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Frontal eye field involvement in sustaining visual attention: Evidence from transcranial magnetic stimulation

Michael Esterman [a,b,*], Guanyu Liu [a], Hidefusa Okabe [a], Andrew Reagan [a], Michelle Thai [a], Joe DeGutis [a,c]

[a] Boston Attention and Learning Laboratory & Neuroimaging Research for Veterans Center (NeRVe), Veterans Administration, Boston Healthcare System, Boston, MA 02130, USA
[b] Department of Psychiatry, Boston University School of Medicine, Boston, MA 02118, USA
[c] Department of Medicine, Harvard Medical School, Boston, MA 02115, USA

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ABSTRACT

The frontal eye field (FEF), particularly the right FEF, is broadly implicated in top–down control of transient acts of attention, but less is known about its involvement in sustained attention. Although neuroimaging studies of sustained attention tasks commonly find FEF activation, it is unclear how this region contributes to moment-to-moment fluctuations in sustained performance. We sought to determine if the FEF plays a critical role in sustained attention, and if that role differs between periods of worse performance (out-of-the-zone) and periods of better performance (in-the-zone). We used offline 1 Hz repetitive transcranial magnetic stimulation (TMS) to temporarily attenuate either right or left FEF excitability while participants performed a go/no-go sustained attention task (the gradual onset continuous performance task). The results demonstrate that following TMS to the right FEF, sustained attention during in-the-zone periods significantly worsened both in terms of lower accuracy and increased reaction time variability. In contrast, applying TMS to the left FEF did not significantly affect accuracy or variability. These results demonstrate that the right FEF plays a crucial role in supporting optimal sustained attention.

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Introduction

Though the frontal eye field (FEF) has been traditionally associated with the control of eye movements (Pierrot-Deseilligny et al., 2004), studies indicate that the FEF regions, particularly the right FEF, are also involved in more general aspects of spatial attention as well as top–down control. For example, in non-human primates, the FEF has been shown to contain neurons that are responsive to covert shifts of spatial attention (Schall, 2004; Thompson et al., 2005b) and micro-stimulating the FEF has been shown to improve attention to regions contralateral to stimulation (Moore and Fallah, 2004). Beyond spatially lateralized aspects of attention, evidence suggests that the right FEF is critical for top–down control of attention to both visual fields (Grosbras and Paus, 2003; Hung et al., 2011; Silvanto et al., 2006). For instance, Hung et al. (2011) found that transcranial magnetic stimulation (TMS) of the right FEF increased distractor interference on both sides of space (i.e., generally reduced attentional control) whereas left FEF TMS had no significant effect on performance. This suggests that while both the left and right FEF regions are involved in spatial attention, the right FEF in particular has an important role in more general aspects of top–down control of attention.

Despite this growing evidence for the role of the FEF in transient acts of selective attention, the involvement of the FEF in sustained attention, the ability to remain focused for prolonged periods of time, has yet to be fully characterized. Studies have demonstrated that the FEF is involved when sustaining attention to spatial locations over short delay intervals (e.g., 2–10 s; Curtis et al., 2005; Geier et al., 2007). Additionally, several core regions of the dorsal attention network (DAN), including the FEF, were associated with sustaining attention over periods of several seconds to many minutes in a recent meta-analysis of 67 tasks (mostly non-spatial tasks; Langner and Eickhoff, 2013). For example, areas consistent with the location of the FEF showed fMRI activation during a variety of sustained attention tasks, including a rapid serial visual presentation task (Lawrence et al., 2003) as well as the classic psychomotor vigilance task (Lim et al., 2010). Moreover, Langner et al. (2011) found that across tactile, auditory, and visual modalities, monitoring for a target in comparison to resting recruited regions consistent with bilateral FEF.

Building on this work, recent studies from our laboratory and others have begun to appreciate that attention fluctuates from moment-to-moment and that different attentional states may reflect different underlying neural mechanisms supporting task performance (e.g., Esterman et al., 2013; Leber et al., 2008; Rosenberg et al., 2014). To better characterize fluctuations in sustained attention, we developed a challenging go/no-go continuous performance task with gradual transitions between stimuli — the gradual onset continuous performance task (gradCPT,

* Corresponding author at: VA Boston Healthcare System, 150 S. Huntington Avenue (182 JP), Boston, MA 02130, USA.
E-mail address: esterman@bu.edu (M. Esterman).

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Esterman et al., 2013, 2014a,b; Rosenberg et al., 2013). These gradual transitions make the task more dependent on intrinsic sustained attention abilities and allow for better examination of fluctuations between periods of better performance (i.e., in-the-zone) and worse performance (i.e., out-of-the-zone). Specifically, these in- vs. out-of-the-zone periods are defined based on intra-individual, moment-to-moment variation in reaction time variability as well as error-proneness. Measuring these fluctuations in attention has allowed us to identify regions associated with relatively successful periods of sustained attention vs. regions associated with relatively worse periods of sustained attention and/or the need for additional cognitive control mechanisms (e.g., to help one get back on task). Recent fMRI studies using the gradCPT demonstrated that not only was the FEF recruited for sustained attention, the FEF was also more active during out-of-the-zone periods than in-the-zone periods (Esterman et al., 2014b). This result challenges the current notion that the degree of right FEF engagement is always associated with more accurate attention performance (Curtis et al., 2004; Thompson et al., 2005a). This paradoxical finding could reflect the difference between the FEF's role in transient acts of top–down control (e.g., trial-based tasks) versus its role in sustaining attention over many seconds to minutes (e.g., continuous performance tasks). Indeed, studies provide evidence that increased recruitment of regions in the dorsal attention network, including the right FEF, may be summoned reactively in response to conflict or errors (e.g., Locke and Braver, 2008). Further, such regions may even be detrimental to sustaining attention or maintaining task set (vs. switching or shifting task set) over time (Leber et al., 2008; Olivers and Nieuwenhuis, 2006; Sadaghiani et al., 2009). Finally, decline in cognitive control, such as that observed in aging, may be linked to increased and potentially inefficient recruitment of these regions, including the FEF (e.g., Paxton et al., 2008).

Based on our work and these previous studies, at least three explanations of the FEF's involvement in sustained attention are plausible. First, the FEF may broadly support sustained performance similarly across attentional states. Alternatively, the finding of less FEF activation while in-the-zone is consistent with an *automaticity hypothesis*, in that optimal sustained attention (being in-the-zone) may actually be accomplished with less reliance on top–down control from the FEF and other DAN regions and instead rely on more engagement of the basal ganglia or default mode network (DMN) — regions associated with automatic, well-practiced tasks (Hazeltine et al., 1997; Mason et al., 2007). The FEF may be more essential when additional top–down control is needed, such as during periods of poor performance caused by distraction or goal-habituation (i.e., out-of-the-zone). According to this hypothesis, in-the-zone periods should be less sensitive to disruption from TMS than out-of-the-zone periods, as the FEF is less essential to in-the-zone performance.

On the other hand, less FEF activation while in-the-zone is also consistent with an *efficient recruitment hypothesis*, in that optimal sustained attention (being in-the-zone) is accomplished with more fine-tuned and economical recruitment of the FEF. Conversely, overactivation while out-of-the-zone may reflect a less efficient processing strategy that more extensively recruits the FEF and other task-positive regions. This is consistent with results showing that lower functioning individuals may recruit more extensive DAN regions (including the FEF) that are typically not activated in healthy young populations (Hedden and Gabrieli, 2004; Paxton et al., 2008). According to this hypothesis, in-the-zone periods should be more sensitive to disruption from TMS than out-of-the-zone periods, as the fine-tuned neural recruitment of the FEF is critical to in-the-zone performance.

To better characterize the FEF's role in sustaining visual attention, we performed repetitive TMS to the right or left FEF immediately followed by a sustained attention task. According to the automaticity hypothesis, disruption of the FEF should have less effect on in-the-zone than out-of-the-zone performance, as less recruitment of the FEF is required to perform optimally. Alternatively, according to the efficient recruitment hypothesis, the FEF is important and efficiently engaged during in-the-zone periods, and thus these states will be highly susceptible to neural disruption from TMS relative to out-of-the-zone periods. Finally, if the role of the FEF is constant across attentional states, both states will be equally disrupted by TMS. An additional prediction is that because the right hemisphere has been shown to be more critical for sustained attention than the left (Langner and Eickhoff, 2013) and the right FEF is more involved in top–down control than the left FEF (Grosbras and Paus, 2003; Hung et al., 2011; Silvanto et al., 2006), TMS of the right FEF should impair performance more than left FEF stimulation.

Materials and methods

Participants

Twenty-eight right-handed participants free of neurological or psychiatric dysfunction (16 males, mean age 20.4, SD 2.4), recruited from Northeastern University and Boston University, participated in this study. The first 14 were assigned to the right FEF stimulation group and the next 14 were assigned to the left FEF stimulation group. All participants met the screening requirement for TMS (Rossi et al., 2009) and completed informed consent. The study was approved by the VA Boston Healthcare System IRB.

Overall experimental procedure

As shown in Fig. 1, participants completed a single 1.5 h TMS session interleaving 4 blocks of 8-minute offline 1 Hz repetitive TMS with 5 min of behavioral task (gradCPT). Two of the four TMS blocks were stimulation (rFEF or lFEF) and the other two were sham (coil oriented 180° away from the scalp). Participants were told they would feel the stimulation more or less depending on the area of stimulation, without direct reference to the sham condition. While it is possible that subjects deduced the use of sham, given the offline design it is unlikely that the sensation during real TMS blocks had a direct effect on performance. TMS and sham were alternated and order was counterbalanced across participants (see Fig. 1). The average time between the end of active TMS (8 mins at 1 Hz) and post-sham gradCPT was 18 min (minimum of 14 min), which is beyond the expected transient duration of rTMS effects (see Discussion).

Localization of TMS targets (right and left FEF)

Prior to the TMS session, each participant completed a T1-weighted structural MRI scan (MPRAGE) at the Neuroimaging Research Center for Veterans (NeRVe) at the VA Boston Healthcare System, which houses a 3 T Siemens Trio Scanner. FEF regions were defined from a previous fMRI study using the same gradCPT task (Esterman et al., 2013), where targets (i.e., mountains) were contrasted to non-targets (i.e., cities), which elicited DAN activation (Fig. 1B). For each subject, the group Talairach map (from Esterman et al., 2013) was transformed into the subject's native space using the Analysis of Functional Neuroimages (AFNI), and subsequent TMS targeted the peak activation of either the right or the left FEF. This prior group map was used because the current subjects did not perform individual gradCPT fMRI. Nevertheless, we examined the individual hotspot of left and right FEF for the 16 subjects from that previous study (Esterman et al., 2013) in order to examine between-subject consistency of these regions. In these 16 subjects, we calculated the average geometric distance of individually-defined hotspots from the group hotspot for both left and right FEF and found no differences (RFEF = 8.3 mm, LFEF = 7.9 mm, $p > .7$). This suggests that the group map for targeting was not likely to be differentially accurate for right vs. left FEF.

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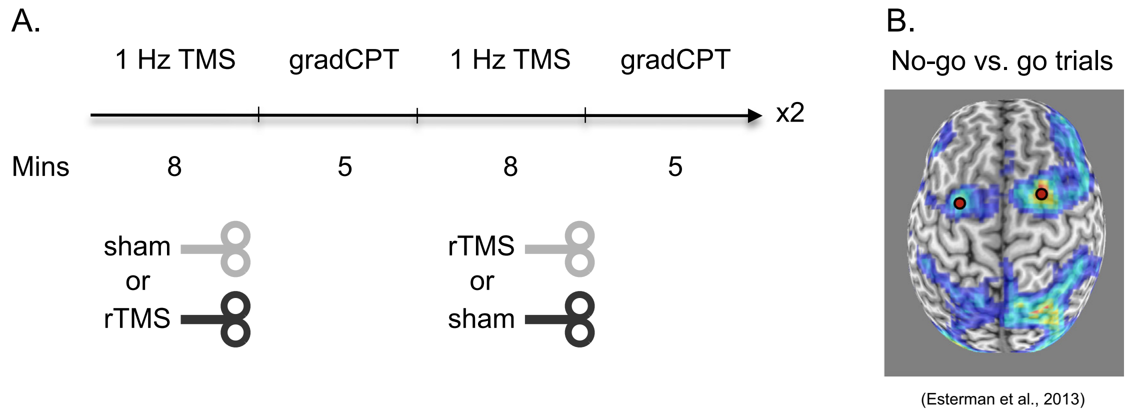

Fig. 1. Overall experimental procedure. (A) Each participant underwent 4 rounds of alternating repetitive TMS (rTMS or sham, 8 min) and gradCPT (5 min). The order of TMS and sham was counterbalanced. (B) TMS target regions were defined in each subject as peak activation for left or right FEF from a reverse normalized group map derived from Esterman et al., 2013.

Transcranial magnetic stimulation

A Magstim Super Rapid Plus with a 70 mm Double Air Film Coil was used to administer the TMS pulses. Brainsight 2 system and software were used for neuronavigation (Rogue-Research Inc., Montreal, Canada). In all cases, the TMS coil was oriented toward the frontal pole during stimulation. Resting motor threshold (RMT) was determined by the minimum amount of stimulator output needed to observe a finger movement for 5/10 single pulses before the main experiment, and 110% RMT was subsequently used (mean 60% stimulator output; range 52% to 65%).

Behavioral task

Participants performed the gradCPT, a go/no-go continuous performance task with gradual transitions between stimuli (Esterman et al., 2013). The stimuli consisted of 20 grayscale photographs of scenes cropped in a circle. Ten photographs were mountain scenes, and the other 10 were city scenes. On any trial, there was a 10% chance that a mountain scene was presented, and a 90% chance that a city scene was presented. Each scene gradually transitioned into the next scene using linear pixel-by-pixel interpolation, with the complete transition occurring over ~800 ms. Participants were instructed to press the comma key on the keyboard for every city scene but withhold their response for the mountain scenes. Response accuracy was emphasized without reference to speed. However, given that the next stimulus would replace the current stimulus in 800 ms, a response deadline was implicit in the task (see Reaction time (RT) and coefficient of variation (CV) below).

The task was presented using an Apple MacBook Pro connected to a 46-in. Sony flat-screen LCD display. MATLAB (MathWorks) and Psychophysics toolbox (Brainard, 1997) were used to present stimuli and collect responses. The participant sat in a chair with a chin rest that ensured that eye level was parallel with the display that was approximately 43 in. (109 cm) from the chin rest. The images subtended approximately 6° of visual angle. The participant responded by making button presses via an Apple Bluetooth keyboard.

Analyses

Reaction time (RT) and coefficient of variation (CV)

RTs were calculated relative to the beginning of each image transition, such that an RT of 800 ms indicates a button press at the moment image n was 100% coherent and not mixed with other images. A shorter RT indicates that the current scene was still in the process of transitioning from the previous, and a longer RT indicates that the current scene was in the process of transitioning to the subsequent scene. For example, an RT of 720 ms would be at the moment of 90% image n and 10% image $n - 1$. On rare trials with highly deviant RTs (before 70% coherence of image n and after 40% coherence of image $n + 1$) or multiple button presses, an iterative algorithm maximized correct responses as follows: the algorithm first assigned unambiguous correct responses, leaving few ambiguous button presses (presses before 70% coherence of the current scene and after 40% coherence of the following scene). Second, ambiguous presses were assigned to an adjacent trial if one of the two had no response. If both adjacent trials had no response, the press was assigned to the closest trial, unless one was a no-go target, in which case subjects were given the benefit of the doubt that they correctly omitted. Slight variations to this algorithm yielded highly similar results, as most button presses showed a 1–1 correspondence with presented images. Raw RTs on correct trials were used to calculate RT variability, or coefficient of variation (CV = standard deviation of RT/meanRT).

Accuracy

Trials in which participants correctly inhibited a button press to mountain scenes (no response was assigned) were considered correct omissions. Trials in which participants erroneously responded to mountains were considered commission errors. Commission error rate (CE) served as our primary measure of accuracy. Errors of omission, or failing to respond to city scenes, occurred rarely and were thus not considered in subsequent analyses.

Variance time course analysis (VTC): defining in-the-zone vs. out-of-the-zone

To assess trial-to-trial changes in RT, we conducted a within-subject block-based analysis called the variance time course (VTC; Esterman et al., 2013, 2014a; Rosenberg et al., 2013). VTCs were computed from the correct responses in each block (following z-transformation of RTs within-subject to normalize the scale of the VTC), where the value assigned to each trial represented the absolute deviation of the trial's RT from the mean RT of the block. Evidence shows that extremely fast RTs often indicate premature responding and inattention to the potential need for response inhibition (Cheyne et al., 2009; Esterman et al., 2013), while extremely slow RTs might indicate reduced attention to or inefficient processing of the ongoing stream of visual stimuli, requiring more time to accurately discriminate scenes (Esterman et al., 2013; Weissman et al., 2006). To emphasize attention-related fluctuations and reduce high frequency noise, based on prior literature (Di Martino et al., 2008; Esterman et al., 2013), the VTC was smoothed using a Gaussian kernel of 13 trials (~10 s) full-width at half-maximum (FWHM). We chose to divide performance into low- or high-variability periods (in-the-zone and out-of-the-zone) with a tertile split on the smoothed VTC for each run. This yielded 1.67 min

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each (per block) of being in-the-zone (lowest tertile of the VTC) and out-of-the-zone (highest tertile of the VTC). We chose this approach because it is a more powerful way to capture differences between these attentional states (Preacher et al., 2005). The patterns of results were identical when considering other divisions of in-the-zone and out-of-the-zone, including a median split. Note that differences in performance measures between in-the-zone and out-of-the-zone were highly significant (and statistically guaranteed in the case of CV), thus we do not report these main effects in the Results section, but rather their interaction with TMS.

Results

Participants

Participants in the right FEF stimulation group had a mean age of 19.43 (SD = 1.70; range: 18–24; 10 males) and participants in the left FEF stimulation group had a mean age of 21.50 (SD = 2.79; range: 18–29; 5 males). A *t*-test revealed that by random sampling, the left FEF group was significantly older than the right FEF stimulation group $t(26) = 2.37$, $p = .03$ (19.43 vs. 21.50 years). A chi-square test demonstrated that the groups did not significantly differ with respect to gender, $X^2(1) = 3.59$, $p = .06$.

Analysis strategy

In this study, our aim was to evaluate the main effect of TMS, as well as adjudicate between the automaticity and the efficient recruitment models of FEF involvement in sustained attention. In particular, the automaticity model predicts that TMS would be more disruptive for sustained attention while out-of-the-zone than in-the-zone. In contrast, the efficient recruitment model predicts that TMS would be more disruptive to sustained attention while in-the-zone than out-of-the-zone. Thus, we included both type of stimulation (TMS, sham) and attentional state (in-the-zone, out-of-the-zone) in our statistical models. We initially assessed the right and left FEF separately (Bonferroni corrected for multiple comparisons; critical $\alpha = .025$). Next, to test our hypothesis of greater effects for the right FEF condition, we conducted analyses with side of stimulation as an additional between-subject factor in our models. Given the limitations of our between-subject design (see Discussion), we conducted a number of control and follow-up analyses to account for potential group differences in composition and baseline performance. Our primary measure of interest was commission error rate (CE), and we examined correct RT variability (CV) as a secondary measure. We did not consider omission errors as they were rare (mean = 1%, STD = 2%) and not present in all subjects.

Right FEF

We began by examining the results in participants who received right FEF stimulation. There was no overall difference in commission error rate between TMS and sham nor differences while out-of-the-zone, but participants performed significantly worse following TMS compared to sham while in-the-zone (Fig. 2). This was confirmed by a significant 2-way (TMS/sham × in-the-zone/out-of-the-zone) interaction in a repeated measures ANOVA, $F(1, 13) = 8.67$, $p = .01$. The interaction was driven by significantly worse performance in-the-zone following TMS stimulation compared to sham (CE Rate = .23, vs. .16, $t(13) = 3.02$, $p = .01$). Although we counterbalanced order of TMS and sham (ABAB vs. BABA), we confirmed that after controlling for order (as a covariate), the 2-way interaction between TMS/sham and in-the-zone/out-of-the-zone was still significant, $F(1, 12) = 11.96$, $p = .005$.

A similar pattern of results for CV was found with participants being more variable following TMS stimulation while in-the-zone (CV = .10, vs. .09, $t(13) = 2.79$, $p = .02$), although there was no significant interaction between TMS/sham and in-/out-of-the-zone, $F(1, 13) = .94$, $p = .35$. Together, these results demonstrate that TMS stimulation of the right FEF increases error rate and variability during in-the-zone periods of sustained attention. These findings provide evidence that the right FEF is important for optimal sustained attention and support the efficient recruitment model rather than the automaticity model.

Given the consistency of the right FEF TMS effects on accuracy and variability during in-the-zone epochs, we conducted an exploratory analysis to examine the average length of each in-the-zone or out-of-the-zone epoch after both right FEF TMS and sham. This analysis revealed that after right FEF TMS relative to sham, average duration of in-the-zone epochs reduced from 13.4 to 11.5 trials ($p < .01$). In contrast, no change was seen in average duration of out-of-the-zone epochs (12.8 vs. 11.9, $p > .3$). Interestingly, this reduced duration of in-the-zone epochs after right FEF TMS was marginally correlated with the increase in commission error rate ($r = .45$, $p = .1$), suggesting a potential common mechanism of both reducing the efficiency *and* duration of optimal periods of sustained attention.

Left FEF

Participants who received left FEF stimulation showed a markedly different pattern from those who received right FEF stimulation. A two-way ANOVA of CE (TMS/sham × in-the-zone/out-of-the-zone) showed no evidence of a main effect of TMS, $F(1, 13) = 3.81$, $p = .07$ (a trend toward fewer errors after left FEF TMS), or an interaction with zone, $F(1, 13) = .55$, $p = .47$. This pattern of results was reflected in CV, where participants showed a nearly identical performance in the TMS and sham conditions (Fig. 2). In particular, there was no main effect of TMS, $F(1, 13) = .27$, $p = .62$, and no significant TMS/sham × in-the-zone/out-of-the-zone interaction, $F(1, 13) = .48$, $p = .50$. These non-significant and less consistent results in the left FEF compared to the right FEF may reflect the fact that the left FEF is less important to sustained attention and top-down control in general (Hung et al., 2011; Langner et al., 2011).

Comparing right and left FEF

To determine if the differing patterns of behavior between the right and left FEF were significant, we conducted mixed 3-way ANOVAs of stimulation (TMS, sham), attentional state (in-the-zone, out-of-the-zone), and side of stimulation (left FEF, right FEF), for both CE and CV. For CE, there were no main effects of stimulation or side of stimulation, but there was a significant 3-way interaction between stimulation, attentional state, and side, $F(1, 26) = 7.52$, $p = 0.01$. This 3-way interaction was driven by differential effects of left and right FEF stimulation while in-the-zone, such that right FEF stimulation significantly increased errors and left FEF stimulation did not (non-significantly reduced errors; Fig. 2). Although CV results showed a pattern similar to CE (see Fig. 2), there were no significant main effects or interactions (all p's > .24). These analyses provide support for a more critical role of the right than left FEF for optimal sustained attention.

A limitation of this between-subject analysis is that the left and right FEF stimulation groups were not perfectly matched. To address differences in age, gender, and baseline performance between groups, we conducted several follow-up analyses. First, we included age or gender as covariates, and in both cases the 3-way interaction for CE was still significant (age: $F(1, 25) = 6.32$, $p = 0.02$; gender: $F(1, 25) = 4.30$, $p < .05$). We also noted the left FEF group had numerically fewer commission errors and was numerically less variable during sham than the right FEF group, but these differences were not significant (main effect of group CE: $F(1, 26) = 2.46$, $p = .13$; CV: $F(1, 26) = .127$, $p = .27$). As such, we correlated the TMS in-the-zone performance effect (CE-in-the-zone-TMS minus CE-in-the-zone-sham) with overall baseline (sham) CE, as well as baseline CE while in-the-zone. These correlations

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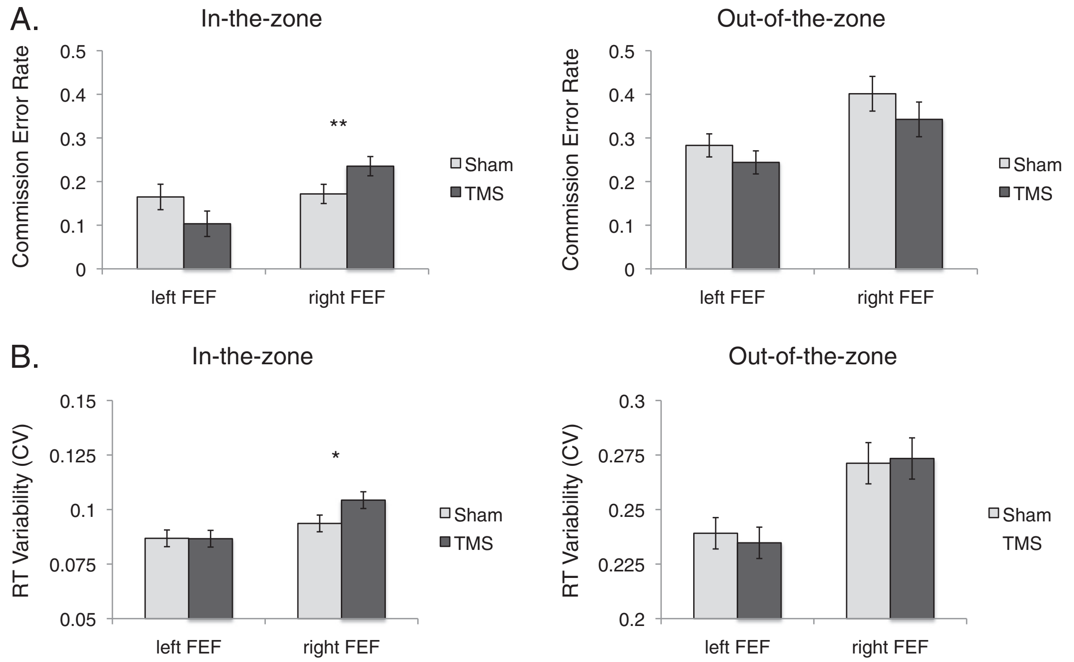

Fig. 2. Overall gradCPT performance. (A) Response accuracy. When in-the-zone, participants made more commission errors (i.e., pressing to mountains) after they received stimulation on the right FEF compared to sham. No effects were observed for out-of-the-zone periods. These effects were observed in the context of a significant 3-way interaction between stimulation (TMS, sham), attentional state (in-the-zone, out-of-the-zone) and side of stimulation (left FEF, right FEF). (B) Reaction time variability. When in-the-zone, participants' RTs were more variable after receiving stimulation of the right FEF compared to sham. * indicates $p < 0.05$; ** indicates $p < 0.01$; error bars reflect standard error of the mean (SEM).

were not significant when collapsing across left and right FEF ($n = 28$; r values $= -.02$ & .16, p values $> .4$). Thus, there was no evidence that worse performers were more disrupted by TMS, regardless of side of stimulation. Together, these follow-up analyses were unable to provide evidence that the relatively small differences in age, the incidental gender differences, and baseline (sham) performance differences were contributing to the laterality effects.

Discussion

We used TMS in order to determine whether the FEF is critical for sustained visual attention, and further if it is differentially important during states of optimal vs. suboptimal attention. This allowed us to tease apart multiple possible neural models of the role of the FEF in sustained attention. First, the role of the FEF could be equivalent across these different attentional states. An alternative is that in-the-zone, optimal periods of sustained attention are accomplished with less reliance on the FEF and attentional control, representing a more automatic attentional state (automaticity hypothesis). On the other hand, in-the-zone periods may be accomplished with more fine-tuned and efficient recruitment of the FEF (efficient recruitment hypothesis), and consequently are more reliant on the FEF's contribution than out-of-the-zone periods. In the current study we observed that TMS of the right FEF selectively impaired performance during in-the-zone periods, as measured by both response accuracy (CE) and variability (CV). This pattern of results significantly differed from the left FEF, where TMS had no effect. Together, these findings highlight the importance of the right FEF in sustained attention and further suggest that optimal sustained attention is accomplished by efficient recruitment of top–down control.

The finding that right FEF TMS selectively impaired in-the-zone performance supports the efficient recruitment model of optimal sustained attention. Specifically, this demonstrates that the right FEF is indeed critical for achieving both high response accuracy as well as consistency, and may even lead to longer periods of maintaining in-the-zone performance. When considering these findings in light of fMRI results showing less activation of the FEF during in-the-zone periods (Esterman et al., 2014a; Rosenberg et al., 2014), this suggests that the right FEF is recruited in a more economical manner during in-the-zone periods. In other words, optimal periods of sustained attention may require smaller but more fine-tuned acts of top-down control (e.g., minor adjustments in response settings, small shifts of attention from distractors back to the task). This may be in contrast to a more reactive strategy, in which cognitive control regions are maximally recruited in response to errors or conflict (such as being out-of-the-zone) (Locke and Braver, 2008). This economical recruitment of the FEF may be particularly important for performing well in continuous tasks compared to trial-based tasks. In trial-based tasks, maximal recruitment of top–down resources can be beneficial in transient bursts because there is time to replenish these resources. However, maximal recruitment of top–down resources in continuous performance tasks and other temporally extended tasks may indicate over-engagement of attentional resources (Olivers and Nieuwenhuis, 2006; Sadaghiani et al., 2009), which can be depleted and lead to worse performance over time (i.e., greater vigilance decrement; Smit et al., 2004; Warm et al., 2008). Though the differences between optimal top–down control of trial-based and continuous performance tasks have yet to be fully characterized, the current results clearly support a model where economical recruitment of top–down control is particularly important for optimal sustained attention performance. More broadly, this highlights the importance of considering the temporal demands of a task when assessing the meaning of over- vs. under-activation of attentional control regions.

In contrast to in-the-zone performance, right FEF TMS did not significantly affect performance during periods of worse, out-of-the-zone sustained attention performance. This is somewhat surprising considering that fMRI showed more activity in the FEF during out-of-the-zone than in-the-zone periods (Esterman et al., 2013; Rosenberg et al., 2014). One explanation is that sustaining attention during out-of-the-zone periods broadly and non-specifically recruits regions distributed across the dorsal attention network. These regions may be involved in more effortful aspects of top-down control (e.g., reorienting to the task after lapses in attention, or major adjustments to response settings). It may be that disrupting any one node in this highly active, distributed network does not substantially impact sustained attention performance because other regions seamlessly compensate. This explanation is consistent with results showing that lower performing individuals recruit more extensive DAN regions that are typically not activated in higher performing populations (Hedden and Gabrieli, 2004; Paxton et al., 2008). Therefore, this more extensive activation may represent inefficient processing strategies, or alternatively more reactivity to errors and conflict, and thus disruption from TMS is not particularly detrimental to performance. The lack of an effect during out-of-the-zone periods could also be a relative floor effect. It may be easier to impair performance when it is at its peak, or when subjects are exerting maximum effort. Nevertheless, even during out-of-the-zone periods, subjects were still correct on well-over 50% of no-go trials, so there numerically was room for additional errors.

Compared to the right FEF, TMS of the left FEF did not significantly influence sustained attention. No effects were observed in performance accuracy and RT variability. This significantly different pattern between left and right FEF TMS is consistent with evidence showing functional differences between these regions (Grosbras and Paus, 2003; Hung et al., 2011; Silvanto et al., 2006). One possible explanation of the lack of effect of left FEF TMS (or even the numerical effect of improved accuracy; CE = .36 vs. .44) is that performing the task with more right hemisphere dominance is optimal. Indeed, our fMRI contrast of go and no-go trials does reflect a right hemisphere-dominant map of task activation (Fig. 1B) in the dorsal attention network including both the FEF and intraparietal cortex (IPS) regions. Right hemisphere dominance in attentional control has more often been attributed to the *ventral* and not dorsal attention network (Corbetta and Shulman, 2011; although see Szczepanski et al., 2010; Vandenberghe et al., 2005 for examples in the DAN). For example, lesions of the right ventral attention network (VAN) selectively cause both lateralized spatial deficits (left hemineglect) as well as non-spatial deficits (poor sustained attention and arousal). However, recent theories have suggested that the critical lesions causing neglect are those connecting the right VAN to the right DAN, and thus neglect symptoms are partly due to an imbalance of activity in the DAN, with the left exceeding the right hemisphere (Corbetta and Shulman, 2011). Our right FEF TMS effects could similarly be due to stimulation-induced inter-hemispheric imbalance in the DAN, with greater right hemisphere activity than left being optimal. This would be consistent with right TMS impairing performance, and if anything, left TMS improving performance.

Though the results of the current study have important implications for sustained attention, there are also limitations. First of all, the mechanism of low frequency TMS is better understood in the motor system than in association cortices. Further, the inhibitory effect of 1 Hz is not completely consistent and can interact with baseline levels of activity (Maeda et al., 2000; Silvanto et al., 2008). Thus, without concurrent neuroimaging, the physiological effects of 1 Hz TMS must be assumed. Carry-over effects are another potential issue with the study design. In this study stimulation lasted 8 min, and the minimum time between the end of active TMS and post-sham gradCPT was 14 min. Studies of cognition have shown that the effects of 1 Hz last approximately as long as stimulation (Thut and Pascual-Leone, 2010). In another study of FEF 1 Hz TMS effects on oculomotor control, effects lasted 8–10 min after 10 min of stimulation (Nyffeler et al., 2006). Thus, although carry-over effects are possible, evidence suggests that effects were likely to have subsided at the time of sham-gradCPT. Another limitation of the study is its between-subject design. Importantly, the significant differences in TMS effects between the left and right FEF were robust to controlling for age and gender differences between groups. While there were no significant baseline differences (during sham) between the groups, numerically the group differences in sham were roughly similar to the significant within-group effects of TMS. While baseline performance did not predict responsiveness to TMS, conclusions regarding the unique role of right vs. left FEF could be better determined with a within-subject design. Such future work, as well as the use of concurrent neuroimaging, complementary stimulation parameters, and variations in tasks will help address these caveats, as well as answer questions regarding the hemispheric interactions caused by unilateral FEF TMS. In addition, exploration of other DAN regions, such as the supplementary eye fields and IPS will strengthen the conclusions drawn in the current study.

In sum, we found that offline TMS of the right FEF impaired in-the-zone sustained attention performance, and thus is the first study to causally implicate the FEF in sustained visual attention, as well as one of few studies to use non-invasive brain stimulation to modulate sustained attention (Lee et al., 2013; McIntire et al., 2014; Nelson et al., 2014). Our results support the importance of this network, and the right FEF in particular, for reaching optimal attentional states and thus have implications for both clinical and human factors applications to modulate and optimize attentional control.

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