

Neck muscle responses evoked by transcranial magnetic stimulation of the human frontal eye fields

Samanthi C. Goonetilleke,¹ Paul L. Gribble,^{1,2} Seyed M. Mirsattari,^{3,4,5} Timothy J. Doherty³ and Brian D. Corneil^{1,2,*}

¹Department of Physiology and Pharmacology, University of Western Ontario, London, Ontario, Canada N6A 5C1

²Department of Psychology, University of Western Ontario, London, Ontario, Canada N6A 5C1

³Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada N6A 5C1

⁴Department of Medical Biophysics, University of Western Ontario, London, Ontario, Canada N6A 5C1

⁵Department of Medical Imaging, University of Western Ontario, London, Ontario, Canada N6A 5C1

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Abstract

Transcranial magnetic stimulation (TMS) provides a non-invasive means of investigating brain function. Whereas TMS of the human frontal eye fields (FEFs) does not induce saccades, electrical stimulation of the monkey FEF evokes eye–head gaze shifts, with neck muscle responses evoked at stimulation levels insufficient to evoke a saccade. These animal results motivated us to examine whether TMS of the FEF (TMS-FEF) in humans evokes a neck muscle response. Subjects performed memory-guided saccades to the left or right while TMS (two pulses at 20 Hz) was delivered on 30% of trials to the left FEF coincident with saccade instruction. As reported previously, TMS-FEF decreased contralateral saccade reaction times. We simultaneously recorded the activity of splenius capitis (SPL) (an ipsilateral head turner). TMS-FEF evoked a lateralized increase in the activity of the right SPL but not the left SPL, consistent with the recruitment of a contralateral head-turning synergy. In some subjects, the evoked neck muscle response was time-locked to stimulation, whereas in others the evoked response occurred around the time of the saccade. Importantly, evoked responses were greater when TMS was applied to the FEF engaged in contralateral saccade preparation, with even greater evoked responses preceding shorter latency saccades. These results provide new insights into both the nature of TMS and the human oculomotor system, demonstrating that TMS-FEF engages brainstem oculomotor circuits in a manner consistent with a general role in eye–head gaze orienting. Our results also suggest that pairing neck muscle recordings with TMS-FEF provides a novel way of assaying the covert preparation of oculomotor plans.

Introduction

The frontal eye fields (FEFs) are a cortical region involved in the control of eye movements, playing an important role in target selection and saccade planning (for review see Schall, 2002). Most FEF research has been performed with the head restrained, but recent neuroimaging studies have suggested that the human FEF may fulfil a more general role in eye–head gaze shifts (Petit & Beauchamp, 2003; Tark & Curtis, 2009). Consistent with this notion, electrical stimulation of the FEF in both humans and monkeys can evoke eye and/or head movements (Rasmussen & Penfield, 1947; Tu & Keating, 2000; Chen, 2006; Elsley *et al.*, 2007; Knight & Fuchs, 2007; Monteon *et al.*, 2010).

Transcranial magnetic stimulation (TMS) provides a non-invasive means to investigate human brain function. Whereas TMS of the

primary motor cortex (M1) evokes a time-locked response on contralateral hand muscles (latency approximately 20 ms) via excitation of corticospinal projections (for review see Hallett, 2007), TMS of the FEF (TMS-FEF) does not evoke a saccade (Muri *et al.*, 1991; Wessel & Kömpf, 1991). Given the absence of a direct behavioural response, many researchers incorporate TMS-FEF in a form of causal chronometry, whereby the FEF's contribution to a given task (and time during a task) is inferred indirectly by the ability of precisely-timed TMS-FEF to modulate task performance (e.g. Grosbras & Paus, 2002; O'Shea *et al.*, 2004; Smith *et al.*, 2005; Olk *et al.*, 2006).

The failure of TMS-FEF to evoke a saccade is not surprising given what is known about the oculomotor brainstem (for review see Scudder *et al.*, 2002). The number and frequency of electrical stimulation pulses required to evoke a saccade from the FEF (300 Hz for 70 ms) (Tehovnik *et al.*, 2000) greatly exceed that delivered by TMS. However, TMS-FEF may evoke other motor responses. Electrical stimulation of the monkey FEF evokes robust neck muscle responses that precede saccades by approximately 20 ms, and persist on trials without evoked saccades or with subsaccadic levels of stimulation current (Elsley *et al.*, 2007; Corneil *et al.*, 2010).

Correspondence: Brian D. Corneil, *present address below.
E-mail: bcorneil@uwo.ca

*Present address: Centre for Brain and Mind, Robarts Research Institute, London, Ontario, Canada N6A 5K8.

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The aim of this study was to investigate whether TMS-FEF evokes a neck muscle response. Specifically, we were interested in the spatiotemporal patterning of any evoked response, and whether any response depends on the engagement of the FEF at the time of stimulation. We are aware of one mapping study, which reported that TMS throughout the frontal cortex, perhaps encompassing the FEF, evoked neck muscle responses (Thompson *et al.*, 1997). However, this study did not deliver TMS in the context of a behavioural task and did not specifically investigate the influence of TMS-FEF on neck muscle responses. We delivered TMS-FEF while subjects performed a memory-guided saccade task, stimulating at a time that decreases contralateral saccade reaction times (SRTs) (Wipfli *et al.*, 2001). Our results establish that TMS-FEF evokes a measurable, task-dependent motor response at the neck, providing insights into the functionality of the FEF not obtainable through behavioural measures.

Some results have been reported previously in abstract form (Goonetilleke *et al.*, 2009).

Materials and methods

Nine healthy subjects (three female, mean age 27 years, SD 5.7, all but one right-handed) participated in the experiment. None reported any neurological symptoms including sensorimotor dysfunction, neck/back pain, or any negative responses to TMS or functional magnetic resonance imaging. Subjects had either normal or corrected-to-normal vision. All procedures were approved by the Research Ethics Board for Health Science Research at the University of Western Ontario and were in accordance with the Declaration of Helsinki. Subjects gave informed consent and were aware that they could terminate testing at any time. Subject S2 was one of the authors and hence was knowledgeable about the specific goals of the experiment, but his results did not differ from the remaining subjects.

Transcranial magnetic stimulation and localization of the frontal eye field

On a separate day prior to the experimental session, all subjects underwent a functional magnetic resonance imaging scan in a 3T Tim Trio scanner with a 32-channel head coil (Siemens, Erlangen, Germany). An anatomical scan was performed encompassing the whole brain, followed by functional scans designed to localize the FEF and M1. These functional scans consisted of sequential 20 s intervals of movement or rest. During the FEF localizer, subjects were instructed to perform memory-guided saccades to the remembered location of a target presented in one of eight locations about a central fixation point (FP). For the M1 localizer, subjects performed a sequential finger tap of their right thumb onto each finger of their right hand. The functional images of FEF or M1 were constructed by comparing the intervals of saccades or finger tapping, respectively, with periods of rest.

The functional images were used to guide the positioning of the TMS coil over the scalp. A three-dimensional reconstruction of each subject's brain with the corresponding functional image overlaid (see Fig. 1A for an example of FEF localization) was co-registered with their head position usingBrainsight frameless stereotaxic software (Rogue Research, Montreal, Canada) and a Polaris infrared motion-tracking camera (Northern Digital, Waterloo, Canada) that co-registered landmarks visible on both the magnetic resonance scan and the head. This equipment allowed us to estimate the position of the centre of the TMS coil with respect to the subject's brain in real-time, permitting us to position the coil over the location of

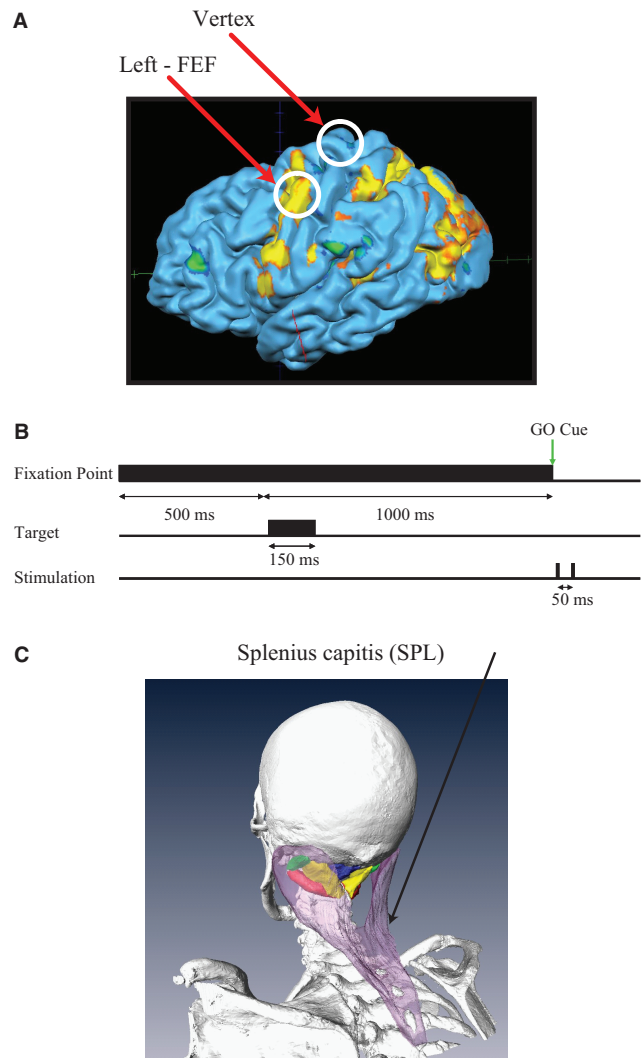


FIG. 1. (A) An example of the area of brain activation as a result of the FEF localizer that subjects performed in the scanner. The location of FEF and vertex stimulation is highlighted. It should be noted that there was no activation at the vertex as a result of the FEF localizer. (B) Schematic representation of the task during a stimulation trial. The FP was illuminated for 500 ms prior to the target being briefly flashed (for 150 ms). The FP remained illuminated for a further 850 ms and the disappearance of the FP served as the GO cue. Stimulation, two pulses at a frequency of 20 Hz, was delivered concurrent with the GO cue. (C) Computerized tomography image on the muscle of interest in purple.

interest. Subjects wore a custom head-band on which three reference markers were mounted. The markers were used to localize the subject's head in space and to co-register the subject's head with their functional magnetic resonance imaging scan using Brainsight frameless stereotaxy. An air-cooled figure-of-eight TMS coil was used for stimulation, which was controlled by a trigger sent from an experimental computer to a rapid rate biphasic stimulator (Magstim Company, Spring Gardens, UK; diameter of each coil 7 cm).

Prior to the start of the experiment, we first determined the lowest setting on the stimulator output sufficient to elicit a response of the contralateral hand muscles following TMS over the hand area of M1. The stimulator output was increased until contraction of the contralateral small hand muscles (e.g. flexor pollicis brevis) was just visible on at least 50% of trials; this was set as the resting motor evoked

potential. During the memory-guided saccade task (described below), TMS-FEF was delivered at a suprathreshold intensity of 110% of resting motor evoked potential (ranging from 51 to 70% of maximum stimulator output). During TMS-FEF the coil was oriented so that the handle was pointing backwards (at an angle of approximately of 45° to the mid-sagittal line) and was held in place on the participant's scalp by a multi-jointed adjustable clamp. Any movement of the coil with respect to the subject's head was identified via our co-registration procedure, and the coil was then appropriately repositioned by hand. During experimental testing, subjects wore ear protection to attenuate the noise of the TMS. This was particularly important to ensure that any neck muscle activity was not simply the result of an acoustic startle response.

Memory-guided saccade task

Subjects were seated in an upright padded chair with their chins stabilized in a chin rest. They performed a memory-guided saccade task that required them to first look at a central FP; 500 ms later a peripheral target was briefly flashed for 150 ms either 20° to the left or right. The FP remained illuminated for a further 850 ms (Fig. 1B). Subjects were instructed to perform a saccade to the remembered location of the target upon the disappearance of the FP, which served as the GO cue. All stimuli in this experiment consisted of light-emitting diodes positioned 1.2 m in front of the subject at a height of 1.2 m to lie on the horizontal meridian from the subject's perspective. Each subject performed a series of practice trials prior to data collection to familiarize themselves with the task. Subjects were instructed to make a saccade to the peripheral target as quickly and accurately as possible following the disappearance of the FP. Subjects completed two blocks of 100 trials (200 trials in total). Within a block of 100 trials, leftward and rightward trials were intermixed and presented an equal number of times. TMS was delivered on 30% of trials and trials were ordered to ensure that there were no sequences with more than two sequential stimulation trials. TMS was delivered to two separate locations, initially to the left FEF (L-FEF) and the vertex (apex) of the head (control site; Fig. 1A). The vertex was chosen as a control site as it is not believed to be involved in saccade control; this was supported by the lack of activation at the vertex during the FEF localizer (Fig. 1A). We were not able to obtain TMS of the vertex in one subject (S9) as the neck electromyographic (EMG) electrodes came out in this subject during repositioning of the TMS coil.

Data collection and analysis

Horizontal eye movements were measured using bitemporal DC electro-oculography with electrodes placed at the outer canthi of the eyes (Carl, 1993), and were filtered and amplified with a P122 AC/DC pre-amplifier (Grass Instruments, Warwick, RI, USA). The horizontal eye position signal was then low-pass filtered (100 Hz), amplified and digitized at a rate of 4 kHz onto a data-collection computer (MotionMonitor system; Innovative Sports Training, Chicago, IL, USA). In some subjects TMS-FEF occasionally evoked a brief blink that did not interfere with our ability to identify saccade onset.

A detailed description of our methodology for recording neck muscle activity is provided elsewhere (Goonetilleke *et al.*, 2010). Briefly, EMG activity of splenius capitis (SPL) (Fig. 1C) was recorded bilaterally using intramuscular fine-wire needle electrodes inserted at the level of the C4/C5 vertebrae, using either commercially available

electrodes (30 mm, 27 gauge, Motion Lab Systems, Baton Rouge, LA, USA) or electrodes made in-house [seven-strand stainless steel wire (A-M Systems Inc., Sequim, WA, USA) threaded into a 30 mm, 25 gauge cannula (Kendal Monoject, Mansfield, MA, USA)]. The commercial electrodes were bipolar hook electrodes and required a single insertion. The in-house electrodes were monopolar, requiring two insertions staggered 3–5 mm apart. These electrodes were used in an attempt to obtain a larger sampling of SPL motor units. Our results did not depend on the type of electrode used. SPL is a dorsal neck muscle that plays a major role in ipsilateral horizontal head rotations as well as a subsidiary role in cervical extension (Mayoux-Benhamou *et al.*, 1997). The placement of the electrode in SPL was confirmed by the presence of strong EMG activity in response to slight ipsilateral head rotation, and the absence of activity in response to shoulder shrugs or contralateral head rotation (André-Deshays *et al.*, 1988). EMG data were recorded with a commercial system (Myopac Jr., Run Technologies, Laguna Hills, CA, USA; customized bandwidth 10 Hz–2 kHz). The EMG data were amplified and sampled at 4 kHz, and digitized with a 16 bit A-D converter by the MotionMonitor system. EMG artefacts as a consequence of TMS stimulation were easily identified, and were removed using a customized template-matching algorithm.

All aspects of the experiment were controlled at a rate of 1 kHz by a customized Labview program that executed in real-time on a PXI box (National Instruments). Off-line analyses were performed using customized Matlab (The Mathworks) programs. Off-line analyses consisted first of downsampling all positional data from 4 to 1 kHz. Saccade onset and offset were identified by a computer algorithm that detected the crossings of a set velocity threshold (50°/s). These marks were used as guides for the placement of interactive marks by an analyst within a customized graphical user interface written in Matlab. Movement amplitudes and peak velocities were extracted for movements bounded by these marks. This interface also permitted the exclusion of trials if classified as anticipatory or too slow due to lack of subject alertness (SRTs < 80 or > 800 ms, respectively), if the subject looked in the wrong direction opposite to the target, if an artefact of TMS obscured saccade onset, or if there were aberrant patterns of EMG activity during the trial (e.g. due to postural shifts). Fewer than 5% of trials were excluded using these criteria.

Results

Influence of transcranial magnetic stimulation of the frontal eye field on saccade latency

The average saccadic reaction time for each subject across the different conditions is shown in Table 1. Consistent with the results of Wipfli *et al.* (2001), TMS-FEF significantly reduced SRTs for contralaterally directed saccades for seven of our nine subjects (*t*-test, $P < 0.05$), and across the population (paired *t*-test, $t = 3.35$, $P = 0.01$; Fig. 2B). For left saccade trials (i.e. ipsilateral to TMS), TMS-FEF did not significantly influence SRTs in the majority of subjects, with most points lying close to the line of unity (Fig. 2A), and across the population there was no significant effect (paired *t*-test; $t = 0.67$, $P = 0.52$). For vertex stimulation, TMS significantly modulated rightward or leftward saccades in only three subjects (*t*-test, $P < 0.05$), and across the population there was no significant effect for saccades to either direction ($t = 0.78$, $P = 0.46$; $t = 0.43$, $P = 0.68$, respectively; Fig. 2C and D). Although vertex stimulation increased SRT in a few subjects, this effect was not consistent across our sample and is in contrast to the consistent decrease in contralateral SRT observed with TMS-FEF.

TABLE 1. Mean \pm SDs of the saccadic reaction time (ms) for each subject and each trial condition for both L-FEF and vertex stimulation

	TMS over L-FEF				TMS over vertex			
	Left saccades		Right saccades		Left saccades		Right saccades	
	Control	TMS	Control	TMS	Control	TMS	Control	TMS
S1	268 \pm 48	285 \pm 41	252 \pm 44	228 \pm 25	251 \pm 46	288 \pm 47	240 \pm 43	271 \pm 59
S2	208 \pm 38	207 \pm 29	231 \pm 49	183 \pm 35	192 \pm 19	186 \pm 26	182 \pm 20	164 \pm 24
S3	215 \pm 39	212 \pm 56	219 \pm 26	197 \pm 40	193 \pm 29	187 \pm 36	210 \pm 50	199 \pm 34
S4	233 \pm 44	270 \pm 52	212 \pm 33	170 \pm 31	227 \pm 34	250 \pm 33	217 \pm 36	258 \pm 49
S5	254 \pm 46	234 \pm 56	252 \pm 42	222 \pm 39	226 \pm 40	219 \pm 37	202 \pm 30	186 \pm 40
S6	345 \pm 53	349 \pm 45	348 \pm 60	294 \pm 66	325 \pm 36	376 \pm 40	369 \pm 53	401 \pm 43
S7	291 \pm 43	282 \pm 56	307 \pm 62	238 \pm 34	342 \pm 45	307 \pm 62	294 \pm 51	267 \pm 54
S8	240 \pm 47	275 \pm 42	236 \pm 39	267 \pm 39	253 \pm 65	232 \pm 31	229 \pm 71	255 \pm 46
S9	200 \pm 46	192 \pm 45	180 \pm 34	157 \pm 28	N/A	N/A	N/A	N/A
Mean	251 \pm 46	255 \pm 49	249 \pm 51	217 \pm 46	251 \pm 56	255 \pm 65	243 \pm 61	250 \pm 73

Representative examples of neck muscle activity evoked by transcranial magnetic stimulation of the frontal eye field

The selective effect of TMS on contralateral SRTs is consistent with previous results of TMS-FEF on the SRT of memory-guided saccades (Wipfli *et al.*, 2001). Having established this, we now describe the profiles of SPL muscle activity observed in this task. If the effect of TMS-FEF on neck muscle activity were to resemble that evoked by

intracortical microstimulation in primates, then we should observe a short-latency increase in activity of the contralateral muscle and a simultaneous decrease in the activity of the ipsilateral muscle (Elsley *et al.*, 2007). Such lateralized recruitment of SPL is a component of a head-turning synergy observed in both monkeys (Corneil *et al.*, 2001) and humans (Zangemeister & Stark, 1982), but differs from the bilateral co-activation of the sternocleidomastoid reported by Thompson *et al.* (1997) following TMS of the frontal cortex. Recall that SPL is an

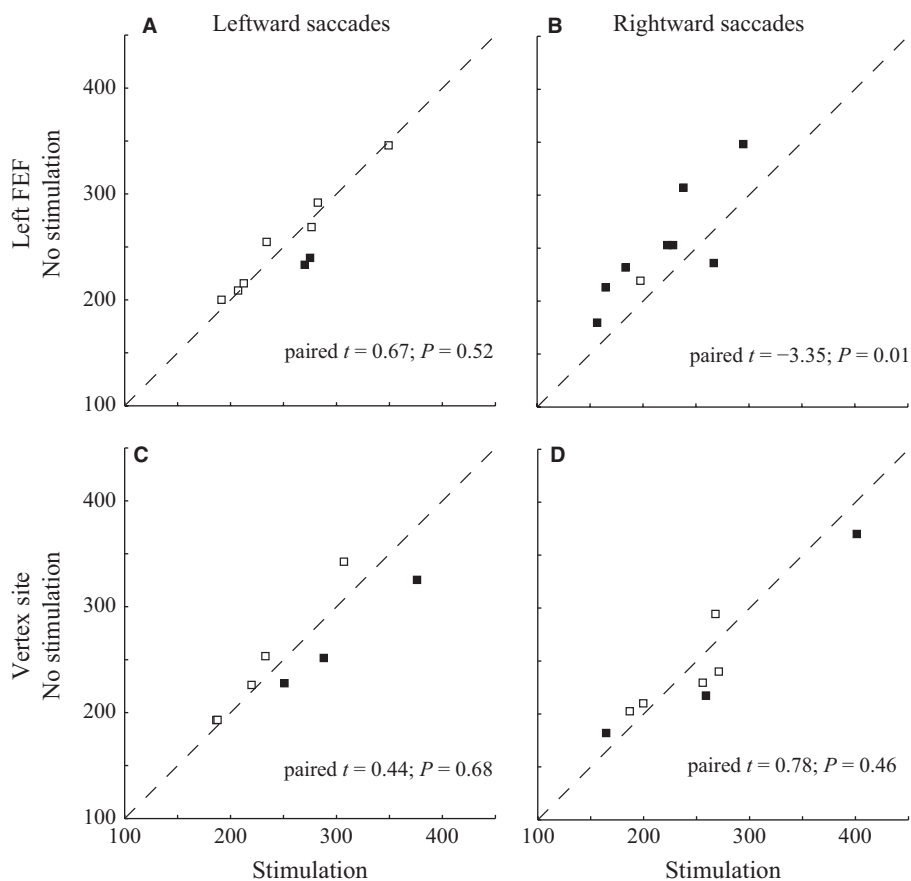


FIG. 2. Scatter plots showing the effect of stimulation over the FEF (A and B) and vertex (C and D) on SRT for both leftward (A and C) and rightward (B and D) saccades for all subjects. The filled points indicate that there was a significant difference (t -test, $P < 0.05$) in the SRT between stimulation and control trials for that subject. The dashed lines indicate the line of unity. A significant effect of stimulation on SRT was only seen for rightward trials when stimulation was applied over the L-FEF (B).

ipsilateral head-turning muscle, hence the right SPL (R-SPL) muscle (contralateral to the side of stimulation) would serve as an agonist for rightward head turns, and the left SPL (L-SPL) as an antagonist.

Across our sample, TMS-FEF evoked one of two patterns of neck muscle responses. In four subjects TMS-FEF evoked an increase in R-SPL activity that was time-locked to the time of stimulation, whereas in the other five subjects TMS-FEF evoked an increase in R-SPL activity that was time-locked to saccade onset. Note that this classification is based on the strongest evoked response; in three of the five subjects where we classified the evoked response as relative to saccade onset, we also observed a weaker response that was time-locked to stimulation (see below).

We begin by showing the profile of neck muscle activity for one representative subject (S4) where TMS-FEF evoked a time-locked recruitment of the R-SPL. Figure 3 shows the rectified activity of the R-SPL aligned to the GO cue (dashed vertical line) for each trial for this subject, sorting trials based on saccade direction and trial type, and ordering them by SRT. It should be noted that there is more activity accompanying rightward (right subplots) compared with leftward (left subplots) saccades even though the subject's head is restrained; this increase in SPL activity with eccentric eye position has been reported previously in humans (André-Deshays *et al.*, 1988, 1991). The bottom subplots show the activity following TMS-FEF, and several aspects of the data need to be emphasized. Firstly, note that TMS-FEF evoked a time-locked increase in R-SPL activity relative to TMS (arrow in bottom-right subplot, Fig. 3), and that such activity only occurred prior to rightward and not leftward saccades. Secondly, this recruitment was observed at around 25–40 ms after the second pulse of TMS, with no apparent response after the first pulse. The latency of the response was thus considerably longer than the latency of the muscle responses evoked by either TMS of the M1 or intracortical microstimulation of the FEF in the monkey, both of which began within ≤ 20 ms of stimulation onset (Elsley *et al.*, 2007; Hallett, 2007). Thirdly, this recruitment was observed in the majority of trials, but not on every trial, with the magnitude and latency of the evoked response varying

from trial to trial. The probabilistic nature and variability of the response evoked by TMS resemble that evoked by low-current microstimulation of the FEF in the monkey (Cornel *et al.*, 2010).

The second pattern of evoked neck muscle activity consisted of an increased probability of R-SPL activity around the time of the saccade. Figure 4A shows the activity of the R-SPL for another representative subject (S3) aligned to the onset of the GO cue (dashed vertical line). In the control trials (top subplots in Fig. 4A), we observed a decrease in R-SPL activity around the time of leftward saccades (solid dots in top-left subplot) and a very moderate increase in activity around the time of rightward saccades. Such phasic sensitivity of SPL activity to saccades has also been reported previously in humans (André-Deshays *et al.*, 1988, 1991). Unlike the previous representative example, the main influence of TMS occurred around the time of rightward saccades (solid dot) on most trials (arrow in lower-right subplot). The increased activity observed on the R-SPL could lag the second pulse of TMS by as little as 70 ms or as much as 200 ms depending on the variability of the SRT. Figure 4B shows the same data as Fig. 4A realigned to saccade onset (dashed vertical line) to emphasize the selective increase in R-SPL muscle activity for rightward saccades following TMS-FEF. These results highlight that the effect of TMS-FEF on the neck muscle activity in this subject was also only evident when the stimulated FEF was engaged in a task.

Figure 5 shows data from an additional subject (S1) from two different test days. On the first test day (Fig. 5A), we observed an effect of TMS that we classified as saccade-locked, as their modulation was stronger than the neck muscle response that appears locked to stimulation onset. On a subsequent test day (Fig. 5B), we observed an effect of TMS that we classified as stimulation-locked. This figure emphasizes that whether TMS-FEF evokes a stimulation-locked or saccade-locked effect is not simply dependent on the subject. Instead, as we consider more thoroughly in the Discussion, we suggest that the type of response evoked by TMS-FEF is more dependent on the sample of splenius motor units that happen to be recorded.

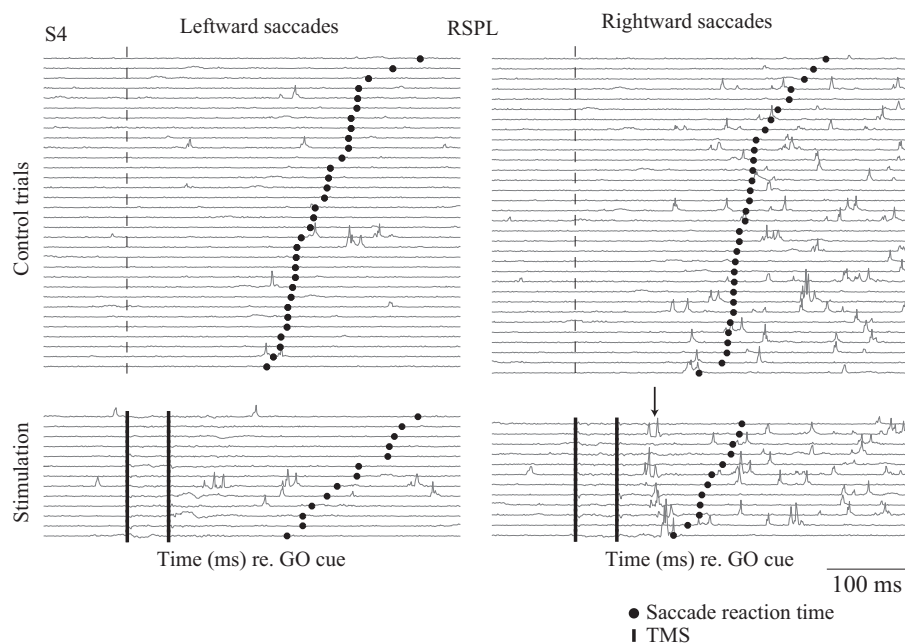


FIG. 3. Intramuscular R-SPL EMG activity on control (top section) and L-FEF stimulation trials (bottom section) for both leftward and rightward saccades from subject S4. Data are aligned to the GO cue (dashed vertical line), and each individual trace is a single trial ordered by SRT (solid circle), with the solid lines on the stimulation trials indicating the onset of stimulation.

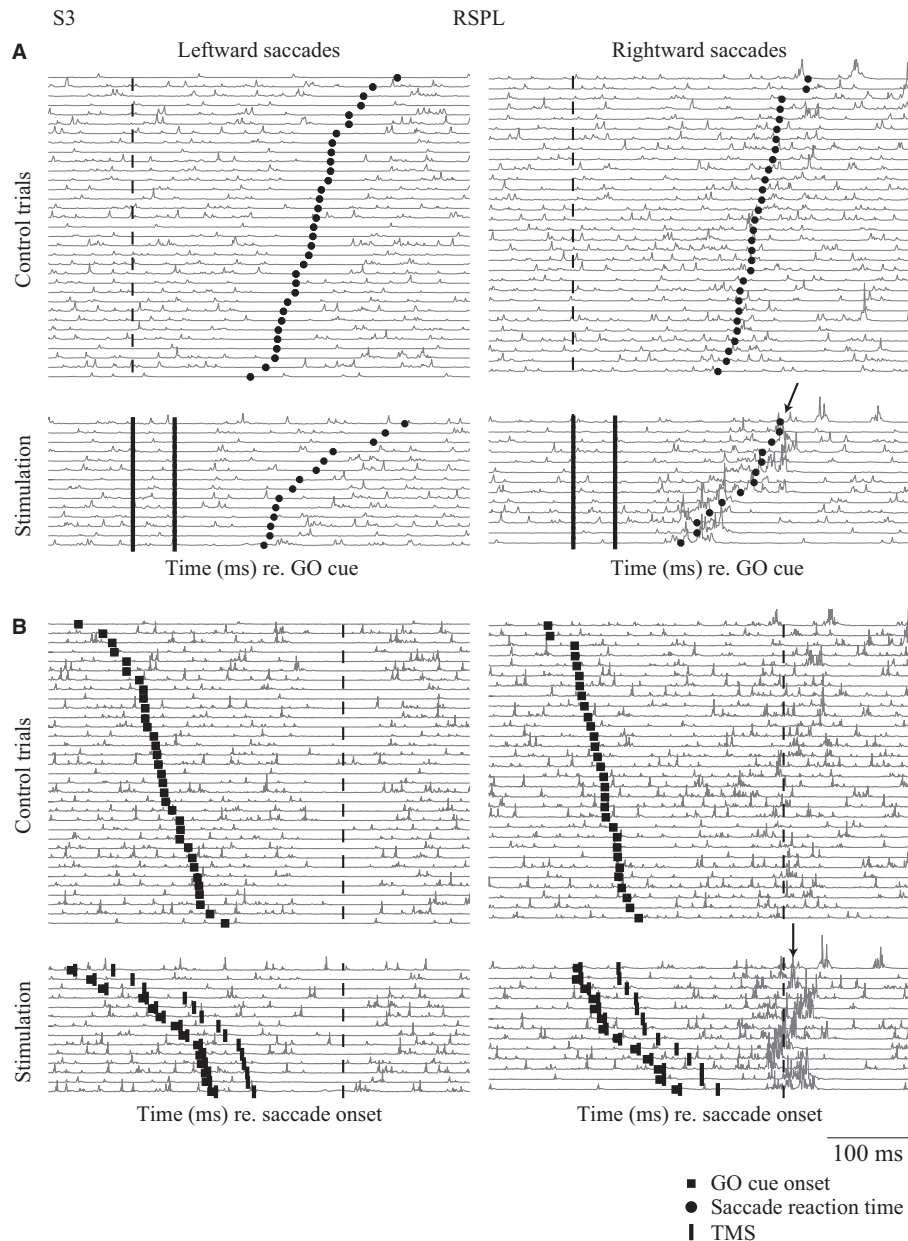


FIG. 4. (A) Intramuscular R-SPL EMG activity on control (top panels) and L-FEF stimulation trials (bottom panels) for both leftward and rightward saccades from subject S3 aligned to GO cue (dashed vertical line). The data are ordered by increasing SRT (solid circle). The solid vertical bars indicate the onset of stimulation. (B) The same data as in A now aligned to SRT (dashed line) with the onset of stimulation indicated by the solid bars and the GO cue indicated by the solid squares.

We also examined the activity of the L-SPL, which is ipsilateral to the side of TMS. We were particularly interested in whether TMS-FEF evokes a bilateral response as seen on the sternocleidomastoid as reported by Thompson *et al.* (1997). Across our sample, we never observed bilateral co-contraction on SPL. Figure 6 shows the activity of the L-SPL for the representative subjects shown previously in Figs 3 and 4 (aligned to the GO cue or saccade onset, respectively). It should be noted that the activity on the L-SPL was similar regardless of whether or not stimulation was applied. In Fig. 6B the increase in recruitment of L-SPL activity with ipsilateral eye position is again consistent with an eye position sensitivity that has been shown to exist in humans (André-Deshays *et al.*, 1988). In subject S3 we observed a slight augmentation of the L-SPL (Fig. 6B, bottom left panel) following TMS, but this was not consistent across our sample. The

absence of a differential effect on L-FEF across our sample emphasizes that TMS-FEF evoked lateralized responses in the R-SPL, consistent with a transient recruitment of a head-turning synergy, rather than bilateral co-activation.

Quantification of selective effects of transcranial magnetic stimulation of the frontal eye field on neck muscle activity

To quantify our results across our sample, we first had to determine for each subject whether the modulation of R-SPL activity with TMS-FEF was aligned to TMS or to the saccade. We then determined the mean and variance of the EMG activity across the different trial types (i.e. leftward and rightward saccade trials with or without TMS). Figure 7 shows the mean and variance of the EMG activity for the

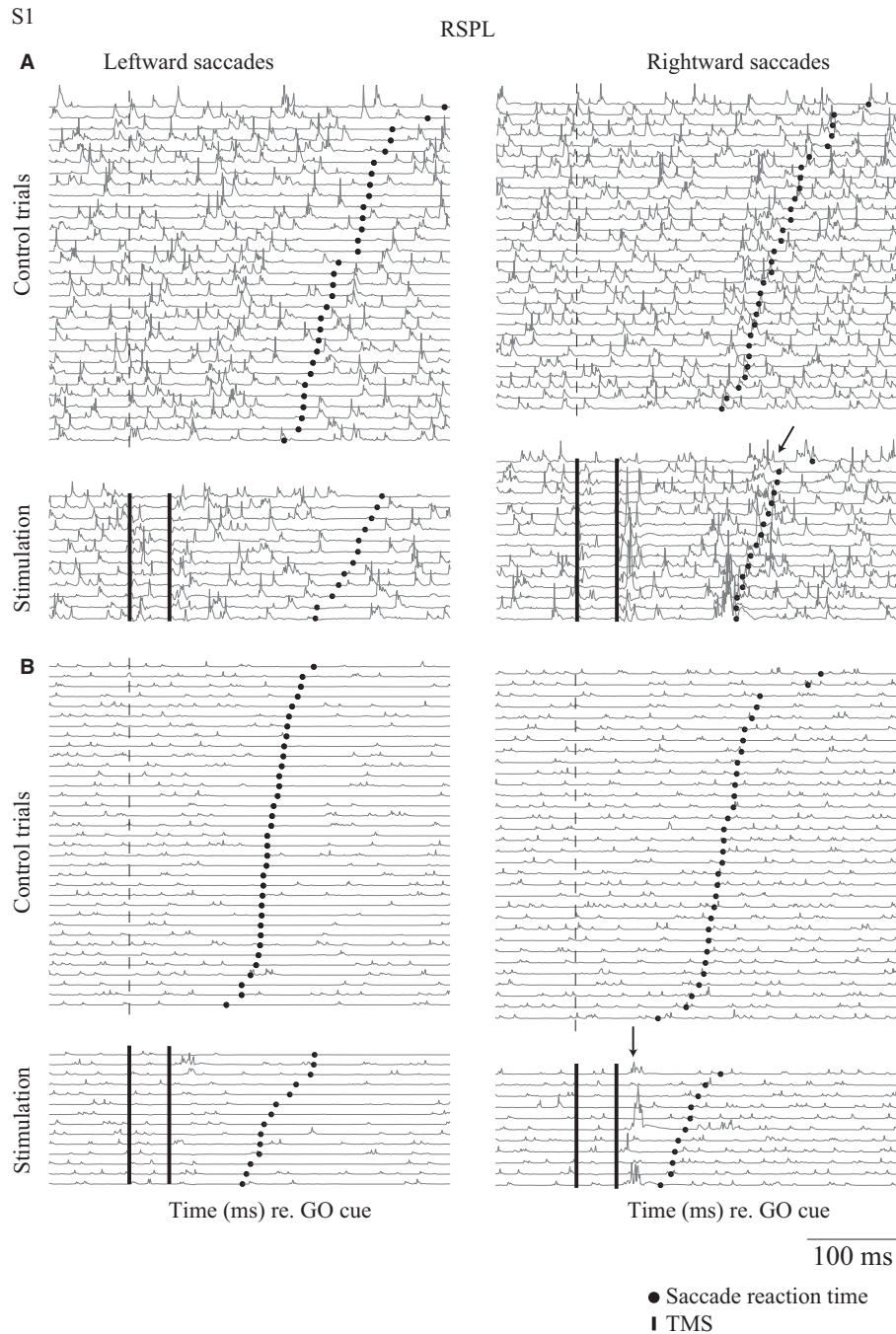


FIG. 5. (A) Intramuscular R-SPL EMG activity for subject S1 for control and L-FEF stimulation trials aligned to the GO cue (dashed vertical line) and ordered with respect to SRT (solid circles). Solid bars indicate stimulation onset for the first test. (B) Intramuscular R-SPL EMG activity for this subject, collected on a different day, for control and stimulation trials ordered and aligned to the SRT (dashed vertical line). Solid bars indicate stimulation onset and GO cue is indicated by the solid squares.

different trial types for both representative subjects aligned to either the GO cue (S4) or saccade onset (S3) (solid vertical line) for both the L-SPL (column I) and R-SPL (column II). For the R-SPL the EMG activity for rightward stimulation trials (black trace) was consistently higher than the EMG activity observed during the other trial types. It should be noted that there was very little difference in the activity of the L-SPL (column I) across all four conditions. We then defined a critical period of 75 ms duration (dashed box) relative to either the GO cue or saccade onset to quantify the effect of

TMS-FEF on neck muscle activity. For subjects where a stimulation-locked effect was observed, the critical period was set from 75 to 150 ms after the GO cue, and for subjects where a saccade-locked effect was observed, the critical period was set from 50 ms before to 25 ms after the SRT. Although the timing of these intervals was arbitrary, changing the width of the interval or its position did not grossly alter the results.

Using these windows, we then integrated the EMG activity for all subjects across the different trial types during our critical period.

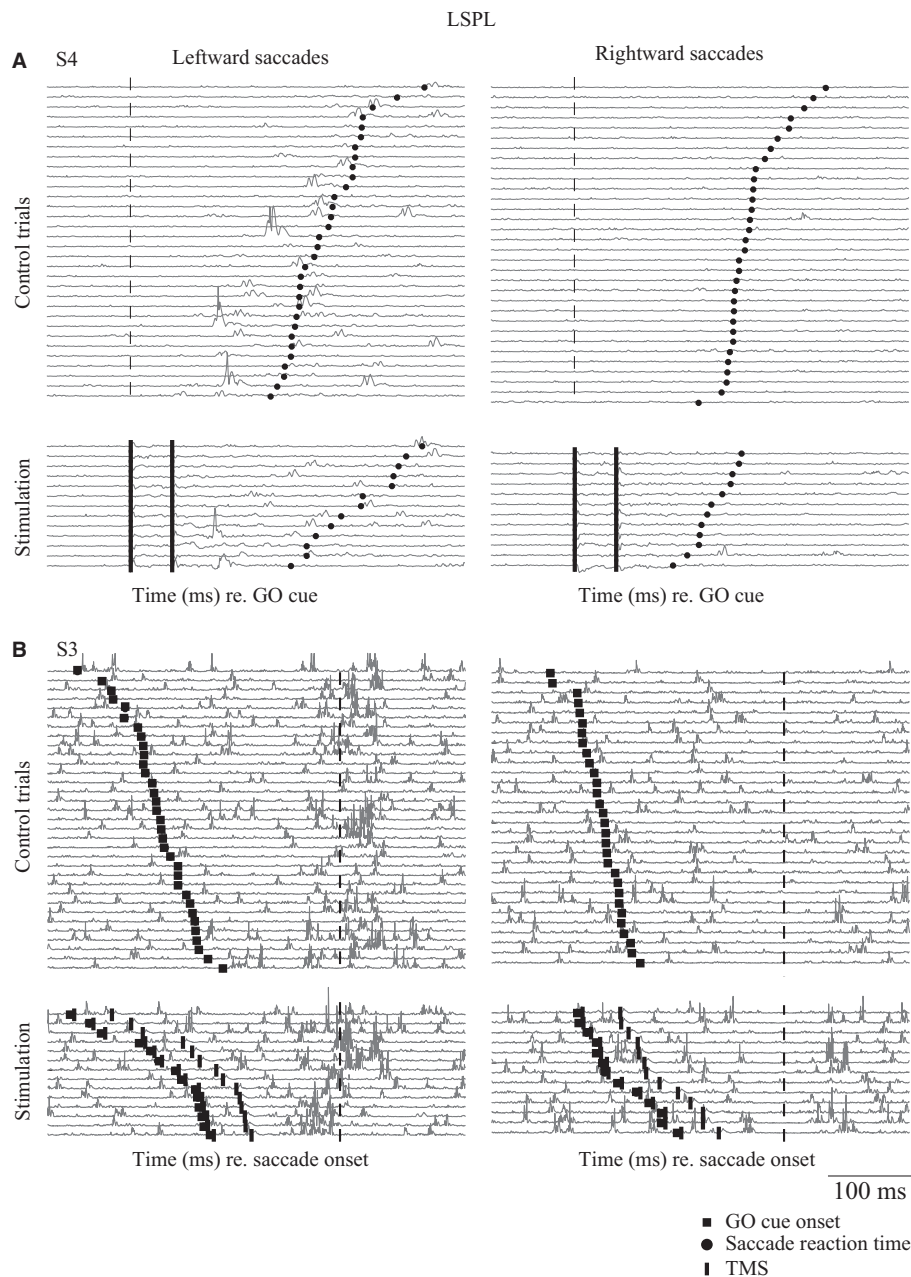


FIG. 6. (A) Intramuscular L-SPL EMG activity for subject S4 for control and stimulation trials aligned to the GO cue (dashed vertical line) and ordered with respect to SRT (solid circles). Solid bars indicate stimulation onset. (B) Intramuscular L-SPL EMG activity for subject S3 for control and stimulation trials ordered and aligned to the SRT (dashed vertical line). Solid bars indicate stimulation onset and GO cue is indicated by the solid squares.

Figure 8A shows the average normalized R-SPL EMG activity in the window of interest for all subjects for each of the four different trial types when TMS was delivered to either the L-FEF (left) or vertex (right). We normalized all activity to the average activity on all trials regardless of saccade direction and whether or not stimulation was delivered; such normalization is necessary to compare EMG magnitude across muscles and subjects. Across all nine subjects we observed greater EMG activity on the R-SPL for rightward saccades with L-FEF stimulation when compared with the other trial types. For TMS-FEF it was seen that there was a significant interaction effect for saccade direction and whether or not stimulation was delivered (two-way repeated-measures ANOVA, $F_{1,8} = 6.73$, $P = 0.03$), with rightward saccades with stimulation having greater motor unit activity than any

other trial type (signed rank test, $P < 0.01$). Statistical analysis showed that there was no effect of vertex stimulation on the recruitment of SPL activity (two-way repeated-measures ANOVA; for both main effects and interaction, $P > 0.05$). This indicates that the effect of TMS-FEF on neck muscle recruitment cannot be explained by the sound affiliated with TMS.

A similar analysis of L-SPL activity (Fig. 8B) revealed a different pattern of results. Unlike R-SPL activity, L-SPL activity was lowest on rightward stimulation trials. This again emphasizes that TMS-FEF did not evoke bilateral co-activation of SPL. For the L-SPL, there was a statistically significant difference in the EMG activity for leftward saccades with stimulation than for the other conditions, but this effect was quite small and not consistent across our sample (only four out of

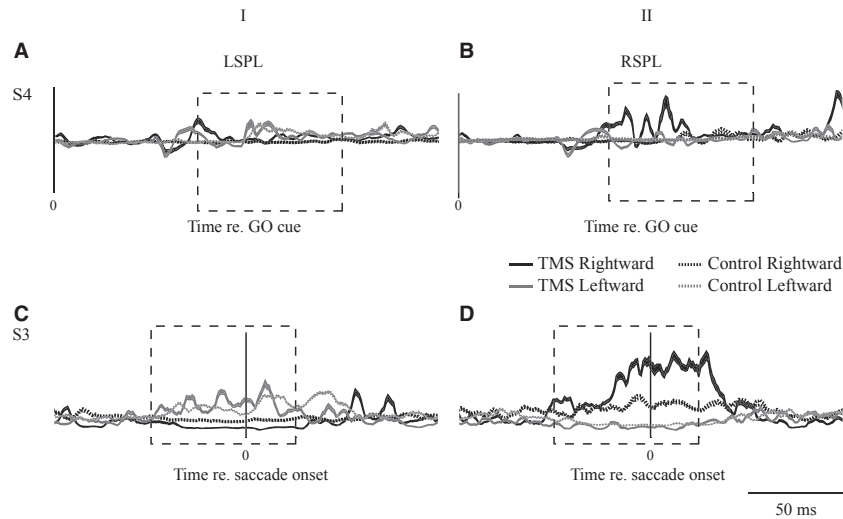


FIG. 7. The average EMG activity subtended by standard error for the L-SPL (A and C) and R-SPL (B and D) for both representative subjects for each of the different trial types, i.e. leftward and rightward trials both with and without L-FEF stimulation. For S4, data are aligned to the GO cue (A and B) and for S3, data are aligned to saccade onset (C and D) (solid vertical line). The solid black line shows rightward saccades with L-FEF stimulation; solid gray trace shows leftward stimulation trials; dashed black trace shows rightward saccades without stimulation; and dashed gray trace shows leftward saccades without stimulation. The 75 ms second window used for the subsequent analysis to quantify the magnitude of the EMG response is also shown (dashed box).

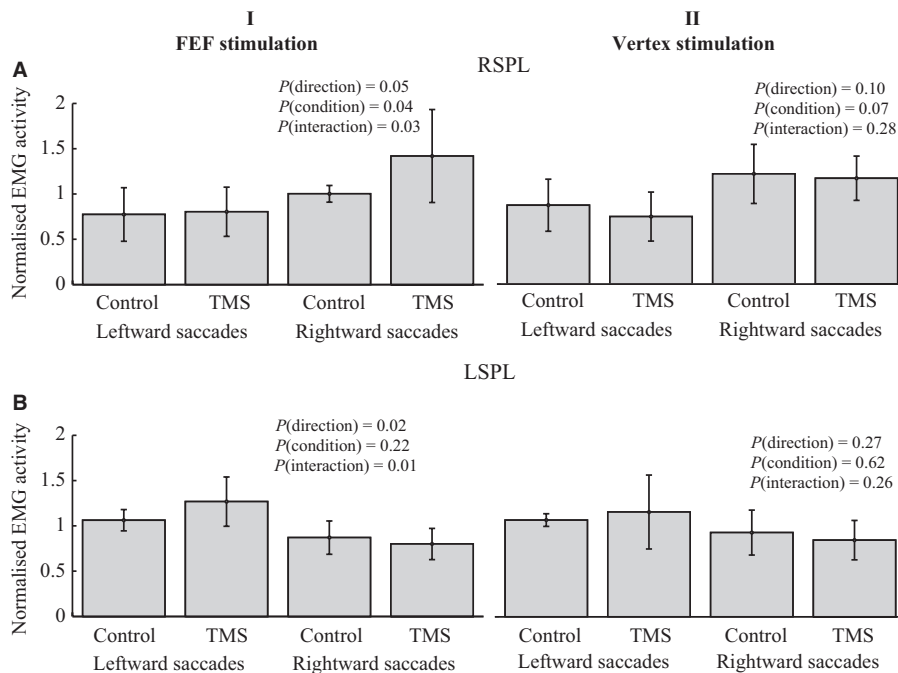


FIG. 8. Histogram of the normalized EMG activity across all subjects on the R-SPL (A) and L-SPL (B) with L-FEF (left panel) or vertex (right panel) stimulation.

nine subjects). There was also no significant difference in the EMG activity on the L-SPL for vertex stimulation.

In summary, across our four conditions (leftward and rightward saccades with or without TMS) we observed the greatest increase in the activity of the R-SPL when TMS of the L-FEF was delivered while subjects were about to generate rightward saccades (i.e. when TMS was delivered to the FEF engaged in the task). This increase in R-SPL activity could present as either time-locked to stimulation, or around the time of the rightward saccade. Such activity was not seen on the L-SPL, or when TMS was applied over the vertex.

Larger evoked neck electromyographic responses precede shorter latency rightward saccades

Finally, we investigated whether increased R-SPL activity depended in any way on ensuing saccade latency. Other studies have shown that greater amounts of EMG activity precede shorter reaction times (Corneil *et al.*, 2004), consistent with neurophysiological correlates of oculomotor preparation (Dorris *et al.*, 1997; Opris *et al.*, 2005; Rezvani & Corneil, 2008). Although these previous studies performed trial-by-trial correlations, such an approach was not feasible given the

low trial count. Therefore, we pooled our normalized EMG activity on the R-SPL across all subjects and compared it with the SRT (normalized to SRT on rightward control trials) for rightward saccades with either L-FEF or vertex stimulation. A highly significant negative trend was seen with L-FEF stimulation ($r = -0.35$, $P = 6 \times 10^{-5}$), which was considerably stronger than the trend observed following vertex stimulation or on rightward control trials ($r = 0.21$, $P = 0.02$; $r = 0.11$, $P = 0.08$, respectively).

Discussion

To our knowledge, this is the first systematic study of neck muscle responses to TMS-FEF during a behavioural task. Despite the diversity of the temporal patterning of the evoked response (i.e. either stimulation- or saccade-locked recruitment of the contralateral SPL), there were common features to the results. Firstly, the effect was lateralized in that TMS-FEF evoked an increase in contralateral (right) SPL activity without influencing the activity of the ipsilateral (left) SPL; TMS-FEF never evoked bilateral co-contraction of SPL. Secondly, the magnitude of the evoked response depended on the behavioural state of the subject, with significantly greater activity observed when TMS was delivered to the FEF engaged in contralateral saccade preparation. Lastly, the magnitude of evoked SPL activity correlated with the ensuing SRT, with greater activity preceding trials with shorter saccade latencies. Our results show that TMS-FEF can evoke an overt response on neck muscles that, when combined with neurophysiological results in monkeys, provides additional support for the role of the FEF in eye-head orienting, and suggests a new way of examining covert processing in the FEF.

Comparison to previous transcranial magnetic stimulation or electrical stimulation studies in humans and monkeys

Although previous studies have established that TMS-FEF does not evoke saccadic eye movements (Muri *et al.*, 1991; Wessel *et al.*, 1991; Zangemeister *et al.*, 1995), such studies have not been able to distinguish amongst possible mechanistic explanations. Perhaps, as suggested by Wessel *et al.* (1991), the inability of TMS-FEF to evoke a saccade is a consequence of the low stimulation frequencies inherent to TMS. The FEF's influence on the saccadic brainstem burst generator is predominantly polysynaptic, probably mediated via the superior colliculus (SC) (Segraves & Goldberg, 1987; Sommer & Wurtz, 2000; Hanes & Wurtz, 2001), and the saccadic burst generator is tonically inhibited by brainstem omnipause neurons (for review see Scudder *et al.*, 2002). Alternatively, there is no guarantee that any descending signal evoked by TMS-FEF is interpretable to brainstem oculomotor circuits. Indeed, to our knowledge it has never been explicitly shown that TMS-FEF induces signals that even propagate to downstream brainstem structures.

The results of this study provide strong evidence that TMS-FEF initiates signals that influence and cascade through brainstem circuits, modulating neck muscle activity either time-locked to stimulation or during the peri-saccadic interval. Although the time-locked effect on neck muscles following TMS-FEF is quite long (70–80 ms after first pulse), these effects lag the second pulse by only 20–30 ms. Assuming that the first pulse primes or facilitates downstream circuits, the latency of the neck EMG response relative to the second pulse is now more similar to that evoked by direct electrical stimulation of the FEF in the monkey (17–20 ms) (Elsley *et al.*, 2007), with the remaining differences in latency attributable to the higher stimulation frequencies and shorter conduction distances in monkeys. The latency of the TMS-FEF evoked neck muscle response relative to the second TMS pulse is

also more similar to motor evoked potentials on neck muscles following TMS of the frontal cortex (10–12 ms) (Thompson *et al.*, 1997) with differences perhaps being due to intervening synapses in the oculomotor pathway. Time-locked neck muscle responses also displayed some variability, both in their probability and parameters (latency and magnitude). These results are also consistent with TMS inducing activity along a polysynaptic pathway, with the evoked response depending not only on the level of FEF activation at the time of TMS, but also on spatial summation at the intervening synapses. This variability is also consistent with monkey neurophysiological studies that have shown less probable and more variable neck muscle responses evoked by progressively lower electrical stimulation currents delivered to the monkey FEF (Cornel *et al.*, 2010). Future studies that parametrically manipulate the number and frequency of TMS pulses in humans or deliver pulses of electrical stimulation in monkeys at frequencies similar to those used in TMS should help provide further mechanistic insights into the effects of both TMS and electrical stimulation in the oculomotor system.

The observed saccade-locked modulation of EMG activity also supports the notion that TMS-FEF initiates activity that cascades through brainstem circuits. The phasic coupling of neck muscle activity with eye movements in humans (André-Deshays *et al.*, 1991) is thought to arise from a population of reticulospinal circuits that distribute collaterals to pre-motor centres for both eye and head movements (Grantyn & Berthoz, 1987; Grantyn, 1989; Isa & Sasaki, 2002). We suggest that TMS-FEF in those subjects primes this pool of reticulospinal neurons, resulting in augmented coupling of neck muscle activity with saccade generation, despite head restraint.

At the current time, we can only speculate as to why TMS-FEF occasionally evokes a stimulation-locked effect on some SPL motor units, and a saccade-locked response in others. Previous work in humans has shown that the recruitment of SPL in a given task can vary substantially across subjects, compared with other neck muscles (Keshner *et al.*, 1989; Mayoux-Benhamou *et al.*, 1997; Blouin *et al.*, 2007). However, the data shown in Fig. 5 demonstrate that both types of responses can be evoked in a single subject; thus the characteristics of SPL motor units that happen to be sampled via intramuscular recordings may also be relevant. The functional heterogeneity of SPL motor units reported previously (André-Deshays *et al.*, 1988, 1991; Bexander *et al.*, 2005) was also apparent in this study; some SPL motor units displayed a tonic eye-in-head position sensitivity, others a phasic eye-in-head sensitivity, and others still no sensitivity to eye-in-head position at all. SPL is also quite a large muscle that displays considerable compartmentalization in humans (Kamibayashi & Richmond, 1998) and, at least in monkeys, a mix of fibre types and the distribution of those types across the muscle's mediolateral extent (Richmond *et al.*, 2001). Finally, the different types of responses evoked by TMS-FEF may arise from the differential amounts of current being delivered to the FEF depending on idiosyncratic factors such as the thickness of the subject's skull, or the exact position and orientation of the FEF within the skull. Now that we have established that there is a measurable behavioural response with TMS-FEF, future studies that manipulate the parameters of TMS or the mediolateral location of SPL recording may be able to identify functional and anatomical factors that determine the type of response recorded.

TMS-FEF resulted in a lateralized increase in EMG activity of SPL contralateral to the side of stimulation but had no effect on the ipsilateral SPL. This is in stark contrast to the findings of Thompson *et al.* (1997) who reported that TMS throughout the frontal cortex evoked bilateral co-contraction of the sternocleidomastoid muscle. The biomechanical and histochemical properties of sternocleidomastoid make it one of the most powerful neck muscles (Kamibayashi &

Richmond, 1998; Vasavada *et al.*, 1998), and it is recruited unilaterally during particularly rapid head turns (Zangemeister *et al.*, 1982). Based on our observation that TMS-FEF evoked lateralized SPL recruitment, we speculate that stimulation in the study of Thompson *et al.* (1997) was being delivered to frontal sites more posterior than the FEF and accordingly not evoking a head-turning synergy.

Plausible neural pathways mediating transcranial magnetic stimulation evoked neck muscle responses

A series of neurophysiological studies have shown that there is a close relationship between low levels of oculomotor activity and the recruitment of neck muscles and head movement regardless of whether this activity is introduced via electrical stimulation or attained during a behavioural task (Tu & Keating, 2000; Pélisson *et al.*, 2001; Corneil *et al.*, 2002, 2008, 2010; Knight & Fuchs, 2007; Rezvani & Corneil, 2008). These results are broadly consistent with a hypothesis where brainstem omnipause neurons tonically inhibit the saccadic burst generator without inhibiting pre-motor head circuits (Galiana & Guitton, 1992); in support of this, omnipause neuron stimulation can arrest an ongoing saccadic gaze shift in mid-flight without influencing the trajectories of ongoing head movements (Gandhi & Sparks, 2007). This hypothesis suggests that one possible explanation of our findings is that TMS-FEF is able to briefly activate head pre-motor circuits through the SC, as is thought to be the case following low-current electrical stimulation (Elsley *et al.*, 2007). A related possibility is that the effects of TMS-FEF may be mediated by pathways that bypass the SC and access brainstem reticulospinal pools either directly or via relays in the paramedian pontine reticular formation (Schnyder *et al.*, 1985; Segraves, 1992; Isa & Sasaki, 2002). The involvement of the SC in responses evoked from the FEF remains a matter of some debate. Although there are anatomical projections from the FEF to the downstream brainstem structures that could underlie preserved oculomotor functions following chronic lesions of the SC (Schiller *et al.*, 1979, 1980), the integrity of the SC appears to be critical for saccades evoked from the FEF in the intact animal (Hanes & Wurtz, 2001). It is impossible to discern between these alternatives in humans, hence we suggest that understanding the mechanistic effects of TMS-FEF requires an animal model that could be combined with neurophysiological recordings or manipulations of the activity in areas such as the SC. The neck muscle responses that we have observed could serve as useful cross-species markers for verifying the effects of TMS-FEF.

Alternatively, could the effects of TMS-FEF be mediated by projections to other cortical regions, or a spread of TMS to nearby cortical areas? TMS or low-current electrical stimulation of the FEF has been shown to influence activity in a host of areas in the striate, extrastriate and parietal cortices (Paus *et al.*, 1997; Moore & Armstrong, 2003; Ruff *et al.*, 2006; Silvanto *et al.*, 2006; Taylor *et al.*, 2007; Ekstrom *et al.*, 2008). Possible candidate areas could be corticospinal projections from M1 or from the ventral pre-motor cortex. Although corticospinal projections from these areas to the upper cervical spinal cord or the SC do exist (Fries, 1984; He *et al.*, 1993), a direct connection between the FEF and either M1 or ventral pre-motor cortex is weak to non-existent (Godschalk *et al.*, 1984; Huerta *et al.*, 1987; Stanton *et al.*, 1993; Ghosh & Gattera, 1995; Dum & Strick, 2005). Furthermore, cervical projections from these areas are frequently bilateral, and prolonged electrical stimulation of the ventral pre-motor cortex in monkeys can evoke ipsilaterally-directed head movements toward the side of stimulation as part of a defensive response (Guitton & Mandl, 1978; Graziano *et al.*, 2002; Boulanger *et al.*, 2009). TMS of the frontal cortex in humans can also provoke a

bilateral co-contraction of neck muscles (Thompson *et al.*, 1997). These profiles of evoked activity differ considerably from the patterns of neck muscle recruitment that we observed, which consisted of a brief expression of a contralateral head-turning synergy away from the side of TMS. Given this, the most parsimonious explanation of all of our results, including the shortening of SRTs, recruitment of a contralateral head-turning synergy and the scaling of such recruitment with ensuing oculomotor behaviour, is that the effects of TMS-FEF propagate through the oculomotor brainstem.

Logothetis *et al.* (2010) recently reported that electrical stimulation of the afferents into the primary visual cortex tends to induce suppression of the activity of retinotopically-matched regions in higher visual areas. These results are important in understanding the propagation of cortical signals following electrical stimulation, establishing, at least for sensory cortices, that inhibition following electrical stimulation is more the rule than the exception. A different set of rules appear to apply following the application of stimulation in the oculomotor system. Regardless of the precise pathway mediating the evoked response, it appears that TMS and low-current electrical stimulation of the oculomotor system, both of which fail to evoke saccades, are able to initiate a cascade of polysynaptic events through the oculomotor brainstem that eventually culminate in motor recruitment.

Implications of our results on the nature and study of the human frontal eye field

Our results emphasize two important perspectives on the human oculomotor system, and on the FEF more specifically. Firstly, our results are consistent with the human FEF fulfilling a more general role in orienting eye-head gaze shifts, as seen in the monkey (Tu & Keating, 2000; Elsley *et al.*, 2007; Knight & Fuchs, 2007; Monteon *et al.*, 2010). Although such a suggestion has been made in recent neuroimaging studies (Petit & Beauchamp, 2003; Tark & Curtis, 2009), the temporal resolution of blood oxygenation level dependent imaging makes it difficult to differentiate between a direct role in generating eye-head gaze shifts and an indirect role in the planning or monitoring of such movements.

Secondly, a central observation in our results is that there was a greater response on the contralateral neck muscle when the stimulated FEF was engaged in a task. This is consistent with electrical stimulation of the FEF or SC in monkeys where the behavioural response varies with the current behavioural state of the monkey (Tehovnik *et al.*, 2000; Opris *et al.*, 2005; Corneil *et al.*, 2007); a likely mechanism common to all of these observations is that stimulation produces a greater response when applied to an already active population. We speculate that this line of reasoning could be exploited to provide a new means of studying the FEF's contribution during covert tasks where the eyes remain stable. In the current paradigm, TMS-FEF was delivered during the maintenance of working memory, but we can imagine extending this technique to other attentional, decision-making, or cognitively-demanding tasks. Although work remains to be done to parameterize the most optimal stimulation parameters for TMS-FEF, the availability of an overt and direct neuromuscular response to TMS-FEF may obviate the need for the sort of causal chronometry whereby the role of the FEF is inferred indirectly by the disruptive influence of TMS.

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Abbreviations

EMG, electromyographic; FEF, frontal eye field; FP, fixation point; L-FEF, left frontal eye field; L-SPL, left splenius capitis; M1, primary motor cortex; R-SPL, right splenius capitis; SC, superior colliculus; SPL, splenius capitis; SRT, saccade reaction time; TMS, transcranial magnetic stimulation; TMS-FEF, transcranial magnetic stimulation of the frontal eye field.

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