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J Neurophysiol 97:701-714, 2007. First published Nov 1, 2006; doi:10.1152/jn.00670.2006

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Priming of Head Premotor Circuits During Oculomotor Preparation

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Submitted 27 June 2006; accepted in final form 27 October 2006

Corneil BD, Munoz DP, Olivier E. Priming of head premotor circuits during oculomotor preparation. *J Neurophysiol* 97: 701–714, 2007. First published November 1, 2006; doi:10.1152/jn.00670.2006. Large, rapid gaze shifts necessitate intricate coordination of the eyes and head. Brief high-frequency bursts of activity within the intermediate and deeper layers of the superior colliculus (dSC) encode desired gaze shifts regardless of component movements of the eyes and head. However, it remains unclear whether low-frequency activity emitted by oculomotor neurons within the dSC and elsewhere has any role in eye-head gaze shifts. Here we test the hypothesis that such low-frequency activity contributes to eye-head coordination by selectively priming head premotor circuits. We exploited the capacity for short-duration (10 ms, 4 pulses) dSC stimulation to evoke neck muscle responses without compromising ocular stability, stimulating at various intervals of a “gap-saccade” task. Low-frequency neural activity in many oculomotor areas (including the dSC) is known to increase during the progression of the gap-saccade task. Stimulation was passed during either a fixation-interval while a central fixation point was illuminated, a 200-ms gap-interval between fixation point offset and target onset, or a movement-interval following target onset. In the two monkeys studied, the amplitude of evoked responses on multiple neck muscles tracked the known increases in low-frequency oculomotor activity during the gap-saccade task, being greater following stimulation passed at the end of the gap- versus the fixation-interval, and greater still when the location of stimulation during the movement interval coincided with the area of the dSC generating the ensuing saccade. In one of these monkeys, we obtained a more detailed timeline of how these results co-varied with low-frequency oculomotor activity by stimulating, across multiple trials, at different times within the fixation-, gap- and movement-intervals. Importantly, in both monkeys, baseline levels of neck EMG taken immediately prior to stimulation onset did not co-vary with the known pattern of low-frequency oculomotor activity up until the arrival of a transient burst associated with visual target onset. These baseline results demonstrate that any priming of the head premotor circuits occurs without affecting the output of neck muscle motoneurons. We conclude that low-frequency oculomotor activity primes head premotor circuits well in advance of gaze shift initiation, and in a manner distinct from its effects on the eye premotor circuits. Such distinctions presumably aid the temporal coordination of the eyes and head despite fundamentally different biomechanics.

INTRODUCTION

Eye-head gaze shifts are a model system for understanding how the brain controls multi-segmental motion. The intermediate and deep layers of the superior colliculus (dSC) constitute a crucial oculomotor node, emitting time-locked bursts of activity shortly before gaze shift onset (Bergeron et al. 2003;

Freedman and Sparks 1997a). However, many neurons in the dSC are not simply silent prior to this high-frequency burst of activity but rather emit persistent levels of low-frequency activity. Indeed, such persistent low-frequency activity is seen in almost every other oculomotor structure with the exception of short-lead burst neurons in the saccadic burst generator (see Scudder et al. 2002 for review). Two lines of evidence implicate a role for low-frequency oculomotor activity in the intermediate stages of sensorimotor transformations. First, low-frequency activity throughout the oculomotor system has been correlated to processes as diverse as oculomotor preparation, target predictability, target or saccade selection, attentional allocation, and representations of reward variables and eye position (e.g., for the dSC: Basso and Wurtz 1997; Campos et al. 2006; Dorris and Munoz 1998; Glimcher and Sparks 1992; Horwitz and Newsome 1999; Ikeda and Hikosaka 2003; Krauzlis and Dill 2002; Kustov and Robinson 1996; McPeck and Keller 2002; Munoz and Wurtz 1995; Paré and Munoz 2001; Van Opstal et al. 1995). Second, electrical stimulation of low current or low frequency within many oculomotor areas, below the current or frequency levels required to evoke gaze shifts, influences behavioral responses presumably through manipulations of decision-making, movement specification, target selection, or attentional allocation (e.g., for the dSC: Carello and Krauzlis 2004; Cavanaugh and Wurtz 2004; Glimcher and Sparks 1993; Horwitz et al. 2004; Muller et al. 2005). However, because the aforementioned studies utilized a head-restrained preparation, the significance of low-frequency oculomotor activity to eye-head gaze shifts has not been addressed.

There are circumstantial reasons to suspect that low-frequency activity throughout the oculomotor system may affect the eyes and head differentially prior to gaze shift onset. Most notably, processes correlated to increased levels of low-frequency oculomotor activity, such as target predictability or varying initial eye position, lower the head's reaction time and increase its contribution to amplitude-matched gaze shifts (Bizzi et al. 1972; Freedman and Sparks 1997b; Oommen et al. 2004; Zangemeister and Stark 1982). This suggests that the brain may exploit low-frequency oculomotor activity prior to movement onset to optimize the head's contribution to the ensuing gaze shift. To test the hypothesis that low-frequency oculomotor activity selectively primes head premotor circuits, we measured electromyographic (EMG) responses from monkey neck muscles after short-duration electrical stimulation of the dSC delivered at various intervals in a gap-saccade task that

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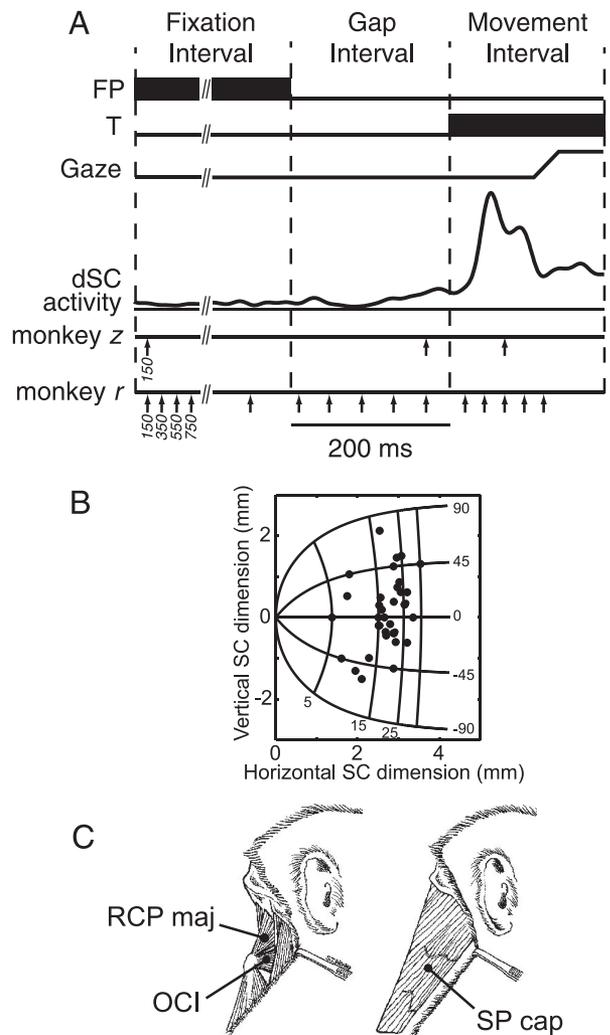


FIG. 1. *A*: the behavioral task required the monkeys to maintain central fixation during both the *fixation interval* [when the fixation point (FP) remained visible] and *gap interval* (after FP disappearance), and then look to a peripheral target (T) after its presentation (during the *movement interval*). As occurs elsewhere in the oculomotor system, activity within the deeper layers of the superior colliculus (dSC) is known to increase during the gap interval (Munoz et al. 2000), represented here by a spike density waveform from a representative dSC neuron (scalebar = 100 spike/s). Stimulation (\uparrow) could be delivered at various times within each of the fixation, gap, or movement intervals. Different protocols were used for the 2 monkeys (see METHODS, \uparrow , all of the possible stimulation times within each monkey across a block of trials). //, breaks in the long fixation interval (>700 ms). Stimulation times to the left of this symbol are given relative to the start of fixation. *B*: depiction of the 35 stimulation locations on a contour map of the dSC (Corneil et al. 2002a). The abscissa represents the rostrocaudal (horizontal) axis of the dSC; the ordinate represents the mediolateral (vertical) axis of the dSC. Iso-amplitude and -direction lines are superimposed with the corresponding values of each line placed within either the lower or rightward portion, respectively. ●, estimated stimulation locations based on the vector of the site-specific gaze shift evoked with a 100-ms stimulation train. Locations have been pooled across both monkeys and side of stimulation. *C*: schematic line drawings of implanted neck muscles examined in this manuscript. OCI, obliquus capitis inferior; RCP maj, rectus capitis posterior major; SP cap, splenius capitis.

enhances oculomotor preparation and is associated with increasing levels of low-frequency activity throughout the oculomotor system (Fig. 1A; METHODS) [dSC and reticular formation: see Munoz et al. 2000 for review; frontal eye fields (FEF): Dias and Bruce 1994; Everling and Munoz 2000; prefrontal cortex: Tinsley and Everling 2002; pedunculo-pontine tegmen-

tal nucleus: Kobayashi et al. 2002]. Because a minimum of four stimulation pulses are sufficient to evoke neck EMG responses from either the rostral or caudal SC without compromising ocular stability (Corneil et al. 2002a), such short-duration electrical stimulation can be applied during various stages of oculomotor preparation to assay the excitability of the head premotor circuitry. Further, recording neck EMG activity circumvents the biomechanical complexities of the head plant (Peterson and Richmond 1988) and permits accurate measurement of the motor command issued to the head (Corneil et al. 2002b, 2004).

METHODS

Experimental procedures

Two male monkeys (*Macaca mulatta*, monkeys *z* and *r*) weighing 5.4–6.7 kg were used in these experiments following procedures approved by the Queen's University Animal Care Committee in compliance with the guidelines of the Canadian Council on Animal Care policy on the use of laboratory animals. The monkeys' weights were monitored daily, and their general health was under the close supervision of the university veterinarian. Each monkey underwent two surgeries to enable chronic recording of gaze position, extracellular recording and microstimulation of the superior colliculus (dSC), and chronic recording of EMG activity from between 10 and 12 neck muscles via chronically implanted bipolar electrodes (see Table 1 for a list of implanted muscles). The procedures have been described in detail elsewhere (Corneil et al. 2001). During these experiments, the monkeys were restrained in a customized primate chair that restricted torso rotation to $\sim \pm 10^\circ$, which was necessary because neck EMG is related to the position of the head relative to the body (Corneil et al. 2001). Monkeys were placed within a dark, sound-attenuated room and faced an array of 49 light-emitting diodes (LEDs; 4.7 cd/m²) or a tangent screen onto which a red laser (8.4 cd/m²) was back-projected. Both displays spanned about $\pm 35^\circ$ of the central visual field. A Pentium computer running a real-time data acquisition system (REX version 5.4) controlled all aspects of the experimental paradigms and visual displays at a rate of 1,000 Hz.

We collected the majority of the data presented in this paper with the head-restrained. Although it may seem odd to examine issues bearing on eye-head gaze shifts with the head restrained, we do not believe this alters the interpretation of our results for the following reasons. First, head restraint has no systematic effect on the basic pattern, latencies, magnitudes, or duration of neck EMG responses evoked by dSC stimulation (see RESULTS); any differences in neck

TABLE 1. Listing of the muscles in which bipolar electromyographic hook electrodes were implanted

Muscle	Monkey <i>z</i>	Monkey <i>r</i>
Splenius capitis (SP cap)	X R ₇₈	L ₃₃ R ₁₂
Biventer cervicis	R	L R
Complexus	R	L R
Atlanto-scapularis anterior	L	
Rectus capitis posterior major (RCP maj)	L ₇₈	L R ₅₉
Obliquus capitis inferior (OCI)	L R	L R
Sternocleidomastoid	R	

The side of the implanted device is denoted by a *L* for a left muscle, and a *R* for a right muscle. An *X* indicates a muscle in which an attempted implant failed due to electrode breakage noted immediately after the surgery. A numerical subscript indicates an implant that was initially viable, but failed after the noted number of days (e.g., L₆₀ denotes a muscle that failed 60 days after the implant). (See Richmond et al. 2001 for morphometric descriptions of these muscles.)

EMG evoked either head restrained or unrestrained stem from differences in baseline (prestimulation) levels of EMG activity consequent to different initial head postures (Corneil et al. 2002b). Second, the very short stimulation train we use evokes only a brief “blip” of neck EMG of ~20 ms in duration. Although we could quantify the latency and magnitude of the evoked neck EMG activity, we saw no evidence it culminated in an observable head movement likely because of the head’s considerable inertia.

Microstimulation parameters

Details of our microstimulation procedures have been described elsewhere (Corneil et al. 2002a). Briefly, bipolar constant current stimulation pulses (each 0.3 ms in duration) were delivered through tungsten microelectrodes (~0.2–1 M Ω at 1 kHz; Frederick Haer) held within a delrin grid (1-mm spacing; Crist Instruments) anchored to a cylinder permitting a surface-normal approach to the dSC. Stimulation duration was controlled by a 10-ms TTL pulse issued by the experimental computer. Stimulation frequency was fixed to 300 Hz and consisted of four biphasic pulses. Prior to the collection of the experimental results, we made an on-line determination of the threshold current required to evoke short-latency, fixed vector gaze shifts on 50% of stimulation trials. Threshold currents ranged from 7 to 50 μ A. We then evoked site-specific gaze shift vectors using 100 ms of dSC stimulation at a current level 1.5 times the predetermined threshold (still at 300 Hz). A threshold for evoking gaze shifts was determined every 500 μ m along the electrode penetration between the dorsal and ventral borders of the dSC, with the head-restrained (Corneil et al. 2002a). After this mapping, the electrode was returned to the stimulation site with the lowest threshold, and the experiments commenced. The stimulation currents passed during the brief stimulation trains ranged from 10 to 75 μ A (median: 30 μ A; stimulation current >50 μ A in only 5 of 35 stimulation sites, and only in *monkey z*). Stimulation currents with the head-unrestrained ranged from 10 to 40 μ A. The position of the electrode within the rostrocaudal and medio-lateral extents of the dSC was estimated by the fixed vector gaze shift evoked using 100 ms of stimulation at a current 1.5 times gaze threshold (Fig. 1B) and determined target placement within a given experimental session. Although using the fixed vector gaze shift evoked from a head-restrained experiment is not ideal, any mislocalizations of our electrode would actually be quite small given the logarithmic scaling of the SC (e.g., Fig. 1B).

Behavioral paradigms

Monkeys were trained on a gap-saccade task (Fig. 1A). Trial onset was signaled by the removal of a background diffuse white light (1.0 cd/m²), followed by the presentation of a central fixation point (FP) 350 ms later. The monkeys were required to look at the FP for either 700 or 1,000 ms (for *monkey z* or *r*, respectively; see following text for more detail), maintain central fixation during a 200-ms “gap” between the disappearance of the FP and the presentation of the peripheral target (T) and then look to and fixate the T within 400 ms of its presentation. Potential T locations were set to either coincide with the endpoint of the site-specific vector (termed the ON location) or at the diametrically opposite location (the OFF location). We kept the durations of all intervals constant because we wanted the monkeys to anticipate the timing of fixation point disappearance and target presentation, since such anticipation is associated with increases in low-frequency dSC activity (Munoz et al. 2000). Note that although the monkeys could predict the time of target appearance, the target could still be presented in one of two locations. Based on previous results (Basso and Wurtz 1997; Dorris and Munoz 1998), we presume that the monkeys were preparing movements to two possible locations. A liquid reward was delivered on successful completion of the task, providing that the animals constrained their eyes with a 3 \times 3° square centered on the appropriate stimulus.

On half of all trials, stimulation was not delivered to the dSC. The patterns of neck EMG recorded during such *control trials* have been presented earlier (Corneil et al. 2004). The other trials consisted of *stimulation trials*, during which short-duration (10 ms, 4 pulses) trains of stimulation were delivered at various intervals. Control and stimulation trials were divided into three intervals: the *fixation-interval* during which the monkeys maintained central fixation while looking at the FP, the *gap-interval* during which the monkeys maintained central fixation even though the FP was not present, and the *movement-interval* after T presentation and encompassing the gaze shift (Fig. 1A).

The precise timing of the three intervals and the timing of stimulation within each interval differed slightly in the two monkeys. However, it is important to note that a subset of stimulation times were studied in both monkeys (e.g., 150 ms after eye entered FP fixation window, 170 ms after FP disappearance, 70 ms after T presentation; see Fig. 1A). Portions of our analysis will focus on these stimulation times, pooling data across both monkeys. For *monkey z*, on a given stimulation trial, stimulation was delivered once in one of the fixation, gap, or movement intervals (Fig. 1A). The fixation interval lasted 700 ms, and stimulation was delivered 150 ms after the eye arrived in the fixation window (i.e., -750 ms relative to T presentation). Within the gap interval, stimulation was delivered 170 ms after FP disappearance (i.e., -30 ms relative to T presentation). Within the movement interval, stimulation time was delivered 70 ms after T presentation in 10 of the 19 stimulation sites in *monkey z* (movement-interval stimulation in the other 9 sites occurred 120 ms after target presentation in the remaining 9 sites. Movement-interval data from these 9 sites was excluded because it occurred after the visual bursts of neck EMG described in the following text).

In *monkey r*, a different approach was used to construct a more precise time course of evoked neck EMG responses during the progression of the trial. Within a given stimulation trial, short-duration stimulation was delivered three times, once each within the fixation, gap, and movement intervals. Over different stimulation trials, the timing of stimulation was varied among five different times within each interval, hence over the entire experimental session, dSC stimulation was delivered at 15 different intervals (Fig. 1A). Within the fixation interval, which lasted 1,000 ms, stimulation could be delivered at 150, 350, 550, 750, or 950 ms after the eye entered the fixation window (i.e., -1,050, -850, -650, -450, or -250 relative to T presentation). Within the 200-ms gap interval, stimulation could be delivered at 10, 50, 90, 130, or 170 ms after FP disappearance (i.e., -190, -150, -110, -70, or -30 relative to T presentation). Within the movement interval, stimulation could be delivered at 20, 45, 70, 95, or 120 ms after T presentation. To avoid sequential stimulation times that were too close together, on a given stimulation trial, a value ranging from 1 to 5 was selected that dictated the time of stimulation within each interval. For example, if the value 1 was selected, stimulation was delivered at the first possible time within each of the fixation, gap and movement intervals (i.e., -1,050, -190, and 20 ms relative to T presentation). With this approach, the minimum time between sequential stimulation trains was 150 ms (i.e., stimulation delivered 30 ms before T presentation in the gap interval and then again 120 ms after T presentation in the movement interval). In RESULTS, we confirm that preceding stimulation had no priming effect on the baseline EMG activity prior to stimulation onset.

For both monkeys, all possible trial combinations (e.g., control vs. stimulation, time of stimulation, T presented at the ON or OFF location) were pseudorandomly varied with a block of 120–180 trials to ensure that each unique trial combination was presented an equal number of times. In *monkey z*, the number of stimulation trials for a given unique trial combination was 36 \pm 15 trials (range: 14–65 trials). In *monkey r*, the number of stimulation trials for a given unique trial combination was 23 \pm 10 trials (range: 10–43 trials). Stimulation trials were pooled across target direction if stimulation was delivered prior to target onset.

Data collection and analysis

Digitized signals of integrated EMG activity and the gaze (eye-in-space) positions derived from the magnetic coil system were acquired simultaneously at 500 Hz as described elsewhere (Corneil et al. 2002a). The signal conditioning steps we used attenuate the peak-to-peak amplitude of the raw EMG signals by approximately a factor of 10. Off-line, computer software determined the beginning and end of each gaze shift using velocity and acceleration thresholds and template-matching criteria. Each gaze shift was verified by an experimenter to ensure accuracy. This method reliably indicated gaze shifts $<0.1^\circ$ in amplitude.

Our analysis focused on examining how the neck EMG evoked by dSC stimulation changed during the progression of the task. We focus our analysis on muscles involved with turning the head (shown in Fig. 1C), as evoked responses on these muscles are more reliable than on muscles involved in vertical head movements, such as biverter cervicis and complexus (Corneil et al. 2002a). We first grouped all stimulation trials from a given stimulation condition, aligned them to the onset of the stimulation train (i.e., the first stimulation pulse), and determined the mean EMG waveforms evoked in response to stimulation. For turning muscles contralateral to the side of stimulation, we determined the peak mean EMG response as the greatest activity after stimulation onset spanning the range of 6–38 ms after stimulation onset. This range corresponds to the minimum and maximum neck EMG response latencies after dSC stimulation with shorter onset latencies stemming from more caudal stimulation locations (Corneil et al. 2002a). We used the time of the peak of the mean EMG waveform to construct a distribution of EMG activity across all trials at the time of peak mean EMG activity. This analysis was done separately for each stimulation condition. A similar approach was used to determine the lowest mean activity on the muscles ipsilateral to stimulation. The onset, offset, and duration of the EMG response was taken as the time the exceeded, fell below, or remained above, respectively, the mean baseline level of neck EMG over the 50-ms interval preceding stimulation ± 2 SDs.

Our interpretations of how the dSC drive to the head plant varies during the progression of the gap task are based critically on whether or not the baseline levels of neck EMG differed during the time course of the task lest the differences in evoked neck EMG responses be attributable simply to preexisting neck EMG differences. To analyze baseline activity, we aligned all stimulation trials as above for each unique stimulation time and extracted the distribution of baseline neck EMG from the 2-ms bin immediately before stimulation onset. We used this approach instead of integrating neck EMG over the 100 ms prior to stimulation onset to ensure that our analyses were sensitive to rapid changes in the baseline levels of neck EMG during the course of the gap task.

RESULTS

Short-duration stimulation (4 pulses, 10 ms) was applied to 35 different dSC stimulation sites in two monkeys (19 sites in *monkey z*, 16 sites in *monkey r*). Previous experiments in monkeys have demonstrated that a minimum of four stimulation pulses are required to evoke a neck EMG responses from either the rostral or caudal SC and that the evoked responses are increased in magnitude with an increasing number of stimulation pulses (Corneil et al. 2002a). Such evoked responses are consistent with results reported from anesthetized cats (Anderson et al. 1971). The head was restrained during stimulation at 31 of the 35 stimulation sites and unrestrained during stimulation at the other 4 stimulation sites. For each muscle, we examined whether head restraint had any effect on the onset latency, peak magnitude, or duration of the evoked neck EMG response by comparing the distribution of these

parameters extracted when the head was restrained to that when the head was unrestrained. This analysis revealed no effect of head restraint (*t*-test of latencies, peak magnitude, and duration across restraint condition for gap-interval stimulation for all muscles, all $P > 0.05$), consistent with previous results, which addressed this issue more directly (Corneil et al. 2002b). Stimulation was applied throughout the dSC, at locations where longer-duration (100 ms) stimulation trains evoked gaze shifts ranging from 5 to 36° in amplitude and from 59° down to 77° up in radial direction (Fig. 1B).

We first confirmed that short-duration dSC stimulation did not evoke gaze shifts. To do this, we examined gaze position surrounding stimulation onset in the fixation and gap intervals (e.g., Fig. 2A). Across all sites, we compared the incidence of gaze shifts in the interval 15–80 ms after stimulation onset to the incidence of gaze shifts made in the 65 ms leading up to stimulation onset, and saw no evidence for more gaze shifts after stimulation onset (paired *t*-test, $P > 0.3$). However, stimulation applied 70 ms after target onset shortened target-directed reaction times (RTs) if the target was presented at the ON location coinciding with the endpoint of the site-specific vector and prolonged RTs if the target was presented at the OFF location [monkey *r*: 2-way ANOVA of RT differences versus control with factors target location (ON and OFF location) and stimulation time (3 stimulation times: 20, 45, and 70 ms after target onset); $P < 10^{-3}$, post hoc corrected Bonferroni *t*-test $P < 0.05$; monkey *z*: *t*-test, $P < 0.02$]. Similar effects in monkey *r* were also observed for stimulation delivered 45 ms, but not 20 ms after target onset, nor during the fixation or gap intervals ($P > 0.64$). Overall, we are confident that ocular stability was not compromised directly by short-duration dSC stimulation, although the RT effects for stimulation during the movement interval indicate that there exists a short temporal window after target presentation during which short-duration dSC stimulation influences RTs, likely by transiently pushing a focal area around the electrode closer to gaze-shifting threshold.

Neck muscle responses evoked by short-duration dSC stimulation

Short-duration stimulation influenced reliably the activity of the suboccipital muscles obliquus capitis inferior (OCI) and rectus capitis major (RCP maj) and the larger SP cap muscle (Fig. 1C), increasing or decreasing the activity of muscles contralateral or ipsilateral to the side of dSC stimulation, respectively (Fig. 2, B–D). These three muscles contribute to volitional and stimulation-evoked horizontal head turns (Corneil et al. 2001, 2002b), and the evoked patterns are consistent with the brief recruitment of a synergy that turns the head in the direction opposite to the side of stimulation. Across all contralateral muscles, the evoked response began 14.0 ± 4.0 ms after the onset of the stimulation train and persisted for 18.3 ± 5.6 ms, peaking 22.1 ± 2.5 ms after stimulation onset (responses tended to be slightly earlier on OCI and RCP maj, consistent with previous results). The inhibitory responses on ipsilateral muscles occurred about simultaneously, beginning 15.3 ± 5.5 ms after stimulation onset and persisting for 19.1 ± 7.2 ms (extracting the time of minimal EMG activity during such inhibitory responses is not meaningful because such EMG activity remained at minimal levels for the duration of the

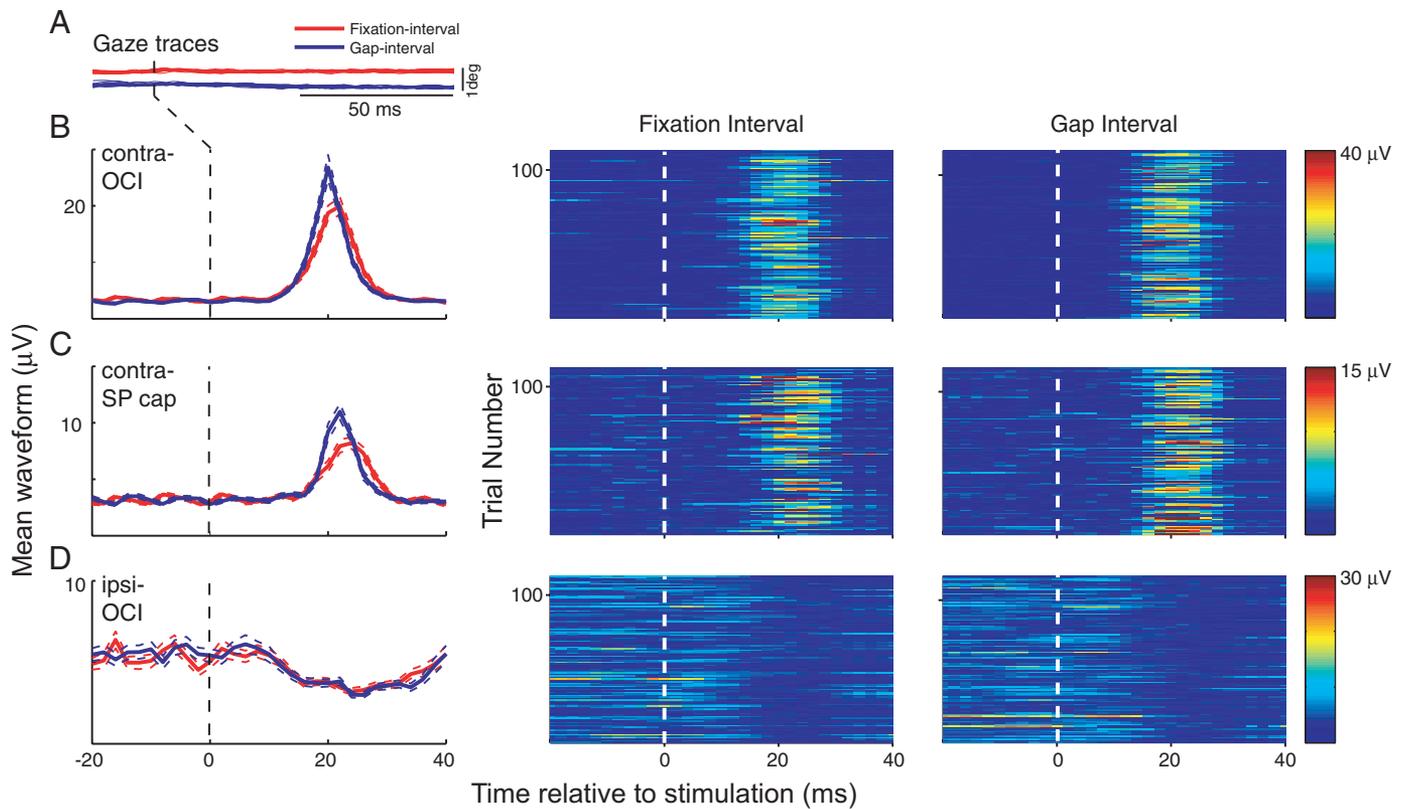


FIG. 2. Comparison of gaze position and muscle responses evoked after gap- and fixation-interval stimulation. *A*: horizontal gaze position traces during either fixation (red solid lines)- or gap (blue solid lines)-interval stimulation, showing that short-duration stimulation did not evoke any gaze shifts. Vertical dashed line shows stimulation onset. *B–D*, left: comparison of mean electromyographic (EMG) waveforms aligned on stimulation onset (vertical dashed lines) of the left-dSC in the fixation interval (red solid lines) and gap interval (blue solid lines) for the contralateral OCI (*B*), contralateral SP cap (*C*), and ipsilateral OCI (*D*). Stimulation was delivered at a site evoking a 20° rightward site-specific gaze shift. Thin dashed lines denote the standard error of the mean. Mean EMG waveforms were derived from 113 trials with fixation-interval stimulation, and 117 trials with gap-interval stimulation. Data in *A* and *B–D* are taken from the same experimental session; note the different time scales. *Middle* and *right*: trial-by-trial EMG activity for the respective muscles for fixation-interval stimulation (*middle*) and gap-interval stimulation (*right*). Within each subplot, each row conveys the EMG activity recorded during a single trial. White, dashed line aligned on stimulation onset.

inhibitory response). These evoked patterns, including the onset latencies and reciprocal appearance of neck EMG evoked on contra- and ipsilateral muscles resemble those elicited by longer stimulation trains (Corneil et al. 2002a,b), although characterized by a shorter duration. Recordings were obtained from contralateral OCI after stimulation at all 35 sites within the dSC, from RCP maj from 18 of these 35 sites, and from contralateral SP-cap from 22 of these 35 sites. These differences reflect both the implantation strategies, and EMG electrode breakage that was noted either immediately postimplant (e.g., we never obtained recordings from L-SP cap in *monkey z*) or at some later point (e.g., recordings from R-RCP maj and R-SP cap were initially viable in *monkey r*, but failed between 1 and 3 mo after implant; see Table 1).

Increased evoked neck EMG after gap- versus fixation-interval stimulation

To test our hypothesis that the level of low-frequency oculomotor activity affects the excitability of the head premotor circuitry, we first compared neck EMG evoked by dSC stimulation delivered around 150–175 ms into either the fixation or gap interval. As predicted, the example shown in Fig. 2, *B* and *C*, demonstrates that the peak magnitude of the evoked EMG response was significantly greater on contralateral mus-

cles after gap- versus fixation-interval stimulation (Wilcoxon rank-sum tests of neck EMG at time of peak of mean EMG traces; $P < 0.05$ for both muscles; note that our analysis picks off the peak EMG value regardless of when it occurs). These augmented evoked responses were not due to preexisting differences in neck EMG in the sample immediately preceding stimulation onset ($P > 0.48$ for both muscles). For the muscle ipsilateral to the side of stimulation (ipsilateral OCI; Fig. 2*D*), the minimum activity value evoked by stimulation did not differ significantly between the fixation and gap interval ($P = 0.45$).

A site-by-site analysis revealed the consistency of this effect in both monkeys in multiple contralateral muscles. The frequency histograms in Fig. 3 express the difference in the peak magnitude of the evoked EMG response between gap- and fixation-interval stimulation (i.e., the difference in the peak values shown in Fig. 2, *B–D*). For all three contralateral muscles, these histograms are shifted toward positive values, implying greater peak evoked activity after gap-interval stimulation. The peak magnitude of evoked neck EMG responses was greater after gap-interval stimulation in 30 of 35 (86%) sites for OCI (Fig. 3*A*, Wilcoxon signed-rank test, $P < 10^{-5}$), 12 of 18 (66%) sites for RCP maj (Fig. 3*B*, $P = 0.02$), and 17 of 22 (77%) sites for SP cap (Fig. 3*C*, $P = 0.008$). No

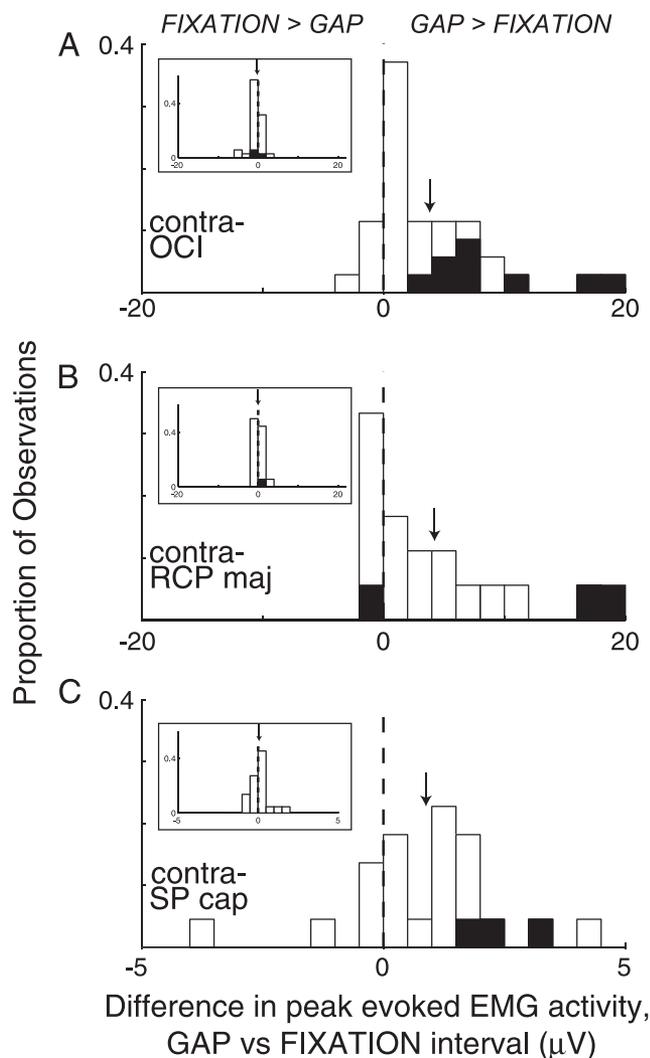


FIG. 3. Normalized frequency histograms expressing differences in peaks of evoked responses across fixation- and gap-interval stimulation for contralateral OCI (A), RCP maj (B), and SP cap (C). Data to the right of the dashed 0 line represents examples where the peak activity after gap-interval stimulation was greater than the peak activity after fixation-interval stimulation. Each observation taken from a separate stimulation site (35, 18, and 22 sites for OCI, RCP maj, and SP cap, respectively). Solid and empty bins represent observations that were significantly different or not, respectively (t -test, $P < 0.05$). All histograms are distributed to the right of the 0 line. Peak EMG activity was significantly greater after gap-interval stimulation across the population (Wilcoxon signed-rank test of peak activity after fixation- vs. gap-interval stimulation, $P < 0.05$). Arrows, mean difference values. Insets: normalized frequency histograms expressing differences in baseline activity prior to fixation- and gap-interval stimulation, using same format. Note that histograms are distributed around 0 ($P = 0.13, 0.79$, and 0.76 for OCI, RCP maj, and SP cap, respectively), implying that levels of neck EMG were not different prior to fixation- and gap-interval stimulation across the population.

consistent differences were found in either the onset time of the evoked response or in the time of the peak response across fixation condition ($P > 0.30$ for all muscles). For muscles ipsilateral to the side of stimulation, the minimum EMG activity did not differ across fixation- and gap-interval (Wilcoxon signed-rank test, $P > 0.05$ for all muscles, results not shown).

The augmented EMG responses after gap-interval stimulation may simply reflect differences in neck EMG that exist prior to stimulation onset (e.g., if neck EMG increased during

the gap interval). We examine this potential confound in a number of ways. First, we performed an analogous site-by-site analysis of the sample of baseline neck EMG immediately before stimulation onset across the fixation and gap intervals and revealed no evidence for preexisting differences in neck EMG prior to stimulation onset (Wilcoxon signed-rank tests, $P = 0.13, 0.79$ and 0.76 for contralateral OCI, RCP maj and SP cap, respectively). Distributions shown in Fig. 3, A–C, insets; by chance one would expect that baseline activity will be greater in the gap- versus fixation-interval in half of the dataset). There was also no consistent relationship between the difference in the prestimulation level of baseline EMG in fixation versus gap intervals and the differences in the peak evoked activity.

We also examined control trials to see if neck EMG had any tendency to increase during the gap interval on trials without stimulation. To do this, we compared the distribution of neck EMG activity for the sample that corresponds to the time that stimulation is delivered in the fixation and gap intervals. Across all of our data, no muscle ever displayed a tendency to increase activity during the gap interval (Wilcoxon signed-rank test, $P > 0.9$ for all muscles). We are therefore confident that the greater magnitude of evoked responses after gap-interval stimulation is not due to preexisting differences in neck EMG before stimulation onset.

One final concern is that the augmented responses following gap-interval stimulation in *monkey r* were due to potentiating effects from the preceding fixation-interval stimulation train (recall that stimulation in this monkey was delivered once in each of the fixation, gap, and movement intervals on a single trial). A comparison of the magnitude of augmentation brought about by gap- versus fixation-interval stimulation revealed no trend for greater augmentation in *monkey r* versus *monkey z* (t -test of percentage increase in peak magnitude evoked by gap- vs. fixation-interval stimulation, $P > 0.65$ for all muscles). Furthermore, for this monkey, we compared the activity in the sample immediately preceding gap-interval stimulation to a time-matched sample from control trials and again observed no evidence for potentiation prior to gap-interval stimulation (Wilcoxon signed-rank test, $P > 0.9$ for all muscles).

Gradual increase of evoked neck EMG during gap-interval

Consistent with our hypothesis, evoked neck EMG in both monkeys is greater after stimulation delivered at the end of the gap versus end of the fixation interval. In the dSC, low-frequency neural activity increases at the locus or loci commanding movements to potential target locations (Munoz et al. 2000), and a similar build-up of activity during the progression of the gap has been observed in the FEF (Everling and Munoz 2000). The stimulation protocol used in *monkey r* allowed us to test whether the excitability of the head premotor circuitry follows a similar time course because short-duration stimulation in *monkey r* was delivered at different times within the fixation, gap, and movement intervals as the monkey prepared for movement initiation (Fig. 1A, METHODS). Here we focus on the changes in evoked neck EMG occurring in the gap and early movement intervals prior to the onset of dSC visual responses after target presentation. We have analyzed stimulation delivered during the early movement interval (e.g., 20 ms after target onset) because such stimulation precedes the

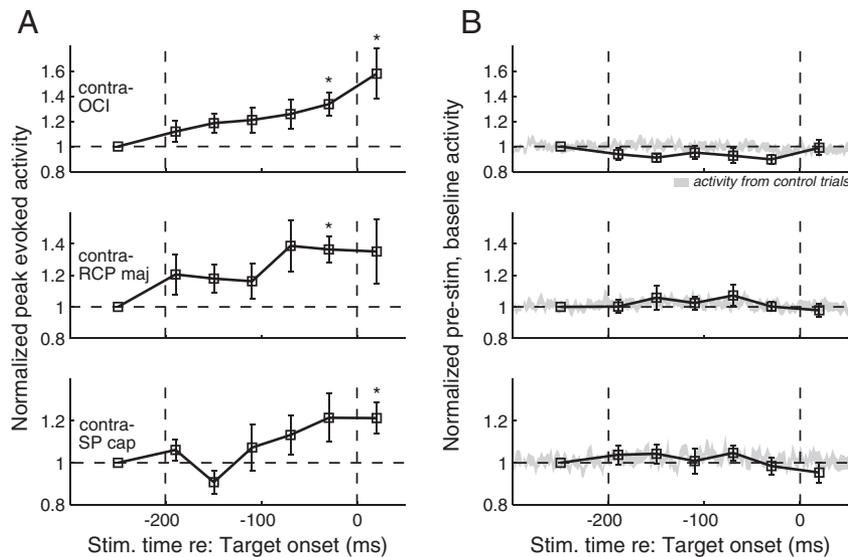


FIG. 4. Time course of changes in evoked EMG activity during gap interval (indicated by the dashed vertical lines). A: mean peak evoked magnitudes for different stimulation times relative to target presentation for contralateral OCI, RCP maj, and SP cap. Data were first normalized to the responses evoked at the end of the fixation interval (-250 ms; horizontal dashed lines) and then averaged from multiple stimulation locations in *monkey r*. Error bars represent SEs of the means. Data points are averages of 15 sites for OCI, 10 for RCP maj, and 11 for SP cap. Asterisk, values determined to be significantly different from the EMG values obtained at the end of the fixation interval (One-way paired t -test, $P < 0.05$, Bonferroni corrected for multiple comparisons). B: baseline levels of neck EMG taken from the sample immediately before stimulation onset. Same format as A. The gray shaded region in the background shows the EMG activity recorded from these muscles on control trials without stimulation, subtending the area between the mean \pm SE.

arrival of visual information in the dSC. dSC neurons can respond to visual stimuli within as little as 40 ms (Wurtz and Goldberg 1972). Similarly short latencies have been observed in our laboratory with the laser and LED stimuli employed here (Bell et al. 2006).

For all contralateral muscles, the magnitude of the evoked neck EMG responses (normalized to responses evoked at the end of the fixation interval) followed a time course similar to low-frequency oculomotor activity, increasing progressively through the gap interval and into the early movement interval (Fig. 4A). To analyze this statistically, we performed a one-way paired t -test of the six normalized evoked values during the gap and early movement interval versus the value evoked at the end of the fixation interval (Bonferroni-corrected for multiple comparisons). This analysis revealed that evoked responses were significantly greater on OCI for the final two stimulation times (i.e., -30 and 20 ms relative to target onset), on RCM for the second last stimulation time (-30 ms relative to target onset), and on SP for the last stimulation time (20 ms relative to target onset; asterisks in Fig. 4A).

Once again, an analogous analysis of baseline neck EMG preceding stimulation revealed no trend for any contralateral muscle to increase in activity during the gap interval (Fig. 4B, $P > 0.3$ for baseline activity prior to all stimulation times on all contralateral muscles). The EMG activity recorded from control trials also did not vary during the progression of the gap task (Fig. 4B shaded contours). These results emphasize that the changes in evoked neck EMG responses during the progression of the gap task were not linked to preexisting differences in neck EMG before stimulation onset.

Neck EMG evoked in movement interval follows lateralized changes in oculomotor activity

Another way to examine the relationship between low-frequency oculomotor activity and the excitability of the head premotor circuitry is to examine the effects of short-duration dSC stimulation during the movement-interval. Within the dSC, and presumably in other oculomotor areas, equal levels of low-frequency activity corresponding to the potential target locations resolve after the arrival of visual activity, increasing

in the area that will ultimately produce the high-frequency burst driving the movement, and decreasing in the other area (Munoz et al. 2000) (Fig. 5A). Our hypothesis predicts that the magnitude of neck EMG responses evoked by stimulation in the movement interval should show similar dependencies, increasing or decreasing if stimulation location coincides with the area of the dSC driving the ensuing movement or not, respectively.¹

Figure 5 shows an example of evoked neck EMG after stimulation delivered to the left-SC, 45 ms after target presentation. In this example, stimulation was timed to coincide approximately with the arrival of visual activity within the dSC (Bell et al. 2006; Wurtz and Goldberg 1972). Stimulation elicited significantly greater activity on the contralateral muscles if the target was presented at the ON versus OFF location (Fig. 5, B and C; Wilcoxon ranksum tests, $P < 0.001$ and < 0.02 for contralateral OCI and SP-cap, respectively). There was no difference in the minimum level of neck EMG in muscles ipsilateral to the side of stimulation (Fig. 5D; $P = 0.69$ for ipsilateral OCI).

We wanted to ensure that there was no difference in the neck EMG activity immediately preceding stimulation onset because we have recently demonstrated lateralized bursts of neck EMG activity after target presentation (Corneil et al. 2004). We therefore derived the latencies of such *visual neck EMG bursts* on control trials without dSC stimulation and restricted our analyses to stimulation delivered before these latencies. For the example in Fig. 5, the latencies of visual neck EMG bursts occurred well after dSC stimulation (stimulation was delivered 45 ms after target onset, and the visual bursts occurred 74 ms after target onset on contralateral OCI, 110 ms on contralateral SP cap, and 64 ms on ipsilateral OCI). Accordingly, an analysis of the baseline levels of neck EMG immediately prior to

¹ Many dSC neurons emit what has been termed a high-frequency burst of activity time-locked after visual target onset. With the exception of express saccades (Dorris et al. 1997; Sparks et al. 2000), the magnitude of this burst is less than the magnitude of the high-frequency motor burst that occurs time-locked prior to movement onset. Rather than having to differentiate between high-frequency "visual" bursts from high-frequency "motor" bursts throughout the manuscript, we use the term low-frequency to denote any activity other than the high-frequency motor burst.

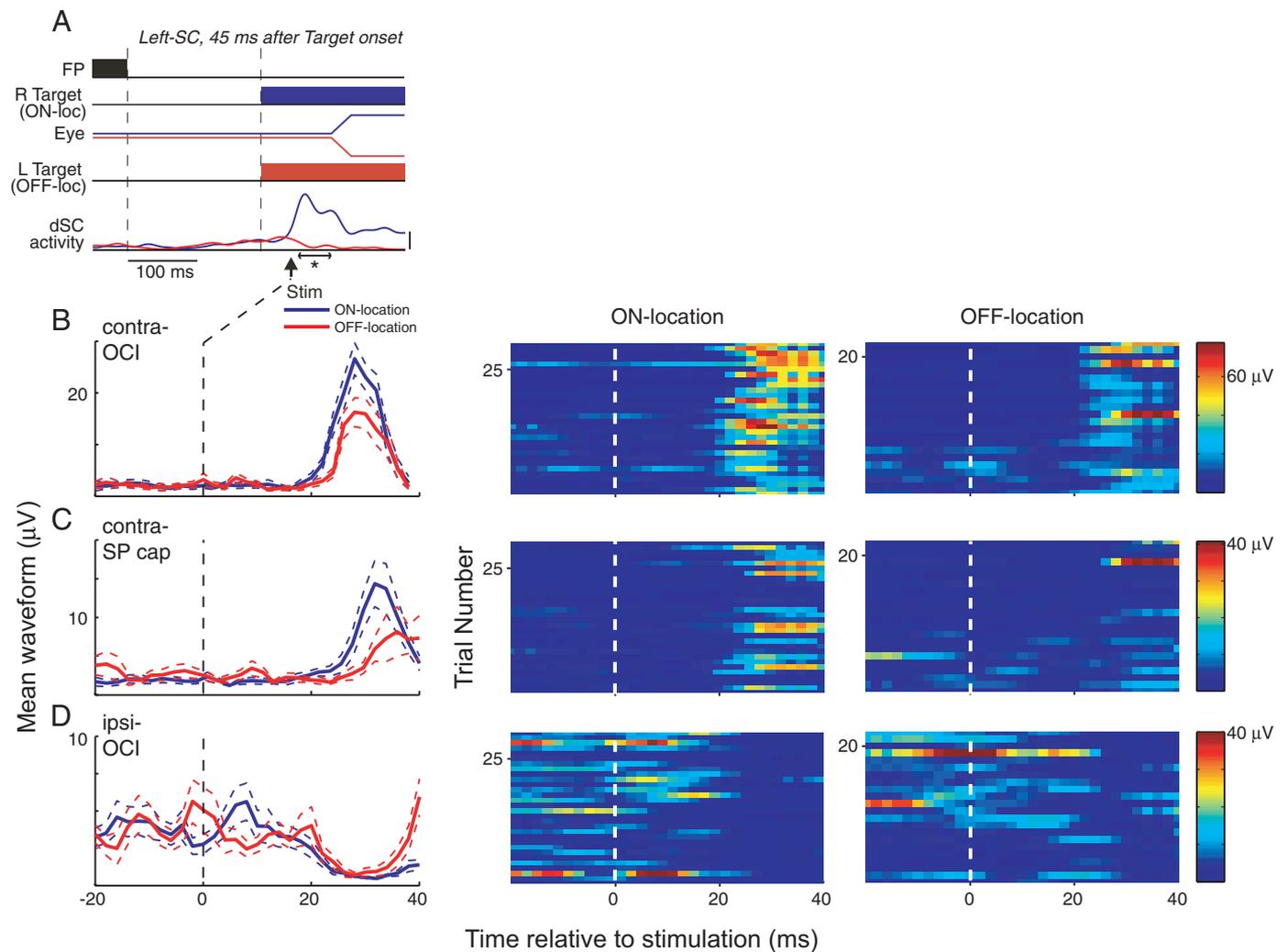


FIG. 5. Neck EMG responses evoked by stimulation delivered 45 ms after target onset to the left dSC. Stimulation was delivered to a location in the left-SC that evoked a 20° rightward site-specific gaze shift angled 7° below the horizontal. **A**: timing and location of stimulation, relative to target location. When the target is presented to the right, matching the endpoint of the site-specific gaze shift, stimulation overlaps with increasing dSC activity, as shown by the spike density function of a representative dSC neuron. In this case, stimulation was delivered to what is termed the ON location (blue lines). In contrast, when the target is presented to the left at the diametrically opposite location, this is termed the OFF location (red lines). Scale bar to the right of the spike density function denotes 100 Hz, a scale coarse enough to obscure increasing low-frequency dSC activity during the gap-interval. The range above the asterisk conveys latencies of visual neck EMG bursts obtained from control trials (Corneil et al. 2004), spanning 55–100 ms after target onset **B–D**. Same format as Fig. 2, with *left* showing evoked responses for contralateral OCI (**B**), contralateral SP cap (**C**), and ipsilateral OCI (**D**) following targets presented at the ON or OFF location. Mean EMG waveforms were derived from 30 trials for ON-location stimulation, and 22 trials for OFF-location stimulation. *Middle and right*: trial-by-trial EMG activity for the respective muscles for ON-location stimulation (*middle*) and OFF-location stimulation (*right*). Within each subplot, each row conveys the EMG activity recorded during a single trial. White, dashed line aligned on stimulation onset.

stimulation onset revealed no differences ($P > 0.36$ for both contra-OCI and -SP).²

² Although the movement-interval stimulation shown in Fig. 5 preceded the arrival of the visual burst of neck EMG, the evoked responses likely result from a summation of the evoked response with the visual burst of neck EMG. Consider for example the records for contra-OCI shown in Fig. 5B. The visual burst on this muscle began 74 ms after target onset. Although stimulation was delivered 45 ms after target onset, the evoked EMG response peaked 30 ms later, coinciding with the latency of the visual burst of neck EMG. In fact, an overlap between the evoked EMG response and the visual burst of neck EMG is unavoidable. The EMG responses evoked by ON- versus OFF-location stimulation can be different only if stimulation is passed simultaneously with or after the arrival of visual transient throughout the oculomotor system, and our previous results demonstrate that it is this visual transient throughout the oculomotor system that leads to the visual bursts of neck EMG (Corneil et al. 2004).

In both monkeys, movement-interval stimulation was delivered 70 ms after target presentation in 26 different experimental sessions. In 14 of these sessions, stimulation occurred *after* the visual bursts of neck EMG, and we therefore constrained our analysis to the remaining 12 stimulation sites (4 in *monkey z*, 8 in *monkey r*). A site-by-site analysis revealed that the peak neck EMG responses on contralateral muscles was greater if stimulation followed target presentation at the ON versus OFF location in 12 of 12 (100%) sites for OCI (Wilcoxon signed-rank test $P < 10^{-3}$, Fig. 6A), at 6 of 6 (100%) sites for RCP maj ($P = 0.04$, Fig. 6B), and 7 of 9 (77%) sites for SP cap ($P = 0.03$; Fig. 6C).

An analogous site-by-site analysis of the baseline neck EMG revealed that this effect was not due to preexisting differences in neck EMG prior to stimulation onset (histograms, Fig. 6,

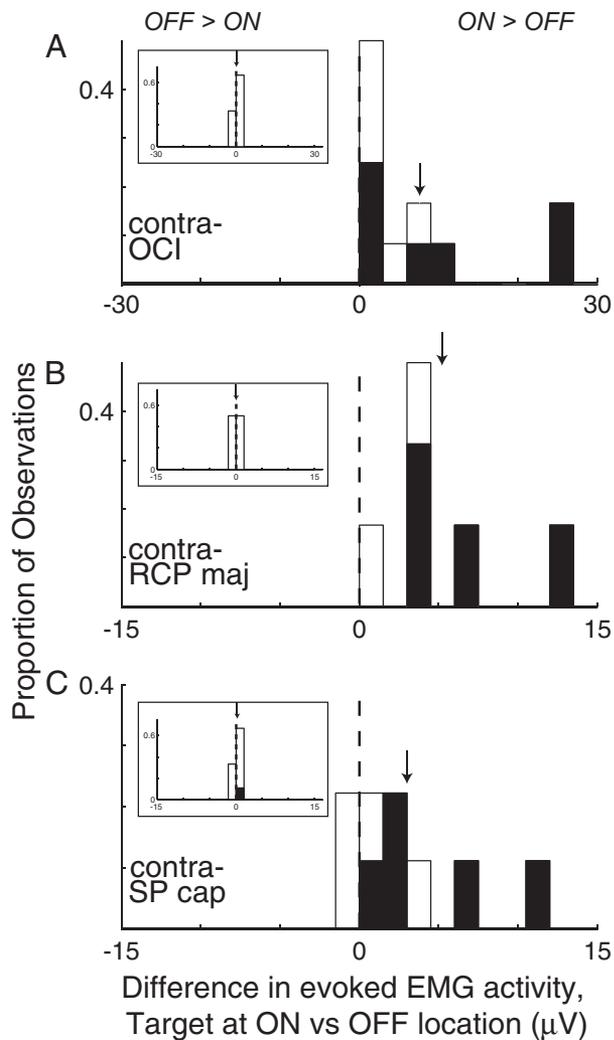


FIG. 6. Normalized frequency histograms expressing differences in peaks of evoked responses across stimulation delivered 70 ms after target presentation at ON and OFF locations in both monkeys. Same format as Fig. 3. Data were only included in this figure if the latency of the visual neck EMG burst determined from control trials exceeded 70 ms, hence the reduced number of points (12 for contralateral OCI, 6 for contralateral RCP maj, 9 for contralateral SP cap). All distributions lay to the right of the zero point (Wilcoxon signed-rank test, $P < 0.05$), whereas those expressing differences in baseline activity (insets) were centered around 0 ($P = 0.38$, 1, and 0.09 for OCI, RCP maj, and SP cap, respectively).

insets, METHODS). By chance, one would expect that the baseline activity will be greater after target presentation at the ON versus OFF location in half of the dataset. Indeed, this trend was observed with baseline activity being greater after target presentation at the ON versus OFF location in 8 of 12 (66%) sites for OCI ($P = 0.38$), 3 of 6 (50%) sites for RCP maj ($P = 1$), and 6 of 9 (66%) of sites for SP cap ($P = 0.09$; histograms in insets in Fig. 6). Importantly, we observed no relationship between the baseline and peak evoked levels of activity across target location.

Although we have already constrained this dataset to ensure that stimulation occurred prior to the visual neck EMG bursts, we re-examined the neck EMG from control trials to ensure that there was no difference in neck muscle activity at the time of stimulation delivery. Across the constrained subset of control data, no muscle ever displayed a tendency to have greater

activity after target presentation in the ON versus OFF direction at the time stimulation is delivered on stimulation trials (Wilcoxon signed-rank test, $P > 0.3$ for all muscles). These baseline analyses emphasize that the augmented neck EMG responses evoked after targets presented at the ON location were not simply a consequence of preexisting differences in neck EMG activity before stimulation.

Given the different stimulation protocols used in the two monkeys, we again compared this result across monkeys and found no significant trend toward greater effects in *monkey r* (t -test of percentage increase in peak magnitude evoked by movement-interval stimulation after targets presented at the ON vs. OFF location, $P > 0.53$ for all muscles) as would have been expected if the preceding stimulation trains were to have a potentiating effect. Furthermore for this monkey, we compared the activity in the sample immediately preceding movement-interval stimulation to a time-matched sample from control trials and again observed no evidence for potentiation prior to movement-interval stimulation ($P > 0.25$ for all muscles).

Gradual divergence of evoked neck EMG during movement-interval

Consistent with our hypothesis, neck muscle activity evoked by movement-interval stimulation in both monkeys is greater after target presentation in the ON versus OFF direction. The stimulation protocol employed in *monkey r* permits us to gain additional insights by constructing a timeline of the divergence in peak evoked neck EMG activity evoked by stimulation delivered at various times during the gap and movement interval, segregated by whether the target was presented at the ON or OFF location (Fig. 7A). The important trend is that the activity evoked on all three muscles was invariant with target location if stimulation was delivered during the gap interval or 20 ms into the movement interval as this precedes the arrival of visual information into the oculomotor system. Evoked responses then diverged depending on the target location, increasing after targets presented at the ON location and decreasing after targets presented at the OFF location. This decrease in the evoked response after OFF-location stimulation is particularly important as it fell below the baseline levels prior to the onset of the gap interval, perhaps consequent to inhibitory interactions stemming from the development of visual burst on the opposing neck muscles. Our statistical analysis of the divergence involved first taking the differences in normalized evoked activity after target presentation at the ON versus OFF direction and then performing Bonferroni-corrected one-way paired t -test of the differences after stimulation at either 45 or 70 ms after target onset versus the difference obtained at 20 ms after target onset. This difference in evoked responses was significantly greater on all muscles for stimulation 70 ms after target onset and additionally on OCI for stimulation 45 ms after target onset (Fig. 7A, asterisks).

We repeated this analysis for the baseline neck EMG activity in *monkey r* as a function of time of stimulation during the movement interval (Fig. 7B). Although baseline neck EMG did tend to increase on contralateral muscles around 70 ms after target presentation in the ON location, this increase only reached significance for OCI (Fig. 7B). The EMG activity recorded from control trials showed similar trends, diverging depending on target location only ~ 70 ms after target presen-

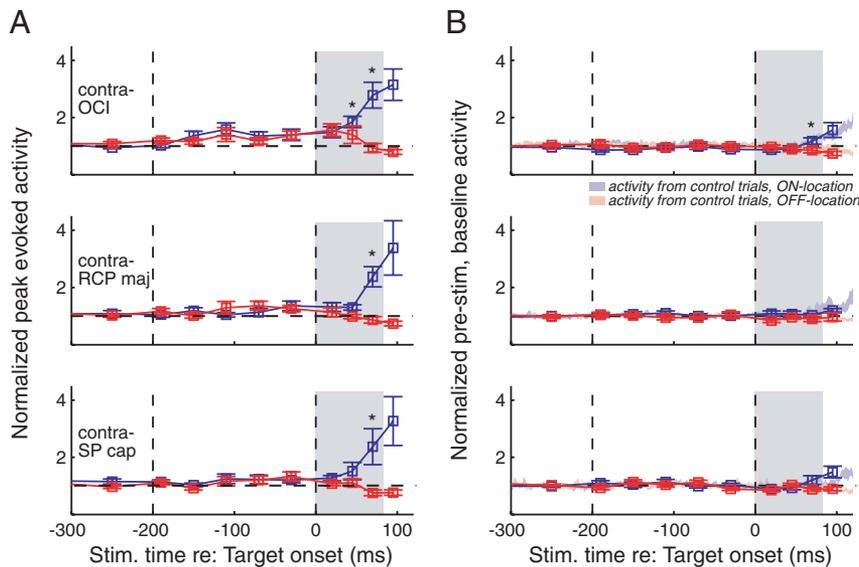


FIG. 7. Time course of changes in evoked activity during movement interval as a function of stimulation time and target location. Same format as Fig. 4. *A*: data segregated by whether the target was presented at the ON location (blue symbols and lines) or the OFF location (red symbols and lines). All activity was normalized to the peak neck EMG for stimulation delivered at the end of the fixation interval. Gray shaded region bounds the three movement-interval stimulation times that were subjected to statistical analyses. Analysis consisted of comparing the difference in the activity evoked 45 and 70 ms after stimulation onset in the ON and OFF location for these intervals, compared with that obtained 20 ms after target onset (* signify significant differences, $P < 0.05$, 1-way paired t -test, Bonferroni-corrected for multiple comparisons). *B*: baseline levels of neck EMG taken from the sample immediately before stimulation onset. Same format as *A* with light blue and red shaded regions denoting EMG activity \pm SEs recorded from these muscles on control trials without stimulation, sorted by whether the target was presented at the ON (blue shaded shapes) or OFF (red shaded shapes) location.

tation (Fig. 7*B*, shaded contours). Therefore although the differential neck EMG responses evoked on OCI 70 ms after target onset could be at least partly due to preexisting differences in neck EMG, the divergence of evoked responses on the other muscles were not.

Influence of stimulation location along the rostrocaudal dSC axis

We investigated all of our data as a function of stimulation location in the dSC as it is well known that progressively larger gaze shifts with larger contributions of the head are evoked from more caudal dSC locations. Although we observed weak trends for the observed effects (e.g., the difference values plotted in Figs. 3 and 6) to increase for more caudal stimulation locations for OCI and RCP maj, these data are confounded with stimulation current. Recall that we set out stimulation current to be 1.5 times the current required to consistently evoke short-latency gaze shifts. Consequently, the absolute level of current that was passed (range: 10–75 μ A) varied between different stimulation sites, and hence the absolute magnitude of the evoked EMG responses also varied. Furthermore the absolute magnitude of the evoked EMG response will also vary muscle by muscle depending on electrode-specific parameters such as impedance or electrode length. These confounds complicate the interpretation of the effects of stimulation location along the rostrocaudal axis of the dSC.

DISCUSSION

Our primary result is that the excitability of the head premotor circuitry, indexed by the EMG responses evoked by short-duration dSC stimulation, follows closely the time course of low-frequency activity within the oculomotor system, being greater following cues informing about impending target presentation (the 200-ms gap), and greater still following target presentation. These observations suggest a role for low-frequency oculomotor activity in priming the premotor circuits of the head. This role may be complementary to other high-level processes related to low-frequency oculomotor activity, such as target predictability and oculomotor preparation, as such

processes affect the onset of the head movement and the head's contribution to a gaze shift (Bizzi et al. 1972; Freedman and Sparks 1997b; Oommen et al. 2004; Zangemeister and Stark 1982). The traditional reliance on head-restrained preparations in the oculomotor literature, for obvious technical reasons, has neglected the control of head motion; if anything, the head is thought to follow the eye slavishly. However, when taken in context with other behavioral and neurophysiological findings (Corneil and Elsley 2005; Corneil et al. 2004; Crawford and Guitton 1997; Oommen et al. 2004; Tweed et al. 1998), our present results implicate low-frequency oculomotor activity in more nuanced control of orienting head movements.

To our knowledge, our results constitute the first neurophysiological evidence for a role of low-frequency oculomotor activity in influencing eye-head gaze shifts. The few recording studies of oculomotor activity in head-unrestrained primates have focused on whether the high-frequency bursts of activity preceding movement onset correlates best with eye, head, or gaze movements (Freedman and Sparks 1997a; Robinson and Jarvis 1974) or have generally been anecdotal in nature (Bizzi and Schiller 1970; Robinson and Jarvis 1974). Although stimulation studies have demonstrated that head movements can be evoked without gaze shifts, such studies have used prolonged stimulation trains that may not engage natural profiles of activity within the oculomotor system (Chen and Walton 2005; Corneil et al. 2002b; Pelisson et al. 2001; Tu and Keating 2000). Here, we used very short-duration stimulation of the dSC as a means to assay the excitability of the head premotor circuitry without disturbing the performance of a well-understood oculomotor task.

Although our results reveal a close temporal correlation between low-frequency oculomotor activity and the excitability of the head premotor circuitry, it is premature to ascribe a causal role to low-frequency activity emanating from a specific neural structure. To advance this issue, future recording experiments should focus on correlating low-frequency oculomotor activity with aspects of either neck EMG or head-movement kinematics. Of note, we have obtained preliminary results that demonstrate a trial-by-trial correlation between low-frequency

activity in the dSC and the magnitude of contralateral neck EMG (Rezvani and Corneil 2006).

Biomechanical realities of moving the head

The eyes and head are fundamentally different motor structures; in particular, the head is characterized by a considerable inertial component that prolongs the interval between muscle activation and movement onset (Zangemeister and Stark 1982) and complicates the inference of neuromuscular events from movement kinematics. Although quite variable and susceptible to behavioral context, the onset of head motion usually lags onset of the high-velocity eye saccade during eye-head gaze shifts (Fuller 1992). Given these onset differences, our evidence for early priming of head premotor circuits appears paradoxical. However, when one considers the biomechanical realities of moving an inertial structure like the head during gaze shifts, selectively priming the premotor circuits of the head may aid the temporal coordination of eye-head movements by potentiating more forceful neck muscle contractions when a commitment is finally made to shift gaze. Indeed there is compelling evidence that the CNS programs and initiates head movements prior to gaze shifts (Corneil and Elsley 2005; Corneil et al. 2004; Crawford and Guitton 1997; Tweed et al. 1998).

How could the CNS utilize selective excitation of head premotor circuits to its strategic advantage? It is well recognized that the brain can generate amplitude-matched gaze shifts with varying contributions of the eyes and head depending on context (e.g., see Constantin et al. 2004; Oommen et al. 2004), but the underlying neural mechanisms remain to be elucidated. Indeed, how the CNS achieves repeatable behavioral goals despite an infinite variety of underlying coordination patterns has long been a central question in motor control (see Todorov and Jordan 2002 for review). We speculate that the head's contribution may depend, at least in part, on the magnitude of low-frequency oculomotor activity prior to gaze shift onset, perhaps integrated over a short time-span (again, determining which specific oculomotor area(s) may be involved require alternative experimental approaches). There is currently very little empirical data to support this contention. Portions of a previous report (Freedman and Sparks 1997a) showed no obvious relationship between low-frequency dSC activity and head motion, but a detailed analysis incorporating neck EMGs is needed to avoid the biomechanical complexities associated with head motion (for example, initial eye-in-head and head-in-space position also affect neck EMG and may alter the linkage among muscle recruitment, kinetics, and head-movement kinematics). With little low-frequency oculomotor activity, the head may move relatively little and/or lag eye motion onset considerably. However, within a different behavioral context associated with increased low-frequency oculomotor activity, the head would move earlier and faster and contribute more to the gaze shift. There are a number of frontal cortical areas that access the oculomotor system that could set up the behavioral contexts to alter strategically the patterns of eye-head coordination (e.g., Everling and DeSouza 2005). Such frontal projections may also access brain stem elements downstream from the dSC that allow the user to voluntarily prevent, or gate out, the head's contribution to a gaze shift (after all, one can easily generate large gaze shifts without moving the head).

Behavioral studies have speculated on the existence of such a gate (Oommen and Stahl 2005), but the underlying neural circuits remain unclear. It is not clear for example whether the lack of a head movement occurs because of the absence of any change in neck EMG (as if the gate functions as a type of switch) or because neck EMG is dampened so that insufficient forces cannot overcome the head's inertia (as if the gate functions as a type of variable resistor). Indeed, the lack of head motion during a small gaze shift does not infer the absence of a change in neck EMG activity (Andre-Deshays et al. 1991; Corneil et al. 2002b, 2004). Recordings of neck EMG should be able to distinguish these possibilities, hence it is possible that the variable patterns of eye-head coordination that characterize real-world gaze shifts can be effected through well-understood and -studied oculomotor structures.

Priming of head circuits occurs upstream of the output of neck muscle motoneurons (neck MNs)

It is important to stress that our results are not simply a reflection of the baseline level of neck EMG preceding stimulation onset (Figs. 3 and 6, insets, and 4B and 7B, shaded contours). In contrast to the magnitudes of neck EMG evoked by dSC stimulation, which increased during trial progression, baseline levels of neck EMG remained unaltered until a sharp divergence following target onset (Corneil et al. 2004). Although at first it may be surprising that neck EMG did not increase during the gap interval (because low-frequency activity in the oculomotor system does increase during the gap), it must be remembered that the target could have been presented at two different locations. Hence although the monkeys could anticipate when the target would appear, they could only predict that it would appear at one of two locations. For example in the dSC, this ambiguity is associated with increasing low-frequency activity in two discrete zones dSC during the gap interval, one in each dSC (see Munoz et al. 2000 for review) [similar bilateral processing also occurs in the FEF (Everling and Munoz 2000)]. We speculate that such accumulating neural populations may exert mutually inhibitory effects within the head premotor circuits, perhaps in the brain stem or spinal cord. If so, neck EMG activity may only increase once these active populations resolve as occurs after dSC stimulation (as reported here) (see also Corneil et al. 2002a,b) or once visual information arrives in the oculomotor system (Corneil et al. 2004). Such a scenario would also predict that neck EMG would increase during the gap period if the amount of low-frequency dSC activity is greater on one side than the other. We have recently obtained preliminary data in support of this prediction using a paradigm that manipulates reward expectancy (Rezvani and Corneil 2006).

We constrained our analysis of evoked neck EMG to the intervals preceding such visual neck EMG bursts, allowing us to be confident that any priming occurred without affecting the output activity of neck MNs. The differential consequences of short-duration dSC stimulation on neck muscle activity (measured directly) and extraocular muscle activity (measured indirectly through eye movements) emphasize important differences in the pathways taking origin from the dSC and terminating at the eye or head plant. Activity within the saccadic burst generator is tightly constrained by brain stem omni-pause neurons (OPNs), which pause only immediately prior to gaze

shift generation (Scudder et al. 2002). OPNs do not decrease their activity during the gap interval analogous to rostral dSC "fixation" neurons but rather maintain a constant firing rate; consequently the premotor short-lead burst neurons in the brain stem burst generator remain inactive during the gap interval (Munoz et al. 2000). The reduction in saccadic reaction times afforded by introducing a 200-ms gap period (the "gap effect") occurs because these premotor elements emit a high-frequency burst sooner after target onset, presumably due to increased low-frequency preparatory activity in the dSC and/or frontal eye fields (Dorris and Munoz 1998; Everling and Munoz 2000).

Our results demonstrate that low-frequency oculomotor activity is manifested in different ways at the eye versus the head plant. The dSC-head plant pathway is almost certainly polysynaptic (Isa and Sasaki 2002; Robinson et al. 1994) and perhaps consists of parallel pathways (Galiana and Guitton 1992). Our results provide further support for the notion that at least a portion of the dSC-head plant pathway bypasses the inhibitory actions of OPNs (Goossens and Van Opstal 1997; Phillips et al. 1995, 1999; Sparks et al. 2002) and demonstrate in addition that the dSC-head plant pathway is comparably more excitable while gaze shifts are being planned but have not yet been executed. Comparative differences in the dSC-eye plant and dSC-head plant pathways likely relate back to the biomechanics of eye and head motion and to the paramount importance of retinal stability for foveal vision; because head movements are characterized by a greater inertial component and compensated for by vestibular reflexes, there is no need to constrain premotor signals from accessing the head plant as tightly as the eye plant.

Our results reveal that increasing levels of low-frequency oculomotor activity prime the head's premotor circuitry, so that a given amount of current injected into the dSC produces a greater output at the neck MNs, despite stable levels of baseline neck EMG prior to stimulation onset. There are a number of plausible mechanisms of this finding that need not be mutually exclusive. First, short-duration dSC stimulation may sum with the preexisting low-frequency dSC activity, resulting in progressively increasing levels of evoked tectal outflow that are relayed onto neck MNs as the trial progresses. Second, increasing levels of low-frequency activity encoding oculomotor preparation (perhaps from the frontal eye fields or elsewhere) may increase the activity within nodes of the head premotor circuits downstream from the dSC prior to stimulation, so that a given input from tectal efferents results in greater output due to increased spatial and/or temporal summation. Finally, increased levels of low-frequency dSC activity may alter either the membrane potential of neck MNs below recruitment threshold or neuromodulatory inputs to neck MNs (Heckman et al. 2004) in effect amplifying the responses to subsequent incoming volleys.

Another important point to consider is whether EMG activity on extraocular muscles, which was not measured in this report, would also display augmented responses to short-duration dSC stimulation. We have previously considered a related question more thoroughly (Corneil et al. 2004), examining the appropriateness of eye movement recordings as a proxy for neuromuscular events at the eye plant. Briefly, a number of results demonstrate that very minor changes in the activity of extraocular motoneurons (even down to single spikes) result in measurable eye movements (Goldberg et al.

1998; Sparks and Gandhi 2003). Because we did not observe any stimulation-evoked eye movements, we are confident that short-duration stimulation of the dSC does not alter the activity of extraocular motoneurons.

Implications for stimulation paradigms

A number of recent studies have used electrical stimulation within oculomotor areas such as the dSC or frontal and parietal cortices as a means of studying higher cognitive processes (Cohen and Newsome 2004). Stimulation is delivered typically at current or frequency levels below the threshold for evoking head-restrained saccades during a behavioral task, presumably manipulating variables such as decision making, target selection, attentional allocation or movement specification (Armstrong et al. 2006; Burman and Bruce 1997; Carello and Krauzlis 2004; Cavanaugh and Wurtz 2004; Glimcher and Sparks 1993; Hanks et al. 2006; Horwitz et al. 2004; Moore and Armstrong 2003; Moore and Fallah 2001; Muller et al. 2005). Because the eyes remain stable, the assumption is that such stimulation influences covert processes removed from motor outputs. Our neck EMG recordings demonstrate that this assumption is unfounded: stimulation paradigms that are below either the duration threshold (as shown here) or current threshold (Corneil et al. 2002a,b) for evoking gaze shift are not divorced from motor output. Of additional concern, afferent information from neck muscles reaches many areas in the oculomotor system (Barbas and Dubrovsky 1980; Edney and Porter 1986; Snyder et al. 1998), raising the possibility that unanticipated or unintended consequences of stimulation confound the interpretation of the stimulation-evoked behavioral results.

Conclusions

We have demonstrated augmented neck muscle responses to short-duration dSC stimulation during the progression of a behavioral task. Such changes closely follow the time course of low-frequency activity throughout the oculomotor system, pointing to a role for low-frequency oculomotor activity in determining head contribution to gaze shifts. Over time, the CNS may optimize the biomechanical differences in eye and head motion by adopting a strategy to begin preparing for head motion while a decision to shift gaze is ongoing. It remains to be seen whether this strategy is unique to orienting eye-head gaze shifts or is also observed in other multisegmental movements with an ocular component such as eye-hand coordination. We note that low-frequency activity is not unique to the oculomotor system but is observed throughout many sensorimotor areas in the intervals leading up to movement initiation (Cisek and Kalaska 2005; Snyder et al. 1997).

ACKNOWLEDGMENTS

We thank Drs. G. E. Loeb and F. J. Richmond for assistance during EMG surgeries and A. Lablans and K. Moore for technical support. We thank Drs. M. Dorris, S. Everling, P. Gribble, and S. Musallam for helpful comments on earlier versions of this manuscript.

GRANTS

This work was supported by the Canadian Institutes of Health Research (CIHR) operating grants to B. D. Corneil and D. P. Munoz. E. Olivier was supported by a short-term fellowship from the Human Frontier Science Program (HFSP). B. D. Corneil was also supported by a doctoral and a New

Investigator award from the CIHR and a long-term fellowship and Career Development Award from the HFSP. D. P. Munoz holds a Canadian Research Chair in Neuroscience.

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