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In addition to its role in shifting the line of sight, the oculomotor system is also involved in the covert orienting of visuospatial attention. Causal evidence supporting this premotor theory of attention, or oculomotor readiness hypothesis, comes from the effect of subsaccadic threshold stimulation of the oculomotor system on behavior and neural activity in the absence of evoked saccades, which parallels the effects of covert attention. Here, by recording neck-muscle activity from monkeys and systematically titrating the level of stimulation current delivered to the frontal eye fields (FEF), we show that such subsaccadic stimulation is not divorced from immediate motor output but instead evokes neck-muscle responses at latencies that approach the minimal conduction time to the motor periphery. On average, neck-muscle thresholds were ~25% lower than saccade thresholds, and this difference is larger for FEF sites associated with progressively larger saccades. Importantly, we commonly observed lower neck-muscle thresholds even at sites evoking saccades ≤5° in magnitude, although such small saccades are not associated with head motion. Neck-muscle thresholds compare well with the current levels used in previous studies to influence behavior or neural activity through activation of FEF neurons feeding back to extrastriate cortex. Our results complement this previous work by suggesting that the neurobiologic substrate that covertly orients visuospatial attention shares this command with head premotor circuits in the brainstem, culminating with recruitment in the motor periphery.

eye–head gaze shifts | oculomotor | visuospatial attention

Our understanding of the functional role of the frontal eye fields (FEF) continues to evolve. Long recognized as a key cortical structure for saccade generation, two sets of recent results emphasize a broader mandate. For example, subsaccadic (in terms of current or frequency) stimulation of the FEF modulates behavior and alters sensory receptive fields in extrastriate visual cortices in a manner paralleling the covert allocation of visuospatial attention (1–6) without evoking saccades. Subsaccadic stimulation also increases the influence of the apparent position illusion on the metrics of voluntary saccades (7), although the deviation of saccades evoked by suprasaccadic currents does not obligatorily reflect the locus of attention (8). Although the precise mechanisms linking the saccade and attention functions of the FEF remain to be determined, these results imply a causal role for the FEF in the covert allocation of visuospatial attention that is presumably mediated by feedback connections to extrastriate cortex (9, 10).

A second line of research shows that the motor contribution of the FEF is not limited to saccadic eye movements. FEF stimulation in head-unrestrained monkeys elicits eye–head gaze saccades (11–13), which is consistent with a more general role for the FEF in orienting. Although the head usually lags the eyes because of inertia, FEF stimulation evokes neck-muscle responses that begin within less than 20 ms of stimulation onset (well before saccades) and increase in magnitude when associated with larger saccades (13). The timing, patterning, and topography of these neck-muscle responses resemble those evoked by stimulation of the superior colliculus (SC), differing mainly by beginning ~3 ms later after FEF stimulation (13, 14). Thus, FEF stimulation most likely evokes neck-muscle responses through feedforward connections to the SC and a subsequent relay in downstream brainstem head premotor areas (14). Furthermore, neck-muscle responses persist in trials in which FEF stimulation failed to evoke a saccade (13). Together, these results suggest that the brainstem mechanisms dictating saccades may be different from those dictating motor output at the neck.

These observations have led us to investigate the current thresholds required to evoke a neck-muscle response, a saccade, or a head movement (in head-unrestrained monkeys) through FEF stimulation. We, therefore, systematically varied the level of stimulation current delivered to the FEF, and we report the current thresholds required to evoke these responses on one-half of all stimulation trials. We also investigated how comparative response thresholds changed with stimulation location given the topography of the FEF.

Results

Two monkeys performed a gap saccade task with stimulation delivered in one-half of all trials 200 ms into the gap period (*Methods*; stimulation = 300 Hz biphasic pulses at 0.3 ms per phase for 100 or 300 ms duration). We examined 60 different sites lying within the anterior bank of the arcuate sulcus (34 head-restrained sites with 18 from monkey *j*; 26 head-unrestrained sites with 20 from monkey *j*). Contralateral saccades (we use this term irrespective of head-restraint) were evoked over one-half of the time with 50 μA of current, confirming localization within the FEF. Such saccades averaged 13.4 ± 7.3° in radial amplitude (range = 3.0–48.3°; all but two sites were less than 25° in amplitude) and 14.7 ± 32.5° in radial angle [range = −58.0° (downward) to 79.1°].

Examples of Evoked Neck-Muscle Responses at Subsaccadic Stimulation Currents. In each site, we varied stimulation current in 5- or 10-μA steps across blocks of trials. Each block was comprised of 30 stimulation and 30 control trials. Fig. 1 shows representative head-restrained and head-unrestrained data after stimulation in two FEF sites (stimulation was prolonged in the latter to permit realization of head movements). In both sites, 50 μA of current elicited saccades on all trials within ~40 ms. Regardless of restraint, stimulation also elicited robust neck electromyographic (EMG) responses on every stimulation trial, increasing activity in agonist muscles contralateral to stimulation and decreasing activity in

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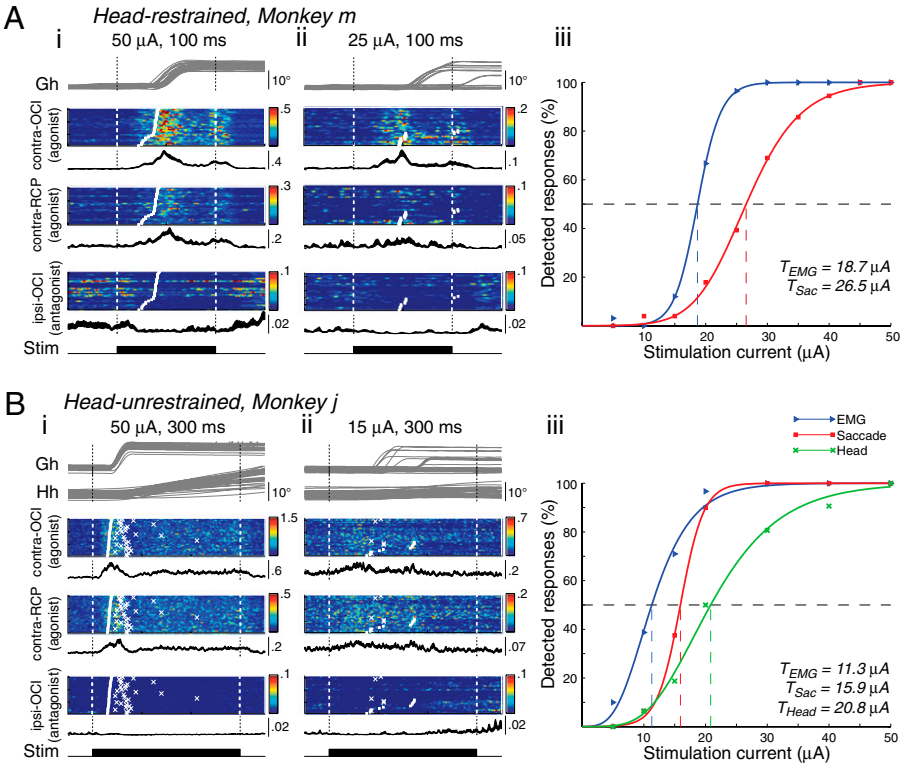

Fig. 1. Examples of head-restrained (*A*; monkey *m*) and head-unrestrained (*B*; monkey *j*) data with currents set at a level that always evoked saccades (*Left*) and at a level that evoked saccades less than one-half of the time (*Center*). *Right* shows plots of percentage of evoked responses versus stimulation current. *Left* and *Center* show horizontal gaze (eye-in-space) and head traces (*Gh* and *Hh*, respectively), with the latter only shown in *B* for ∼30 stimulation trials (upward deflections denote rightward movements). *Left* and *Center* also show EMG activity for three muscles, two agonists contralateral to side of stimulation, and one antagonist ipsilateral to stimulation. Color plots show EMG activity aligned on stimulation onset with each row showing EMG activity from a single trial ordered by saccade onset (white superimposed squares). White × in *B* shows head-movement onset. Black contours show mean evoked EMG activity subtended by SE. The horizontal dashed line in the right plot shows the response-threshold level at which a given response is evoked on 50% of stimulation trials.

antagonist muscles ipsilateral to stimulation. These evoked EMG responses began within ∼15–20 ms of stimulation (i.e., before saccades), peaked during saccades, and ceased ∼20 ms after stimulation offset. When head-unrestrained, evoked head movements started ∼50–100 ms after stimulation onset and continued for the duration of stimulation (Fig. 1*B Left*). We have previously characterized the saccades, neck EMG responses, and head movements evoked by 50 μA of current, and have also described the differences between evoked neck EMG responses and those observed during control trials (13).

At both sites, neck EMG responses persisted at lower currents that failed to consistently evoke saccades. In the head-restrained example (Fig. 1*A Center*), 25 μA of current elicited saccades on 11 of 28 (39%) trials but appeared to elicit neck-muscle responses on most if not all trials. In the head-unrestrained example (Fig. 1*B Center*), 15 μA of current evoked saccades on 12 of 31 (39%) trials, but also elicited neck EMG responses on most stimulation trials. Such stimulation occasionally elicited head movements either before saccades or on trials without saccades; if so, a compensatory eye-in-head movement maintained gaze stability (13). Although the general pattern of the evoked neck EMG response remained consistent, the latency of the response increased, and the magnitude of agonist muscle recruitment decreased compared with that evoked at 50 μA (note the changes in scale bars). Thus, FEF stimulation at current levels below that required for saccades evoked neck-muscle responses that could culminate in head turning when head was not restrained.

Determination of Response Thresholds. We sought to determine the percentage of trials in which a given current evoked saccades, neck EMG responses, or head movements. The classification of an evoked saccade is straightforward, simply requiring detection of contralateral saccades evoked either during stimulation or within 20 ms of stimulation cessation. The determination of whether or not a neck EMG response or head movement is evoked on a given trial is more difficult, because the evoked response can be quite subtle at lower currents. We, therefore, devised the following methodology. For neck EMG responses, we first classified every muscle as an agonist, an antagonist, or a nonresponder based on responses at the highest current. Then, we produced a cumulative EMG trace by summing the normalized agonist activity to the inverted normalized antagonist activity (Fig. S1). We repeated this process for data from control trials using the same interval in which stimulation was passed on stimulation trials. For head movements, we extracted horizontal head-velocity traces for the duration of stimulation and from an equivalent interval from control trials (head movements evoked from the FEF tend to have small vertical components, hence our focus on the horizontal component) (12, 13).

We then employed a template-matching methodology to determine whether or not an evoked response occurred on a given stimulation trial. This determination was based on a linear regression of the cumulative EMG activity (or head-velocity trace) on a given stimulation trial and the mean cumulative EMG response (or head-velocity trace) evoked by the maximum current used at a given site. Our logic was based on the similarity of responses evoked at lower or higher stimulation currents, despite large decreases in response magnitude and modest increases in

response latency (Fig. S2). Evoked latencies increased by <10 ms on average for the lowest current. Across our sample, the complement of agonist and antagonist muscle responses evoked from a given stimulation site remained constant with lowering stimulation currents, as did the vectorial direction of evoked saccades or head movements. The regression provided a slope value for an individual stimulation trial that we compared with the distribution of slopes from the regression of control trial versus the mean evoked response. Stimulation-trial slopes that lay above or below the 90% confidence interval of control trials were flagged as response or no-response trials, respectively. All trials were inspected by an analyst, enabling reclassification of false-positive or false-negative trials (required on <5% of all stimulation trials). For the head-restrained data (Fig. 1*A*), 50 and 25 μA of current evoked neck EMG responses on 31 of 31 (100%) trials and 27 of 28 (96%) trials, respectively. For the head-unrestrained data (Fig. 1*B*), 50 and 15 μA of stimulation current evoked neck EMG responses on 31 of 31 (100%) trials and 22 of 31 (72%) trials and head movements on 31 of 31 (100%) trials and 6 of 31 (19%) trials, respectively.

We then constructed plots of percentage of evoked responses as a function of stimulation current (Fig. 1 *A Right* and *B Right*). From these plots, it is clear that lower currents evoked neck EMG responses more readily than saccades. We fitted these plots with a generalized logistic curve (*Methods*) and extracted the current levels that evoked saccades, neck EMG responses, or head movements on 50% of stimulation trials as well as the slopes of these relationships near the threshold levels. For the head-restrained dataset, the saccade threshold was 26.5 μA and the neck EMG threshold was 18.7 μA; equivalently, the neck EMG threshold was 29.4% lower than the saccade threshold. For the head-unrestrained dataset, the saccade threshold was 15.9 μA, the neck EMG threshold was 11.3 μA, and the head movement threshold was 20.8 μA; equivalently, the neck EMG threshold was 28.9% lower and the head-movement threshold was 30.8% higher than the saccade threshold. Steeper slopes near thresholds were observed for the neck EMG versus saccade functions in the head-restrained dataset (13.2% vs. 5.8% per μA, respectively), whereas steeper slopes were observed for the saccade versus neck EMG and head-movement functions in the head-unrestrained dataset (13.2%, 7.8%, and 4.5% per μA, respectively).

Lower Thresholds for Neck EMG Responses Versus Saccadic Responses. We repeated this analysis for every FEF site and extracted the various response thresholds (Fig. 2 *A–C*). Across our head-restrained sample, thresholds were lower for neck EMG responses [median (interquartile range spanning 25th to 75th percentile) = 20.1 (18.06) μA; range = 5–55 μA] (Fig. 2*B*) than for saccades [30.1 (15.4) μA; range = 5–48 μA] (Fig. 2*A*). A site-by-site analysis revealed that this difference was significant, and neck EMG thresholds, on average, were 25.5% lower than saccade thresholds; equivalently, saccade thresholds were 34.2% greater than neck EMG thresholds (Fig. 2*D*) (Wilcoxon signed rank test; $P < 0.001$). Similar results emerged from our head-unrestrained sample, wherein thresholds were significantly lower for neck EMG responses [12.6 (6.1) μA; range = 7.6–34.0 μA] (Fig. 2*B*) than for saccades [19.1 (8.5) μA; range = 7.1–41.8 μA; $P < 0.001$] (Fig. 2 *A* and *D*). Head-movement thresholds [18.3 (14.5) μA; range = 9.1–42.3 μA] (Fig. 2*C*) were significantly greater than neck EMG thresholds (Fig. 2*F*) ($P < 10^{-5}$); on average, neck EMG thresholds were 27.3% lower than saccade thresholds, and equivalently, saccade thresholds were 37.6% greater than neck EMG thresholds when head was not restrained. Across our head-unrestrained sample, saccade and head-movement thresholds did not differ ($P = 0.79$) (Fig. 2*E*).

Response thresholds also tended to be positively correlated, meaning that sites with smaller saccade thresholds tended to have smaller neck EMG and head-movement thresholds ($r = 0.66, 0.68$, and 0.87 for regression lines in Fig. 2 *D–F*, respectively; all are $P < 10^{-4}$). Importantly, neck EMG and saccade thresholds tended to be lower if obtained with the head-unrestrained [Kolmogorov–Smirnov (KS) test; both $P < 0.001$], likely because prolonged stimulation permits more time for an evoked response. Consistent with this observation, we saw no significant difference across head restraint if neck EMG thresholds were expressed as a percentage of saccade thresholds (KS test; $P = 0.62$). Across our sample, neck EMG thresholds were 26.1% and 31.5% lower than saccade and head-movement thresholds, respectively; equivalently, saccade and head-movement thresholds were 35.2% and 45.2% higher than neck EMG thresholds, respectively.

The slopes of the response/current relationships near threshold are presented in Fig. S3. Briefly, slopes were steeper for the neck EMG compared with saccade curves with the head restrained [5.02% (10.3%) per μA versus 3.7% (3.4%) per μA, respectively; $P < 0.05$] but not unrestrained [18.5% (22.5%) per μA versus 15.0% (20.0%) per μA, respectively; $P = 0.53$]. The slopes for both the neck EMG and saccade relationships tended to be much steeper with the head not restrained, likely because of prolonged stimulation (KS test; both $P < 10^{-4}$).

We repeated all analyses with an alternative technique based on a receiver-operating characteristic (ROC) comparison of neck EMG activity (or head movements) on stimulation and control trials. This technique has the advantage of being objective (i.e., the derived metric expresses the difference between distributions drawn from stimulation versus control trials without inspection), but it does not discriminate whether or not a response is evoked on a given trial (relevant below). The threshold values derived from this ROC-based analysis are presented in Fig. S4 (mirroring Fig. 2) and show all of the same trends.

Comparative Thresholds Depend on the Size of the Evoked Saccade. Although neck EMG thresholds tended to be lower than saccade thresholds, our sample of comparative response thresholds displays substantial variability (e.g., Fig. 2*D*). Neck EMG thresholds could be as much as 39 μA below or 12 μA above saccade threshold, respectively (mean difference ± SD; 6.8 ± 9.7 μA with lower neck EMG thresholds on average). Head-movement thresholds could be as much as 22 μA above or below saccade threshold (4.4 ± 11.3 μA with lower head-movement thresholds on average). We wondered if some of this variability could be caused by the size of the saccade evoked by 50 μA of current at a given site (the characteristic saccade), because sites evoking larger characteristic saccades are associated with larger neck EMG responses and head

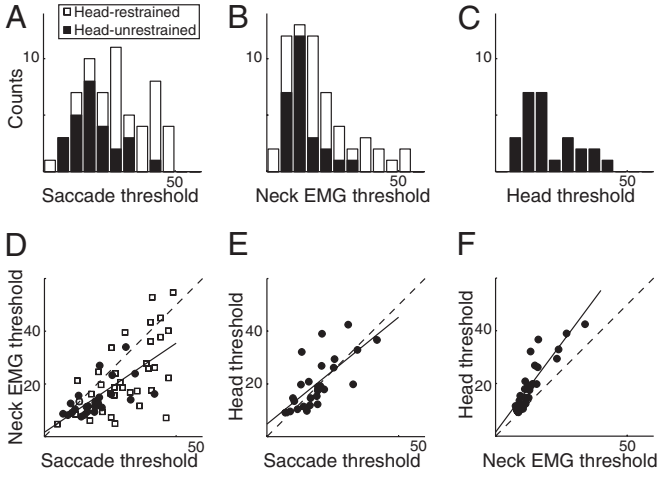

Fig. 2. (*A–C*) Histograms of response thresholds grouped in 5-μA bins. (*D–F*) Comparative response thresholds plotted on a site-by-site basis. Dashed or solid lines show line of unity or linear regression line, respectively.

movements (13). Accordingly, we plotted the percent difference between saccade thresholds and either neck EMG thresholds or head-movement thresholds as a function of the amplitude of the characteristic saccade (Fig. 3 *A* and *B*) (calculating percentage differences simplifies comparison regardless of head restraint).

Recasting the data in this manner resolved some of the variability in comparative-response thresholds. Briefly, both neck EMG and head-movement thresholds get progressively lower compared with saccade thresholds at sites associated with progressively larger characteristic saccades. Importantly, we frequently observed lower neck EMG versus saccade thresholds even at sites evoking moderately sized saccades not typically associated with head motion (lower neck EMG responses were observed in 2/5 cases for <5° characteristic saccades, 9/15 cases for 5–10° characteristic saccades, 25/30 cases for 10–20° characteristic saccades, and 10/10 cases for >20° characteristic saccades). Head-movement thresholds tended to be lower than saccadic thresholds for characteristic saccades ≥20° in amplitude (Fig. 3*B*) (lower head-movement thresholds were observed in 1/4, 8/16, and 5/6 cases for 5–10°, 10–20°, and >20° characteristic saccades, respectively). Comparing neck EMG and head-movement thresholds revealed no relationship with characteristic saccade amplitude (Fig. 3*C*).

Performing a similar analysis using an ROC analysis to determine neck EMG and head-movement response thresholds revealed all of the same trends (Fig. S5).

Persistent Neck-Muscle Responses Below Saccade Threshold. Previous studies employing low-current FEF stimulation have generally adopted a current level of 50% saccade threshold. Although we observed lower neck versus saccade thresholds, the differences in the slopes of the response/current relationships lead to the question of how often stimulation at 50% saccade threshold evoked neck-muscle responses. We extracted this value from the fit of evoked neck-muscle responses versus stimulation current (e.g., the blue curves in Fig. 1 *A Right* and *B Right*). For our representative data, a current of 50% saccade threshold evoked a neck-muscle response in 5% and 23% of trials with the head restrained or unrestrained, respectively. Across our sample, neck EMG responses were evoked at 50% saccade threshold in 30% ± 33% and 18% ± 24% of trials with the head restrained or unrestrained, respectively. As stated above, part of this variability depended on the site of stimulation, because EMG responses at 50% saccade threshold were more likely for sites associated with larger characteristic saccades (Fig. 3*D*).

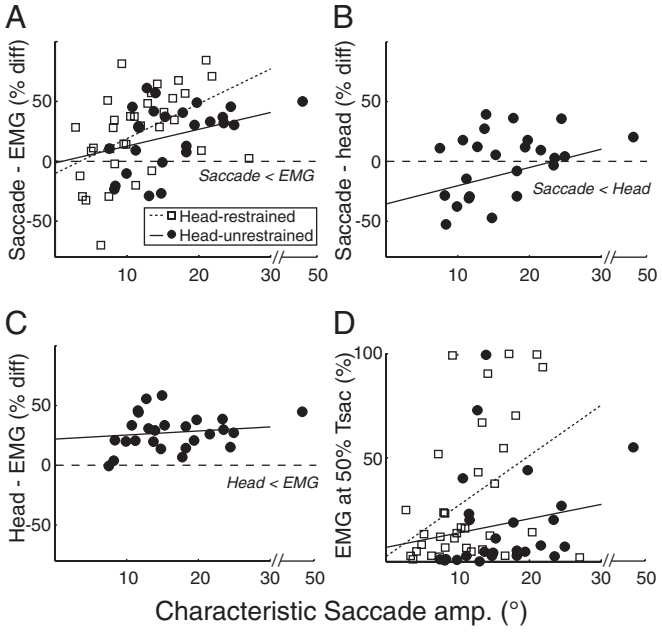

Fig. 3. (*A–C*) Comparative thresholds (expressed as a percent difference) vary with magnitude of the characteristic saccade. (*D*) Percentage of trials with evoked neck-muscle activity at a current that is 50% of saccade threshold and plotted as a function of the magnitude of the characteristic saccade. Each point is from a different stimulation site. Dashed or solid oblique lines show the linear regression lines of head-restrained or head-unrestrained data, respectively.

Stronger and More Probable Neck EMG Responses on Trials with Evoked Saccades. We also compared the magnitude and probability of evoked neck EMG responses with the presence of evoked saccades (Fig. S6 has a description and presentation of this analysis). Very briefly, neck EMG responses were both greater in magnitude and more probable on stimulation trials that evoked saccades.

Discussion

Our results show that subsaccadic levels of FEF stimulation directly activate motor circuits; the absence of saccades clearly cannot be used to infer the absence of evoked responses in the motor periphery. That the expression of such motor commands appeared on neck muscles is not surprising given the role for head movements in orienting the visual axis. What is perhaps surprising is that activation of motor circuits persisted at currents well below saccade threshold, even for FEF sites evoking relatively small saccades not typically associated with head motion.

The use of subsaccadic levels of stimulation current has become an increasingly popular methodology in cognitive neuroscience, in part because the causal effects of stimulation on both behavior and neural processing are usually divorced from saccades (15). Our results are not the first to show motor consequences of low-current FEF stimulation, as such stimulation increases both the probability of saccades and the influence of the apparent position illusion on such saccades (7). However, the latencies of neck-muscle responses evoked by low-current FEF stimulation approach the minimal conduction time to the motor periphery (Fig. S2) (13). The directness of such evoked responses prompts the following questions. Is it possible that previous studies incorporating low-current FEF stimulation, which have always restrained the head, unknowingly evoked neck-muscle responses? If so, does this alter the interpretation of these results? Finally, what are the implications of our results regarding the neurobiologic substrate underlying covert orienting? We tackle these questions separately.

A direct comparison with our results is hindered by differences in stimulation parameters (particularly stimulation duration, which lowers thresholds) and protocol (many studies determined saccade thresholds in a separate set of trials). However, our median neck EMG thresholds are in the range of currents used in other studies (e.g., 20.1 and 12.6 μA when head is restrained or not restrained, respectively, compared with median currents of 10 μA in ref. 1 and median detection thresholds of 13 μA in ref. 16). The amplitudes of characteristic saccades that we observed (~13°) also compared favorably to these reports; thus, we did not preferentially target FEF sites encoding larger saccades. The analysis presented in Fig. 3*D* shows that neck-muscle responses can be evoked even at currents well below saccade threshold. Thus, the levels of current delivered to the FEF in previous studies are certainly within the range sufficient to evoke neck-muscle responses on at least some stimulation trials.

Although the muscles that we recorded have a particularly dense complement of sensory receptors (17) that influences activity within oculomotor areas (18), it is difficult to conceive how sensations arising from evoked neck-muscle responses could produce the well-documented consequences of low-current FEF stimulation in extrastriate cortex. Such consequences are simply too rapid (5), widespread (19), and spatially restricted (4). Studies

showing that low-current stimulation affords behavioral benefits by focusing attention have generally concluded that such benefits could not have arisen by unintended sensory effects such as phosphenes. Indeed, arguments marshaled to address potential confounds of evoked phosphenes (see ref. 20 for considerations related to SC) can be applied equally to address potential confounds of sensations arising secondary to evoked neck-muscle activity. Thus, the conclusions in previous studies on the behavioral and neural consequences of low-current FEF stimulation are not grossly altered by our results.

Our results bear on recent work which required monkeys to report the presence of low current FEF stimulation in one of two intervals (16). In this task, detection thresholds are less than saccade thresholds by a range similar to the differences between neck EMG and saccade thresholds. It seems possible that the monkeys could use sensations arising from evoked neck-muscle responses to identify the stimulation interval, particularly at stimulation sites associated with larger saccades. Indeed, such sensations may prove to be distracting and could underlie the observations that the beneficial effects of subsaccadic FEF stimulation on attention decrease as the current approaches saccade threshold (2). However, if perceptions arising from neck muscle contraction are the sole cue being used to detect stimulation, then the detection thresholds should get lower compared with saccade thresholds for sites associated with progressively larger saccades (i.e., mirroring the relationship plotted in Fig. 3*A*). Indeed, any explanation of behavioral or neural phenomena that hinges on evoked neck-muscle activity should display such a dependency with the site of stimulation. This prediction provides a clear test for how potential confounds of neck-muscle contraction can be addressed.

Although our results do not grossly alter the interpretation of previous studies using subsaccadic FEF stimulation, they provide further experimental evidence that covert orienting of visuospatial attention recruits head-orienting circuits. We and others have speculated that brainstem omni-pause neurons (OPNs) selectively inhibit saccade but not head-premotor circuits (21–23), which is consistent with many neurophysiologic and behavioral results (14, 23–25), and as such, they may represent the neurobiologic substrate for lower neck EMG versus saccade thresholds. OPNs reside downstream of the SC, and given that the patterning of neck-muscle responses evoked from the FEF differs only by an ~3-ms interval appropriate for FEF–SC communication (13, 26), the implications of our results likely generalize to the SC (27, 28). Indeed, reported relationships between neck-muscle activity and visual transients (29), representations of motivation and reward (30), or reflexive allocation of visuospatial attention (31) reflect both the diversity of signal content within the oculomotor areas such as the FEF and SC and the distribution of such signals to downstream areas (32, 33). Neck-muscle activity in a variety of behavioral paradigms is predictive of the ensuing saccadic reaction time on a trial-by-trial basis (29–31), supporting a functional linkage between the nascent oculomotor programs that manifest in neck-muscle recruitment and the overt movement of the gaze axis. Recordings of neck-muscle activity may, therefore, prove to be a useful means of indexing otherwise covert processes, as the trial-by-trial and temporally refined nature of such recordings differ from probabilistic measures of microsaccade propensity and orientation (34).

The premotor theory of attention (35) and oculomotor readiness hypothesis (36) posit that the same circuits responsible for shifting the line of sight can also covertly orient attention. Delivering subsaccadic levels of stimulation to the FEF and SC has provided important causal evidence for these ideas by suggesting that the nascent oculomotor program arising from stimulation focuses attention without requiring saccade execution. However, other studies have shown that spatial attention and saccade preparation can be dissociated within the FEF (8, 37), and recent anatomic work has placed limitations on the underlying neural substrates within the FEF by showing that separate FEF neurons project to the SC or area V4 (38). One implication of our results is that low-current FEF stimulation likely does not selectively activate cortico-cortical projections feeding back to extrastriate visual cortex without activating cortico-fugal projections feeding forward to the brainstem. Conjoined activation of feedforward and feedback circuits is also consistent with recent work showing that low-current cortical stimulation similar to what we have used activates a sparse and distributed population of neurons (39).

In summary, our results suggest that the neurobiologic machinery that covertly orients visuospatial attention shares a command with the motor periphery. The dominant view that covert orienting of attention is divorced from motor output may have arisen, at least in part, because of a preference for examining saccades with the head restrained. Such a preference affords obvious technical simplification; however, the oculomotor system evolved with the head free to move. Although corticofugal and corticocortical pathways are segregated at a neuroanatomic level within the FEF, the functional content of signals conveyed along these pathways during attentional tasks remains undetermined. A number of observations, including those presented here, show an overt manifestation of otherwise covert oculomotor processes on neck muscles. Such a strategy seems to be a compromise between behavioral and biomechanical demands given the importance of retinal stability for foveal vision and the head's substantial inertia.

Methods

Surgical and Experimental Procedures. Two male monkeys (*Macaca mulatta*; monkeys *j* and *m*) weighing 5.4 and 6.8 kg were used in these experiments. All training, surgical, and experimental procedures were in accordance with the Canadian Council on Animal Care policy on the use of laboratory animals and approved by the Animal Use Subcommittee of the University of Western Ontario Council on Animal Care. Both monkeys underwent two surgeries (13). The first prepared the animal for recording of gaze position and extracellular stimulation in the left FEF. The second prepared the animal for recording of neck EMG activity through bipolar electrodes implanted chronically in the following muscles: obliquus capitis inferior (OCI), rectus capitis posterior major (RCP), splenius capitis, biventer cervicis, and complexus.

Behavioral Paradigm and Stimulation Parameters. Monkeys performed a gap-saccade paradigm requiring them to look from a central fixation point (FP) to a peripheral target (13). A gap of 300 (head-restrained trial) or 500 ms (head-unrestrained trial) was interposed between FP disappearance and target presentation. Stimulation (300-Hz biphasic pulses at 0.3 ms per phase) was delivered on one-half of all trials through a tungsten microelectrode (~0.2–1 MΩ at 1 kHz; Frederick Haer); the other trials were control trials. Stimulation started 200 ms into the gap interval and persisted for 100 (head-restrained trial) or 300 ms (head-unrestrained trial), and thus, the gap duration was equivalent on both control and stimulation trials. We first confirmed that the electrode was in the FEF (evoked saccades on >50% of stimulation trials with a current of 50μA) and then ran a series of blocks of 60 trials (30 intermixed stimulation and control trials) with varying levels of current in each block. Across blocks, current was varied in steps of either 5 or 10 μA in either increasing (22 series) or decreasing (38 series) order. The maximum current was usually 50 μA, although we occasionally went up to 75 μA. If evoked responses persisted at 5 μA, we lowered current to 2.5 or 1 μA to abolish all responses.

Determining Response Thresholds. Trials were excluded if there were aberrant patterns of saccades or EMG activity (e.g., if the animal was shifting position) or if evoked saccades began within <5 ms of stimulation onset. Overall, trials were rejected at a rate of <3%. Evoked saccades were detected if they were directed contralateral to the side of stimulation, proceeded in a direction matching saccades evoked at higher currents, and began within 20 ms after stimulation onset to 20 ms after stimulation cessation. A graphical depiction of the template-based classification of EMG responses on one trial is given in Fig. S1. Briefly, we compared the evoked response on a given trial with the mean response evoked at the highest stimulation current, and the boundaries determining significance were set by an identical analysis of control trials. The relationship of percentage of evoked responses versus stimulation current was fit with a general logistic curve (Eq. **1**)

$$y = Q + \frac{R}{\left(1 + Te^{-S(x-P)}\right)^{1/T}} \quad [1]$$

where Q is the lower asymptote, R is the upper asymptote minus Q, S defines the overall slope of the curve, P is the location of maximum slope, and T defines the magnitude of the curve's asymmetry. We set Q to 0 and R to 100. Response thresholds were then extracted by the current level at which movements would be evoked 50% of the time.

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1. Moore T, Fallah M (2001) Control of eye movements and spatial attention. *Proc Natl Acad Sci USA* 98:1273–1276.
2. Moore T, Fallah M (2004) Microstimulation of the frontal eye field and its effects on covert spatial attention. *J Neurophysiol* 91:152–162.
3. Moore T, Armstrong KM (2003) Selective gating of visual signals by microstimulation of frontal cortex. *Nature* 421:370–373.
4. Armstrong KM, Fitzgerald JK, Moore T (2006) Changes in visual receptive fields with microstimulation of frontal cortex. *Neuron* 50:791–798.
5. Armstrong KM, Moore T (2007) Rapid enhancement of visual cortical response discriminability by microstimulation of the frontal eye field. *Proc Natl Acad Sci USA* 104:9499–9504.
6. Ekstrom LB, Roelfsema PR, Arsenault JT, Kolster H, Vanduffel W (2009) Modulation of the contrast response function by electrical microstimulation of the macaque frontal eye field. *J Neurosci* 29:10683–10694.
7. Schafer RJ, Moore T (2007) Attention governs action in the primate frontal eye field. *Neuron* 56:541–551.
8. Juan CH, Shorter-Jacobi SM, Schall JD (2004) Dissociation of spatial attention and saccade preparation. *Proc Natl Acad Sci USA* 101:15541–15544.
9. Stanton GB, Bruce CJ, Goldberg ME (1995) Topography of projections to posterior cortical areas from the macaque frontal eye fields. *J Comp Neurol* 353:291–305.
10. Huerta MF, Krubitzer LA, Kaas JH (1987) Frontal eye field as defined by intracortical microstimulation in squirrel monkeys, owl monkeys, and macaque monkeys. II. Cortical connections. *J Comp Neurol* 265:332–361.
11. Tu TA, Keating EG (2000) Electrical stimulation of the frontal eye field in a monkey produces combined eye and head movements. *J Neurophysiol* 84:1103–1106.
12. Knight TA, Fuchs AF (2007) Contribution of the frontal eye field to gaze shifts in the head-unrestrained monkey: Effects of microstimulation. *J Neurophysiol* 97:618–634.
13. Elsley JK, Nagy B, Cushing SL, Corneil BD (2007) Widespread presaccadic recruitment of neck muscles by stimulation of the primate frontal eye fields. *J Neurophysiol* 98: 1333–1354.
14. Corneil BD, Olivier E, Munoz DP (2002) Neck muscle responses to stimulation of monkey superior colliculus. I. Topography and manipulation of stimulation parameters. *J Neurophysiol* 88:1980–1999.
15. Cohen MR, Newsome WT (2004) What electrical microstimulation has revealed about the neural basis of cognition. *Curr Opin Neurobiol* 14:169–177.
16. Murphey DK, Maunsell JH (2008) Electrical microstimulation thresholds for behavioral detection and saccades in monkey frontal eye fields. *Proc Natl Acad Sci USA* 105: 7315–7320.
17. Richmond FJ, Singh K, Corneil BD (1999) Marked non-uniformity of fiber-type composition in the primate suboccipital muscle obliquus capitis inferior. *Exp Brain Res* 125:14–18.
18. Nagy B, Corneil BD (2010) Representation of horizontal head-on-body position in the primate superior colliculus. *J Neurophysiol* 103:858–874.
19. Ekstrom LB, Roelfsema PR, Arsenault JT, Bonmassar G, Vanduffel W (2008) Bottom-up dependent gating of frontal signals in early visual cortex. *Science* 321:414–417.
20. Cavanaugh J, Alvarez BD, Wurtz RH (2006) Enhanced performance with brain stimulation: Attentional shift or visual cue? *J Neurosci* 26:11347–11358.
21. Galiana HL, Guitton D (1992) Central organization and modeling of eye-head coordination during orienting gaze shifts. *Ann NY Acad Sci* 656:452–471.
22. Corneil BD, Munoz DP (1999) Human eye-head gaze shifts in a distractor task. II. Reduced threshold for initiation of early head movements. *J Neurophysiol* 82: 1406–1421.
23. Pélisson D, Goffart L, Guillaume A, Catz N, Raboyeau G (2001) Early head movements elicited by visual stimuli or collicular electrical stimulation in the cat. *Vision Res* 41: 3283–3294.
24. Corneil BD, Elsley JK (2005) Countermanding eye-head gaze shifts in humans: Marching orders are delivered to the head first. *J Neurophysiol* 94:883–895.
25. Gandhi NJ, Sparks DL (2007) Dissociation of eye and head components of gaze shifts by stimulation of the omnipause neuron region. *J Neurophysiol* 98:360–373.
26. Segraves MA, Goldberg ME (1987) Functional properties of corticotectal neurons in the monkey's frontal eye field. *J Neurophysiol* 58:1387–1419.
27. Cavanaugh J, Wurtz RH (2004) Subcortical modulation of attention counters change blindness. *J Neurosci* 24:11236–11243.
28. Müller JR, Philiastides MG, Newsome WT (2005) Microstimulation of the superior colliculus focuses attention without moving the eyes. *Proc Natl Acad Sci USA* 102: 524–529.
29. Corneil BD, Olivier E, Munoz DP (2004) Visual responses on neck muscles reveal selective gating that prevents express saccades. *Neuron* 42:831–841.
30. Rezvani S, Corneil BD (2008) Recruitment of a head-turning synergy by low-frequency activity in the primate superior colliculus. *J Neurophysiol* 100:397–411.
31. Corneil BD, Munoz DP, Chapman BB, Admans T, Cushing SL (2008) Neuromuscular consequences of reflexive covert orienting. *Nat Neurosci* 11:13–15.
32. Rodgers CK, Munoz DP, Scott SH, Paré M (2006) Discharge properties of monkey tectoreticular neurons. *J Neurophysiol* 95:3502–3511.
33. Sommer MA, Wurtz RH (2000) Composition and topographic organization of signals sent from the frontal eye field to the superior colliculus. *J Neurophysiol* 83:1979–2001.
34. Engbert R, Kliegl R (2003) Microsaccades uncover the orientation of covert attention. *Vision Res* 43:1035–1045.
35. Rizzolatti G, Riggio L, Dascola I, Umiltá C (1987) Reorienting attention across the horizontal and vertical meridians: Evidence in favor of a premotor theory of attention. *Neuropsychologia* 25:31–40.
36. Klein RM, Nickerson RS (1980) *Does Oculomotor Readiness Mediate Cognitive Control of Visual Attention? Attention and Performance VIII* (Lawrence Erlbaum Associates, Hillsdale, NJ), pp 259–276.
37. Sato TR, Schall JD (2003) Effects of stimulus-response compatibility on neural selection in frontal eye field. *Neuron* 38:637–648.
38. Pouget P, et al. (2009) Visual and motor connectivity and the distribution of calcium-binding proteins in macaque frontal eye field: Implications for saccade target selection. *Front Neuroanat* 3:2.
39. Histed MH, Bonin V, Reid RC (2009) Direct activation of sparse, distributed populations of cortical neurons by electrical microstimulation. *Neuron* 63:508–522.