INVITED REVIEW

ABSTRACT: The prerequisite for behavioral self-control is the ability to initiate actions and to cancel planned actions. A rational choice about which action to initiate or to withhold must be informed by the consequences of prior actions. The neuronal correlates of these processes have been studied with the countermanding paradigm. This task requires subjects to withhold planned movements in response to an imperative stop signal, which they can do with varying success. By recording the activity of single neurons in different parts of the frontal cortex of macaque monkeys performing this task, signals that are sufficient for controlling the initiation and inhibition of movements and other signals that evaluate the consequences of these movements have been identified.

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NEURONAL CONTROL AND MONITORING OF INITIATION OF MOVEMENTS

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In our everyday life, we take for granted the control of our actions. Within the limits of the laws of physics, we seem to be masters of what we do. But what specifically is meant by "controlling an action"? Voluntary control over behavior starts with the ability to decide between alternatives. Even for a single act, voluntary control always entails at least a choice between acting and not acting. In other words, the salient feature of a behavioral act over which one has control is that one can decide not to do it or to do something else instead. For example, at each moment, one is able to express an opinion in a number of ways or alternatively one might decide to be silent. In this sense, speech is under voluntary control. On the other hand, one might find that "one couldn't help but laugh." There was an involuntary behavior beyond the individual's control. Therefore, control seems to be essentially the ability to decide to initiate or to inhibit movements or thoughts.

The most general aspects of the voluntary control of behavior are independent of the particular effector of the motor system. Strategically, it is most effective to begin to elucidate this brain function in a system with a basic organization that is reasonably well understood. The oculomotor system is an ideal model system for this purpose.

A number of lines of behavioral evidence indicate that the high-level control of gaze operates according to similar principles as the high-level control of limb movements or speech. For example, when asked to generate a sequence of saccades, the latency of the first saccade increases with the number of movements in the sequence,[123] following the same pattern observed for speech and typing.[115] Also, a signal warning that a trigger signal will occur after a predictable interval reduces saccade latency[31,45] in the same way as manual response times are reduced.[75] However, if the intervals between the warning and the trigger signal are unpredictable, then the reduction of latency does not occur for either saccades [45] or manual movements.[72,74] Saccade latency is influenced profoundly by a particular warning signal, that of removing the fixation spot; this has been referred to as the "gap" paradigm, because there is an interval during which no visual stimulus is visible. The subject is required to maintain central fixation during the gap period. When a target is presented shortly (~200 ms) after the fixation spot is removed, saccade latencies can be reduced so much that they have been referred to as "express saccades."[32] The disappearance of the fixation point

Abbreviations: FEF, frontal eye field; LIP, lateral intraparietal area; MST, medial superior temporal area; MT, medial temporal area; SC, superior colliculus; SEF, supplementary eye field; SRBN, saccade-related burst neuron; TEO, occipital part of temporal area TE

Key words: control of movement; countermand; movement initiation; reaction time; saccade

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seems to have two consequences. On the one hand, it releases the fixation system, and on the other hand, it allows the subject to prepare for the impending target appearance.[70] A similar effect has been demonstrated for arm movements.[5] Thus, the high-level programming and behavioral control of eye movements seem indistinguishable from that of manual movements or even speech.

The study of the production of eye movements provides a number of advantages over comparable types of movements, such as limb movements or speech. The kinetic description of an eye movement is given by a system of only three parameters. This compares favorably with the movements of multijointed limbs, with their many degrees of freedom. Likewise, the eye position is controlled by a set of three pairs of antagonistic muscles. As a result of this relative simplicity, much progress has been made in describing the underlying neural systems responsible for gaze control.[12,121] The same is true to a lesser degree for neural correlates of visual perception[80] and attention[19,65,92]

AN OVERVIEW OF THE OCULOMOTOR SYSTEM

Figure 1 is a schematic diagram of some key structures and connections in the brain circuits responsible for the production of visually guided saccades. Visual processing in the cortex begins in primary visual cortex (V1) from which issue two processing streams.[36,119] One stream that is responsible in general for form and object recognition proceeds into the inferior temporal lobe through areas V2, V4, and the occipital part of temporal area TE (TEO). The second stream that is responsible for guiding action in space proceeds into the posterior parietal cortex through the medial temporal area (MT) among other areas. Neurons in posterior parietal cortex represent the location and motion of stimuli needed to guide accurate movements. The scheme in Figure 1

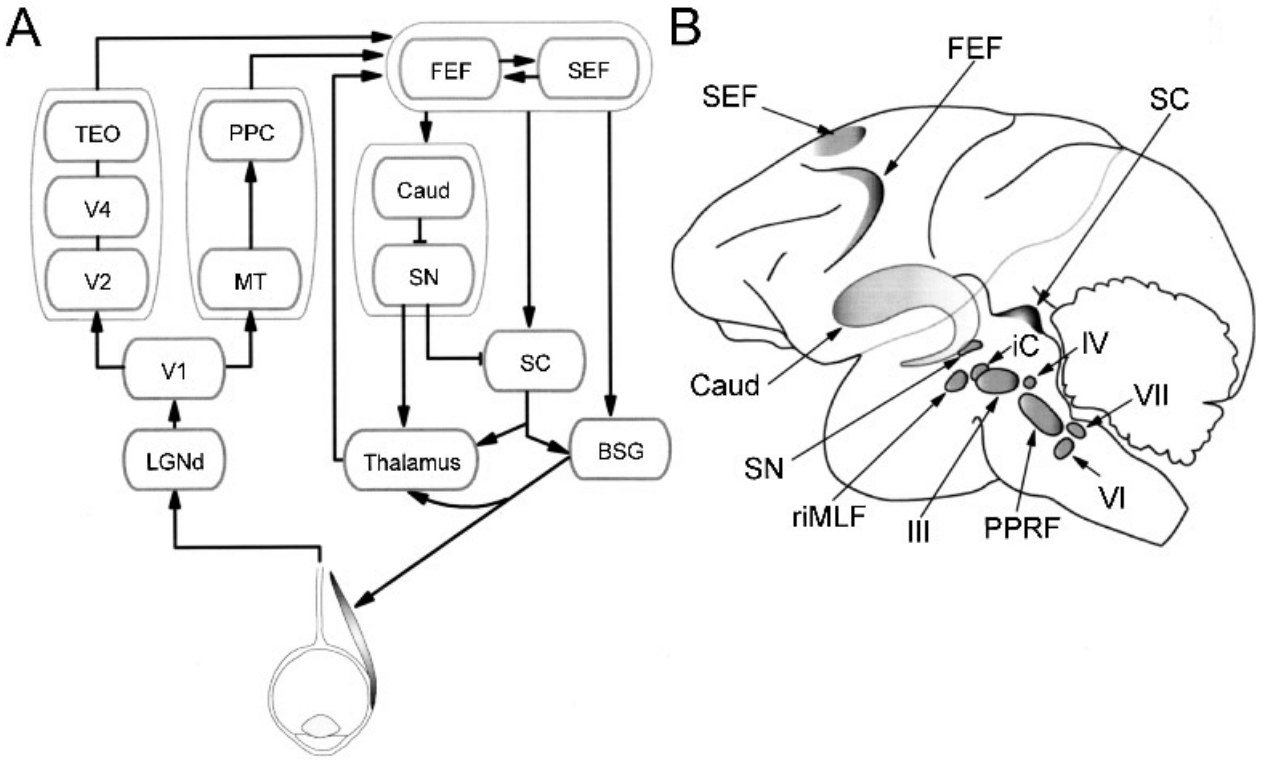

FIGURE 1. The visuo-oculomotor system of the primate brain. **(A)** Overview of some of the major stations of visual and oculomotor system in the primate brain. Incoming visual information is processed by a hierarchy of neuronal areas, as depicted by the ascending stream on the left side of the diagram. The neuronal system, which controls saccadic movements of the eye, is represented by the descending stream on the left side. (Note that this diagram is not intended to be complete.) **(B):** Macaque brain showing the localization of the major oculomotor structures. The occipital, parietal and temporal lobes are removed to allow view of the subcortical structures. (Abbreviations: TEO, occipital part of temporal area TE; V2 and V4, extrastriate visual areas 2 and 4; V1, primary visual cortex; LGNd, dorsal lateral geniculate nucleus; MT, medial temporal area; PPC, posterior parietal cortex; FEF, frontal eye field; SEF, supplementary eye field; Caud, caudatum, a part of the striatum in primates; SN, substantia nigra; SC, superior colliculus; BSG, brainstem saccade generator; riMLF, rostral interstitial nucleus of the median longitudinal fasciculus (MLF); III, oculomotor nucleus; PPRF, paramedian pontine reticular formation; VI, abducens nucleus; VII, facial nucleus; IV, trochlear nucleus; iC, interstitial nucleus of Cajal.)

is, of course, not meant to indicate a strictly serial and hierarchical form of information processing. There are reciprocal connections between areas of different hierarchical status and also across the two processing streams. The visual neurons in both streams project (in different degrees) to two frontal oculomotor areas: the frontal eye field (FEF) and the supplementary eye field (SEF).[54,55,90]

The FEF is located in prefrontal cortex (Fig. 1B). The ventrolateral FEF generates shorter saccades, whereas the dorsomedial FEF generates progressively longer saccades. The part of the FEF that generates longer saccades receives inputs from parts of TEO, MT, and associated areas that represent peripheral vision and from posterior parietal cortex, including the lateral intraparietal area (LIP). The part of FEF that generates shorter saccades receives inputs from areas in the caudal temporal lobe and parts of MT that represent central vision, and from posterior parietal cortex. Thus, ventral FEF is one site of convergence of the two visual processing streams.[90]

The SEF is an area in the dorsomedial frontal cortex (Fig. 1B). It is innervated by fewer visual cortical areas than is FEF. In contrast to the extensive array of prestriate visual areas connected with FEF, SEF receives afferents only from the medial superior temporal area (MST), the superior temporal polysensory area, and LIP.[54] The prestriate visual areas projecting to SEF also project mainly to the dorsomedial but not the ventrolateral FEF[90]; conversely, the visual areas associated with the ventral visual processing stream do not project to SEF.[54] The SEF is reciprocally connected with anterior and posterior cingulate cortex, postarcuate premotor areas, the supplementary motor area, and prefrontal cortex in areas 12 and 46.[54]

Another source of signals into FEF and SEF are thalamic afferents. The FEF and SEF receive dense input from the segments of the ventroanterior and mediodorsal thalamic nuclei adjacent to the internal medullary lamina. These thalamic nuclei are themselves mainly innervated by afferents from the superior colliculus (SC) and the substantia nigra as well as certain cerebellar nuclei.[63]

There are three possible routes for cortical eye fields to influence the saccade generator network in the brainstem. First, there is a direct route from both FEF and SEF to the brainstem.[54,58,103] Second, the frontal and SEF are among a number of cortical areas that innervate the SC. The SC is a structure in the midbrain that, like the FEF, plays a direct role in producing saccadic eye movement.[68–70,111] The connection between FEF and SC seems to be especially essential for saccade production in normal primates. Activity in the FEF modulates the discharge of neurons in the SC.[98] The ability to electrically evoke saccades from the FEF is abolished after acute SC inactivation[46] but can recover after some time following a lesion of SC.[94] Lesion of both FEF and SC results in a complete loss of the ability to generate saccades. Third, an oculomotor circuit also passes through the basal ganglia, through which FEF and SEF may regulate the activity of neurons in the SC. Movement cells in the SC receive tonic inhibition from the substantia nigra pars reticulata.[52,53] Neurons in the substantia nigra pars reticulata are themselves largely inhibited by an oculomotor region of the caudate nucleus.[48–51] This oculomotor region of the caudate nucleus is innervated by both FEF and SEF.[81,104,114]

Thus, the oculomotor system throughout the brain is connected through three loops each starting in saccade-related areas in the frontal cortex (Fig.1A). One loop processes through the brainstem, the thalamus, and back to the cortex. The second loop processes through the caudate nucleus, the substantia nigra pars reticulata, to the thalamus, and back to the cortex. The third loop processes through the SC, the thalamus, and back to the cortex. In addition, there are cross-connections between these loops. The second loop through the substantia nigra modulates the third loop at the level of the SC, and the third loop through the SC is strongly connected to the first loop at the level of the brainstem.

Prior to saccade initiation, the entire oculomotor network is active in concert. The rising activity in cortical movement cells activates neurons in the caudate nucleus. Their activation inhibits tonically active neurons in the substantia nigra pars reticulata, which normally damp down activity in the SC. This release on the excitability of the SC coincides with the input through the corticotectal projection and enables the rise of movement-related activity in the SC in concert with the cortex. The SC activity combines in the brainstem with other direct inputs from the cortex and activates the saccade generator. In addition, the signals from the substantia nigra, SC, and the saccade generator project to the mediodorsal thalamus. From there they get relayed back to the cortex. Through this closed loop the different parts of the oculomotor network are able to communicate and to coordinate their respective states. It has recently been shown that the FEF sends not only movement-related signals to the SC[102] but also phasic visual signals[107] and diverse tonic signals during a delay period that are of preparatory, memory, or visual nature.[109] The flow of

these signals enables the FEF to influence the activity in the SC through each step of saccade preparation from target selection to saccade initiation. Conversely, the SC sends predominantly visual and premotor signals to the FEF via relay neurons in the thalamus.[106,122]. The estimated conduction latency between SC and FEF is very fast (2.1–2.3 ms). The FEF neurons receiving this thalamic projection show visual and premotor activity similar to the input signals.[108]

In general, the process of movement preparation can be divided into an earlier controlled and a later ballistic phase. The ballistic phase is inextricably linked to overt movement. In other words, once this step has begun, it must proceed to completion with production of an overt movement. The controlled phase, preceding the ballistic phase, can be interrupted without producing the movement. The cusp of a "point of no return" divides the two stages. The question of movement initiation then becomes the question: When is the point of no return reached, making voluntary control through inhibition impossible? More specifically, in the context of eye movement control, we can ask: Is there such a point of no return in the neuronal processes preceding a saccadic eye movement? A preliminary answer is provided by our current knowledge about the neuronal system in the brainstem that generates saccades.[47]

This saccade generation network requires two inputs: one signaling the desired direction and amplitude of the movement ("where"), and the other triggering the initiation of the movement ("when"). This brainstem circuit, once activated, generates a complete saccade and cannot be stopped by any naturally occurring event. Therefore, triggering this circuit represents a point of no return for saccade production. Whereas both signals are necessary to produce a saccade, the "where" signal alone is not sufficient. A study of eye movements evoked by electrical microstimulation of the paramedian pontine reticular formation shows that the "where" signal develops gradually in the brainstem. Only after the formation of this signal does the trigger signal occur that releases the saccade.[112] At least in principle, it is possible that the location of a desired eye movement may be selected for some tens or even hundreds of milliseconds but that no saccade to that location is produced until a trigger signal occurs. Because the activity of omnipause neurons arrests the eye, most agree that the trigger signal is probably an inhibitory influence on these neurons.

THE SOURCE OF TRIGGER INPUTS INTO THE SACCADE GENERATOR

One main source of signals into the brainstem saccade generator is the SC.[70,111] Saccade-related burst neurons (SRBN) in the intermediate layers of the SC have axons innervating pontine premotor neurons. They generate a high-frequency burst of activity synchronous with saccade initiation.[22,100,110] Antidromic stimulation of the omnipause region activates the vast majority of SRBNs.[56] The intermediate layers of the SC receive descending inputs from many cortical areas, originating most particularly for the present discussion from the FEF and the SEF in the frontal lobe.

The FEF also projects directly to the brainstem and is an additional source of the signals required by the saccade generator.[55] Recent work has demonstrated that reversible inactivation of FEF or SC impairs monkeys' ability to make saccades.[21,46,105] Ablation of either structure impairs saccades and fixations for a few days or weeks, but animals then recover and exhibit only a few long-term deficits. If both FEF and SC are ablated bilaterally, however, the ability to make saccades is permanently devastated.[94] Clearly, as described above, both FEF and SC are components of a larger, integrated system, functioning in parallel with each other and a number of other cortical and subcortical structures.[88]

THE FRONTAL EYE FIELD

The FEF, located in the rostral bank of the arcuate sulcus in the frontal cortex of macaque monkeys, participates in the transformation of visual computations guided by cognitive processes into saccade motor commands.[88,92] Physiological recordings in the FEF of monkeys trained in visual tracking tasks have found that roughly half of the neurons have visual responses.[10,67,87] Unlike neurons in other visual cortical areas, the responses of FEF neurons are not selective for the features of stimuli such as color, form, or motion. The FEF receptive fields are localized, emphasizing the contralateral hemifield but occasionally extending into the ipsilateral hemifield. These visual responses participate in the selection of targets for saccades.[92]

The FEF plays a role in producing saccadic eye movements. Saccades are elicited by low-intensity intracortical microstimulation of FEF.[11] This influence is mediated by a subpopulation of neurons in FEF that discharge specifically before and during saccades[10,44] and innervate the SC[102,106] and the brainstem saccade-generating circuit.[101] Burst neurons in the brainstem begin to be active at more or less the same time that FEF movement cells begin to fire.

High-frequency, short-duration electrical stimulation of the FEF activates burst neurons in the paramedian pontine reticular formation (the "where" signal) and inhibits the activity of omnipause neurons in the nucleus raphe interpositus (the "when" signal). The latency of these effects suggests that the FEF influence on both burst and pause cells is mediated by interneurons.[101]

By innervating brainstem omnipause neurons, FEF is in a position to directly trigger saccades. Still to be characterized, though, is the specific signal generated by FEF (as well as other structures) that reliably predicts when a saccade will be initiated. In developing hypotheses about particular trigger signals, it is important to account for the distribution of saccade latencies observed under different circumstances.[14,32]

RISE TO THRESHOLD MECHANISM FOR REACTION TIME

Over the years, many models have been developed to explain the stochastic variability of reaction time,[62] only some of which are appropriate to evaluate in relation to brain function. One such class of models supposes that in response to a stimulus, a signal in the brain grows until it reaches a threshold, at which point a movement is produced (Fig. 2). Models of this sort have at least two sources of stochastic variability. According to one type of accumulator model, the variability in reaction time arises from randomness in the level of the trigger threshold.[38] According to another type of accumulator model, the threshold is constant, but the rate of growth of the accumulator is random across trials.[13,84] Both architectures can account for reaction time data distributions under a range of conditions.[14,73,84] Indeed, it has been shown mathematically that random accumulator and random threshold models generate indistinguishable predictions.[24]

A recent study has examined movement-related activity recorded in the FEF to evaluate these alternative models of reaction time.[44] It was found that once movement-related activity in FEF reached a particular level, saccades were initiated. This level did not vary with saccade latency in the task (Fig. 3). The same conclusion has been drawn from an analysis of the amplitude of a particular scalp potential, called the lateralized readiness potential, that precedes movements.[37] Recordings in motor cortex indicate that this mechanism also holds for the control of skeletomotor movements.[57]

In the FEF data, the variability in reaction time was accounted for by variation in the rate of growth of the premovement activity, which began at a fairly constant interval after target presentation, toward the threshold.[92] Accordingly, the movement-related

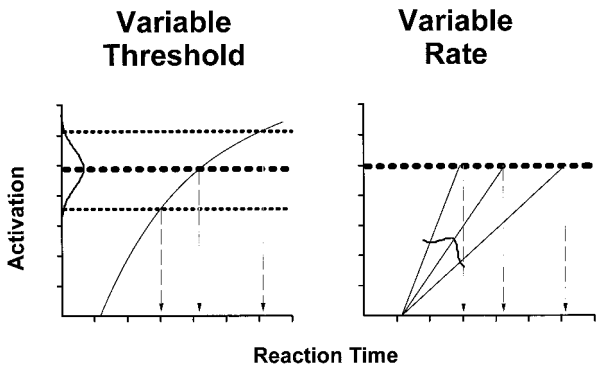

FIGURE 2. The two accumulator models. The variable threshold and the variable-rate models and their respective predictions of the threshold activation and the rate of growth of the accumulator for different reaction times (RT). Solid lines represent the activation functions; dotted lines represent the movement-trigger-activation threshold. In the variable-threshold model, the activation function does not vary, but the threshold level varies across trials. Short RTs result from a low threshold level. With increasing threshold level, longer RTs occur. In the variable-rate model, the threshold level does not vary across trials. Instead, the rate of growth of the activation function varies across trials. Short RTs result from a high rate of growth of the activation function. Long RTs occur when the rate of growth is low. (Modified from Hanes and Schall, 1996.)

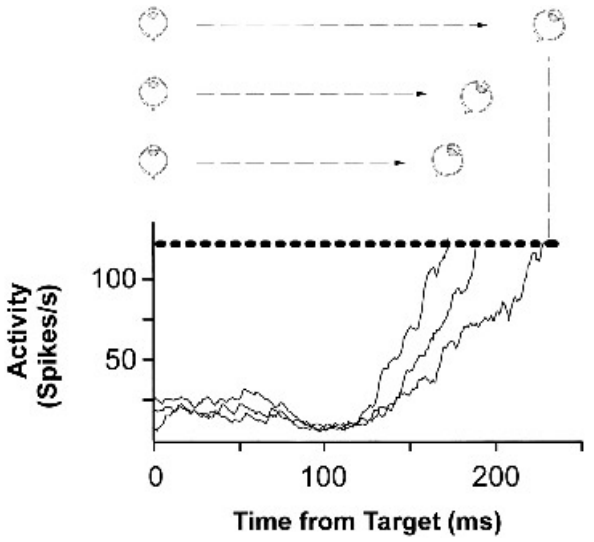

FIGURE 3. Relationship between movement-related FEF activity and saccade initiation. Time course of activation of a single movement–related FEF neuron is shown for three subsets of trials having different saccade latencies. Plots are aligned on target presentation and stop at saccade initiation. The level of activity at which the saccade is triggered (thick dotted line) is fairly constant across saccade latencies. Variability in saccade latency is accounted for by the time taken by the neuron to reach the threshold activation. (Modified from Schall and Thompson, 1999.)

neural activity in FEF corresponds to an accumulator model architecture with variable growth to a fixed threshold, and the data directly contradict the architecture with a fixed growth process and random threshold. A recent study in SC shows the same fixed activity level at the time of saccade initiation both for build-up and for burst neurons.[79]

IS THE TRIGGER THRESHOLD TASK DEPENDENT?

How general is this finding? Does it hold for eye movements in other conditions? Preliminary data indicate that saccades made in a visual search task are also produced when movement-related activity in FEF reaches a fixed level.[89] Evidence also indicates that a common threshold level is observed before regular and express saccades for neurons in the SC[22,41] and the FEF.[28] However, evidence from other studies indicates that a fixed threshold of some absolute value may not hold in all cases. One line of evidence on this question was obtained in a study using electrical stimulation to investigate how the FEF in opposite hemispheres interact in producing saccades.[96] A condition was created in which a burst of action potentials of a certain magnitude may or may not be associated with a saccade. This would appear to violate the fixed threshold hypothesis. Another line of evidence was obtained in monkeys making saccades that were of a more voluntary or self-generated nature. Movement neurons in the SC are reported to show a lower level of activity before anticipatory saccades than before regular visually guided saccades.[22] Similarly, saccade-related neurons recorded in the SC[26] and the FEF[28] were less active before antisaccades as compared with prosaccades. In the antisaccade task, subjects must generate saccades to the site opposite the visual stimulus.[39] The interpretation of these results is complicated by the fact that antisaccades are slower and less accurate than are prosaccades.[1,6,26] Therefore, the lower activity on average for antisaccades may have occurred because the saccades were scattered about the perimeter of each neuron's movement field. This can be evaluated by analyzing neural activity for saccades with precisely matched metrics and dynamics. Even accounting for variation in saccade metrics and dynamics, it appears that the level of activity of many neurons in the SC preceding saccade initiation is lower if the saccade is not guided by a visual stimulus.[25]

Granting, then, that there is a genuine task-dependent difference in the level of activity in FEF and SC necessary to produce saccades, what are the implications? Ultimately, a fixed threshold for all types of saccades might be realized only at the level of the final pathway in the brainstem saccade generator, possibly at the level of the long-lead burst neurons. A number of higher areas in the brain (such as SC, FEF, and SEF) innervate directly or indirectly this population. One can imagine how the level of activity in these higher areas might be independent of one another due to different functional specializations. However, it may be that the activity at the brainstem level reflects the total output of these multiple areas, but the relative contribution of a given area may vary depending on its functional specialization. According to this hypothesis, the lower contribution of activation from the FEF and the SC during antisaccades must be compensated by higher activity from another oculomotor area.

A possible candidate is the SEF, which contains neurons that are more active during antisaccades than during regular saccades.[97] It seems that SEF alone is unable to activate the brainstem saccade generator, because saccade initiation is completely abolished after a combined lesion of FEF and SC.[94] Nevertheless, SEF could modulate the activity coming from the SC and the FEF. The SEF projects to the brainstem into the region containing omnipause neurons[54,103] and bilaterally to a region containing burst neurons.[103] Preliminary evidence indicates that electrical stimulation of at least some sites in the SEF inhibits neuronal activity in FEF[86] and saccade production.[116] Such connections could enable the SEF to influence the FEF, the SC, and the brainstem in two ways. First, it could exert a global inhibitory influence on FEF and SC, which would explain the generally lower level of activity during antisaccades and would enable the suppression of the reflexive saccades to the visual target. Indeed, an analysis of error trials shows that almost all the erroneous saccades are express saccades that have a very short latency associated with higher activity of build-up neurons in the SC.[2729] Before the generation of an erroneous express saccade, movement neurons in the FEF reach the same activity level as before regular saccades.[26] Second, through the projection of SEF to the brainstem, it might enhance long-lead burst neurons generating saccades with a metric appropriate for the desired antisaccade. At the same time, it could contribute to the inhibition of the omnipause cells. This scheme would indicate that the FEF and SC are more concerned with visually guided saccades, whereas SEF is more responsible for internally generated saccades.

Taken together, these data indicate that the hypothesis that saccades are produced when the activity of certain neurons reaches a fixed threshold is useful but merits further scrutiny. Despite these

complications, it seems noteworthy that the constant threshold model of saccade initiation successfully describes the response of movement-related cells in FEF and SC during visually guided saccades for a wide range of latencies from express saccades to regular saccades.

PREPARATORY SHIFTS IN BASELINE ACTIVITY

The data just reviewed indicate that saccades are produced when the activity of certain neurons in the FEF or the SC reaches a fixed threshold.[44,79,110] If this is true, the point of no return may be earlier in time and more central in the oculomotor system than the brainstem. But must we stop here? Do other, earlier events inevitably lead to the crossing of the threshold and therefore mark the point of no return?

It has been reported that the low-frequency activity of a class of movement-related neurons in the SC, the so-called build-up or prelude neurons, is correlated significantly with saccadic reaction time. Preparatory processes can produce a shift in the baseline activity of populations of neurons residing in localized regions of the motor map in the SC[3,22,23,26,35] and in FEF.[20,28] This baseline shift can start in advance of the target presentation, long before the movement neurons begin to rise towards the trigger threshold.

At first, these findings might seem to argue that a process earlier than the crossing of the threshold determines the time of the eye movement initiation, that is, the reaction time. One would therefore be allowed to propose an even earlier point of no return in the chain of events leading up to the saccade. However, a number of points argue against a necessary causal role of this low-frequency activity in saccade initiation.

First, the relationship between baseline shifts and the average reaction time can be explained within a rise-to-threshold framework.[14,84,85] In the variable-rate model, the threshold level is fixed, whereas the rate of growth of the activation function varies across trials (Fig. 4A; left panel). Variability in reaction time is accounted for by the time taken by the accumulator to reach the threshold activation. Figure 4A shows the consequences of different baseline activity levels. Elevated starting levels lead to reaction time distributions that are on average shorter and of lower variability, but even so, there is no difference in the variability of the growth rate. In other words, a trial starting at a higher baseline level has a higher probability of producing shorter reaction times. The model therefore predicts a decreasing average reaction time with increasing baseline activity (Fig. 4B). However, on a single trial, the threshold introduces a strong nonlinearity in the relationship between the instantaneous activity of the accumulator and the instantaneous probability of saccade initiation. As long as the activity is below the critical level, the probability of saccade initiation remains zero. In this interpretation, the smoothly increasing probability of saccade initiation on average (the decreasing average reaction time) is the result of the averaging of many single trials each being governed by a highly nonlinear function.

This interpretation is supported by the low variance of the activity level that movement neurons reach just before saccade onset, implying a fixed

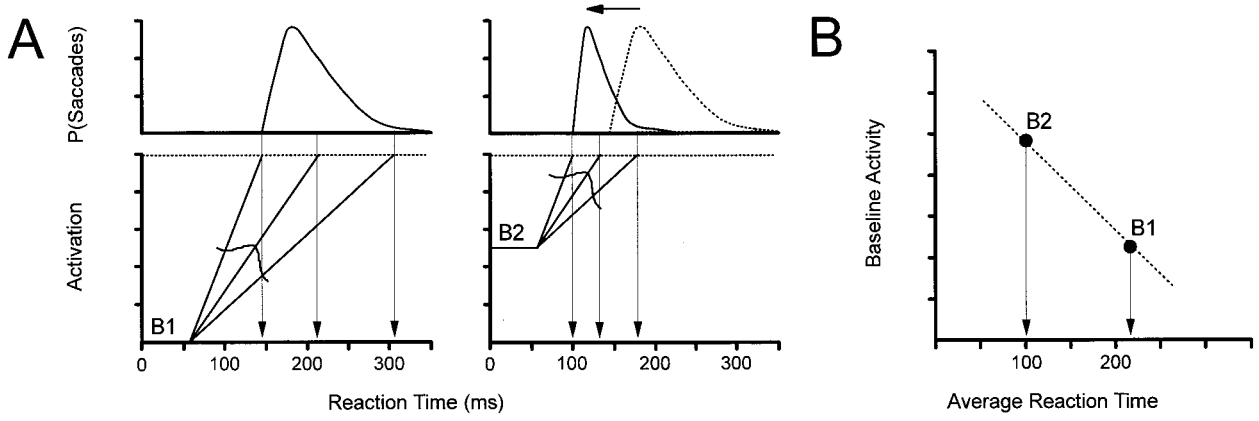

FIGURE 4. Relationship between activity levels and the reaction time in a race-to-threshold model. **(A)** In the variable-rate model, the threshold level is fixed across trials, whereas the rate of growth of the activation function varies. Variability in RT is accounted for by the time taken by the accumulator to reach the threshold activation (see left panel). In the right panel, the baseline activity level is increased (see B2). This leads to RT distributions that are on average shorter (see arrow) and of lower variability; even so, there is no difference in the variability of growth rate. **(B)** The model described in A predicts a decreasing average RT with increasing baseline activity.

threshold, at least for regular and express saccades to visual targets.[9,44,79,110] In addition, experiments with low-level electrical stimulation influence the location but not the timing of spontaneous saccades.[35] Furthermore, more recent recordings demonstrate cases in which the low-frequency collicular activity is not followed by a saccade into the movement field of the cell.[79,113] This shows that the build-up, prelude activity can influence but is not sufficient for saccade initiation.

Nevertheless, none of these experiments tested directly the ability of a subject to control saccade production. A critical characteristic of the phase before the point of no return is the fact that the movement preparation can be aborted. So the question remains open: Are the neural events that lead to reaching the threshold compulsory? Or can movements be partially prepared but not executed? Further research has investigated these questions by comparing neural activity when saccades were made or withheld after different degrees of preparation.

THE COUNTERMANDING PARADIGM

To investigate the neural control of movement initiation, we used a behavioral paradigm with behaving monkeys, referred to as the countermanding paradigm, that was originally developed to investigate human performance.[62] The countermanding paradigm tests a subject's ability to control the initiation of movements in a reaction-time task by infrequently presenting an imperative stop signal. In the oculomotor version, monkeys were trained to make a saccade to a peripheral target unless a stop signal was presented, in which case they were supposed to withhold the movement; the stop signal was the reappearance of the fixation spot[43] (Fig. 5). Performance on this task can be accounted for by a race between a process that generates the movement and a process that inhibits the movement.[61] This race model, which is referred to as "the stop signal reaction time," provides an estimate of the time needed to cancel the planned movement. Oculomotor stop signal reaction times average around 100 ms in monkeys[43] and are slightly longer in humans.[40] The stop signal reaction time corresponds theoretically and quantitatively to estimates of the time needed to reprogram a saccade in double-step saccade tasks.[4,60]

GAZE CONTROL SIGNALS IN FRONTAL EYE FIELD

The countermanding paradigm provides a means by which to determine whether single neurons generate signals that are logically sufficient to control the production of movements. The logic of the countermanding paradigm establishes two criteria a neuron must meet to play a direct role in the control of movement. First, the neuron must discharge differently when a saccade is initiated than when a saccade is withheld. Second, the difference in activity must occur by the time the movement has been canceled, that is, the stop-signal reaction time.

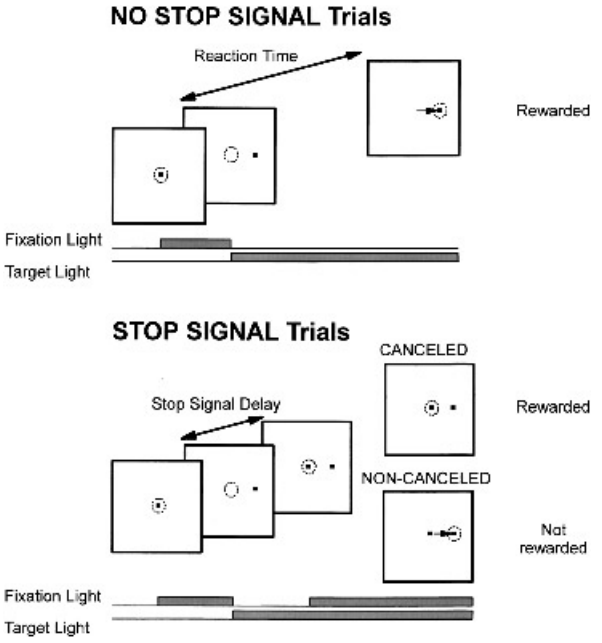

FIGURE 5. The countermanding paradigm. The dotted circle indicates the focus of gaze at each interval. All trials began with the presentation of a central fixation spot. After fixation of this spot for a variable interval, it disappeared. Simultaneously, a target appeared either in the cell's response field or in the opposite hemifield. On a fraction of trials after a delay, referred to as the stop-signal delay, the fixation spot reappeared, instructing the monkey to withhold movement initiation (stop-signal trials). During the trials in which the stop signal was not presented (NO STOP SIGNAL trials), monkeys were rewarded for generating a single saccade to the peripheral target. During stop-signal trials, monkeys were rewarded for maintaining fixation on the central spot (CANCELED trials). If the monkeys did generate a saccade to the peripheral target during stop-signal trials, no reward was given (NON-CANCELED trials). (Modified from Hanes et al., 1998.)

This approach was applied to neural activity recorded in FEF.[42] The main finding was that movement-related activity in FEF, which began to grow toward the trigger threshold, failed to reach the threshold when movements were canceled but instead decreased rapidly after the stop signal was presented (Fig. 6A). Moreover, the movement-related activity differentiated between execution and inhibition of the movement before the stop-signal reaction time had elapsed. Therefore, according to the logic of the countermanding paradigm, movement-related activity in FEF was logically sufficient to specify whether the saccade would be produced. A

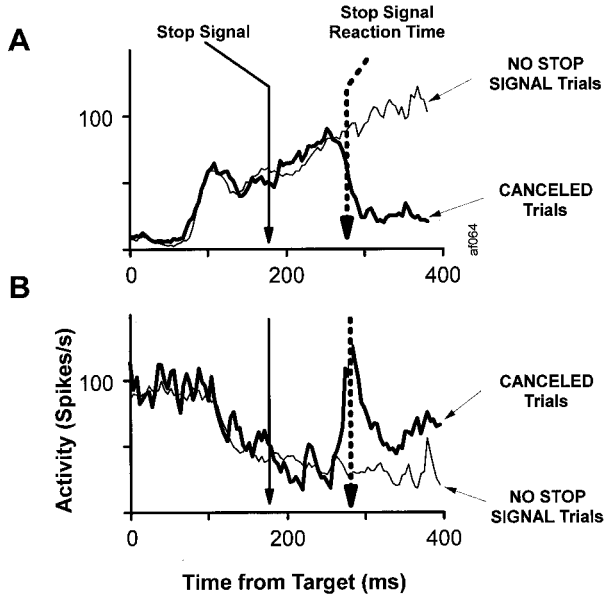

FIGURE 6. Relationship between FEF activity and canceling a movement. **(A)** Activity of a movement neuron in FEF in trials in which the movement was produced but would have been canceled if the stop signal had been presented (thin line) is compared with activity on trials when the planned saccade was canceled because the stop signal appeared (thick line). The time of the stop signal is indicated by the solid vertical arrow. The time needed to cancel the planned movement, the stop signal reaction time is indicated by the dashed vertical arrow. The activity when the movement was canceled decayed immediately before the stop-signal RT. **(B)** Comparison of the activity of a fixation neuron in FEF when saccades were initiated or canceled. (Modified from Hanes et al., 1998.)

complementary pattern of neural activity was observed in fixation neurons (Fig. 6B), another class of cells in FEF. If eye movements were canceled, fixation neurons that had decreased firing in preparation for the saccade generated a rapid increase of activity before the stop-signal reaction time. Such modulation before the stop-signal reaction time was not observed in neurons with only visual activity. Movement- and fixation-related activity in the SC of monkeys performing the oculomotor countermanding task show qualitatively similar patterns of activity.[41] The findings from the countermanding experiment indicate that the preparation of a movement is a controlled process; it can be canceled because the growth of the activation toward the trigger threshold is sufficiently slow. In other words, this phase of the saccade preparation is before the point of no return. But why, then, does the control sometimes fail, allowing errors? The answer, we believe, is because the growth of activity of the movement neurons is variable. If on a particular trial the activity increases rapidly, then the level of activity is already close to the threshold when the stop signal is presented. This shortens the time available for the completion of the stop process. Under such circumstances, the neural activity that produces the movement is more likely to reach the threshold before the stop process exerts its influence. In FEF, no difference was found between activity associated with movements executed without or in spite of the stop signal. This finding is consistent with the premise that the go and the stop processes are independent.[61] This means that the border between the controlled and the ballistic phase does not occur at a particular, discrete time during saccade preparation. The closer the activity of a movement neuron is to its threshold, the shorter the time period during which the movement can still be canceled and the less controllable becomes saccade initiation. However, only the crossing of the threshold makes the eye movement truly inevitable.

To perform the task well in the long run, subjects must know when errors are made and adapt their behavior to minimize future errors. Thus, some part of the brain must monitor the consequences of action and exert a controlling influence on the part of the brain responsible for producing the movement, that is, some form of supervisory or executive control.

SUPERVISORY CONTROL SYSTEM

After making an error, subjects commonly respond more carefully so that, for example, the response time increases.[83] Such self-adjustments have been interpreted in terms of a supervisory control system that monitors and controls the perception and production systems.[77] When a situation is novel or highly competitive, this system intervenes and provides additional inhibition to neurons responsible for the preparation of an inappropriate behavior and additional activation to neurons preparing an appropriate action. Norman and Shallice[77] argued that the executive control of the supervisory system is necessary during decision making, error correction, production of responses that are not well-learned, and in overcoming habitual responses. Certain regularities in performance across sequences of trials of monkey and human subjects performing the countermanding task provide clear evidence of performance adjustments across trials.[8,91]

This model bears on the question of the source and nature of the supervisory controller. Clearly there are at least two different controlling influences on behavior in the countermanding paradigm. One of them, the stop signal, is external. Its potency in the task we used is probably because it was a flash of a light in the fovea that directly activated the gaze

fixation system.[29,71] The other one is internal and reflects expectations based on past experiences, the motivation to do the task and other factors. What is its origin?

PERFORMANCE MONITORING IN THE SUPPLEMENTARY EYE FIELD

We recorded neural activity in the SEF in monkeys performing the countermanding task.[118] It was thought that SEF operates in parallel with FEF in producing saccades. However, we found that surprisingly few neurons in SEF generate signals that are sufficient to control gaze according to the logic of the countermanding paradigm.[9,82] In fact, SEF is not necessary for producing accurate, visually guided saccades.[95] Instead, distinct groups of neurons were active after errors, after successful withholding of a partially prepared movement, or in association with reinforcement.[118] These three forms of activation could not be explained by sensory or motor factors.

Error-related neurons are modulated specifically in trials in which a planned movement is not canceled as it should be (Fig. 7). This signal from single neurons corresponds to a particular scalp potential referred to as the error-related negativity, which was the earliest physiological evidence for a supervisory control system.[30,33] Current evidence suggests that this signal corresponds to the detection but not necessarily the correction of errors.[93] The source generator of the error-related negativity seems centered in the anterior cingulate cortex but may include the supplementary motor area.[18,66] In fact, we have recorded error-related neurons in the part of the anterior cingulate cortex that underlies SEF.[117] Error-related activity has also been observed in other studies in the medial frontal cortex.[34,76]

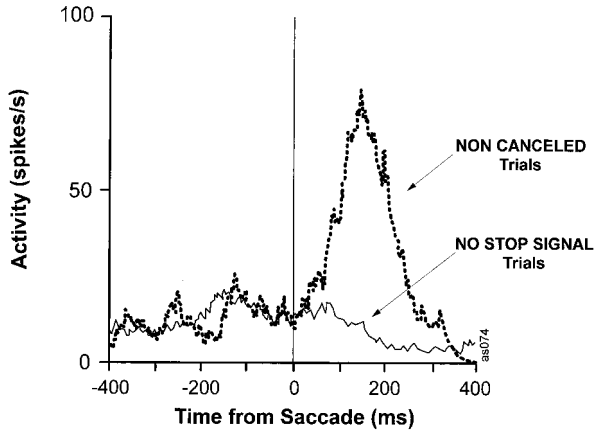

FIGURE 7. Error neuron in the SEF. Neural activity following initiation of rightward eye movements in trials without a stop signal (thin solid line) is compared with activity on trials in which the saccade was not canceled despite the stop signal (thick dotted line). The neuron became active after the erroneous saccade. (Modified from Stuphorn et al., 2000.)

Another kind of SEF neuron is illustrated in Figure 8. It exhibited an elevated discharge rate during stop-signal trials in which the saccade was correctly canceled, but the activity occurred after the stop-signal reaction time had elapsed. This modulation cannot be involved in canceling the movement, because it occurred too late. Furthermore, the magnitude of the activation was greater following a longer stop-signal delay when canceling the movement was less likely. This variation with performance motivates the hypothesis that this signal may register the amount of process conflict invoked during the task. This interpretation was motivated by neuroimaging work that identified activation in mesial frontal cortex in correct trials under challenging conditions when strong competition between responses occurred.[16] This dissociation led to the hypothesis that the medial frontal cortex was signaling conflict, defined specifically as coactivation of mutually incompatible processes that cannot both run to completion.[7,15]

During the countermanding task, gaze-shifting and gaze-holding neurons are activated concurrently when movements are canceled.[41,42] Because they are mutually incompatible, coactivation of the gaze-holding and gaze-shifting systems engenders a conflict in processing that is proportional to the magnitude of coactivation. The probability of canceling a planned eye movement is dictated by the balance of activation of gaze-holding and gaze-shifting neurons, because movements are canceled only if the magnitude of gaze-holding activation exceeds the magnitude of gaze-shifting activation. Thus, the probability of failing to cancel increases as gaze-shifting activation grows. Accordingly, as the probability of failing to cancel increases, the combined magnitude of gaze-shifting and gaze-holding activation sufficient to cancel a planned movement will be higher, thereby generating more conflict. The relationship we observed in SEF neurons of the second type corresponds to this measure of conflict. The hypothesis that medial frontal cortex monitors conflict has not gone unchallenged.[64] Finding distinct error- and conflict-related signals at the level of single neurons may provide a reconciliation of these competing hypotheses.

Reinforcement-related activity was observed after trials with no stop signal or after successfully canceled movements (Fig. 9). The countermanding task dissociates behavior from reinforcement. Identical actions (saccades to the target) can yield different

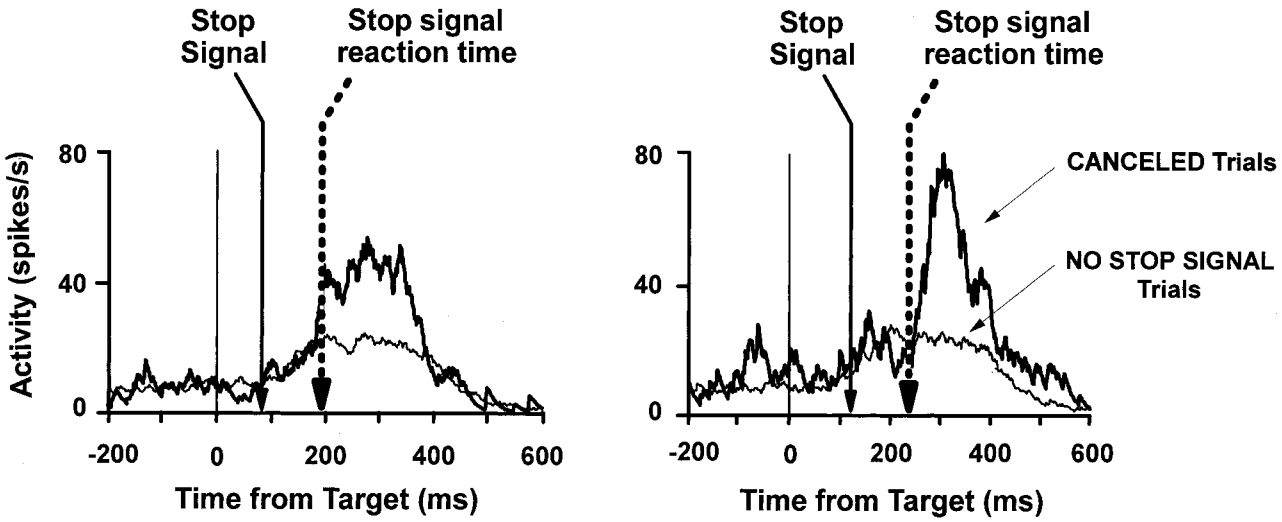

FIGURE 8. Conflict neuron in the SEF. Activity in trials in which the movement was produced (thin line) is compared with activity in trials when the planned saccade was canceled because the stop signal appeared (thick line). Presented are stop signal delays of 93 ms (left) and 144 ms (right), yielding 3% and 27% noncanceled errors. The time of the stop signal is indicated by the solid vertical arrow. The time needed to cancel the planned movement, the stop-signal reaction time, is indicated by the dashed vertical arrow. Note that the modulation starts after the stop-signal RT and increases with higher probability to commit an error. (Modified from Stuphorn et al., 2000.)

outcomes (successful no-stop-signal trials or unsuccessful noncanceled trials). Conversely, different actions (saccades when no stop signal was presented or holding fixation when the stop signal was presented) lead to the same outcome (reinforcement). These conditions permit the distinction between neuronal signals related to producing the behavioral response and those related to the reinforcement of that response. Neural activity associated with reinforcement has been described in many brain areas[99] including SEF.[2] However, an absence of reward-related modulation has been reported in FEF.[59] The presence of reward-related activity in SEF but not in FEF is consistent with the differential innervation by dopamine.[120] Thus, neurons of the third type were the functional complements of the putative error-related neurons, signaling the expectation and receipt of reinforcement.

These observations suggest a new framework for understanding SEF function. Our new results indicate that when monkeys must exert control over the initiation of an eye movement, neurons in SEF signal

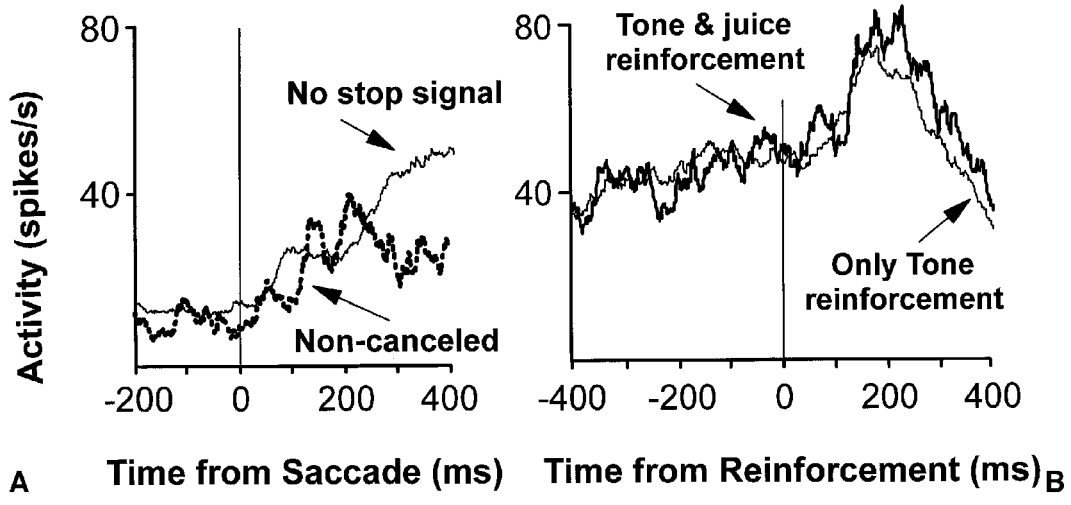

FIGURE 9. Reinforcement neuron in the SEF. **(A)** Activation grew after successful no-stop-signal trials (thin line) but was not sustained in erroneous noncanceled trials (thick dotted line). **(B)** Activation was elevated while the monkey awaited reinforcement and peaked after delivery of primary plus secondary (thick line) or only secondary (thin line) reinforcement. (Modified from Stuphorn et al., 2000.).

the production of an error, the anticipation of reinforcement, or the presence of processing conflict. Indeed, SEF activity is observed in other tasks that require suppressing prepotent responses to produce arbitrary conditional responses.[17,78,97]

CONCLUSIONS

Saccades are produced by a distributed network that extends from the cerebral cortex to the brainstem. The high-level control of saccades has been investigated with notable success over the last decade. Data from a countermanding task have provided additional insights into how the brain produces and controls movements of the eyes. Whereas neural activity in FEF was sufficient to cancel motor planning or to initiate saccades, neural modulation in SEF appears to signal the production of an error, the anticipation of reinforcement, or the presence of processing conflict. The work we reviewed demonstrates how much we have learned about how the brain controls actions. We are hopeful that the insights from basic research will translate into clinical applications.

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