

Human Frontal Eye Fields and Spatial Priming of Pop-out

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Abstract

■ “Priming of pop-out” is a form of implicit memory that facilitates detection of a recently inspected search target. Repeated presentation of a target’s features or its spatial position improves detection speed (feature/spatial priming). This study investigated a role for the human frontal eye fields (FEFs) in the priming of color pop-out. To test the hypothesis that the FEFs play a role in short-term memory storage, transcranial magnetic stimulation (TMS) was applied during the intertrial interval. There was no effect of TMS on either spatial or feature priming. To test whether the FEFs are important when

a saccade is being programmed to a repeated target color or location, TMS was applied during the search array. TMS over the left but not the right FEFs abolished spatial priming, but had no effect on feature priming. These findings demonstrate functional specialization of the left FEFs for spatial priming, and distinguish this role from target discrimination and saccade-related processes. The results suggest that the left FEFs integrate a spatial memory signal with an evolving saccade program, which facilitates saccades to a recently inspected location. ■

INTRODUCTION

“Priming of pop-out” (PoP) describes the detection benefit (speed/accuracy) that accrues when an observer searches repeatedly for the same odd-one-out target (e.g., red) among the same distractors (e.g., green), compared with the cost when the target–distractor combinations change across trials (Maljkovic & Nakayama, 1994, 1996). If the target on the current trial has the same features or spatial location as the target on the previous trial, detection is faster. Manual and saccadic reaction time (RT) benefits of up to 50 msec have been demonstrated in both humans and monkeys (McPeck & Keller, 2001; McPeck, Maljkovic, & Nakayama, 1999). Priming has been attributed to “a decaying memory trace” of the search target that is laid down on each trial. It is proposed to reflect an implicit memory system that is specialized for rapid, automatic target selection for saccades (Maljkovic & Nakayama, 2000). One challenge is to disentangle the mechanisms in fronto-parietal cortex that appear to be common to search, eye movements, and spatial working memory (LaBar, Gitelman, Parrish, & Mesulam, 1999; Corbetta et al., 1998). Tonic neural activity in the delay period of spatial working memory tasks has been shown to reflect visual, mnemonic, and oculomotor signals (Curtis & D’Esposito, 2006; Sommer & Wurtz, 2001). Because PoP is passive, automatic, and not subject to conscious

control, this paradigm eliminates task strategy complications from the effort to dissociate memory mechanisms from search and saccade-related processes.

In a functional magnetic resonance imaging (fMRI) study, Kristjansson, Vuilleumier, Schwartz, Macaluso, and Driver (2006) (see also Yoshida, Tsubomi, Osaka, & Osaka, 2003) found that repetition of a target’s features or location induced bilateral suppression of blood oxygen level-dependent (BOLD) signal in the frontal eye fields (FEFs) and a number of parietal regions (including the angular gyrus [AG]). Feature priming induced additional suppression in infero-temporal areas involved in color processing. Repetition suppression is believed to reflect reduced neuronal discharge on repeated stimulus presentation and has been shown to correlate with priming in a variety of paradigms (Henson & Rugg, 2003; Kourtzi & Kanwisher, 2000; Wiggs & Martin, 1998; Desimone, 1996). One question posed by these fMRI data is whether fronto-parietal repetition suppression is task-critical. Because FEF neurons are not color-selective (Mohler, Goldberg, & Wurtz, 1973), they would not be expected to mediate color priming. Nevertheless, it has been shown that color priming modulates FEF activity. Bichot and Schall (2002) recorded from FEF visuomotor neurons and showed that on color-repeat trials, target selection activity developed earlier, and there was a greater difference between target- and distractor-related activity in the post-selection period. These effects seem best interpreted as downstream influences of adaptation in sensory visual cortex. Much evidence suggests

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that the cortical visual areas selective for a particular feature (e.g., color) also support perceptual memory for that feature (Tulving & Schacter, 1990). Three studies have shown that V4 lesions abolish color PoP (Girard, Choitel, & Bullier, 2001; Rossi, Bichot, Desimone, & Ungerleider, 2001; Walsh, Le Mare, Blaimire, & Cowey, 2000). Even after complete removal of the unilateral prefrontal cortex, the corpus callosum, and the anterior commissure, Rossi et al. showed that color PoP remained unaffected. Collectively, these studies suggest that color priming requires intact V4, and that repetition suppression in the FEFs reflects changes in the efficiency of target selection, but that these depend on sensory adaptation in color-selective cortex.

There are reasons to expect that spatial priming may require a causal contribution from the FEFs. Whereas changes in target selection activity in FEF visual neurons can be considered in terms of a “visual salience map,” spatial priming can also be conceptualized as maintaining or switching task set (Fecteau & Munoz, 2003). When the same saccade program must be re-executed (“stay” trials), performance is easier than when a new saccade must be programmed (“switch” trials). Thus, spatial priming may be thought of as a form of oculomotor memory. By contrast with the spatial PoP paradigm, cueing paradigms have reported “inhibition of return,” a slowing of saccadic responses when a target location is pre-cued (for a review, see Klein, 2000). Both facilitation and inhibition effects can be measured in a PoP paradigm, but target-position facilitation appears to always be stronger than distractor-position inhibition (Maljkovic & Nakayama, 1996). Consistent with this, PoP studies almost unanimously report facilitation at the primed location (e.g., Kristjansson et al., 2006; Kristjansson, Vuilleumier, Malhotra, Husain, & Driver, 2005; McPeck et al., 1999). Saccadic priming has been shown to correlate with changes in the baseline firing rate of superior colliculus neurons, altering the threshold for saccade initiation (Gore, Dorris, & Munoz, 2002; Dorris, Pare, & Munoz, 2000). Location switch costs have also been ascribed to competing oculomotor programs within the superior colliculus (McPeck, Han, & Keller, 2003; McPeck & Keller, 2002). The FEFs also play a role in oculomotor preparatory set (Connolly, Goodale, Menon, & Munoz, 2002; Cornelissen et al., 2002; Everling & Munoz, 2000). Applying transcranial magnetic stimulation (TMS) over the right or left FEFs has been shown to reduce or increase spatial cueing costs for oculomotor or manual responses (Smith, Jackson, & Rorden, 2005; Ro, Farne, & Chang, 2003; Grosbras & Paus, 2002). The proposal that areas specialized for spatial selection (like the FEFs) might also subservise short-term memory for selected locations is a natural extension of the sensory memory hypothesis to visuomotor cortex (Awh & Jonides, 2001).

Oculomotor regions of parietal cortex (areas 7a/LIP) are densely interconnected and appear to be closely functionally coupled with the FEFs during search, eye move-

ment, and spatial memory tasks (Chafee & Goldman-Rakic, 1998, 2000). During search tasks, patients with right parietal lesions frequently return to previously inspected items and show no awareness of having done so (Pisella, Berberovic, & Mattingley, 2004; Husain et al., 2001). This “revisiting” behavior has been interpreted as a failure to maintain or update searched locations across saccades. Revisiting behavior has been argued to depend on damage to the right AG and/or the intraparietal sulcus (Mannan et al., 2005), but monkeys with FEF (but not superior colliculus) lesions also show revisiting behavior (Collin, Cowey, Latto, & Marzi, 1982). The data on “revisiting” behavior would predict that AG lesions or TMS should disrupt spatial PoP. However, to our knowledge, only one study has tested right parietal patients on implicit spatial memory using color PoP. Kristjansson et al. (2005), using manual responses, reported that both feature and spatial priming were intact in both of their patients who had neglect and extinction. Spatial priming occurred as long as the patient had detected the target on the previous trial, but feature priming occurred irrespective of prior target detection. Hence, the role of the AG in spatial PoP requires further investigation.

The central aim of the present study was to investigate whether the FEFs make causal contributions to feature or spatial PoP with saccadic responses. We hypothesized that TMS applied over the FEFs would disrupt spatial but not feature priming. In addition, we investigated a potential role for the AGs in spatial priming. Because the AGs form a functionally integrated circuit with the FEFs during tasks that require visual search, target selection, saccade programming, and spatial memory, we expected some interference at both TMS sites. Hence, we asked whether any such effects might dissociate across timing conditions, or whether the FEFs or the AGs might have a dominant role. To test for a role in primed memory storage across trials, TMS was applied in the intertrial interval (ITI). To test whether the FEFs are important when a saccade is repeated toward a primed feature or location, TMS was applied during presentation of the search array. Four experiments were conducted, with controls for task (feature/spatial), TMS site (FEFs/AGs), hemisphere (left/right), and TMS timing (ITI/during search array).

METHODS

Subjects

Five subjects were tested in each of the four experiments. Two subjects participated in three experiments, four participated in two—one feature and one spatial priming experiment. All subjects were naïve to the purpose of each experiment. All were right-handed and had normal or corrected-to-normal vision. All gave written informed consent and reported an absence of any neurological condition in their known family history. All procedures were approved by the Oxford Research

Visual Stimuli

Two varieties of search arrays were used in the feature and spatial priming experiments (Figure 1A). Each array contained one target and two distractors, as the fewer the distractors, the harder it is to select the odd target (McPeck et al., 1999; Bravo & Nakayama, 1992). All three stimuli ($1.4^\circ \times 1.4^\circ$) were positioned equidistant from each other on an imaginary ellipse (14.8° horizontally \times 11.7° vertically), each at one of six possible locations (1, 3, 5, 7, 9, and 11 o'clock). Arrays were presented on

a 16-in. screen (100 Hz refresh rate) of uniform white (177 cd/m^2). Spatial priming stimuli were X-shaped with a black spot in the center, and came in three different luminance-matched (71 cd/m^2) color pairings: (1) blue (CIE: $x = 0.209, y = 0.311$) and orange (CIE: $x = 0.480, y = 0.384$); (2) green (CIE: $x = 0.285, y = 0.590$) and brown (CIE: $x = 0.338, y = 0.319$); and (3) pink (CIE: $x = 0.295, y = 0.185$) and purple (CIE: $x = 0.249, y = 0.195$). On 50% of trials, target location was repeated on consecutive trials, otherwise it switched. Feature priming stimuli were luminance-matched (12.5 cd/m^2) green (CIE: $x = 0.287, y = 0.581$) and mauve (CIE: $x = 0.459, y = 0.252$) diamond shapes with a small white square at the center. On 50% of trials, the target-distractor color pairing was repeated on consecutive trials, otherwise it switched. In all experiments, target color and location were randomized across trials with the constraint that the non-primed target dimension (color/location) never repeated on consecutive trials. That is, in the feature priming experiments, target color had a 0.5 switch probability but target location switched on every trial; in the spatial priming experiments, target location had a 0.5 switch probability but target color switched on every trial. Thus, feature priming was not contaminated by spatial priming, and vice versa.

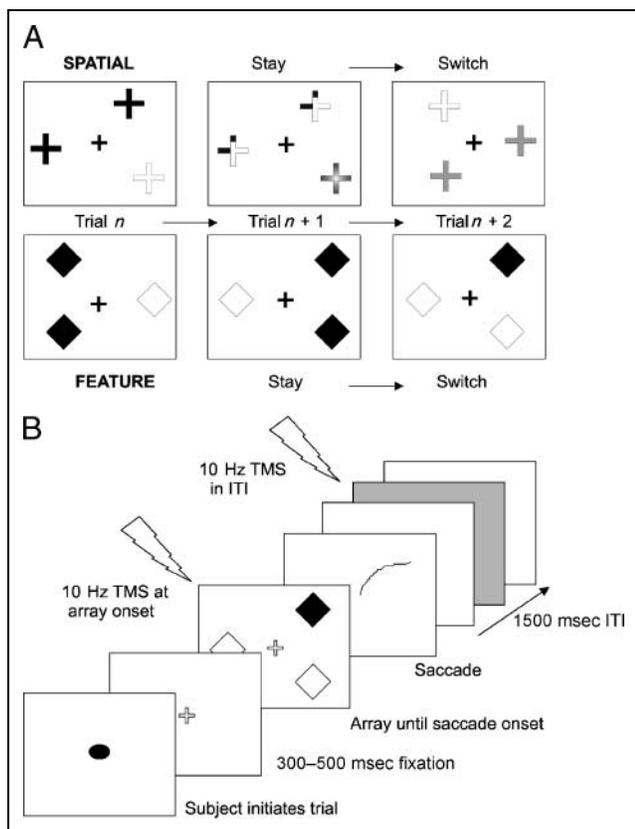


Figure 1. (A) Visual search arrays. Subjects were instructed to make a saccade to the odd-colored target on every trial. In the spatial priming experiments, the target-distractor color pairings (blue/orange, brown/green, pink/purple—rendered schematically in gray) always switched across consecutive trials so there was no feature priming. Target location had a 0.5 switch probability. In the feature priming experiments, target location always switched across consecutive trials so there was no spatial priming. Target color (green/mauve—rendered in black and white) had a 0.5 switch probability. (B) Time course of a single trial. Subjects pressed a key to initiate a trial. A fixation cross was presented for a variable duration (300–500 msec) followed by the search array, which terminated when a saccade was initiated. Following the saccade, there was a 1500-msec ITI. In the “TMS during the Search Array” experiments, 10 Hz TMS (500 msec) was applied at the onset of the search array. In the “TMS in the ITI” experiments, TMS was applied in the middle 500-msec period of the ITI.

Procedure

The experimental procedure was adapted from McPeck et al. (1999). Subjects sat in a dimly lit room at a distance of 57 cm from the screen. The experiment started with eye movement calibration, which was repeated at the start of each block. Subjects then performed two practice blocks (40 trials each) to stabilize saccadic reaction times (SRTs). Each experimental block began with five practice trials, followed by 40 trials, the data from which were subjected to statistical analysis. At the start of each trial, a fixation circle appeared (Figure 1B). Subjects initiated the trial by pressing a key. A fixation cross (variable duration 300–500 msec) then appeared, after which the search array was presented. Subjects were instructed to make a saccade to the odd target as quickly and accurately as possible. The array was removed once a saccade was initiated. Following the response, there was a 1500-msec ITI. After the ITI, the fixation circle reappeared, signaling the start of the next trial.

In the two “TMS during the Search Array” experiments, 10 Hz TMS (500 msec) was triggered by the onset of the visual search array. In the two “TMS in the ITI” experiments, 10 Hz TMS (500 msec) was applied during the middle 500-msec period of the ITI. The “TMS in ITI” protocol replicated Campana, Cowey, and Walsh (2002), who disrupted priming of visual motion direction with TMS over area V5. Four experiments were conducted (feature/spatial priming \times TMS during the Search Array/in the ITI) with controls for task (feature/spatial), TMS site (FEFs/AGs), hemisphere (left/right), and TMS timing

(ITI/onset). Subjects performed 12 blocks in each experiment, totalling 80 trials per TMS condition: right or left FEFs, right or left AG, right or left sham TMS.

Eye Movement Recording

Eye movements were recorded using the Eyelink I System (SR Research, Ontario, Canada) sampling at 250 Hz using corneal reflection to define pupil position. The head movement compensation system was removed to enable TMS application, and the eye tracker was bolted to a chinrest. Head movement was restricted by a forehead and chin rest and was compensated for by an automated drift correction procedure at the start of each trial. A standard 9-point calibration procedure was used. Saccades were detected by an automated algorithm using minimum velocity and acceleration criteria of 35 deg/sec and 9500 deg/sec², respectively. Eye position data were analyzed off-line. SRTs were analyzed only for those trials in which inclusion criteria for saccade latency, vector, and amplitude were fulfilled. Because each trial featured three stimuli (presented at equidistant locations on an imaginary ellipse), a saccade was classified as correct if its landing position fell within that third of the array containing the target, and was classified as incorrect if the landing position fell within one of the other two-third sectors, each of which contained a distractor. Data from trials in which the saccade amplitude in the correct (target) direction did not exceed 1° of visual angle, or in which saccade latency was below 80 msec or above 1000 msec, were excluded from the analysis. Trials in which subjects blinked or broke fixation were automatically terminated and the search array was removed from the screen. On average, 5% of trials were rejected for this reason. There was no difference in blink rates across conditions.

Transcranial Magnetic Stimulation

TMS sites were localized using frameless stereotaxy (Brainsight, Rogue Research, Montreal, Canada). Stimulation was applied at the location of the probabilistic human FEFs, just rostral to the junction of the superior frontal sulcus and the ventral branch of the precentral sulcus at mean MNI coordinates $x = 31$ ($SE = 1.4$), $y = -1$ ($SE = 1.2$), and $z = 60$ ($SE = 2.2$), which correspond well with previous work that has identified FEF location using either extensive single-subject fMRI-based mapping (Amiez, Kostopoulos, Champod, & Petrides, 2006) or by means of a large-scale meta-analysis across a variety of fMRI studies (Grosbras, Laird, & Paus, 2005) (Figure 2A). FEF localization was further confirmed in three subjects using fMRI by showing that these anatomically targeted sites were activated when subjects made saccades as opposed to maintaining fixation. The right and left AGs were localized using group mean MNI coordinates from previous studies that reported TMS interfer-

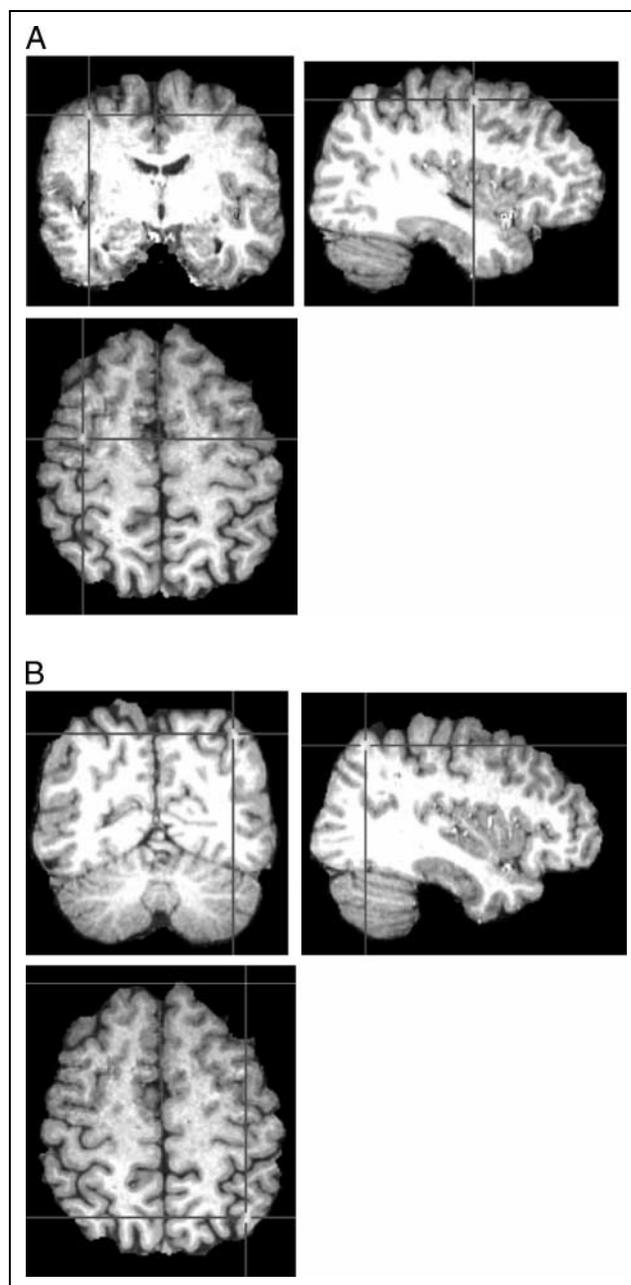


Figure 2. TMS sites. Cortical areas were targeted for TMS using frameless stereotaxy. Cross-hairs show the location of each TMS site on an anatomical MRI scan from a single subject. (A) Frontal eye fields. Cross-hairs are centered on the left FEFs, located at the junction of the precentral and superior frontal sulci, anterior to the motor hand area. (B) Angular gyrus. Cross-hairs are centered on the dorsal part of the right AG, inferior to the intraparietal sulcus and superior to the posterior end of the superior temporal sulcus.

ence on visual search, visuospatial orienting, and target selection tasks (Hung, Driver, & Walsh, 2005; Rushworth, Ellison, & Walsh, 2001). Each subject's anatomical MRI scan was normalized against the MNI 152-mean brain T1 template. The coordinates were then converted into each subject's own image space and plotted within Brainsight. The locations marked by this method were

confirmed against anatomical landmarks for the AG. By combining these two methods, the area stimulated by TMS was located inferior to the intraparietal sulcus and superior to the posterior end of the superior temporal sulcus, which bisects the AG (mean MNI coordinates: $x = 39, y = 68, z = 53$; Figure 2B).

A Magstim Super Rapid machine (Magstim Company, Dyfed, UK) was used to deliver TMS through a 50-mm figure-of-eight coil. Each coil was replaced at the end of each block of trials and was air-cooled to prevent overheating. In the FEF conditions, the coil was oriented tangential to the skull and the coil handle was oriented parallel to the floor, resulting in a posterior–anterior direction of induced current flow. Over the AG, the coil was held tangential to the skull, oriented ca. 45° to the mid-sagittal axis. During sham TMS, the coil was placed over the FEFs and oriented perpendicular to the floor, such that the magnetic field was orthogonal to the subjects' skull. TMS (500 msec) of 10 Hz was applied at 65% of maximum stimulator output. We chose to stimulate at this fixed intensity for all participants on two grounds: (1) neither motor nor visual phosphene thresholds are a reliable guide to what stimulation intensity will be effective in other regions of cortex (Stokes et al., 2005; Stewart, Walsh, & Rothwell, 2001); (2) we and others have previously shown that TMS at an intensity of 65% of maximum effectively interferes with search performance when applied over the right AG or the right FEFs (see, for example, Hung, Driver, & Walsh, 2005; Rushworth, Ellison, et al., 2001). In the “TMS during the Search Array” experiments, stimulation was triggered by the onset of the search array. In the “TMS

in the ITI” experiments, TMS was applied during the middle 500 msec of the 1500-msec ITI.

RESULTS

We first assessed whether TMS induced a generalized delay in contralateral saccades, an effect that has been reported on some, but not all, saccade tasks (e.g., Ro, Henik, Machado, & Rafal, 1997). Saccade latencies were pooled over stay and switch trials and separated by target hemifield. There was no difference in saccade latencies to either hemifield when TMS was applied in the ITI or during the search array in either the feature or spatial priming experiments. This analysis demonstrates that any effects of FEF TMS on priming are not confounded by a generalized delay in SRT (see Figure 4C and D). Each trial was next classified and analyzed according to the target on the preceding trial. On “stay” trials, the target was either the same color (feature priming) or had been at the same location (spatial priming) as the target on the previous trial. If the previous trial target differed, this was classified as a “switch” trial. Trials were sorted into “stay” or “switch” categories and median SRTs were calculated for each subject for each category and experimental condition (Table 1).

Spatial Priming

Experiment 1 (Spatial Priming—TMS in the ITI)

SRTs were entered into a three-way repeated-measures analysis of variance (ANOVA) [TMS site (sham/FEF/AG) *

Table 1. Mean Saccadic Reaction Times for Stay and Switch Trials in Every Experiment

<i>Saccade Latencies (msec)</i>	<i>RSham</i>	<i>LSham</i>	<i>Right FEF</i>	<i>Left FEF</i>	<i>Right AG</i>	<i>Left AG</i>
<i>Experiment 1: Spatial Priming—TMS in the Intertrial Interval</i>						
Switch	304.4 (14.69)	296.2 (13.03)	298.8 (11.22)	289.5 (11.87)	293.9 (18.81)	300.9 (15.11)
Stay	279.2 (16.02)	273.4 (15.42)	269.4 (11.94)	268.3 (12.59)	276.2 (13.7)	277.4 (15.48)
<i>Experiment 2: Spatial Priming—TMS during the Search Array</i>						
Switch	355.5 (40.58)	347.2 (33.01)	357.6 (32.29)	348.4 (36.92)	350.5 (34.59)	346 (30.21)
Stay	318 (31.47)	305.2 (23.35)	335.3 (32.36)	346.2 (34.9)	335.2 (37.62)	328.3 (30.02)
<i>Experiment 3: Feature Priming—TMS in the Intertrial Interval</i>						
Switch	328.6 (10.94)	314.4 (10.48)	310 (17.22)	315.2 (14.68)	320.5 (7.55)	320.4 (15.72)
Stay	282.8 (8.65)	285 (13.16)	284 (11.82)	295.8 (14.97)	290.3 (9.47)	288.3 (11.77)
<i>Experiment 4: Feature Priming—TMS during the Search Array</i>						
Switch	341.4 (34.1)	355.2 (36.48)	356.2 (35.19)	348.4 (26.4)	333.6 (19.37)	340.5 (31.91)
Stay	317.6 (30.17)	312.6 (25.22)	319.3 (34.69)	324.1 (28.96)	311 (24.69)	312.4 (34.75)

The table shows mean of median saccade latencies (msec) and standard errors (in parentheses) for each TMS condition in each of the four experiments.

Hemisphere (left/right) * Prime (stay/switch)]. There was a significant effect of prime [$F(1, 4) = 40.202, p = .003$], with switch trial latencies being significantly longer than stay latencies (mean difference: 23.3 msec, 95% confidence intervals [CI]: 13.09, 33.50; Figure 3A). The pattern of errors matched that of SRT. There was a significant effect of prime [$F(1, 4) = 176.942, p < .001$], with greater accuracy on stay trials versus switch trials (ca. 90%/70%). There were no other effects, trends, or interactions.

Experiment 2 (Spatial Priming—TMS during the Search Array)

SRTs were submitted to a three-way repeated-measures ANOVA [TMS site (sham/FEF/AG) * Hemisphere (left/right) * Prime (stay/switch)]. There was a main effect of prime [$F(1, 4) = 15.589, p = .017$]. Switch trial latencies were significantly longer than stay trial latencies (mean difference: 22.83 msec, 95% CI: 38.89, 6.77). There was also an effect of TMS site [$F(2, 8) = 7.575, p = .014$], with planned contrasts showing that FEF latencies were significantly longer than baseline sham TMS latencies [$F(1, 4) = 33.378, p = .004$; mean difference: 15.4 msec, 95% CI: 22.80, 7.99]. AG latencies did not differ significantly from baseline [$F(1, 4) = 2.608, p = .182$]. There was a two-way interaction of Site * Prime [$F(2, 8) = 4.654, p = .046$

and a three-way interaction of Site * Hemisphere * Prime [$F(2, 8) = 10.419, p = .006$] (Figure 3B).

These interactions were explored further by decomposing the data according to hemisphere. A two-way ANOVA on the right hemisphere TMS sites [TMS Site (right sham/FEF/AG) * Prime] revealed an effect of prime [$F(1, 4) = 40.049, p = .003$], but no effect of TMS site [$F(2, 8) = 0.641, p = .552$], nor a Site * Prime interaction [$F(2, 8) = 1.776, p = .230$] (Figure 4A). A two-way ANOVA on the left hemisphere sites [TMS site (left sham/FEF/AG) * Prime] showed that the priming effect was not significant [$F(1, 4) = 5.794, p = .074$]. There was no effect of TMS site [$F(2, 8) = 3.349, p = .088$], but there was a significant Site * Prime interaction [$F(2, 8) = 13.174, p = .003$]. Inspection of the means showed there was no difference between switch trial latencies in the left sham, FEF, and AG conditions (Figure 4B). Two paired-samples *t* tests compared the stay trial latencies of the left FEF and left AG against the left sham baseline. There was a trend for left AG latencies to be longer than baseline [$t(4) = -2.459, p = .07$] (mean difference: 23.1 msec, 95% CI: 2.98, 49.18). Left FEF latencies were significantly longer than baseline [$t(4) = -3.083, p = .04$] (mean difference: 41 msec, 95% CI: 3.08, 78.92). The difference between these two sites was marginally significant [$t(4) = 2.733, p = .052$] (mean difference: 17.9 msec, 95% CI: -0.29,

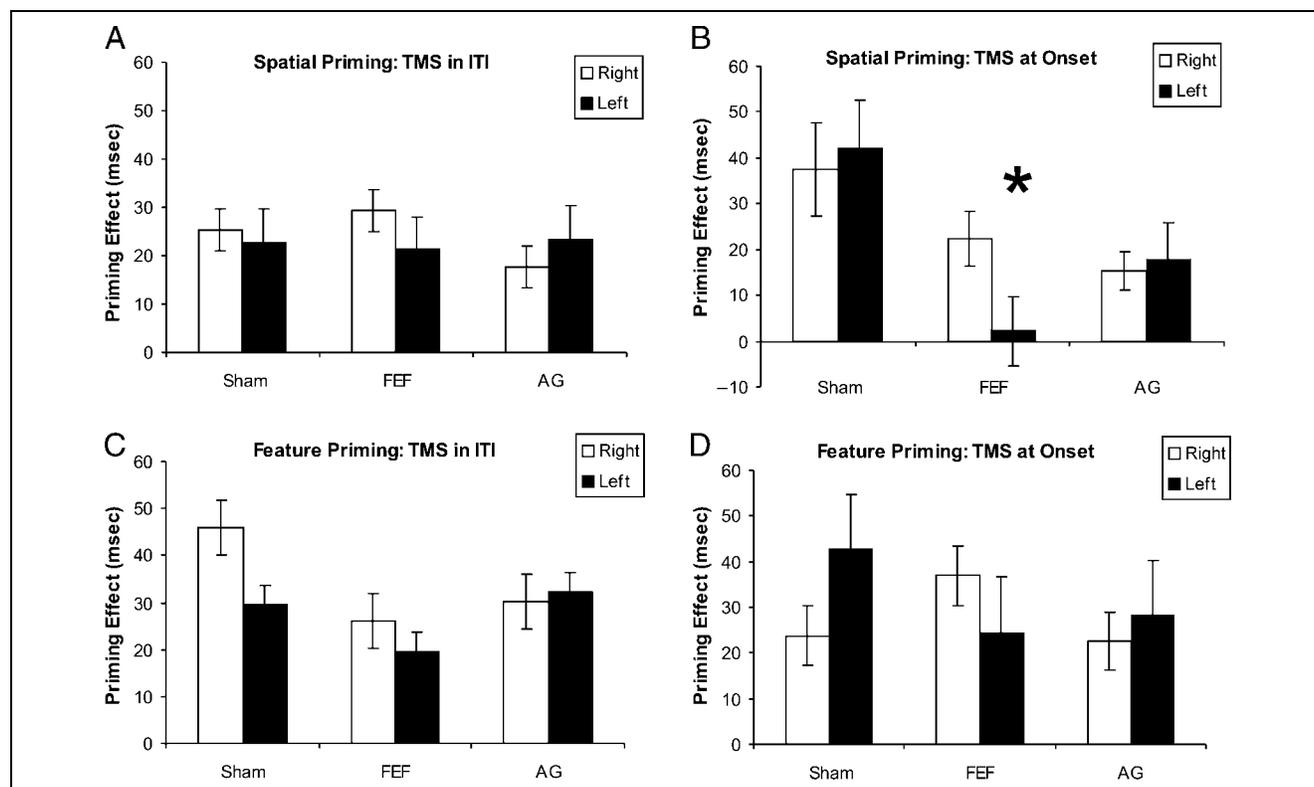


Figure 3. Effect of TMS on priming. Each graph plots the size of the priming effect in each TMS condition (right and left sham/FEFs/AG) in each experiment. The size of the priming effect is calculated by subtracting the group mean SRT on stay trials from the group mean switch trial SRT (error bars = 1 SEM). (A) Spatial priming: TMS in the ITI—there was no effect of TMS. (B) Spatial priming: TMS during the search array—TMS applied over the left FEFs abolished spatial priming. (C) Feature priming: TMS in the ITI—there was no effect of TMS. (D) Feature priming: TMS during the search array—there was no effect of TMS.

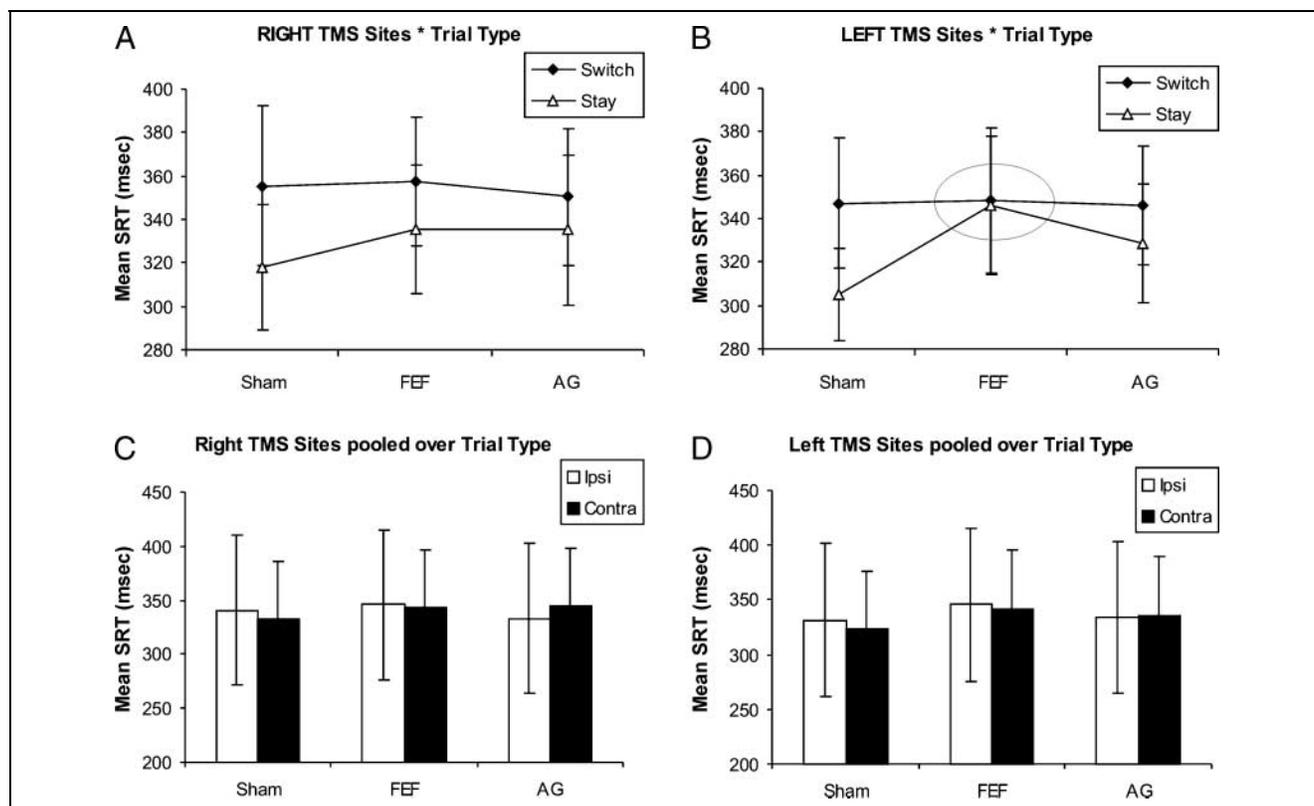


Figure 4. The left FEF TMS effect is specific to stay trials. TMS applied over the left FEFs during the search array (Experiment 2) abolished spatial priming (mean stay/switch difference in SRT). Panels A and B show the specificity of this effect: left FEF TMS caused a selective increase in SRT on stay trials, but no change in SRT on switch trials (B, circled). There was no such effect in the left sham or left AG conditions, nor was there any effect of TMS in the right sham, right FEF, or right AG conditions (A). Panels C and D demonstrate further the specificity of this effect: When the data were collapsed over trial type (stay/switch), there was no effect of TMS at any site on SRT to the ipsi- or contralateral hemifield.

36.09). That is, TMS over the left FEF produced a greater reduction in saccade latency than TMS over the left AG. Hence, we focus here only on the significant reduction in spatial priming induced by the left FEF TMS. TMS over the left FEFs increased stay trial latencies such that the stay/switch difference was abolished. This reduction in spatial priming was present in every single subject. In four out of five subjects, this effect was unambiguously due to a selective increase in stay trial latencies. This result is plotted for the raw mean data in Figure 4B. Analysis of error data revealed a significant effect of prime [$F(1, 4) = 23.870, p = .008$], with greater accuracy on stay versus switch trials (ca. 90%/70%), but no other effects, trends, or interactions. This shows that the left FEF TMS effect did not result from a speed-accuracy tradeoff.

To test whether the left FEF effect was specific to trials in which the target was in the contralateral hemifield, the data were analyzed by target location. The pattern of results tended to correspond with the overall analysis, showing an effect of TMS over the left FEF. A four-way ANOVA (TMS Site * Hemisphere * Prime * Hemifield) revealed significant priming in both hemifields [Prime: $F(1, 4) = 29.68, p = .006$]. There was also a main effect of TMS site [$F(1, 8) = 8.227, p = .042$, Huynh-Feldt corrected], with planned contrasts showing that FEF la-

tencies were significantly longer than baseline latencies [$F(1, 4) = 27.742, p = .006$; mean difference: 13.95 msec, 95% CI: 6.6, 21.3]. Importantly, there was no main effect of hemifield. Nor was there any interaction of hemifield with TMS site, prime, or hemisphere (all $ps > .2$). This demonstrates that left FEF TMS disrupted spatial priming for targets located in either the contralateral or the ipsilateral hemifield.

To further confirm our findings for mean saccade latencies (that TMS over the left FEFs abolishes spatial priming), we tested whether this was also true for the distribution of saccade latencies. We generated cumulative frequency curves for the distribution of stay versus switch trial saccade latencies for each subject in each condition. Each switch trial curve was then subtracted from the corresponding stay trial curve to yield a difference curve, which represented the size of the priming effect (Proportionate Stay – Switch SRT difference) for each subject in each time bin. Group mean difference curves were calculated and plotted with 95% CIs. Right and left sham data were combined to yield a baseline priming curve of 160 trials; TMS priming curves consisted of 80 trials. The area under each priming curve was calculated and submitted to a one-way repeated-measures ANOVA. The main effect (TMS site) was not

significant [$F(4, 16) = 1.77, p = .184$], but planned contrasts showed that the left FEF curve was significantly smaller than the baseline priming curve [$F(1, 4) = 14.452, p = .019$] (mean difference: 1.266 units², 95% CI: 0.34, 2.19]. No other condition approached significance (all $p > .14$, uncorrected). This effect can be seen in Figure 5 where the 95% CIs in the left FEF condition overlap the x -axis in every time bin (the x -axis represents no stay/switch difference, i.e., zero priming). This does not occur in any other condition. This suggests that left FEF TMS disrupts spatial priming throughout the distribution of saccade latencies. Similar analyses were performed on the saccade latency data from each of the

other three experiments (Spatial priming – TMS in the ITI, Feature Priming – TMS in the ITI/during the search array). There was no effect, trend, or interaction of TMS at any site, at any time, or on any priming task (all $p > .1$), further confirming the specificity of our findings for the left FEFs.

Feature Priming

Experiment 3 (Feature Priming—TMS in the ITI)

SRTs were entered into a three-way repeated-measures ANOVA [TMS site (sham/FEF/AG) * Hemisphere (left/

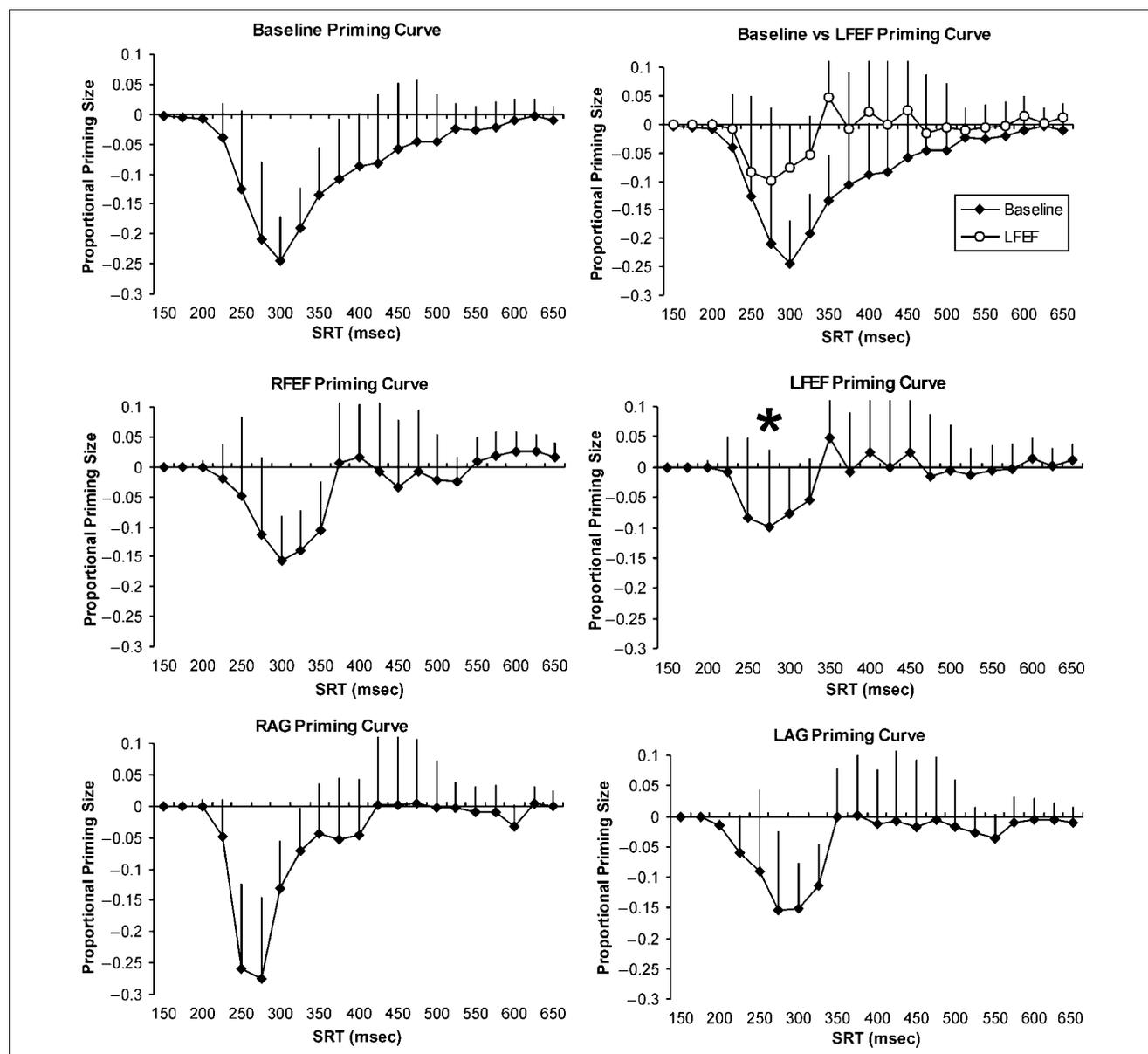


Figure 5. Effect of left FEF TMS on the distribution of saccade latencies (priming curves for Experiment 2: Spatial priming—TMS during the search array). This graph shows the effect of left FEF TMS on the distribution of SRT. Each graph plots the proportional stay-switch trial difference in SRT (y -axis), showing the size of the priming effect in each time bin. Left FEF TMS abolished spatial priming across the distribution of saccadic latencies (note the overlap with the x -axis, indicating zero priming, in every time bin). The baseline priming curve consists of 160 trials. Each TMS condition sampled 80 trials. Error bars = 95% confidence intervals.

right) * Prime (stay/switch)]. There was a significant effect of prime [$F(1, 4) = 82.181, p = .001$] with switch trial latencies being significantly longer than stay trial latencies (mean difference: 30.48 msec, 95% CI: 21.14, 39.81). The pattern of errors matched that of SRT. There was a significant effect of prime [$F(1, 4) = 112.061, p < .001$], with greater accuracy on stay versus switch trials (ca. 90%/70%). There were no other effects, trends, or interactions (Figure 3C).

Experiment 4 (Feature Priming—TMS during the Search Array)

SRTs were entered into a three-way repeated-measures ANOVA [TMS site (sham/FEF/AG) * Hemisphere (left/right) * Prime (stay/switch)]. There was a significant effect of prime [$F(1, 4) = 61.052, p = .001$], with switch trial latencies being significantly longer than stay trial latencies (mean difference: 29.71 msec, 95% CI: 19.15, 40.27). The pattern of errors matched that of SRT. There was a significant effect of prime [$F(1, 4) = 7.694, p = .05$], with greater accuracy on stay versus switch trials (ca. 90%/70%). There were no other effects, trends, or interactions (Figure 3D).

DISCUSSION

TMS applied over the left FEFs during the search array, but not during the ITI, abolished spatial PoP. Priming was disrupted across the distribution of saccade latencies. The effect was specific to trials on which the target location was repeated. Because the target–distractor color pairs always switched across consecutive trials, there was no color priming. Hence, the only difference between stay and switch trials was the influence of a spatial memory signal, which resulted in faster saccade latencies on stay trials. TMS over the left FEFs removed this benefit of location repetition by increasing stay trial latencies, while leaving switch trials unaffected. This indicates that TMS abolished a spatial memory signal in the left FEFs that is required for spatial priming. The absence of an effect of TMS in the ITI argues against a memory storage interpretation. The selective increase in stay trial latencies rules out generalized disruption of target discrimination, response selection, or oculomotor programming as the basis for the left FEF effect. If those processes had been disrupted, then TMS during the search array would have also affected feature priming, but it did not. Rather, the data suggest that the left FEFs integrate a spatial memory signal when a saccade is being programmed to a repeated location.

That TMS interference was selective to the within-trial and not the between-trial period concurs with prior data on behavioral priming. Repetition suppression, a well-documented neural correlate of priming, occurs during the repeated presentation of a stimulus, and not during

the interval between presentations. During stay trials, a persisting trace of the saccade executed on the previous trial appears to be integrated with the presently evolving saccade program, speeding reorienting to the same location. By applying TMS to the left FEFs during this period, it appears that this integration was disrupted, abolishing the behavioral priming effect. One important difference between spatial PoP and spatial working memory is that explicit memorization is not required. This may explain why TMS in the ITI had no effect: There was no process of active memory storage for TMS to disrupt. Consistent with this, in their study of PoP, Bichot and Schall (2002) observed no change in the baseline discharge rate of FEF neurons in the interval between trials. Rather, within-trial processes of target discrimination and saccade programming were speeded or slowed as a function of location repeats and switches. It seems probable that, like a representation of behavioral salience, a decaying implicit memory trace of where a target was last detected, and where a person last looked, would be distributed throughout the network of visual and oculomotor areas that are recruited for those behaviors (e.g., Dorris, Klein, Everling, & Munoz, 2002; Bichot & Schall, 1999; Umeno & Goldberg, 1997; Duhamel, Colby, & Goldberg, 1992). If this memory trace is so distributed (e.g., across retinotopic visual areas), it follows that it might be disrupted by TMS in a downstream visuomotor structure like the FEFs—when the information converges and is integrated with an evolving oculomotor output command.

The absence of an effect of TMS in the ITI suggests that the FEFs do not mediate between-trial storage of the kind of implicit memory on which spatial priming depends. However, it could be argued that implicit spatial memory traces were stored in the FEFs and transiently disrupted by TMS, but that there was sufficient time for the trace to recover prior to the next trial (Opris, Barborica, & Ferrera, 2005). In our experiment, the ITI was 1500 msec, onset of the next trial was self-initiated, and then there was a further 300–500 msec fixation period before presentation of the next search array. Throughout this period, TMS was applied only during the middle 500 msec of the ITI. To test this hypothesis, the ITI could be shortened to prevent a recovery period, which might produce an interference effect. However, the concept of recovery itself seems to implicate reliance on a spatial memory buffer located outside the FEFs. Consistent with this, it has been shown that when monkeys make saccades during the delay period of an oculomotor spatial match-to-sample task, sustained spatial memory signals are modulated by those gaze shifts. Following recentering saccades, the sustained signal was abolished and FEF neurons exhibited a loss of tuning. The sustained spatial signal then re-emerged over the next few hundred milliseconds (Balan & Ferrera, 2003a, 2003b). In our study, subjects' gaze in the ITI was unconstrained. Gaze shifts between trials

would be associated with a host of movement-related signals in the FEFs that could be deleterious to an implicit spatial memory trace. Hence, it may be that perturbation of sustained signals by gaze shifts makes the FEFs an unsuitable storage site for the kind of implicit memory on which spatial priming depends.

We have argued that a decaying trace of spatial salience from the previous trial (where the target was, where the person looked) is likely to be distributed throughout the visual and oculomotor systems. The reason that left FEF TMS during stay trials disrupts priming is because it disrupts this memory trace (of trial “ n ”) at the point of use: that is, when it is being integrated with a developing saccade command (on trial “ $n + 1$ ”). In order to maximize statistical power in our experiments, TMS was applied on every trial. Hence, we cannot preclude the possibility that TMS disrupted the initial laying-down of a memory trace (on stay trial “ n ”) rather than the subsequent read-out of that memory (on stay trial “ $n + 1$ ”) as we have argued. However, if TMS had disrupted an initial trace in the left FEFs, as long as the saccade was successfully executed, there would seem to be a surfeit of additional visual and oculomotor structures from which a spatial trace could be read-out (over the subsequent 1800–2000 msec) to facilitate the next saccade. Interference seems more likely to be task-critical on trial “ $n + 1$,” during the decision period when distributed spatial signals are integrated into a single oculomotor command (Schall, 2003).

We have previously argued that the right FEFs are functionally specialized for *visuospatial* processes (O’Shea, Muggleton, Cowey, & Walsh, 2004; Muggleton, Juan, Cowey, & Walsh, 2003). The present data suggest complementary specialization in the left FEFs for *spatiomotoric* memory processes. This echoes previous TMS data from the posterior parietal cortex, showing right hemisphere specialization for “visuospatial attention” and left specialization for “motor attention” (Rushworth, Krams, & Passingham, 2001). The selective effect of left but not right FEF TMS is also consistent with other previous work. Kristjansson et al.’s (2006) fMRI study reported significantly greater repetition suppression effects in the left hemisphere (left FEFs, left AG) than in the right. Also, Gaymard, Ploner, Rivaud-Pechoux, and Pierrot-Deseilligny (1999) reported data from a patient with a discrete left FEF lesion. The patient made normal contralateral saccades, but showed a marked reduction in memory-guided saccade gain, which worsened as the delay increased. The authors argued that the lesion had impaired a spatial memory signal in oculomotor coordinates and suggested that the (left) FEFs may be important for spatial memory during short delays that do not depend on the dorsolateral prefrontal cortex.

We also investigated a potential role for the AGs in spatial priming, as the FEFs and the AGs are densely interconnected and form a functionally integrated network subserving visual search performance. Because

all four TMS sites contribute to search, we expected (and we found) that TMS at each of the targeted sites would produce some interference effect (Muggleton et al., 2003; Ashbridge, Walsh, & Cowey, 1997). Because no such effect was observed in Experiment 4 (Feature Priming: TMS during the search array; Figure 3D), where the TMS protocol was the same, such interference cannot be explained by somatosensory or acoustic artifacts. Rather, the data suggest that priming is reduced across all four TMS sites because at the time that TMS is applied (during the search array), these areas are working together as a functionally integrated circuit to mediate target selection, saccade programming, and spatial priming. Thus, the non-significant reduction in spatial priming in the right FEF and the right and left AG conditions confirms that each of our TMS sites was effectively stimulated (Figure 3B). It is against this backdrop of *generalized* disruption of priming that the *relative prominence* of the left FEFs within the circuit is novel and interesting—only with left FEF TMS (for both the mean and the distribution of saccade latencies) is there a clear, statistically significant abolition of spatial priming. Hence, our results demonstrate that, within this bilateral parietal–premotor circuit, the left FEFs have a dominant role in integrating a spatial memory signal with an evolving saccade command.

The absence of a significant reduction in spatial priming following right AG TMS is consistent with previous reports that feature and spatial priming remain intact after right parietal lesions or TMS (Kristjansson et al., 2005; Campana et al., 2002). It also concurs with findings that the FEFs, but not the parietal cortex, are important for oculomotor preparatory set (Connolly et al., 2002) and for mnemonic coding in oculomotor coordinates (Curtis & D’Esposito, 2006). However, although the effects of AG stimulation were not significant, the trend (especially in the left hemisphere) was in the same direction as the effect of left FEF TMS. Because the present study was designed to investigate functional dissociations *across* conditions, it necessarily lacks the sensitivity to investigate the question of relative functional specialization *within* the within-trial spatial priming condition. For this reason, we have planned a series of studies to further explore this issue. One potentially fruitful approach would be to capitalize on the proposed distinction, demonstrated in delayed oculomotor memory tasks, between prospective/motor coding in the FEFs and retrospective/sensory coding in the parietal cortex (Curtis & D’Esposito, 2006). This could be further investigated using a TMS protocol in which pulse timing was anchored to the period of search array presentation versus the period of saccade programming. Neither TMS over the FEFs nor the AGs during the search array or in the ITI had any effect on feature priming. The absence of an effect is consistent with claims that the critical substrate for color PoP is color-selective cortex. It also supports the contention that fronto-parietal repetition suppression during

color PoP may simply reflect downstream effects of earlier sensory adaptation. Taken together with previous work (Kristjansson et al., 2005), the present findings suggest that spatial and feature priming derive from (at least partially) distinct causal mechanisms.

Recent imaging (Curtis, Rao, & D'Esposito, 2004; Donner et al., 2000) and TMS studies (O'Shea, Muggleton, Cowey, & Walsh, 2006; Taylor, Nobre, & Rushworth, 2006) have extended to the human brain findings from the macaque monkey that the FEFs do not merely issue oculomotor commands but compute a range of additional visuo-motor functions (Schall, 2002). To dissociate such processes from eye movement signals, previous TMS studies have used manual responses. The present study extends this line of work to the oculomotor domain. Our findings demonstrate hemispheric specialization in the human FEFs: the left, but not the right, FEFs integrate a spatial memory signal that facilitates saccades to a recently inspected location.

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