Functional Distinction Between Visuomovement and Movement Neurons in Macaque Frontal Eye Field During Saccade Countermanding

Supriya Ray, Pierre Pouget and Jeffrey D. Schall

J Neurophysiol 102:3091-3100, 2009. First published 23 September 2009; doi:10.1152/jn.00270.2009

J Neurophysiol 102: 3091–3100, 2009.
First published September 23, 2009; doi:10.1152/jn.00270.2009.

Functional Distinction Between Visuomovement and Movement Neurons in Macaque Frontal Eye Field During Saccade Countermanding

Supriya Ray, Pierre Pouget, and Jeffrey D. Schall
Vanderbilt Vision Research Center, Center for Integrative and Cognitive Neuroscience, Department of Psychology, Vanderbilt University, Nashville, Tennessee

Submitted 27 March 2009; accepted in final form 17 September 2009

Ray S, Pouget P, Schall JD. Functional distinction between visuomovement and movement neurons in macaque frontal eye field during saccade countermanding. *J Neurophysiol* 102: 3091–3100, 2009. First published September 23, 2009; doi:10.1152/jn.00270.2009. In the previous studies on the neural control of saccade initiation using the countermanding paradigm, movement and visuomovement neurons in the frontal eye field were grouped as movement-related neurons. The activity of both types of neurons was modulated when a saccade was inhibited in response to a stop signal, and this modulation occurred early enough to contribute to the control of the saccade initiation. We now report a functional difference between these two classes of neurons when saccades are produced. Movement neurons exhibited a progressive accumulation of discharge rate following target presentation that triggered a saccade when it reached a threshold. When saccades were inhibited with lower probability in response to a stop signal appearing at longer delays, this accumulating activity was interrupted at levels progressively closer to the threshold. In contrast, visuomovement neurons exhibited a maintained elevated discharge rate following target presentation that was followed by a further enhancement immediately before the saccade initiation. When saccades were inhibited in response to a stop signal, the late enhancement was absent and the maintained activity decayed regardless of stop-signal delay. These results demonstrate that the activity of movement neurons realizes the progressive commitment to the saccade initiation modeled by the activation of the GO unit in computational models of countermanding performance. The lack of correspondence of the activity of visuomovement neurons with any elements of these models indicates that visuomovement neurons perform a function other than the saccade preparation such as a corollary discharge to update visual processing.

INTRODUCTION

Efficient interactions with a dynamic visual environment require the ability to reconstruct the stable visual space when saccades are produced and to prevent saccades that are no longer relevant because the context in which they are planned changes. Inhibition of the saccade production has been studied using a stop-signal (countermanding) task in which subjects are instructed to refrain from their gaze shift in response to a stop signal that infrequently follows the appearance of the target after a random delay (e.g., Armstrong and Munoz 2003; Cabel et al. 2000; Colonius et al. 2001; Hanes and Carpenter 1999; Logan and Irwin 2000; Morein-Zamir and Kingstone 2006; Özyurt et al. 2003; Stevenson et al. 2009; Walton and Gandhi 2006). Performance in the countermanding task can be understood as the outcome of a race between stochastically independent GO and STOP processes; movements are initiated if the GO process finishes before the STOP process and are inhibited if the STOP process finishes first (Logan and Cowan 1984).

When macaque monkeys inhibit a saccade to a target in response to a stop signal, the activity of movement and visuomovement neurons in the frontal eye field (FEF) and superior colliculus (SC) diverges from the activity that approaches a fixed threshold to trigger the saccade (Brown et al. 2008; Hanes et al. 1998; Paré and Hanes 2003). Boucher et al. (2007) developed an interactive race model consisting of mutually inhibitory GO and STOP units to reconcile the independence premise of the race model with the functional inhibitory interactions that occur in motor systems of the brain. According to the interactive race model, saccades are produced when the stochastic activation of the GO unit reaches a threshold. Saccades are inhibited if the STOP unit responds to the stop signal and inhibits the GO unit before it reaches the threshold. The late, potent inhibition embodied by this interactive race model can be replicated by a biophysically plausible network of GO and STOP units comprised of hundreds of leaky integrate-and-fire units (Lo et al. 2009). One of the key sources of validation of these neural network models is that the form and timing of activation of the GO units correspond to what is observed in presaccadic movement neurons in both FEF (Hanes et al. 1998) and SC (Paré and Hanes 2003).

Such simulation studies have prompted a re-examination of the presaccadic movement-related activity in FEF. Previous studies have identified two populations of neurons, movement and visuomovement neurons, that increase activity before the saccade initiation (Bruce and Goldberg 1985; Schall 1991). Both of these populations exhibit differential discharge rates when saccades are cancelled; therefore they have been analyzed together as if they are a homogeneous population of neurons (Brown et al. 2008; Hanes et al. 1998). However, several lines of evidence indicate that they may not be homogeneous biophysically or functionally. For example, a recent study has shown that the spike widths generated by visuomovement neurons are significantly narrower than those produced by movement neurons (Cohen et al. 2009). Also, visuomovement and movement neurons exhibit different patterns of modulation. Here we demonstrate that visuomovement and movement neurons in FEF can be distinguished based on the time course of their activation before saccades are initiated or cancelled. First we show that visuomovement neurons exhibit a moderately elevated discharge rate after the target appears that is maintained until it either increases immediately before a saccade is initiated or subsides when the saccade is cancelled. In contrast, movement neurons exhibit a monotonic, stochastic

Address for reprint requests and other correspondence: S. Ray, Dept. of Psychology, Vanderbilt University, PMB 407817, 2301 Vanderbilt Place, Nashville, TN 37240-7817 (E-mail: supriya.ray@vanderbilt.edu).

accumulation of discharge rate that reaches a fixed threshold immediately before a saccade is initiated or is interrupted at progressively higher levels following the stop signal at progressively longer delays when the saccade is cancelled. Second, we show that while the activity of movement neurons began to increase a relatively fixed interval after target presentation, the beginning of the presaccadic increase in activity of visuomovement neurons varied with the latency of a saccade. These findings indicate that movement and visuomovement neurons in FEF have different functions. The activity of movement neurons can be understood as instantiating the function of the GO units in the race model. But if movement neurons produce saccades, what is there for visuomovement neurons to do? We speculate that the modulation of visuomovement neurons in FEF as well as in other sensory-motor and extrastriate areas is an effect, not a cause, of the saccade production. This effect may represent the corollary discharge hypothesized to update visual processing before, during, and after each saccade.

METHODS

Data collection

Two male macaque monkeys (*Macaca mulatta*) were prepared using conventional surgical methods as described previously (Hanes and Schall 1995; Hanes et al. 1998). All experimental procedures conformed to United States Public Health Service guidelines as interpreted by the Vanderbilt University Institute for Animal Care and Use Committee (IACUC).

Countermanding task

The saccade version of the countermanding task was used for this study (Hanes et al. 1998). To summarize, the monkeys were trained to stare at a central fixation spot, which instigated the trial. Once the trial began, the fixation spot disappeared simultaneously with the presentation of a peripheral target either in the neuron's response field or in the opposite hemifield of the neuron's response field at the same eccentricity. On a fraction of trials, referred to as the stop-signal trials, the fixation spot reappeared after a variable delay instructing the monkeys to withhold their saccades. The delay between the appearance of the target and the stop signal is referred to as the stop-signal delay (SSD). During trials in which the stop signal was not presented, referred to as no-stop-signal trials, the monkeys were rewarded for generating a saccade to the target. During stop-signal trials, however, the monkeys were rewarded for maintaining fixation on the central fixation spot (i.e., cancelled trials). If the monkeys generated a saccade to the target during a stop-signal trial (i.e., noncancelled trials), no reward was given.

Analysis of behavioral data

An inhibition function was obtained by fitting the plot of the ratio of noncancelled trials to the total number of trials against the SSD with a function of the form $W(t) = \gamma - (\gamma - \delta)\cdot\exp[-(t/\alpha)^{\beta}]$ where t ranges from the minimum to the maximum SSD, α is the time at which the inhibition function reaches the sum of 63.2% of its maximum value γ and 36.8% of its minimum value δ, β is the slope. One way to quantify the time the monkey takes to inhibit partially prepared saccades during stop-signal trials is by measuring the *stop-signal reaction time* (SSRT). SSRT was calculated by subtracting the SSD at which the generation of a saccade and the inhibition of the saccade were equally likely, from the mean saccade latency across all trials in which the stop signal did not appear (Logan and Cowan 1984). The procedures for measuring SSRT have been described in detail previously (Hanes and Schall 1995; Logan and Cowan 1984). SSRTs for saccades averaged ~80–100 ms (Hanes et al. 1998).

Cell classification

A memory-guided saccade task was used to distinguish the visually evoked activity from saccade-related activity through established criteria (Bruce and Goldberg 1985) as previously described in detail (Hanes et al. 1998). In the memory-guided saccade task, after the monkey fixated on a central spot for a variable interval (500–800 ms), the target was flashed either in the neuron's response field or in the opposite hemifield for 50–100 ms. The monkey was required to maintain fixation on the central spot for another 500–1,000 ms until the spot disappeared. Reward was contingent on the monkey making a saccade to the remembered location of the target only after the fixation spot was extinguished. The target then reappeared at the same location once the monkey made a saccade. Movement neurons were classified by a pronounced increase of discharge rate before the production of saccade but not to the visual stimulus. Neurons with pronounced visual responses followed by a presaccadic increase of discharge rate were classified as visuomovement neurons. Activity of a representative visuomovement neuron and a movement neuron aligned on the target and saccade onsets during the memory-guided saccade task are shown in Fig. 1, *A* and *B,* respectively.

To quantify the relative magnitude of visual and movement activity in memory-guided saccades, a visual-movement index (VMI) was calculated for each neuron. Visual activity (VA) was defined as the mean firing rate of the neuron during the time window of 50–200 ms after the stimulus onset. Movement activity (MA) was defined as the mean firing rate during the time window 100 ms before to 50 ms after the saccade onset. VMI is calculated as VMI = (MA − VA)/(VA + MA). Neurons with strong visually evoked responses would have a VMI closer to −1.0 and those with strong saccade-related activity would have a VMI closer to 1.0. Visual-movement index across the population of movement neurons [0.65 ± 0.21 (mean ± SD), min = 0.22, max = 0.89] was significantly [t (50) = 4.8, $P < 0.001$] higher than that of visuomovement neurons (0.2 ± 0.3, min = −0.52, max = 0.69).

Analysis of neural activity

Spike density functions were obtained by convolving the spike train with a function resembling a postsynaptic potential $R(t) = [1 - \exp(-t/\tau_g)]\cdot[\exp(-t/\tau_d)]$, where τ_g is the time constant for the growth phase, and τ_d is the time constant for the decay phase. Physiological data from excitatory synapses indicate that 1 and 20 ms are optimum values for τ_g and τ_d, respectively (Sayer et al. 1990).

The average firing rate in cancelled stop-signal trials was compared with that in latency-matched no-stop-signal trials and noncancelled stop-signal trials as a function of time from the target presentation. To perform this time-course analysis, we subtracted the spike density function during cancelled stop-signal trials from the average spike density function during either latency-matched no-stop-signal trials or noncancelled stop-signal trials. The resulting spike density function is referred to as the differential spike density function. The time at which activity in the two conditions, when saccades were produced and when saccades were cancelled, began to diverge was defined as the instant when the differential spike density function exceeded 2 SDs of the difference in activity over the 200-ms interval before the target presentation, provided that this differential spike density function reached 6 SD and remained >2 SD for 50 ms.

The time of modulation of neurons was also determined using a receiver operating characteristic (ROC) analysis (Green and Swets 1966) as described elsewhere (Murthy et al. 2007, 2009). The spike density function from a set of at least five cancelled stop-signal trials was compared with the spike density function from a set of at least five either noncancelled stop-signal trials or latency-matched no-stop-

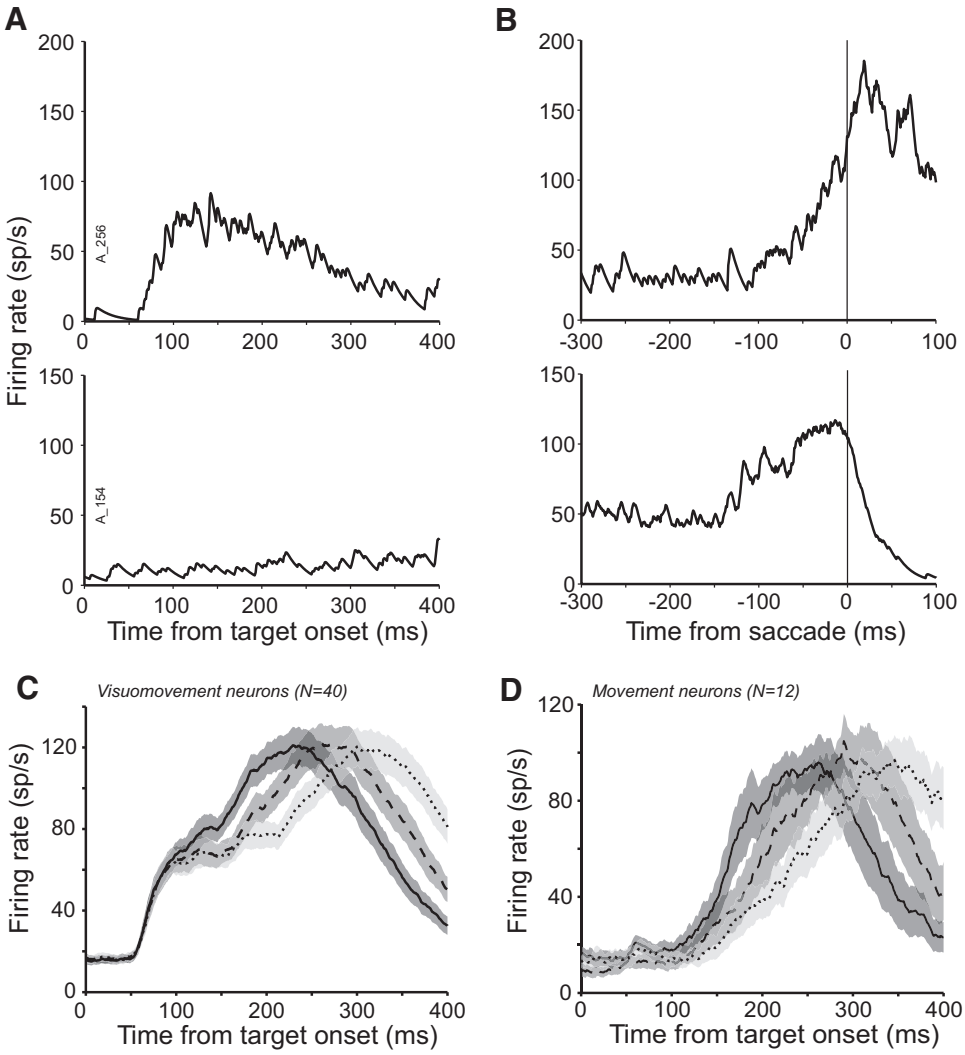

FIG. 1. Activity of a representative visuomovement (*top*) and movement (*bottom*) neuron during a memory-guided saccade task is aligned on target onset (*A*) and on saccade (*B*). Average (± SE) firing rate across the population of visuomovement neurons (*C*) and movement neurons (*D*) during no-stop-signal trials with fast (—), medium (- - -), and slow (· · ·) saccade latencies. As the saccade latency increased, the growth rate of the firing rate of movement neurons decreased while the onset of increased firing rate of visuomovement neurons delayed.

signal trials. Spike trains from the original sets of trials were bootstrapped to construct 500 simulated spike trains in each set for reliable comparison. A simulated spike train was constructed by randomly selecting one trial from the set of original trials at every 1 ms time bin. If a spike occurred in that trial at that instant, the spike was added to the simulated spike train. Comparisons were conducted by calculating ROC curves for successive 1-ms bins starting at the time of target presentation and continuing until all saccades were initiated during one set of trials. The area under the ROC curve provides a quantitative measure of the separation between two distributions of activity. An area under the ROC curve value of 0.5 signifies that the two distributions are completely overlapped, whereas an extreme value of 0.0 or 1.0 signifies that the two distributions do not overlap. To describe the growth in the area under the ROC curve over time, the data were fit with a cumulative Weibull distribution function of the form $W(t) = \gamma - (\gamma - \delta)\cdot\exp[-(t/\alpha)^{\beta}]$, where t is the time that ranges from when the area under the ROC curve attains its minimum to when the area under the ROC curve reaches its maximum. α is the time at which the area under the ROC curve reached the sum of 63.2% of its maximum value γ and 36.8% of its minimum value δ, β is the slope. The time of differential activity was determined from the growth of the ROC area over time and is defined as the time when the ROC area reached a value of 0.7.

RESULTS

For this study, we analyzed the activity of 40 visuomovement and 12 movement neurons recorded from two monkeys. This proportion of neurons in the overall sample corresponded to proportions previously reported (Bruce and Goldberg 1985; Schall 1991). Neurons were classified using a memory-guided saccade task. In the memory-guided saccade task, visuomovement and movement neurons discharged rapidly before the production of saccades, but only visuomovement neurons responded to the appearance of the target. Figure 1 shows the average discharge rate of representative visuomovement and movement neurons during memory-guided saccades. As expected, the discharge rate of visuomovement neurons increased earlier than the discharge rate of movement neurons when the target appeared inside their receptive fields. In correct no-stop-signal trials, the discharge rate of visuomovement neurons increased in two phases, first in response to the appearance of the target and then again immediately before the saccade initiation. This is illustrated by plotting the average firing rate across the population of visuomovement neurons during trials that yielded short, moderate and long saccade latencies (Fig. 1*C*). This pattern of visuomovement activity was different from the pattern of movement activity that increased monotonically before the monkey produced a saccade. Previous studies have established an inverse relationship between the saccade latency and the rate at which the activity of movement neurons rise from baseline to a fixed threshold (Brown et al.

2008; Hanes and Schall 1996). The rate of growth of activity of these neurons decreased gradually as the saccade latency increased; this is illustrated by plotting the average firing rate across the population of movement neurons during trials that yielded short, moderate and long saccade latencies (Fig. 1*D*). In contrast, for visuomovement neurons the increase of presaccadic discharge rate was progressively delayed with longer saccade latencies (Fig. 1*C*).

To test the relationship between neural activity and saccade production, we compared the firing rate of movement and visuomovement neurons when monkeys produced a saccade with the firing rate when monkeys did not produce a saccade in response to the stop signal. Hanes et al. (1998) have shown that when a saccade is withheld in response to the stop signal, the activity of both movement and visuomovement neurons diverge from the activity during a subset of correct no-stop-signal trials in which saccades *would* have been inhibited if the stop signal had appeared. In practice, this subset of correct no-stop-signal trials are trials that produced saccades with latencies longer than the sum of SSD and SSRT. Because SSRT is the time required to cancel the preparation of a saccade following the appearance of the stop signal, the activity of movement neurons that are involved in inhibition of a saccade must modulate at or before SSD + SSRT during stop-signal trials when the monkey cancelled the saccade. When a saccade is inhibited, the modulation of visuomovement neurons should occur in unison with the modulation of the movement neurons if the late augmentation of visuomovement activity is an effect of saccade. On the contrary, the modulation of visuomovement and movement neurons may occur independently if the augmentation of visuomovement activity is the cause of saccade.

We measured the *cancellation time*, which is the time when this divergence began relative to SSD + SSRT, for each neuron at each SSD that provided at least five cancelled stop-signal trials. Negative cancellation time indicates that the divergence began before SSD + SSRT. We followed the same method and conventions used by Hanes et al. (1998) to measure the cancellation time. Figure 2 illustrates the difference in the pattern of activity of movement and visuomovement neurons in stop-signal trials with cancelled saccades relative to latency-matched no-stop-signal trials. These neurons discharged differentially when the monkey withheld saccades in comparison to when the monkey produced saccades. The movement neuron attenuated activity 92 ms after the stop signal appeared and 8 ms before SSD + SSRT. Meanwhile, the visuomovement neuron exhibited differential activity 89 ms after the stop signal appeared and 20 ms before SSD + SSRT. Figure 2*C* shows the cumulative distribution of the cancellation time of all visuomovement and movement neurons measured at each SSD that provided adequate number of trials. Modulation of discharge rate occurred before SSD + SSRT for at least one SSD in 88% of visuomovement neurons and 100% of movement neurons. In all, visuomovement neurons modulated before SSD + SSRT in 60% of SSDs, while movement neurons modulated in 72% of SSDs. The average ± SE cancellation time for all visuomovement neurons (−10 ± 3.1 ms) was not different from that of movement neurons [−15 ± 5.3 ms; $t(190) = 0.7$; Fig. 2*C*]. Hanes et al. (1998) reported an average of −1.1 ± 2.6 (SE) ms across all visuomovement and movement neurons for all SSDs. The difference between SE in their result and our findings is due to our classification of these neurons into two separate smaller groups, and the difference between the mean cancellation time in their result and our findings is due to a more conservative selection of SSDs that provided at least five cancelled stop-signal trials.

The inverse relationship between the growth rate of FEF movement activity and the saccade latency, given the fixed threshold for triggering a saccade, suggests that if the accumulation of activity of these neurons is interrupted sooner, only the fraction of fastest saccades will be initiated. Therefore we should predict that the earlier the differential activity relative to the target onset, the higher the probability of canceling initiation of the saccade. Because visuomovement neurons modulate in unison with movement neurons when saccades are inhibited, the relation between the probability of saccade inhibition and the modulation visuomovement activity is also expected if both types of neurons modulate to accomplish a common objective that is saccade inhibition. In fact, a significant correlation between the probability of saccade inhibition and the time of differential activity was observed for both visuomovement [$r = -0.52$, $F(145) = 52.5$, $P < 0.001$] and movement neurons [$r = -0.56$, $F(45) = 19.6$, $P < 0.001$].

The modulation of discharge rate occurring before SSD + SSRT could arise from the attenuation of the accumulating activity when saccades were cancelled or from the enhancement of activity when saccades were produced. To distinguish between these two possibilities, we measured the peak discharge rate of each neuron in each SSD during stop-signal trials when saccades were inhibited. Assuming that the STOP process takes a constant time, independent of SSD, to interrupt the progressing preparation of saccades, a higher peak discharge rate should be measured with longer SSDs. Alternatively, if neurons did not exhibit an accumulating discharge rate during stop-signal trials with cancelled saccades, the peak discharge rate would not vary with SSD. Figure 3 plots the firing rate of movement and visuomovement neurons during cancelled stop-signal trials. The peak discharge rate of movement but not visuomovement neurons increased monotonically with SSD. We found a significant correlation between the peak firing rate and SSD for movement neurons [$r = 0.54$, $F(42) = 17.1$, $P < 0.001$] but not visuomovement neurons [$r = 0.013$, $F(145) = 2.7$, $P = 0.1$].

While Fig. 3*B* shows the invariance of the peak discharge rate of the representative visuomovement neuron during stop-signal trials with cancelled saccades at different SSDs, Fig. 4*A* shows that the peak discharge rate increased when the monkey produced saccades in stop-signal trials, which suggests that the saccade-related modulation of visuomovement activity happens only when saccades are irrevocable. To measure when visuomovement neurons began to increase discharge rate following the initial visually evoked activity in stop-signal trials, we compared the average discharge rate of visuomovement neurons during stop-signal trials that produced saccades with the average discharge rate when saccades were inhibited. The average discharge rate of the visuomovement neuron increased when saccades were directed to the target despite that the stop signal appeared 167 ms after the appearance of the target (Fig. 4*A*). We included visuomovement neurons that provided at least five stop-signal trials with cancelled saccades and five stop-signal trials that produced saccades at each SSD for a ROC analysis across the population of neurons to measure the

modulation time relative to the target onset, which is the time right from when the visuomovement activity in two conditions appeared to be distinguishable from each other. Altogether 28 visuomovement neurons modulated in 45 SSDs. To measure how early these neurons modulated relative to the saccade onset, we plotted the modulation time against the corresponding mean saccade latency (Fig. 4*B*). In the scatter plot, 80% of the data points fell below the diagonal. On average (±SD), visuomovement neurons modulated 29 ± 50 ms before the saccade onset. We found a significant correlation between the modulation time and the saccade latency [coefficient = 0.6, $F(44) = 25.3$, $P < 0.001$]. A least-square linear fit weighted by the fraction of stop-signal trials that produced saccades intersected the abscissa at 25 ms and remained parallel to the diagonal (slope = 0.998).

To ensure that the conclusion drawn from the preceding analysis was not susceptible to the particularities of the measurement, we used a different criterion to measure the time when the activity during stop-signal trials that produced saccades began to diverge from the activity during stop-signal trials that did not produce saccades. This time was defined as the instant when the differential spike density function exceeded 2 SD of the difference in activity over the 200-ms interval before the target presentation, provided that this differential spike density function reached 6 SD and remained >2 SD for 50 ms. Among the sample of 40 visuomovement neurons, 36 modulated significantly in a total of 88 SSDs. On average (±SD), visuomovement neurons modulated 40 ± 86 ms before the saccade initiation in stop-signal trials. Irrespective of the technique used, the relationship between the modulation time and the saccade latency was still found [coefficient = 0.35, $F(87) = 11.7$, $P = 0.001$].

To test the hypothesis that the onset of presaccadic visuomovement activity is related to the saccade latency regardless of the context in which the saccade is produced, we sorted correct no-stop-signal trials according to their corresponding saccade latency and grouped them into three sets of equal size corresponding to short, medium, and long saccade latencies. We measured the modulation time relative to the target onset, which was the time when the activity during no-stop-signal trials that produced correct saccades began to diverge from the activity during stop-signal trials that did not produce saccades, for each visuomovement neuron using a ROC analysis (see METHODS). Because the number of cancelled stop-signal trials was highest at the shortest SSD and the peak visuomovement activity during cancelled stop-signal trials did not vary with SSD, we used the set of stop-signal trials with cancelled saccades at the shortest SSD that provided at least five trials to measure the baseline of activity for comparison. The representative visuomovement neuron progressively postponed the onset of presaccadic activity as saccade latency increased (Fig. 4*C*). Figure 4*E* plots the linear regression fits of the modulation time as a function of the saccade latency for the population of visuomovement neurons. Among 40 sampled visuomovement neurons, 35 neurons always modulated before the saccade initiation, as evident from the corresponding regression lines fell below the diagonal. The mean (± SD) slope of regression fits was 0.53 ± 0.4, which was significantly >0 [$t(39) = 8.6$,

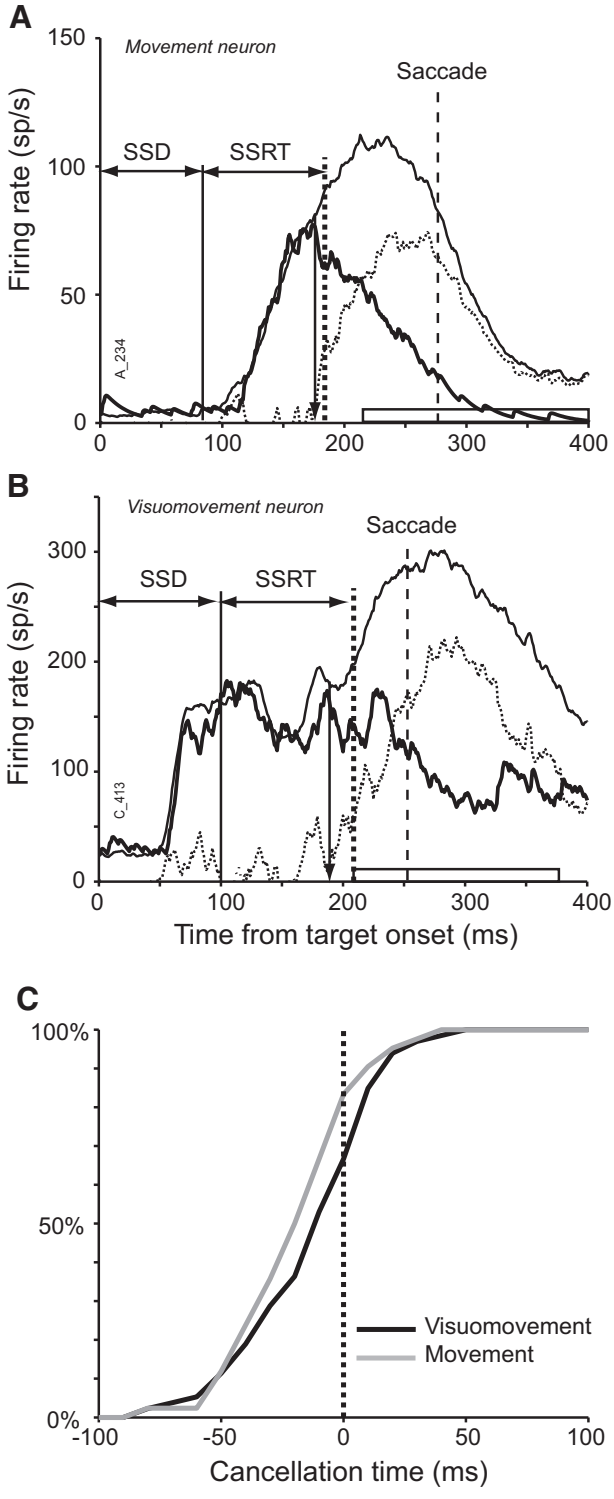

FIG. 2. Comparison of the activity of a movement (*A*) neuron and a visuomovement (*B*) neuron aligned on the target onset during cancelled stop-signal trials (thick) and latency matched correct no-stop-signal trials (thin) in the countermanding task. The spread and the mean of saccade latencies across correct no stop-signal trials are indicated by the rectangle on the abscissa and the dashed vertical line, respectively. The differential activity (thin dotted) began, as indicated by the downward vertical arrow, after the stop-signal delay (SSD) but before the stop-signal reaction time (SSRT) and the mean saccadic reaction time, which suggests their role in inhibition of the saccade. *C*: the cumulative distribution of the *cancellation time*, i.e., the onset of the differential activity relative to (SSD + SSRT) across the population of visuomovement (black) and movement (gray) neurons show these 2 classes of neurons modulated at the same time when the monkeys inhibited saccades.

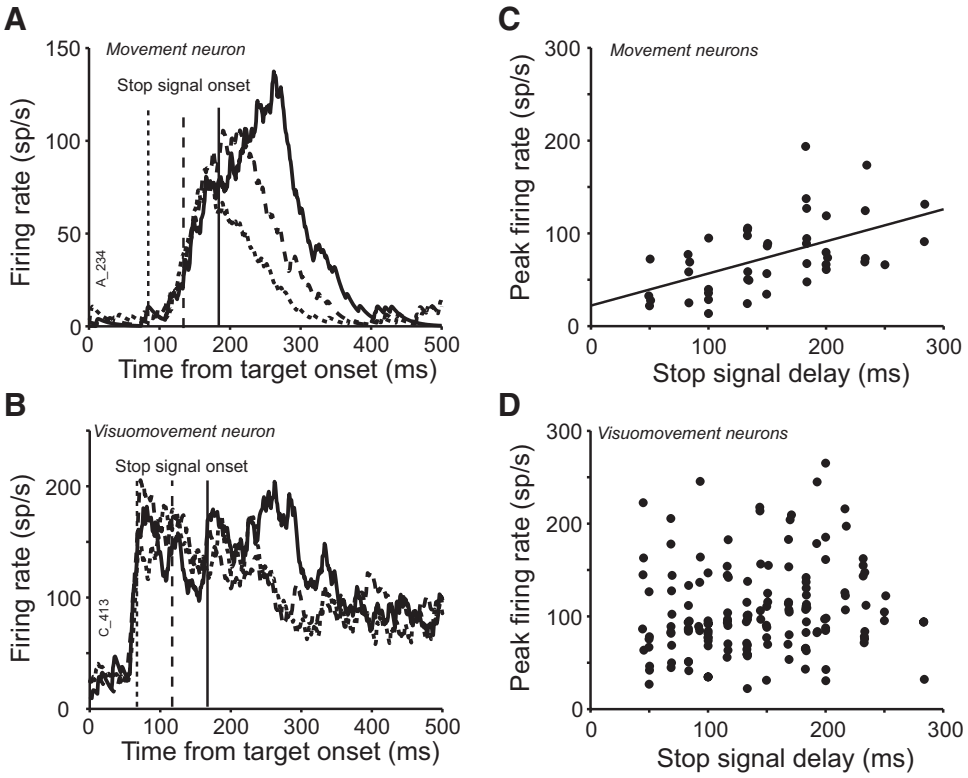

FIG. 3. Relation of the peak firing rate of movement and visuomovement neurons to the SSD. The average firing rate of a movement neuron (*A*) and a visuomovement neuron (*B*) during cancelled stop-signal trials with short (···), moderate (- - -), and long (—) SSDs. Peak firing rates are plotted against SSD for the population of movement (*C*) and visuomovement neurons (*D*). Each data-point corresponds to the peak activity of a sampled (*C*) movement and (*D*) visuomovement neuron at a given SSD. The peak firing rate of movement neurons but not visuomovement neurons varied significantly with SSD.

$P < 0.001$] but significantly <1 [$t(39) = 7.8$, $P < 0.001$]. This analysis has not been conducted for movement neurons because the time when their activity corresponding to correct no-stop-signal trials diverges from the activity corresponding to stop-signal trials with cancelled saccades does not demarcate the onset of saccade preparation; rather this time represents when the STOP process successfully inhibits the saccade. Figure 4*D* shows the activity of the representative visuomovement neuron aligned on saccade initiation during correct no-stop-signal trials with short, medium, and long reaction times. Note that unlike in Fig. 4*C*, the visuomovement activity during correct stop-signal trials has not been plotted here as the reference activity because those trials did not produce saccades. Instead we measured the difference between the modulation time and the mean saccade latency, as described in Fig. 4*C*, to estimate the period when visuomovement neurons were most active. The rates of change of firing rate during this period for three sets of trials that yielded short, medium, and long saccade latencies are calculated for each neuron. In Fig. 4*F,* each line represents the regression fit of the growth rate of visuomovement activity aligned on saccade as a function of the saccade latency for one visuomovement neuron. The average ($\pm$ SD) slope of these lines was 0.18 $\pm$ 15.5 spike$\cdot s^{-2}\cdot ms^{-1}$, which was not different from 0.

DISCUSSION

We distinguished visuomovement and movement neurons in the FEF in relation to the control of saccades during the countermanding task. Both types of neurons exhibited a differential discharge rate before a critical temporal boundary when the monkeys successfully stopped their planned saccades. However, we found a difference between the pattern of activity of visuomovement and movement neurons when saccades were produced. While movement neurons steadily increased activity to a threshold, visuomovement neurons increased their activity in two phases. Visuomovement neurons initially had an increased discharge rate to an intermediate level in response to the appearance of the target followed by a period when the discharge rate did not increase until the saccade-related activity began.

Visuomovement neurons were functionally distinguished from movement neurons based on three critical findings. First, the onset of saccade-related visuomovement activity was proportional to the saccade latency regardless of whether the saccade was a correct or wrong response. Second, in cancelled stop-signal trials, while the peak discharge rate of movement neurons progressively increased when the monkeys inhibited saccades in response to the stop signal that appeared late, the peak discharge rate of visuomovement neurons remained uninfluenced by the stop signal. Third, in stop-signal trials, visuomovement neurons increased activity only when saccades escaped inhibition, but movement neurons attenuated activity when saccades were cancelled. The preceding findings suggest that the movement and visuomovement neurons play different roles when saccades are produced.

Activity of movement-related neurons in relation to the countermanding performance

On the premise of the previous finding that movement-related neurons in FEF accumulated activity steadily to a fixed threshold to trigger a saccade at a rate that varies with the saccade latency (Hanes and Schall 1996), Brown et al. (2008) constructed a neurometric function from the probability of the maximum discharge rate of crossing the criterion (threshold)

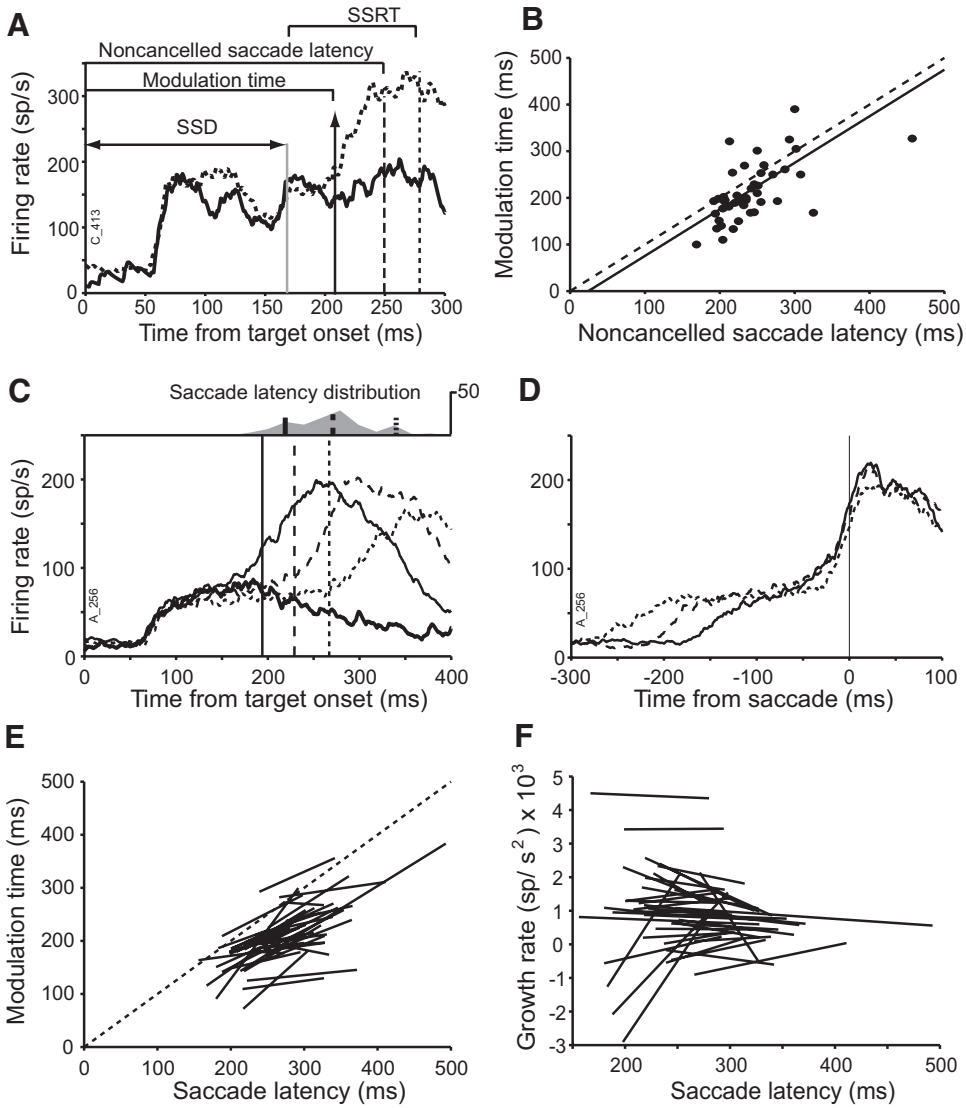

FIG. 4. Relation of visuomovement modulation to saccade latency. *A*: the average firing rate of a visuomovement neuron during noncancelled stop-signal trials (dotted) is compared with the average firing rate of the neuron during cancelled stop-signal trials (solid) at 167-ms SSD. Visuomovement activity during noncancelled stop-signal trials began to diverge, as indicated (up arrow), from the average firing rate during cancelled stop-signal trials 40 ms after the appearance of the stop signal but 69 ms before SSD plus SSRT and 40 ms before the saccade onset. This neuron modulated only during noncancelled stop-signal trials with 56% probability. *B*: the modulation time relative to the target onset increased with the saccade latency. The diagonal dashed line represents the condition when the neural modulation occurred at the same time of the saccade onset. Most of the visuomovement neurons modulated before the saccade onset. On average visuomovement neurons modulated 25 ms before the saccade onset as measured from the intersection of the best fitted line on the abscissa. *C*: the activity of a visuomovement neuron aligned on target presentation during no-stop-signal trials that produced fast (solid), medium (dashed), and slow (dotted) correct saccades are compared with the activity during stop-signal trials with cancelled saccades (thick black) when the stop signal appeared 84 ms after the target onset. The reaction time distribution across all trials is shown above the plot. The modulation times relative to the target onset (thin) and the corresponding mean saccade latencies (thick) for the three sets of trials are shown by solid, dashed, and dotted vertical lines. This neuron modulated 194, 229, and 267 ms after the target onset to produce saccades with mean latencies of 219, 271, and 340 ms, respectively. *D*: the activity of the neuron aligned on the saccade onset during no-stop-signal trials that produced fast (solid), medium (dashed), and slow (dotted) correct saccades. A period of rapid growth of discharge rate was observed immediately before the saccade initiation. *E*: linear regression fits of the modulation time of each visuomovement neuron as a function of mean saccade latency. The regressions had positive slopes demonstrating that the time of presaccadic visuomovement modulation varied with the reaction time. The regressions fell below the diagonal demonstrating that the visuomovement modulation preceded the saccade initiation. *F*: linear regression fits of the growth rate of the firing rate preceding the saccade initiation as a function of mean saccade latency. The average slope of these fits was not different from 0, demonstrating a stereotyped growth of presaccadic activation of visuomovement neurons.

that corresponded best to the probability of canceling a saccade for a given SSD. In the present study, we found that only the movement neurons accumulate activity steadily to the threshold; visuomovement neurons discontinued the steady increase of discharge rate for a period of time before the saccade onset, which was proportional to the saccade latency. This result allows us to speculate that in the previous study some neurons that mapped the neurometric function to the inhibition function might have had stronger saccade-related response than visually evoked response.

Possible functions of visuomovement modulation

The late enhancement or presaccadic elevation of discharge rate of visually responsive neurons has been observed in a number of extrastriate areas and sensorimotor structures in-

cluding area V4 (Fischer and Boch 1981, 1985; Moore 1999; Moore et al. 1998), lateral intraparietal area (LIP) (Churchland et al. 2008; Roitman and Shadlen 2002), area 46 in dorsolateral prefrontal cortex (Boch and Goldberg 1989), and pulvinar (Robinson et al. 1986). Given the reciprocal connectivity between FEF, area V4, LIP and area 46 (Huerta et al. 1987; Pouget et al. 2009; Schall et al. 1995; Stanton et al. 1995), it seems possible that this late modulation is a common signal that is distributed across these areas. Accordingly, we reason that if this late presaccadic activity in FEF neurons is not responsible for the saccade production, then the same is plausible for the other areas that are anatomically more remote from the saccade generators in the brain stem. In other words, this late enhancement is an effect, not a cause, of saccades. What are the functions that must be accomplished to produce a visually guided saccade?

Two major related functions have been suggested. The first is related to the attenuation of visual processing and the reconstruction of the visual space perturbed by each saccade. The second is related to the allocation of attention at the endpoint of a saccade. With every saccade, the projection of the visual world sweeps across the retina in the opposite direction of the saccade. Consequently, visual perception is attenuated around the time of saccadic eye movement (e.g., Burr and Morrone 1996; Burr et al. 1994; Ross et al. 2001; Volkmann 1986) coupled with systematic patterns of mislocalization (Awater et al. 2005; Boucher et al. 2001; Dassonville et al. 1992; Honda 1989; Jeffries et al. 2007; Kaiser and Lappe 2004; Schlag and Schlag-Rey 1995). Neural correlates of the attenuation of visual perception during saccades have been described in early visual structures (Royal et al. 2006). A presaccadic shifting of receptive fields (RFs) in the SC (Walker et al. 1994), LIP (Colby et al. 1996; Duhamel et al. 1992), and FEF (Sommer and Wurtz 2006; Umeno and Goldberg 1997) has been considered as the neural basis for the mislocalization and reconstruction of visual space. Further evidence in support of the hypothesis that the presaccadic elevation of the discharge rate of visuomovement neurons is an effect of an imminent saccade was found in the observation that the majority of FEF neurons receiving signals through the thalamus from the SC were visuomovement (62%) with some visual (32%) and no movement neurons (Sommer and Wurtz 2004).

Sommer and Wurtz (2008) argued that " . . . if the shifting RF is concerned with maintaining perceptual visual stability, it would be important for it to occur only if the generation of the saccade were inevitable . . . therefore is to delay their onset to begin only after the 'point of no return' for moving." The stop-signal task provides a means of identifying neural signals with controlled and ballistic programming (Bartlett 1958; De Jong et al. 1990; Logan and Cowan 1984; McGarry and Franks 1997; Osman et al. 1986). Because no control can influence the preparation of a movement after the point of no return is crossed, if the transition from the controlled to the ballistic programming stage is registered by a neural signal, it should occur only when the movement is inevitable. We have demonstrated that FEF visuomovement neurons exhibit an elevation of discharge rate above the visually evoked activity only when saccades are inevitable. Hence we speculate that the late enhancement of visuomovement activity begins at a time coinciding with the transition from controlled to ballistic programming to contribute to the attenuation of visual processing as well as to update the visual representation associated with visually guided saccades.

The relationship between covert orientation of attention and overt orientation of gaze is well known (Deubel and Schneider 1996; Doré-Mazars et al. 2004; Henderson 1991; Hoffman and Subramaniam 1995; Hunt and Kingstone 2003; Kowler et al. 1995; Peterson et al. 2004; Rizzolatti 1983; Sheliga et al. 1994; Shepherd et al. 1986). The oculomotor readiness, also known as the premotor theory of attention, explains this relationship by positing that orienting attention is accomplished by the same mechanism that shifts gaze. Accordingly, the presaccadic enhancement of activity in V4 (Fischer and Boch 1981, 1985; Moore 1999; Moore et al. 1998) has been identified with the allocation of attention to enhance visual processing at the endpoint of the saccade (McAdams and Maunsell 1999; Tolias et al. 2001; reviewed by Reynolds and Chelazzi 2004). In fact, intracortical microstimulation of FEF with current below the threshold necessary to evoke saccades improves visual discrimination possibly through enhanced visual activity in area V4 (Moore and Armstrong 2003; Moore and Chang 2009). Neuroanatomical studies demonstrate that this influence of FEF activity on extrastriate visual cortex arises predominantly from neurons in supragranular layers and not from the layer 5 neurons that project to the superior colliculus (e.g., Pouget et al. 2009). Therefore we propose that these data are consistent with the hypothesis that the signal that extrastriate cortex receives from FEF is not specifically the saccade preparation, rather, is the target selection and late enhancement of visuomovement activity.

ACKNOWLEDGMENTS

Present address of P. Pouget, Laboratoire de Thérapeutique Expérimentale, Université Pierre et Marie Curie, Paris, France.

GRANTS

This work was supported by National Institutes of Health Grants R01-MH-55806, P30-EY-08126, and P30-HD-015052 and Robin and Richard Patton through the E. Bronson Ingram Chair in Neuroscience.

REFERENCES

Armstrong IT, Munoz DP. Inhibitory control of eye movements during oculomotor countermanding in adults with attention-deficit hyperactivity disorder. *Exp Brain Res* 152: 444–452, 2003.

Awater H, Burr D, Lappe M, Morrone MC, Goldberg ME. Effect of saccadic adaptation on localization of visual targets. *J Neurophysiol* 93: 3605–3614, 2005.

Bartlett FC. *Thinking: An Experimental and Social Study.* New York: Basic Books, 1958.

Boch RA, Goldberg ME. Participation of prefrontal neurons in the preparation of visually guided eye movements in the rhesus monkey. *J Neurophysiol* 61: 1064–1084, 1989.

Boucher L, Groh JM, Hughes HC. Afferent delays and the mislocalization of perisaccadic stimuli. *Vision Res* 41: 2631–2644, 2001.

Boucher L, Palmeri TJ, Logan GD, Schall JD. Inhibitory control in mind and brain: an interactive race model of countermanding saccades. *Psychol Rev* 114: 376–397, 2007.

Brown JW, Hanes DP, Schall JD, Stuphorn V. Relation of frontal eye field activity to saccade initiation during a countermanding task. *Exp Brain Res* 190: 135–151, 2008.

Bruce CJ, Goldberg ME. Primate frontal eye fields. I. Single neurons discharging before saccades. *J Neurophysiol* 53: 603–635, 1985.

Burr DC, Morrone C. Temporal impulse response functions for luminance and color during saccades. *Vision Res* 36: 2069–2078, 1996.

Burr DC, Morrone MC, Ross J. Selective suppression of the magnocellular visual pathway during saccadic eye movements. *Nature* 371: 511–513, 1994.

Cabel DW, Armstrong IT, Reingold E, Munoz DP. Control of saccade initiation in a countermanding task using visual and auditory stop signals. *Exp Brain Res* 133: 431–441, 2000.

Churchland AK, Kiani R, Shadlen MN. Decision-making with multiple alternatives. *Nat Neurosci* 11: 693–702, 2008.

Cohen JY, Pouget P, Heitz RP, Woodman GF, Schall JD. Biophysical support for functionally distinct cell types in the frontal eye field. *J Neurophysiol* 101: 912–916, 2009.

Colby CL, Duhamel JR, Goldberg ME. Visual, presaccadic, and cognitive activation of single neurons in monkey lateral intraparietal area. *J Neurophysiol* 76: 2841–2852, 1996.

Colonius H, Özyurt J, Arndt PA. Countermanding saccades with auditory stop signals: testing the race model. *Vision Res* 41: 1951–1968, 2001.

Dassonville P, Schlag J, Schlag-Rey M. Oculomotor localization relies on a damped representation of saccadic eye movement displacement in human and nonhuman primates. *Vis Neurosci* 9: 261–269, 1992.

Deubel H, Schneider WX. Saccade target selection and object recognition: Evidence for a common attentional mechanism. *Vision Res* 36: 1827–1837, 1996.

De Jong R, Coles MG, Logan GD, Gratton G. In search of the point of no return: the control of response processes. *J Exp Psychol Hum Percept Perform* 16: 164–182, 1990.

Doré-Mazars K, Pouget P, Beauvillain C. Attentional selection during preparation of eye movements. *Psychol Res* 69: 67–76, 2004.

Duhamel JR, Colby CL, Goldberg ME. The updating of the representation of visual space in parietal cortex by intended eye movements. *Science* 255: 90–92, 1992.

Fischer B, Boch R. Enhanced activation of neurons in prelunate cortex before visually guided saccades of trained rhesus monkeys. *Exp Brain Res* 44: 129–137, 1981.

Fischer B, Boch R. Peripheral attention versus central fixation: modulation of the visual activity of prelunate cortical cells of the rhesus monkey. *Brain Res* 345: 111–123, 1985.

Green DM, Swets JA. *Signal Detection Theory and Psychophysics.* New York: WiIey, 1966.

Hanes DP, Carpenter RHS. Countermanding saccades in humans. *Vision Res* 39: 2777–2791, 1999.

Hanes DP, Patterson WF, Schall JD. Role of frontal eye fields in countermanding saccades: visual, movement, and fixation activity. *J Neurophysiol* 79: 817–834, 1998.

Hanes DP, Schall JD. Countermanding saccades in macaque. *Vis Neurosci* 12: 929–937, 1995.

Hanes DP, Schall JD. Neural control of voluntary movement initiation. *Science* 274: 427–430, 1996.

Henderson JM. Stimulus discrimination following covert attentional orienting to an exogenous cue. *J Exp Psychol* 17: 91–106, 1991.

Hoffman JE, Subramaniam B. The role of visual attention in saccadic eye movements. *Percept Psychophys* 57: 787–795, 1995.

Honda H. Perceptual localization of visual stimuli flashed during saccades. *Percept Psychophys* 45: 162–174, 1989.

Huerta MF, Krubitzer LA, Kaas JH. 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, 1987.

Hunt AR, Kingstone A. Covert and overt voluntary attention: linked or independent? *Cogn Brain Res* 18: 102–105, 2003.

Jeffries SM, Kusunoki M, Bisley JW, Cohen IS, Goldberg ME. Rhesus monkeys mislocalize saccade targets flashed for 100 ms around the time of a saccade. *Vision Res* 47: 1924–1934, 2007.

Kaiser M, Lappe M. Perisaccadic mislocalization orthogonal to saccade direction. *Neuron* 41: 293–300, 2004.

Kowler E, Anderson E, Dosher B, Blaser E. The role of attention in the programming of saccades. *Vision Res* 35: 1897–1916, 1995.

Lo C-C, Boucher L, Paré M, Schall JD, Wang X-J. Proactive inhibitory control and attractor dynamics in countermanding action: a spiking neural circuit model. *J Neurosci* 29: 9059–9071, 2009.

Logan GD, Cowan WB. On the ability to inhibit thought and action: a theory of an act of control. *Psychol Rev* 91: 295–327, 1984.

Logan GD, Irwin DE. Don't look! Don't touch! Inhibitory control of eye and hand movements. *Psychonom Bull Rev* 7: 107–112, 2000.

McAdams CJ, Maunsell JHR. Effects of attention on orientation-tuning functions of single neurons in macaque cortical area V4. *J Neurosci* 19: 431–441, 1999.

McGarry T, Franks IM. A horse race between independent processes: evidence for a phantom point of no return in preparation of a speeded motor response. *J Exp Psychol Hum Percept Perform* 23: 1533–1542, 1997.

Moore T. Shape representations and visual guidance of saccadic eye movements. *Science* 285: 1914–1917, 1999.

Moore T, Armstrong KM. Selective gating of visual signals by microstimulation of frontal cortex. *Nature* 421: 370–373, 2003.

Moore T, Chang MH. Presaccadic discrimination of receptive field stimuli by area V4 neurons. *Vision Res* 49: 1227–1232, 2009.

Moore T, Tolias AS, Schiller PH. Visual representations during saccadic eye movements. *Proc Natl Acad Sci USA* 95: 8981–8984, 1998.

Morein-Zamir S, Kingstone A. Fixation offset and stop signal intensity effects on saccadic countermanding: a crossmodal investigation. *Exp Brain Res* 175: 453–462, 2006.

Murthy A, Ray S, Shorter SM, Priddy EG, Schall JD, Thompson KG. Frontal eye field contributions to rapid corrective saccades. *J Neurophysiol* 97: 1457–1469, 2007.

Murthy A, Ray S, Shorter SM, Schall JD, Thompson KG. Neural control of visual search by frontal eye field: effects of unexpected target displacement on visual selection and saccade preparation. *J Neurophysiol* 101: 2485–2506, 2009.

Osman A, Kornblum S, Meyer DE. The point of no return in choice reaction time: controlled and ballistic stages of response preparation. *J Exp Psychol Hum Percept Perform* 12: 243–258, 1986.

Özyurt J, Colonius H, Arndt PA. Countermanding saccades: evidence against independent processing of go and stop signals. *Percept Psychophys* 65: 420–428, 2003.

Paré M, Hanes DP. Controlled movement processing: superior colliculus activity associated with countermanded saccades. *J Neurosci* 23: 6480–6489, 2003.

Peterson MS, Kramer AF, Irwin DE. Covert shifts of attention precede involuntary eye movements. *Percept Psychophys* 66: 398–405, 2004.

Pouget P, Stepniewska I, Crowder EA, Leslie MW, Emeric EE, Nelson MJ, Schall JD. Visual and motor connectivity and the distribution of calcium-binding proteins in macaque frontal eye field: Implsications for saccade target selection. *Front Neuroanat* 3:2, 1–14. doi:10.3389/neuro.05.002.2009.

Reynolds JH, Chelazzi L. Attentional modulation of visual processing. *Annu Rev Neurosci* 27: 611–647, 2004.

Rizzolatti G. Mechanisms of selective attention in mammals. In: *Advances in Vertebrate Neuroethology*, edited by Ewert JP, Capranica RR, Ingle DJ. London: Plenum, 1983, p. 261–297.

Robinson DL, Petersen SE, Keys W. Saccade-related and visual activities in the pulvinar nuclei of the behaving rhesus monkey. *Exp Brain Res* 62: 625–634, 1986.

Roitman JD, Shadlen MN. Response of neurons in the lateral intraparietal area during a combined visual discrimination reaction time task. *J Neurosci* 22: 9475–9489, 2002.

Ross J, Morrone MC, Goldberg ME, Burr DC. Changes in visual perception at the time of saccades. *Trends Neurosci* 24: 113–121, 2001.

Royal DW, Sáry G, Schall JD, Casagrande VA. Correlates of motor planning and postsaccadic fixation in the macaque monkey lateral geniculate nucleus. *Exp Brain Res* 168: 62–75, 2006.

Sayer RJ, Friedlander MJ, Redman SJ. The time course and amplitude of EPSPs evoked at synapses between pairs of CA3/CA1 neurons in the hippocampal slice. *J Neurosci* 10: 826–836, 1990.

Schall JD. Neuronal activity related to visually guided saccades in the frontal eye fields of rhesus monkeys: comparison with supplementary eye fields. *J Neurophysiol* 66: 559–579, 1991.

Schall JD. Neural basis of saccade target selection. *Reviews in the Neurosciences* 6: 63–85, 1995.

Schall JD, Morel A, King DJ, Bullier J. Topography of visual cortex connections with frontal eye field in macaque: convergence and segregation of processing streams. *J Neurosci* 15: 4464–4487, 1995.

Schlag J, Schlag-Rey M. Illusory localization of stimuli flashed in the dark before saccades. *Vision Res* 35: 2347–2357, 1995.

Sheliga BM, Riggio L, Rizzolatti G. Orienting of attention and eye movements. *Exp Brain Res* 98: 507–522, 1994.

Shepherd M, Findlay JM, Hockey RJ. The relationship between eye movements and spatial attention. *Q J Exp Psychol A* 38: 475–491, 1986.

Sommer MA, Wurtz RH. What the brain stem tells the frontal cortex. I. Oculomotor signals sent from superior colliculus to frontal eye field via mediodorsal thalamus. *J Neurophysiol* 91: 1381–1402, 2004.

Sommer MA, Wurtz RH. Influence of the thalamus on spatial visual processing in frontal cortex. *Nature* 444: 374–377, 2006.

Sommer MA, Wurtz RH. Brain circuits for the internal monitoring of movements. *Annu Rev Neurosci* 31: 317–338, 2008.

Stanton GB, Bruce CJ, Goldberg ME. Topography of projections to posterior cortical areas from the macaque frontal eye fields. *J Comp Neurol* 353: 291–305, 1995.

Stevenson SA, Elsley JK, Corneil BD. A" gap effect" on stop signal reaction times in a human saccadic countermanding task. *J Neurophysiol* 101: 580–590, 2009.

Tolias AS, Moore T, Smirnakis SM, Tehovnik EJ, Siapas AG, Schiller PH. Eye movements modulate visual receptive fields of V4 neurons. *Neuron* 29: 757–767, 2001.

Umeno MM, Goldberg ME. Spatial processing in the monkey frontal eye field. I. Predictive visual responses. *J Neurophysiol* 78: 1373–1383, 1997.

Volkmann F. Human visual suppression. *Vision Res* 26: 1401–1416, 1986.

Walker MF, FitzGibbon EJ, Goldberg ME. Predictive visual responses in monkey superior colliculus. In: *Contemporary Oculomotor and Vestibular Research: A Tribute to David A Robinson*, edited by Fuchs AF, Brandt T, Buttner U, Zee D. Stuttgart: Thieme, 1994, p. 512–519.

Walton MMG, Gandhi NJ. Behavioral evaluation of movement cancellation. *J Neurophysiol* 96: 2011–2024, 2006.