Saalman et al. 2007).

The TMS effects we observed when stimulating the FEF could be partially explained by TMS disrupting any of these visuospatial processing. For instance, our TMS results may reflect interference strictly to working memory regardless of any intervening saccade made during the memory interval as in the *Saccade Task*. Such an explanation would seem consistent with previous studies that show TMS applied over the FEF can disrupt spatial memory in the absence of eye movements (Kessels et al. 2000; Oliveri et al. 2001; Tanaka 2005; Campana et al. 2007; O’Shea et al. 2007). Furthermore, the close proximity of other prefrontal neurons associated with maintaining memory of object identity and location as shown in the monkey (Rayner 1998), one might suggest that the area of cortical stimulation by the TMS pulse aimed at the FEF may have included these neighboring prefrontal neurons. An alternative explanation may be related to the attentional control process mediated by the FEF. The FEF has been implicated as part of a top-down attentional control network of higher cortical regions in the visual system’s processing hierarchy that modulates stimulus selection processes in earlier visual areas (Hopfinger et al. 2000; Hamker 2005a, b; Bressler et al. 2008; for review see Kastner and Ungerleider 2000). The TMS effects we observed could be due to TMS disrupting these top-down attentional control signals originating from the FEF and disrupting the stimulus-selection processes in the visual cortex involved in encoding targets in memory. Indeed, top-down modulation of visual cortex activity has been found when the FEF was microstimulated in the monkey (Moore and Armstrong 2003) and magnetically stimulated in the human (Ruff et al. 2006, 2008). We cannot completely discount the possibility that the TMS effect in the *Saccade Task* is not at least partially attributable to either of these 2 potential explanations.

However, none of these explanations accounts for our finding that the disruptive effects of TMS were most robust in the *Saccade Task*, particularly when timed to coincide with the saccade. In our trans-saccadic memory task, object features

must be spatially updated across saccades. The FEF is known to be involved in the spatial remapping of remembered saccade targets during intervening saccades (Umeno and Goldberg 1997, 2001; Sommer and Wurtz 2006). Rather than proposing a new mechanism to explain our TMS effect, it seems most parsimonious to propose that this effect was caused by the injection of neural noise into this same spatial updating mechanism. Thus, we propose that the same spatial remapping mechanisms that arise in the FEF for saccade targets might also be used for updating the spatial component of trans-saccadic memory, perhaps in combination with signals originating in the PEF (Prime et al. 2008). Again, our finding here that FEF perturbation had less effect on the memory of one object compared with PEF perturbation suggests that the signal affected by FEF TMS might be more purely motor or spatial in nature, whereas the PEF may play additional roles.

This efference/spatial updating theory does not contradict our finding that TMS to the FEF also had borderline effects on visual memory during fixation in the current experiment, or the findings of other visual memory experiments during fixation (Kessels et al. 2000; Oliveri et al. 2001; Tanaka 2005; Campana et al. 2007; O’Shea et al. 2007). First, the TMS effect in the *Fixation Task* may reflect a general reduction in visual working memory. However, this can also be explained in terms of the role of the FEF in spatial updating. The eye is almost always transitioning from movement to fixation during normal vision. To work properly, spatial updating system should not disappear during fixation, but rather should *inform* the visual system that the eyes are fixating. From a computational standpoint, it is equally important for the visual system to know that the eye is moving at zero velocity as it is to know that it is making a saccade, microsaccade, or smooth pursuit eye movement. The FEF appears to be involved in all of these movements (Petit and Haxby 1999; Rosano et al. 2002). Thus, injection of noise into these signals could still produce spatial errors in working memory during fixation, by reducing certainty about eye position. However the effect of TMS on the FEF appears to be less during fixation compared with saccades, either because lower levels of neural activity or less susceptible to TMS-induced noise, or because this noise is likely to be somewhat damped by inhibitory inputs from the fixation system (Munoz and Everling 2004).

The central problem of trans-saccadic memory is that it requires spatial information to update object feature information across a saccade—that is, feature information must be synthesized with saccade signals somewhere in the visual system. It is widely believed that different aspects of visual processing are broadly segregated into 2 separate visual streams in the brain, the ventral stream for object feature analysis that projects from the visual cortex to the temporal cortex, and the dorsal stream for visuospatial processing for perception and action that projects from the visual cortex to the posterior parietal cortex (Ungerleider and Mishkin 1982; Goodale and Milner 1992). Thus, the issue of how object information is spatially updated in trans-saccadic memory is synonymous with how these 2 visual streams interact.

In the case of trans-saccadic integration, the targets of the “dorsal stream” spatial updating signals perturbed in our experiments is likely the normal network for visual object memory originating in the ventral stream of vision and culminating in the frontal cortex (Baker et al. 1996; Courtney et al. 1996; McCarthy et al. 1996). The FEF in particular is known to be connected

to areas throughout this network, from visual area V4 to dorsolateral prefrontal cortex (Moore and Armstrong 2003; Pierrot-Deseilligny et al. 2004; Ruff et al. 2008). Thus, as argued in our previous paper (Prime et al. 2008), these “dorsal-ventral” interactions might take different forms, depending more on top-down mechanisms in multiple object tasks such as ours, and perhaps relying partially on automated feedback mechanisms through earlier levels of visual cortex for the processing of low-level feature properties within objects (Melcher 2005; Melcher and Vidnyánszky 2006; Wittenberg et al. 2008). Consistent with our latter proposal, a recent fMRI study showed that activity related to the maintenance of feature information in working memory is retained in early retinotopic visual areas in the human (Harrison and Tong 2009). But whichever mechanism is used for visuospatial memory, because humans make several saccades per second, it can only be valid in real world circumstances if it accounts for eye movement. Our studies suggest that it does this with the use of signals from both the PEF and FEF.

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References

Andersen RA, Buneo CA. 2002. Intentional maps in posterior parietal cortex. *Annu Rev Neurosci.* 25:189-220.

Anderson EJ, Mannan SK, Husain M, Rees G, Sumner P, Mort DJ, McRobbie D, Kennard C. 2007. Involvement of prefrontal cortex in visual search. *Exp Brain Res.* 180(2):289-302.

Asselen M, van Kessels RPC, Neggers SFW, Kapelle LJ, Frijns CJM, Postma A. 2006. Brain areas involved in spatial working memory. *Neuropsychologia.* 44:1185-1194.

Baker SC, Frith CD, Frackowiak RS, Dolan RJ. 1996. Active representation of shape and spatial location in man. *Cereb Cortex.* 6:612-619.

Bays PM, Husain M. 2008. Dynamic shifts of limited working memory resources in human vision. *Science.* 321:851-854.

Beauchamp MS, Petit L, Ellmore TM, Ingeholm J, Haxby JV. 2001. A parametric fMRI study of overt and covert shifts of visuospatial attention. *Neuroimage.* 14(2):310-321.

Bledowski C, Kadosh KC, Wibrall M, Rahm B, Bittner RA, Hoechstetter K, Scherg M, Maurer K, Goebel R, Linden DEJ. 2006. Mental chronometry of working memory retrieval: a combined functional magnetic resonance imaging and event-related potentials approach. *J Neurosci.* 26(3):821-829.

Borojerdi B, Meister IG, Foltys H, Sparing R, Cohen LG, Topper R. 2002. Visual and motor cortex excitability: a transcranial magnetic stimulation study. *Clin Neurophysiol.* 113:1501-1504.

Brasil-Neto JP, McShane LM, Fuhr P, Hallett M, Cohen LG. 1992. Topographic mapping of the human motor cortex with magnetic stimulation: factors affecting accuracy and reproducibility. *Electroencephalogr Clin Neurophysiol.* 85:9-16.

Bressler SL, Tang W, Sylvester CM, Shulman GL, Corbetta M. 2008. Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention. *J Neurosci.* 28:10056-10061.

Bullier J. 2001. Integrated model of visual processing. *Brain Res Rev.* 36(2-3):96-107.

Buschman TJ, Miller EK. 2007. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science.* 315:1860-1862.

Campana G, Cowey A, Casco C, Oudsen I, Walsh V. 2007. Left frontal eye field remembers “where” but not “what. *Neuropsychologia.* 45:2340-2345.

Colby CL, Goldberg ME. 1999. Space and attention in parietal cortex. *Annu Rev Neurosci.* 22:319-349.

Connolly JD, Goodale MA, Menon RS, Munoz DP. 2002. Human fMRI evidence for the neural correlates of preparatory set. *Nat Neurosci.* 5:1345-1352.

Corbetta M, Akbudak E, Conturo TE, Snyder AZ, Ollinger JM, Drury HA, Linenweber MR, Petersen SE, Raichle ME, van Essen DC, et al. 1998. A common network of functional areas for attention and eye movements. *Neuron.* 21(4):761-773.

Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV. 1998. An area specialized for spatial working memory in human frontal cortex. *Science.* 279:1347-1351.

Courtney SM, Ungerleider LG, Keil K, Haxby JV. 1996. Object and spatial visual working memory activate separate neural systems in human cortex. *Cereb Cortex.* 6:39-49.

Curtis CE. 2006. Prefrontal and parietal contributions to spatial working memory. *Neuroscience.* 139:173-180.

Curtis CE, D’Esposito M. 2006. Selection and maintenance of saccade goals in the human eye fields. *J Neurophysiol.* 95:3923-3927.

Duhamel J, Colby CL, Goldberg ME. 1992. The updating of the representation of visual space in parietal cortex by intended eye movements. *Science.* 255:90-92.

Epstein CM, Schwartzberg DG, Davey KR, Sudderth DB. 1990. Localizing the site of magnetic brain stimulation in humans. *Neurology.* 40:666-670.

Gaymard B, Ploner CJ, Rivaud-Pechoux S, Pierrot-Deseilligny C. 1999. The frontal eye field is involved in spatial short-term memory but not in reflexive saccade inhibition. *Exp Brain Res.* 129:288-301.

Goldberg ME, Bisley JW, Powell KD, Gottlieb J. 2006. Saccades, salience, and attention: the role of the lateral intraparietal area in visual behavior. *Prog Brain Res.* 155:157-175.

Goodale MA, Milner AD. 1992. Separate visual pathways for perception and action. *Trends Neurosci.* 15(1):20-25.

Gottlieb J. 2007. From thought to action: the parietal cortex as a bridge between perception, action, and cognition. *Neuron.* 53:9-16.

Grosbras MH, Laird AR, Paus T. 2005. Cortical regions involved in eye movements, shifts of attention, and gaze perception. *Hum Brain Mapp.* 25:140-154.

Grosbras MH, Paus T. 2002. Transcranial magnetic stimulation of the human frontal eye field: effects on visual perception and attention. *J Cogn Neurosci.* 14(7):1109-1120.

Hamker FH. 2005a. The reentry hypothesis: the putative interaction of the frontal eye field, ventrolateral prefrontal cortex, and areas V4, IT for attention and eye movement. *Cereb Cortex.* 15(4):431-447.

Hamker FH. 2005b. A computational model of visual stability and change detection during eye movements in real world scenes. *Vis Cogn.* 12:1161-1176.

Harris IM, Benito CT, Ruzzoli M, Miniussi C. 2008. Effects of right parietal transcranial magnetic stimulation on object identification and orientation judgments. *J Cogn Neurosci.* 20(5):916-926.

Harrison SA, Tong F. 2009. Decoding reveals the contents of visual working memory in early visual areas. *Nature.* 458:632-635.

Hayhoe M, Lachter J, Feldman J. 1991. Integration of form across saccadic eye movements. *Perception.* 20:393-402.

Honda H. 1991. The time courses of visual mislocalization and of extraretinal eye position signals at the time of vertical saccades. *Vis Res.* 31:1915-1921.

Honda H. 1999. Modification of saccade-contingent visual mislocalization by the presence of a visual frame of reference. *Vis Res.* 39:51-57.

Honda M, Wise SP, Weeks RA, Deiber MP, Hallett M. 1998. Cortical areas with enhanced activation during object-centered spatial information processing: a PET study. *Brain.* 121(11):2145-2158.

Hopfinger JB, Buonocore MH, Mangun GR. 2000. The neural mechanisms of top-down attentional control. *Nat Neurosci.* 3(3):284-291.

Hubbard EM, Piazza M, Pinel P, Dehaene S. 2005. Interactions between number and space in parietal cortex. *Nat Rev Neurosci.* 6(6):435-448.

Huerta MF, Krubitzer LA, Kaas JH. 1987. Frontal eye field as defined by intracortical microstimulation in squirrel monkeys, owl monkeys

- and macaque monkeys. II. Cortical connections. *J Comp Neurol*. 265:332-361.
- Irwin DE. 1991. Information integration across saccadic eye movements. *Cogn Psychol*. 23:420-456.
- Irwin DE. 1992. Memory for position and identity across eye movements. *J Exp Psychol Learn Mem Cogn*. 18:307-317.
- Irwin DE. 1996. Integrating information across saccadic eye movements. *Curr Dir Psychol Sci*. 5:94-100.
- Irwin DE, Andrews R. 1996. Integration and accumulation of information across saccadic eye movements. In: Inui T, McClelland JL, editors. *Attention and performance XVI: information integration in perception and communication*. Cambridge (MA): MIT Press. p. 125-155.
- Irwin DE, Gordon RD. 1998. Eye movements, attention, and transsaccadic memory. *Vis Cogn*. 5(1/2):127-155.
- Jonides J, Smith EE, Koeppel RA, Awh E, Minoshima S, Mintun MA. 1993. Spatial working memory in humans as revealed by PET. *Nature*. 363:623-625.
- Juan CH, Muggleton NG, Tzeng OJL, Hung DL, Cowey A, Walsh V. 2008. Segregation of visual selection and saccades in human frontal eye fields. *Cereb Cortex*. 18(10):2410-2415.
- Juan CH, Shorter-Jacobi SM, Schall JD. 2004. Dissociation of spatial attention and saccade preparation. *Proc Natl Acad Sci U S A*. 101:15541-15544.
- Karnath HO, Berger MF, Kuker W, Rorden C. 2004. The anatomy of spatial neglect based on voxelwise statistical analysis: a study of 140 patients. *Cereb Cortex*. 14:1164-1172.
- Kastner S, Ungerleider LG. 2000. Mechanisms of visual attention in the human cortex. *Annu Rev Neurosci*. 23:315-341.
- Kessels RPC, d'Alfonso AAL, Postma A, de Haan EH. 2000. Spatial working memory performance after high-frequency repetitive transcranial magnetic stimulation of the left and right posterior parietal cortex in humans. *Neurosci Lett*. 287:68-70.
- Lappe M, Awater H, Krekelberg B. 2000. Postsaccadic visual references generate presaccadic compression of space. *Nature*. 403:892-895.
- Leff AP, Scott SK, Rothwell JC, Wise RJS. 2001. The planning and guiding of reading saccades: a repetitive transcranial magnetic stimulation study. *Cereb Cortex*. 11:918-923.
- Leichnetz GR, Goldberg ME. 1988. Higher centres concerned with eye movement and visual attention: cerebral cortex and thalamus. In: Buttner-Ennever JA, editor. *Neuroanatomy of the oculomotor system*. New York (NY): Elsevier. p. 365-429.
- Luck SJ, Vogel EK. 1997. The capacity of visual working memory for features and conjunctions. *Nature*. 399:279-281.
- Matin E. 1974. Saccadic suppression: a review and an analysis. *Psychol Bull*. 81:899-917.
- Maunsell JH, van Essen DC. 1987. Topographic organization of the middle temporal visual area in the macaque monkey: representational biases and the relationship to callosal connections and myeloarchitectonic boundaries. *J Comp Neurol*. 266(4):535-555.
- McCarthy G, Puce A, Constable RT, Krystal JH, Gore JC, Goldman-Rakic P. 1996. Activation of human prefrontal cortex during spatial and nonspatial working memory tasks measured by functional MRI. *Cereb Cortex*. 6:600-611.
- Medendorp WP, Goltz H, Vilis T, Crawford JD. 2003. Gaze-centered updating of visual space in human parietal cortex. *J Neurosci*. 23:6209-6214.
- Melcher D. 2005. Spatiotopic transfer of visual-form adaptation across saccadic eye movements. *Curr Biol*. 15:1745-1748.
- Melcher D, Colby CL. 2008. Trans-saccadic perception. *Trends Cogn Neurosci*. 12(12):466-473.
- Melcher D, Vidnyánszky Z. 2006. Subthreshold features of visual objects: unseen but not unbound. *Vis Res*. 46:1863-1867.
- Merriam EP, Genovaese CR, Colby CL. 2003. Spatial updating in human parietal cortex. *Neuron*. 39:361-373.
- Milea D, Lobel E, Lehericy S, Leboucher P, Pochon JB, Pierrot-Deseilligny C, Berthoz A. 2007. Prefrontal cortex is involved in internal decision of forthcoming saccades. *Neuroreport*. 18(12):1221-1224.
- Miller JM. 1996. Egocentric localization of a perisaccadic flash by manual pointing. *Vis Res*. 36:837-851.
- Moore T, Armstrong KM. 2003. Selective gating of visual signals by microstimulation of frontal cortex. *Nature*. 421:370-373.
- Muggleton NG, Juan CH, Cowey A, Walsh V. 2003. Human frontal eye fields and visual search. *J Neurophysiol*. 89:3340-3343.
- Munoz DP, Everling S. 2004. Look away: the anti-saccade task and the voluntary control of eye movements. *Nat Neurosci*. 5(3):218-228.
- Muri RM, Hess CW, Meienberg O. 1991. Transcranial stimulation of the human frontal eye field by magnetic pulses. *Exp Brain Res*. 86:219-223.
- Neggers SFW, Huijbers W, Vrijlandt CM, Vlaskamp BNS, Schutter DJLG, Kenemans JL. 2007. TMS pulses on the frontal eye fields break coupling between visuospatial attention and eye movements. *J Neurophysiol*. 98(5):2765-2778.
- Nieder A, Miller EK. 2004. A parieto-frontal network for visual numerical information in the monkey. *Proc Natl Acad Sci U S A*. 101(19):7457-7462.
- Nowak LG, Bullier J. 1997. The timing of information transfer in the visual system. In: Rockland EA, editor. *Cerebral cortex*. Vol. 12. New York: Plenum Press. p. 205-241.
- O'Shea J, Muggleton NG, Cowey A, Walsh V. 2004. Timing of target discrimination in human frontal eye fields. *J Cogn Neurosci*. 16(6):1060-1067.
- O'Shea J, Muggleton NG, Cowey A, Walsh V. 2006. On the roles of the human frontal eye fields and parietal cortex in visual search. *Vis Cogn*. 14(4-8):934-957.
- O'Shea J, Muggleton NG, Cowey A, Walsh V. 2007. Human frontal eye fields and spatial priming of pop-out. *J Cogn Neurosci*. 19(7):1140-1151.
- Oliveri M, Turriziani P, Carlesimo GA, Koch G, Tomaiuolo F, Panella M, Caltagirone C. 2001. Parieto-frontal interactions in visual-object and visual-spatial working memory: evidence from transcranial magnetic stimulation. *Cereb Cortex*. 11:606-618.
- Olk B, Chang E, Kingston A, Ro T. 2006. Modulation of antisaccades by transcranial magnetic stimulation of the human frontal eye field. *Cereb Cortex*. 16:76-82.
- Park J, Lee J, Lee C. 2001. Non-veridical visual motion perception immediately after saccades. *Vis Res*. 41:3751-3761.
- Pascual-Leone A, Bartres-Faz D, Keenan JP. 1999. Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of 'virtual lesions'. *Philos Trans R Soc Lond B Biol Sci*. 354:129-1238.
- Pascual-Leone A, Walsh V, Rothwell J. 2000. Transcranial magnetic stimulation in cognitive neuroscience—virtual lesion, chronometry, and functional connectivity. *Curr Opin Neurobiol*. 10:232-237.
- Paus T. 1996. Location of function of the human frontal eye field: a selective review. *Neuropsychologia*. 34:475-483.
- Paus T. 1999. Imaging the brain before, during, and after transcranial magnetic stimulation. *Neuropsychologia*. 37:219-224.
- Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC. 1997. Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. *J Neurosci*. 17(9):3178-3184.
- Petersen SE, Corbetta M, Miazan FM, Shulman GL. 1994. PET studies of parietal involvement in spatial attention: comparison of different task types. *Can J Exp Psychol*. 48:319-338.
- Petit L, Haxby JV. 1999. Functional anatomy of pursuit eye movements in humans as revealed by fMRI. *J Neurophysiol*. 82:463-471.
- Pierrot-Deseilligny C, Milea D, Muri RM. 2004. Eye movement control by the cerebral cortex. *Curr Opin Neurobiol*. 17:17-25.
- Pierrot-Deseilligny C, Muri R. 1997. Posterior parietal cortex control of saccades in humans. In: Thier P, Karnath HO, editors. *Parietal lobe contributions to orientation in 3D space*. Heidelberg: Springer-Verlag. p. 135-148.
- Pierrot-Deseilligny C, Rivaud S, Gaymard B, Muri R, Vermersch A-I. 1995. Cortical control of saccades. *Ann Neurol*. 37(5):557-567.
- Postle BR. 2005. Delay-period activity in the prefrontal cortex: one function is sensory gating. *J Cogn Neurosci*. 17:1679-1690.
- Prime SL, Niemeier M, Crawford JD. 2006. Transsaccadic integration of visual features in a line intersection task. *Exp Brain Res*. 169:532-548.

- Prime SL, Niemeier M, Crawford JD. 2007. Transsaccadic memory of visual features. In: Harris LR, Jenkins M, editors. *Computational vision in neural and machine systems*. New York (NY): Cambridge University Press. p. 167-182.
- Prime SL, Tsotsos L, Keith GP, Crawford JD. 2007. Visual memory capacity in transsaccadic integration. *Exp Brain Res*. 180:609-628.
- Prime SL, Vesia M, Crawford JD. 2008. Transcranial magnetic stimulation over posterior parietal cortex disrupts transsaccadic memory of multiple objects. *J Neurosci*. 28(27):6938-6949.
- Rayner K. 1998. Eye movements in reading and information processing: 20 years of research. *Psychol Bull*. 124(3):372-422.
- Ro T, Cheifet S, Ingle H, Shoup R, Rafal R. 1999. Localization of the human frontal eye fields and motor hand area with transcranial magnetic stimulation and magnetic resonance imaging. *Neuropsychologia*. 37:225-231.
- Ro T, Farnè A, Chang E. 2002. Locating the human frontal eye fields with transcranial magnetic stimulation. *J Clin Exp Neuropsychol*. 24(7):968-976.
- Ro T, Henik A, Machado L, Rafal RD. 1997. Transcranial magnetic stimulation of the prefrontal cortex delays contralateral endogenous saccades. *J Cogn Neurosci*. 9(4):433-440.
- Robertson EM, Theoret H, Pascual-Leone A. 2003. Studies in cognition: the problems solved and created by transcranial magnetic stimulation. *J Cogn Neurosci*. 15:948-960.
- Rosano C, Krisky CM, Welling JS, Eddy WF, Luna B, Thulborn KR, Sweeney JA. 2002. Pursuit and saccadic eye movement subregions in human frontal eye field: a high-resolution fMRI investigation. *Cereb Cortex*. 12:107-115.
- Ruchkin DS, Johnson JRR, Grafman J, Canoune H, Ritter W. 1997. Multiple visuospatial working memory buffers: evidence from spatiotemporal patterns of brain activity. *Neuropsychologia*. 35:195-209.
- Rudiak D, Marg E. 1994. Finding the depth of magnetic brain stimulation: a re-evaluation. *Electroencephalogr Clin Neurophysiol*. 93:358-371.
- Ruff CC, Bestmann S, Blankenburg F, Bjoertomt O, Josephs O, Weiskopf N, Deichmann R, Driver J. 2008. Distinct causal influences of parietal versus frontal areas on human visual cortex: evidence from concurrent TMS-fMRI. *Cereb Cortex*. 18:817-827.
- Ruff CC, Blankenburg F, Bjoertomt O, Bestmann S, Freeman E, Haynes JD, Rees G, Josephs O, Deichmann R, Driver J. 2006. Concurrent TMS-fMRI and psychophysicals reveal frontal influences on human retinotopic visual cortex. *Curr Biol*. 16:1479-1488.
- Saalman YB, Pigarev IN, Vidyasagar TR. 2007. Neural mechanisms of visual attention: how top-down feedback highlights relevant locations. *Science*. 316:1612-1615.
- Sawamura H, Shima K, Tanji J. 2002. Numerical representation for action in the parietal cortex of the monkey. *Nature*. 415(6874):918-922.
- Schall JD, Hanes DP. 1993. Neural basis of saccade target selection in frontal eye field during visual search. *Nature*. 366:467-469.
- Schall JD, Morel A, King DJ, Bullier J. 1995. Topography of visual cortical afferents to frontal eye field in macaque: functional convergence and segregation of processing streams. *J Neurosci*. 15:4464-4487.
- Schlag J, Schlag-Rey M. 1995. Illusory localization of stimuli flashed in the dark before saccades. *Vis Res*. 35:2347-2357.
- Schmolsky MT, Wang Y, Hanes DP, Thompson KG, Leutgeb S, Schall JD, Leventhal AG. 1998. Signal timing across the macaque visual system. *J Neurophysiol*. 79(6):3272-3278.
- Shomstein S, Behrmann M, McClelland JL. 2006. Cortical systems mediating visual attention to both objects and spatial locations. *Proc Natl Acad Sci U S A*. 130:11387-11392.
- Silvanto J, Lavie N, Walsh V. 2006. Stimulation of the human frontal eye fields modulates sensitivity of extrastriate visual cortex. *J Neurophysiol*. 96:941-945.
- Smith DT, Jackson SR, Rorden C. 2005. Transcranial magnetic stimulation of the left human frontal eye fields eliminates the cost of invalid endogenous cues. *Neuropsychologia*. 43:1288-1296.
- Smith EE, Jonides J, Koeppel RA, Awh E, Schumacher EH, Minoshima S. 1995. Spatial versus object working memory: PET investigations. *J Cogn Neurosci*. 7:337-356.
- Sommer MA, Wurtz RH. 2006. Influence of the thalamus on spatial visual processing in frontal cortex. *Nature*. 444:374-377.
- Sommer MA, Wurtz RH. 2008. Brain circuits for the internal monitoring of movements. *Annu Rev Neurosci*. 31:317-338.
- Stanton GB, Bruce CJ, Goldberg ME. 1995. Topography of projections to posterior cortical areas from the macaque frontal eye fields. *J Comp Neurol*. 353:291-305.
- Stewart LM, Walsh V, Rothwell JC. 2001. Motor and phosphene thresholds: a transcranial magnetic stimulation correlation study. *Neuropsychologia*. 39:415-419.
- Stokes MG, Chambers CD, Gould IC, Henderson TR, Janko NE, Allen NB, Mattingley JB. 2005. Simple metric for scaling motor threshold based on scalp-cortex distance: application to studies using transcranial magnetic stimulation. *J Neurophysiol*. 94:4520-4527.
- Talairach J, Tournoux P. 1988. *Co-planar stereotaxic atlas of the human brain*. New York: Thieme.
- Tanaka S. 2005. Transcranial magnetic stimulation studies of human working memory. *Jap Psychol Rev*. 48(4):482-497.
- Terao Y, Fukuda H, Ugawa Y, Hikosaka O, Hanajima R, Furubayashi T, Sakai K, Miyauchi S, Sasaki Y, Kanazawa I. 1998. Visualization of the information flow through human oculomotor cortical regions by transcranial magnetic stimulation. *J Neurophysiol*. 80:936-946.
- Todd JJ, Marois R. 2004. Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature*. 428:751-754.
- Umeno MM, Goldberg ME. 1997. Spatial processing in the monkey frontal eye field I. Predictive visual responses. *J Neurophysiol*. 78:1373-1383.
- Umeno MM, Goldberg ME. 2001. Spatial processing in the monkey frontal eye field: II Memory responses. *J Neurophysiol*. 86(5):2344-2352.
- Ungerleider LG, Mishkin M. 1982. Two cortical visual systems. In: Ingle DJ, Goodale MA, Mansfield RJW, editors. *Analysis of visual behavior*. Cambridge (MA): MIT Press. p. 549-586.
- Vogel EK, Machizawa MG. 2004. Neural activity predicts individual differences in visual working memory capacity. *Nature*. 428:748-751.
- Vogel EK, Woodman GF, Luck SJ. 2001. Storage of features, conjunctions, and objects in visual working memory. *J Exp Psychol Hum Percept Perform*. 27(1):92-114.
- Wardak C, Ibos G, Duhamel JR, Olivier E. 2006. Contribution of the monkey frontal eye field to covert visual attention. *J Neurosci*. 26:4228-4235.
- Wassermann EM. 1998. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalogr Clin Neurophysiol*. 108:1-16.
- Weidner R, Fink GR. 2007. The neural mechanisms underlying the Müller-Lyer illusion and its interaction with visuospatial judgments. *Cereb Cortex*. 17(4):878-884.
- Wessel K, Kompf D. 1991. Transcranial magnetic brain stimulation: lack of oculomotor response. *Exp Brain Res*. 86:216-218.
- Wilson SA, Thickbroom GW, Mastaglia FL. 1993. Transcranial magnetic stimulation mapping of the motor cortex in normal subjects. The representation of two intrinsic hand muscles. *J Neurol Sci*. 118:134-144.
- Wipfli M, Felblinger J, Mosimann UP, Hess CW, Schlaepfer TE, Muri RM. 2001. Double-pulse transcranial magnetic stimulation over the frontal eye field facilitates triggering of memory-guided saccades. *Eur J Neurosci*. 14:571-575.
- Wittenberg M, Bremmer F, Wachtler T. 2008. Perceptual evidence for saccadic updating of color stimuli. *J Vis*. 8(14):1-9.
- Wurtz RH. 2008. Neuronal mechanisms of visual stability. *Vis Res*. 48:2070-2089.
- Xu Y, Chun MM. 2006. Dissociable neural mechanisms supporting visual short term memory for objects. *Nature*. 440:91-95.