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Neural control of behavior: countermanding eye movements

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Abstract Understanding the self-control of action entails knowledge about how actions are initiated, how planned actions are canceled and how the consequences of actions are registered. We have investigated neural correlates of these processes using the countermanding paradigm – a task that required subjects to occasionally cancel a planned speeded response, and an analysis that provides an estimate of the time needed to cancel a planned movement. By monitoring the activity of single neurons in the frontal cortex of macaque monkeys performing this task we have distinguished signals responding to the visual stimuli, other signals that control the production of movements, and still other signals that seem to monitor behavior.

Introduction

A fundamental goal of cognitive neuroscience is to explain the relationship between brain function and behavior. The initiation of a movement is a basic action that it seems we ought to be able to understand. A characteristic of movement initiation is that the precise time of occurrence is somewhat random. This leads to the general problem of reaction time that has occupied

experimental psychology since its birth. The general framework in cognitive psychology that guides research on reaction time posits the existence of more or less distinct stages of processing. For example, a perceptual stage locates and identifies at least some of the objects in the environment, and a response stage prepares and produces movements to acquire or avoid the objects. Quantitative models have been developed in this framework to account for performance measured by reaction time and the probability of generating certain responses (e.g., Luce, 1986). The proliferation of models has led to redundancy; more than one model can produce realistic reaction time distributions. A scientific approach requires us to ask which model is more accurate. However, additional behavioral data and continuously refined models of the black box ultimately cannot answer the question.

This reasoning motivates us to open the black box by asking what neural processes correspond to the stages of the cognitive models. Do the patterns of neural processes provide insights into the architecture of cognition? The black box of cognition can be opened today because of technical developments in methods to record the activity of individual neurons in monkeys trained to perform tasks inspired by cognitive psychology.

We have investigated movements of the eyes for several reasons. First, the primary sensory input is very well understood (e.g. Parker & Newsome, 1998). Anatomical and physiological studies have elucidated how visual signals are routed through a variety of cerebral areas to compute what is where in an image. Second, the eye movement production system is very well understood (e.g., Carpenter, 1991; Wurtz & Goldberg, 1989). Neural recordings, electrical stimulation, inactivation or lesions as well as quantitative modeling have provided a detailed understanding of the neural network in the brain stem that produces saccadic eye movements. Thus, we know more about and have easier access to every stage of eye movement production than we do for limb or vocal movements, for example. Third, several lines of evidence indicate that the knowledge gained about the

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high level control of eye movements will be applicable to other systems and more complex behaviors. 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 (Zingale & Kowler, 1987) following the same pattern observed for speech and typing (Sternberg, Monsell, Knoll & Wright, 1978). In addition, the influence of foreperiod on reaction time is the same for movements of the eyes (Findlay, 1981; Hanes, Tu & Schall, 1992) as it is for movements of the limbs (e.g., Niemi & Näätänen, 1981). These are just two examples among many which demonstrate that the high-level programming and behavioral control of eye movements seems indistinguishable from that of manual movements or even speech.

Eye fields in frontal cortex

Before describing our experimental data, we provide some background on the cortical areas from which the data were collected. The frontal eye field (FEF) is an area in prefrontal cortex, located in the rostral bank of the arcuate sulcus in macaque monkeys. Broadly considered, this cortical area participates in the transformation of visual signals into saccade motor commands (reviewed by Schall, 1997). FEF is innervated in a topographic fashion by areas in both the dorsal and ventral streams of extrastriate visual cortex (e.g., Schall, Morel, King & Bullier, 1995b). As a result of this extensive connectivity with extrastriate visual cortical areas, many neurons in FEF respond to visual stimuli. Physiological recordings in the FEF of monkeys trained to shift gaze to visual targets have found that roughly half of the neurons have visual responses (e.g., Mohler, Goldberg & Wurtz, 1973; Bruce & Goldberg, 1985). Recent research has demonstrated how these visually responsive neurons in FEF participate in the selection of visual targets for saccades (reviewed by Schall & Thompson, 1999; see also Thompson & Schall, 1999; Bichot & Schall, 1999; Kim & Shadlen, 1999).

FEF is also known to play a direct role in producing saccadic eye movements. Low-intensity microstimulation of FEF elicits saccades (e.g., Bruce, Goldberg, Bushnell & Stanton, 1985). This direct influence is mediated by a subpopulation of neurons in FEF that discharge specifically before and during saccades (Bruce & Goldberg, 1985; Hanes & Schall, 1996). These neurons that generate movement-related activity innervate the superior colliculus (Segraves & Goldberg, 1987) and the neural circuit in the brain stem that generates saccades (Segraves, 1992). Recent work has demonstrated that reversible inactivation of FEF impairs monkeys' ability to make saccades (Dias, Kiesau & Segraves, 1995; Sommer & Tehovnik, 1997) and complements earlier observations that ablation of FEF causes an initial severe impairment in saccade production that recovers over time (e.g., Schiller, Sandell & Maunsell, 1987; Schiller & Chou, 1998).

The supplementary eye field (SEF) is an area in dorsomedial frontal cortex that may be considered an extension of the supplementary motor area. In several respects SEF seems to parallel FEF. Neurons in SEF are responsive to visual or auditory stimulation, and other neurons in SEF discharge in relation to saccades (Schlag & Schlag-Rey, 1987; Schall, 1991). Saccades can be elicited by low-intensity microstimulation of SEF (Schlag & Schlag-Rey, 1987). SEF innervates oculomotor centers in the striatum, superior colliculus and brainstem (reviewed in Schall, 1997).

The countermanding paradigm

To investigate the neural control of movement production, we have employed the countermanding paradigm with behaving monkeys. Originally developed to investigate human performance, the countermanding paradigm probes a subject's ability to control the initiation of movements by infrequently presenting an imperative stop signal in a reaction time task (Vince, 1948; Lappin & Eriksen, 1966; Osman, Kornblum & Meyer, 1986, 1990; DeJong, Coles, Logan & Gratton, 1990; DeJong, Coles & Logan, 1995; reviewed by Logan & Cowan, 1984; Logan, 1994). The subjects' task is to cancel the planned movement if the stop signal is presented. In the oculomotor version, monkeys were trained to make a saccade to a peripheral target that appeared when the fixation spot disappeared unless a "stop signal" was

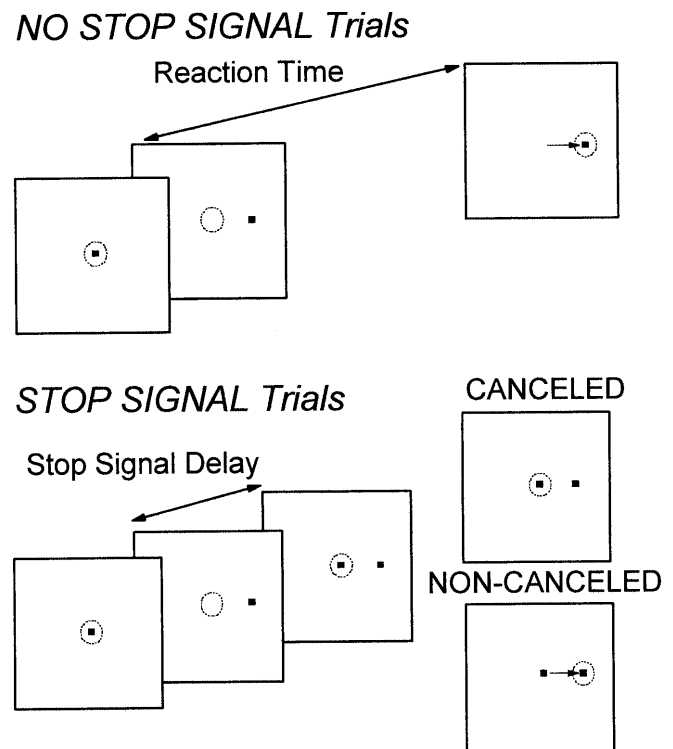


Fig. 1 The countermanding task. Details in the text

presented (Fig. 1). In response to the stop signal, the monkeys were to withhold the movement; the stop signal was the reappearance of the fixation spot (Hanes & Schall, 1995). Logan and Cowan (1984) showed that performance on this task can be accounted for by a race between a process that generates the movement and a process that cancels the movement. This race model provides an estimate of the “stop signal reaction time”, which is the time needed to cancel the planned movement. The stop signal reaction time corresponds theoretically and quantitatively to estimates of the time needed to reprogram a saccade in double-step saccade tasks (Lisberger, Fuchs, King & Evinger, 1975; Becker & Jurgens, 1979). Oculomotor stop signal reaction times average around 100 ms in monkeys (Hanes & Schall, 1995).

The extent to which the information obtained in monkeys can be used to help understand the generation of movements in humans depends on the similarity of monkey and human performance in the oculomotor countermanding task. Recently, Hanes and Carpenter (1999) showed that human performance in the saccade countermanding task is quite similar to that of monkeys. One difference, however, was that the duration required to cancel the movement was around 30 ms longer for humans than for monkeys. This may not be surprising in view of the common observation that macaque saccade latencies are somewhat shorter than humans.

Neural control of saccade initiation by frontal eye field

Rise to threshold mechanism for reaction time

Over the years many models have been developed to explain the stochastic variability of reaction time (reviewed by Luce, 1986). Because their aim was more purely theoretical, a good number of these models incorporate assumptions that are not physiologically plausible. One class of models known as accumulator models, does seem appropriate to evaluate in terms of brain function. Accumulator models suppose that in response to a stimulus, a signal in the brain grows until it reaches a threshold, thereby triggering a motor response to the stimulus. In models of this sort there are at least two sources of the stochastic variability evident in reaction times. One type of accumulator model supposes that the variability in reaction time arises from randomness in the level of the trigger threshold (e.g., Grice, Nullmeyer & Spiker, 1982). This model has been shown to account for reaction times in a saccade task (Nazir & Jacobs, 1991). Another type of accumulator model assumes that the threshold is constant, but that the average rate of growth of the accumulator is random across trials (e.g., Ratcliff, 1978; Carpenter, 1988). This architecture can account for a broad range of reaction times measured in a variety of tasks (Carpenter & Williams, 1995; Ratcliff, Van Zandt & McKoon, 1999). Thus, the two alternative models cannot be distinguished on the

basis of performance data alone. As a matter of fact, it has been shown that random accumulator and random threshold models generate equivalent predictions (Dzhafarov, 1993).

We have investigated movement-related activity recorded in FEF to evaluate these alternative models of reaction time (Hanes & Schall, 1996). We found that saccadic eye movements were initiated when movement-related activity in FEF reached a particular level, but that this threshold level did not vary with reaction time (Fig. 2A). The variability in reaction time was accounted for mainly by variation in the rate of growth of the premovement activity towards the trigger threshold. Accordingly, the movement-related neural activity in FEF appears to correspond to an accumulator model architecture with variable growth to a fixed threshold, and directly contradicts the architecture with a fixed growth process and random threshold.

What is the logical relationship between the movement activity of neurons in FEF and saccade production? It is well known that many neurons across multiple structures contribute to each movement (e.g., Georgeopoulos, 1996; Lee, Rohrer & Sparks, 1988). Moreover, the inevitable destruction of single neurons by the microelectrode during the recording sessions goes completely unnoticed by the monkey or the investigator monitoring its behavior. Therefore, the activity of a single movement neuron is not *necessary* for movement production. Nevertheless, an important test of the fixed threshold model was to determine whether the quantitative variation in the rate of growth of the activity of individual neurons could account for the actual range of reaction times generated by the monkeys. The distribution of the behavioral reaction times collected while recording from each individual FEF cell was compared to a distribution of reaction times generated by a Monte-Carlo simulation run with parameters derived from that neuron's activity (Fig. 2B). The parameters put in the simulation were derived from the average threshold level and the rates of growth measured from premovement activity obtained from each neuron individually. For almost all comparisons, the mean reaction time derived from the simulation corresponded precisely with the mean reaction time observed in the trials while each neuron was recorded (Fig. 2C). In many but not all cases the simulated distribution of reaction times was indistinguishable from the observed distribution of reaction times. Thus, the activity of a single FEF movement neuron appears to be *sufficient* to account for when movements are produced. In other words, the activity of a single FEF movement neuron is a very accurate index of the state of preparation of the whole oculomotor system.

Does the same relationship between the growth of movement-related neural activity and the time of movement initiation hold for neurons in other motor structures? Although not investigated in exactly the same way as in our study, recordings in motor cortex (Lecas, Requin, Anger & Vitton, 1986) and superior

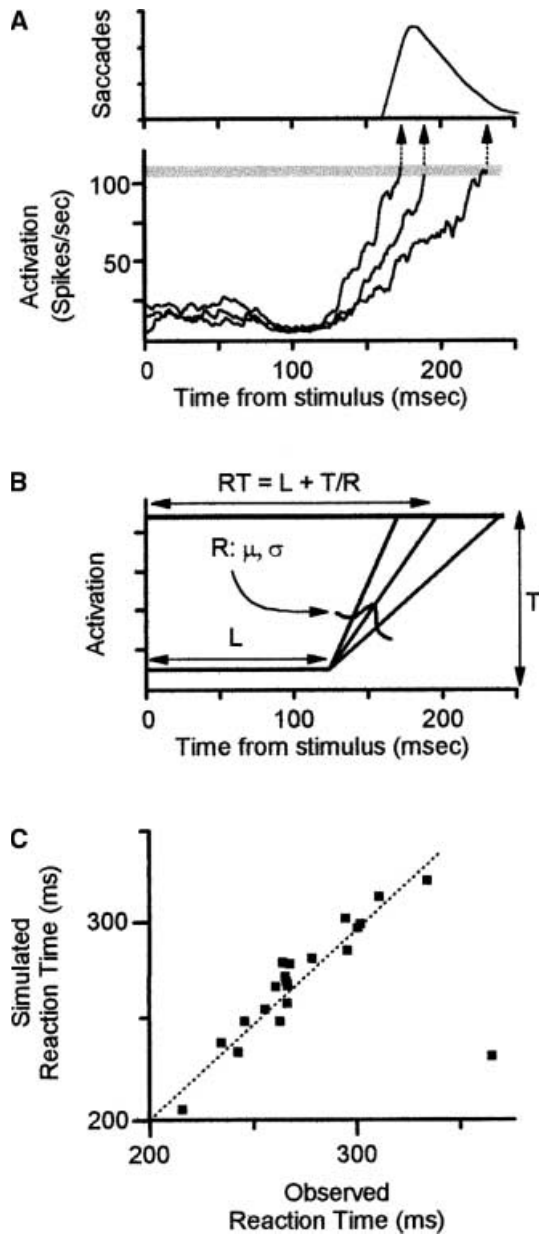


Fig. 2A–C Relationship between movement-related FEF activity and saccade initiation. **A** Time course of activation of a single movement-related FEF neuron is shown for three subsets of trials having different saccade latencies. Plots are aligned on target presentation and stop at saccade initiation. The level of activity at which the saccade is triggered (*gray bar*) 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. **B** Elements of a simple variable rate rise to threshold model of reaction time. **C** Comparison of the mean reaction times produced by a monkey while the activity of single movement-related neurons in FEF were recorded and the mean reaction time produced by the simple model based on parameters derived from the activity of each neuron (*FEF* frontal eye field)

colliculus (Sparks, 1978; Dorris, Paré & Munoz, 1997) indicate that movements are produced when neural activity reaches a rather fixed threshold. Similar evidence has been presented measuring the amplitude of the lat-

eralized readiness potential, a scalp potential concomitant of movement preparation (Gratton, Coles, Sirevaag, Eriksen & Donchin, 1988). From this, we can infer that each neuron contributing to a given movement may have an idiosyncratic threshold but that the time at which the activity reaches that threshold is correlated within and across structures. While a matter for empirical verification, this inference has important implications for the functional organization of the neural motor system, chief among which is the question of how coordinated growth of movement-related activity across the brain might be achieved. One possibility is that rapid interactions between oculomotor structures coordinate the growth of movement activation such that neurons lagging behind are accelerated and those speeding ahead are decelerated. Another possibility is that an external source such as the catecholaminergic systems may influence the state of activation of the whole system.

To test the hypothesis that the growth of movement-related activity in multiple neurons is correlated, one would need to record simultaneously from multiple movement cells in FEF and other structures to determine whether a particular constant level of activation is achieved by all neurons before movements of all latencies. This would be stronger evidence for the hypothesis that movements are produced when the response preparation process in the motor system reaches a specific threshold. One can then determine how the rate of growth of the activation across a population of neurons varies as a function of movement latency. Finding that the rate of growth covaries across neurons, i.e., on long latency trials the rate is slower across areas and structures, and vice versa, may be taken as evidence for coordination within circuits that produce eye movements. More subtle relationships may hold as well. For instance, one can determine whether variations in behavioral reaction times are associated with changes in the cross-correlation of activity among neurons. Recent studies have shown subtle changes in the relationship between neurons within an ensemble synchronized with covert processing leading to behavioral responses (e.g., Vaadia, Haalman, Abeles, Bergman, Prut, Slovin & Aertsen, 1995; Riehle, Gran, Diesmann & Aertsen, 1997).

In summary, the evidence from FEF indicates a particular architecture for motor response production that includes some random variability. Numerous performance studies have shown that reaction times can be reduced as conditions become more predictable, although some fraction of variability in reaction times remains. Why is the growth of movement-related activity variable? Is it the best possible or is it the most desirable performance of the system? From a design perspective random variability may permit more adaptive behavior. The world is an ever-changing place; an action chosen at one instant may in the next become a bad choice. Occasional procrastination may allow the perceptual system to reevaluate the environment and specify a different action. Also, random behavior facilitates deception, evasion and discovery.

These speculations rest on the validity of the hypothesis that eye movements are produced when oculomotor activity reaches a fixed threshold. Further research has tested the validity of the threshold conception by comparing neural activity when saccades were either made or withheld after different degrees of preparation.

Gaze control signals in frontal eye field

Commonly brain structures are attributed a function in motor control if it can be shown that they play a role in producing movements. The stop signal paradigm permits us to investigate another facet of control, the cancellation of a planned movement. The chief virtue of the countermanding paradigm is that one can determine whether single neurons generate signals that are logically sufficient not only to initiate movements but also to prevent 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 and most obviously, the neuron must discharge differently when a saccade is initiated versus when a saccade is withheld. Second, and most importantly, this difference in activity must occur by the time that the movement is canceled, i.e., within the stop signal reaction time.

Examining neural activity recorded in FEF, we found that movement-related activity, which began to grow toward the trigger threshold, failed to reach the threshold activation level when movements were canceled (Fig. 3A) (Hanes, Patterson & Schall, 1998). Instead, when planned movements were canceled, the movement-related activity decreased rapidly after the stop signal was presented. Moreover, the movement-related activity associated with canceling as compared to executing the movement became different just before the stop signal reaction time had elapsed. Therefore, the activity of single FEF movement neurons is logically sufficient to specify whether or not a saccade will be produced. This pattern of results was observed in almost all cells with movement-related activity.

A complementary pattern of neural activity was observed in another class of neuron in FEF called fixation neurons (Fig. 3B). If eye movements were canceled, fixation neurons that had decreased firing generated a rapid burst of activity before the stop signal reaction time. The modulation before the stop signal reaction time was never observed in neurons with only visual responses. The different results observed for the different functional classes of neurons is entirely consistent with the fact that movement and fixation neurons in FEF provide direct input to the brain structures that produce eye movements, but the visual neurons do not (Segraves & Goldberg, 1987; Segraves, 1992). Recently, neurons from the superior colliculus have been recorded while monkeys performed the oculomotor countermanding task (Hanes & Paré, 1998). Preliminary results indicate

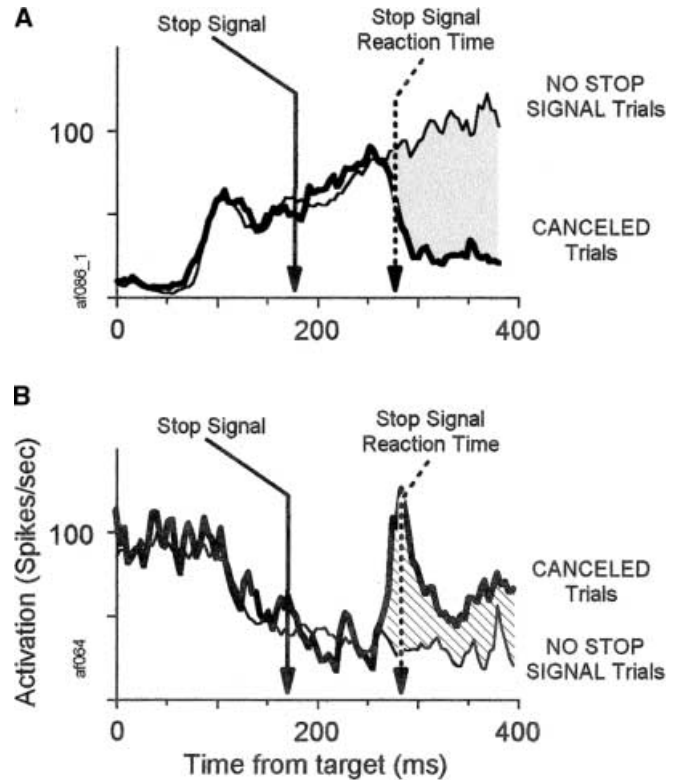


Fig. 3A, B Relationship between FEF neural activity and canceling a movement. **A** Activity of a movement neuron in FEF in trials in which the movement was produced but would have been canceled if the stop signal had been presented (*thin line*) is compared with activity on trials when the planned saccade 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 precipitously immediately before the stop signal reaction time. **B** Comparison of the activity of a fixation neuron in FEF when saccades were initiated or canceled. (Modified from Hanes et al., 1998)

that the activity in the superior colliculus is qualitatively similar to that in FEF.

The findings from FEF using the countermanding paradigm indicate that the preparation of a movement can be a controlled process; it can be canceled if the growth of the activation toward the trigger threshold is sufficiently slow. What if errors are made because the movement is not canceled? In FEF we found no difference in neural activity associated with movements executed without or in spite of the stop signal. In other words, FEF neurons that are involved in producing an eye movement discharge in the same fashion for correct saccades made when no stop signal was presented, as for errant saccades made even though the stop signal was presented. This finding is consistent with the fundamental premise of the race model used to account for countermanding performance, which is that the finish times of the go and of the stop process are independent (Logan & Cowan, 1984). To perform the task well, though, 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 to adjust performance.

Performance monitoring by supplementary eye field

A number of investigators have begun to focus on executive processes that monitor and control the perception, selection and production systems (e.g., Coles, Scheffers & Fournier, 1995; Cohen, Braver & O'Reilla, 1996; Meyer & Kieras, 1997). This framework has guided our interpretation of new and unexpected results we have obtained in neural recordings from SEF in monkeys performing the countermanding task (Stuphorn, Taylor & Schall, 1999). Despite the numerous parallels in anatomical connections, neuronal activation profiles and stimulation effects observed for SEF and FEF (reviewed by Schall, 1997), we have found that, unlike their counterparts in FEF, remarkably few neurons in SEF generate signals that are sufficient to control gaze according to the logic of the countermanding paradigm. This observation is consistent with recent observations that SEF lesions cause only a relatively modest impairment of gaze (Schiller & Chou, 1998) and that following combined ablation of the FEF and the superior colliculus, leaving the SEF intact, monkeys cannot make eye movements (Schiller, True & Conway, 1980). In spite of evidently playing little role in the control and production of eye movements, neurons in SEF did generate interesting signals during the countermanding task.

Figure 4 illustrates two of the signals that were observed in SEF. The neuron illustrated in Fig. 4A 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 occurs too late. The latency and magnitude of the activation after the stop signal reaction time were reduced following short stop signal delays when most movements were canceled. Both the latency and the magnitude of the activation increased following longer stop signal delays when canceling the movement was less likely. The timing of this neural activation in SEF and its variation with performance motivate the hypothesis that this signal may register successful performance of the task.

Another signal generated by SEF neurons occurred specifically in stop signal trials in which the saccade was not canceled (Fig. 4B). Some SEF neurons discharged after the errant saccade was completed. One hypothesis is that this signal registers the occurrence of an error. A prelude to testing whether the signals generated in SEF have any relation to adjustments in performance involves determining whether monkeys modify their behavior according to what they have done. Preliminary evidence indicates that, despite much idiosyncrasy, sequential effects can be observed in the performance of

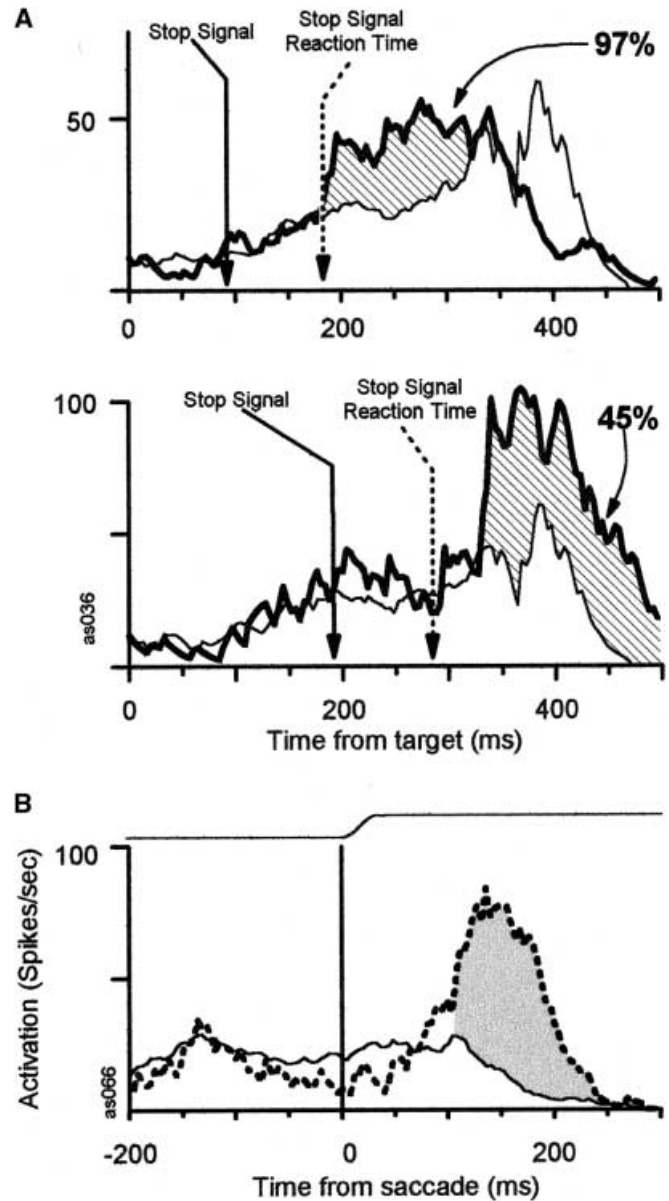


Fig. 4A, B Supplementary eye field activity during the countermanding task. **A** Comparison of activity between trials when the movement was canceled (*thick line*) and trials when the movement was produced but would have been canceled if the stop signal had been presented (*thin line*). The *top panel* shows data from shorter stop signal delays in which the monkey canceled the movement on 97% of the stop signal trials. The *lower panel* shows data from longer stop signal delays in which the monkey canceled the movement on 45% of the stop signal trials. The time of the stop signal and the estimated stop signal reaction time are shown. This neuron was activated after the movement was canceled. **B** Comparison of activity between trials when the eye movement was made because no stop signal was given (*solid line*) and trials when the eye movement was made in spite of the stop signal (*thick dashed line*). This neuron discharged following errant but not correct saccades

monkeys during the countermanding task (Schall & Taylor, 1998). A movement was more likely to be canceled if a stop signal had been presented in the immediately preceding trial, and this trend was strongest if the

movement had failed to be canceled on the previous trial. The increased probability of canceling the movement coincided with an increase in the reaction time observed on trials with no stop signal following a stop signal trial.

The discharge of SEF neurons following noncanceled movements is reminiscent of a scalp potential recorded in humans called the error-related negativity (ERN) (Falkenstein, Hohnsbein & Hoormann, 1991; Gehring, Goss Coles & Meyer, 1993; Coles et al., 1995). The ERN has been observed when subjects made errors in a choice reaction time task or failed to withhold the response in a go-no-go task or when subjects receive feedback that they made an error in a time estimation task (Miltner, Braun & Coles, 1997; Scheffers, Coles, Bernstein, Gehring & Donchin, 1996; Falkenstein et al., 1995). A correlation between the magnitude of the ERN and the degree to which subjects modify their behavior on subsequent trials – greater adjustment in performance associated with larger ERN magnitude – has been observed under some (Gehring, Coles, Meyer & Donchin, 1995) but not all conditions (Scheffers et al., 1996; Miltner et al., 1997). For this reason, the ERN has been regarded as detecting errors between desired and produced behavior, and the adjustment of performance depends on strategy and task conditions. The source of the ERN has been localized to the anterior cingulate cortex but may also include the supplementary motor area of which SEF is part (Dehaene, Posner & Tucker, 1994; Miltner et al., 1997). A recent functional magnetic resonance imaging study demonstrated activation in anterior cingulate during a task in which subject made errors, but the activation was interpreted as monitoring response competition rather than only detecting errors (Carter, Braver, Barch, Botvinick, Noll & Cohen, 1998).

If SEF generates signals that are not observed in FEF related to correct performance and error, what is the origin of the difference? Neural activity associated with the receipt, withholding or unexpected delivery of reward has been recorded in the dorsal and ventral striatum (Shidara, Aigner & Richmond, 1998; Kawagoe, Takikawa & Hikosaka, 1998; Schultz, 1997), dorsolateral prefrontal cortex (Watanabe, 1996), orbital frontal cortex (Thorpe, Rolls & Maddison, 1983) in dopamine neurons in the ventral tegmental area and substantia nigra (Schultz, 1997, 1998) and in anterior cingulate cortex (Shima & Tanji, 1998; Niki & Watanabe, 1976; Gamba, Sasaki & Brooks, 1986). Anatomical studies have shown that SEF is interconnected with anterior cingulate cortex much more heavily than is FEF (Huerta, Krubitzer & Kaas, 1987; Huerta & Kaas, 1990). Also, FEF and SEF receive different patterns of innervation from dopamine neurons in the brain stem (Gaspar, Stepniewska & Kaas, 1992) – SEF and the supplementary motor area are more heavily innervated by the ventral tegmental area than by the substantia nigra pars compacta; in contrast, FEF is more heavily innervated by the substantia nigra pars compacta than by the ventral tegmental area. Neurophysiological

studies have reported a slightly higher incidence of reward-related activity in the ventral tegmental area as compared to the other dopamine cell groups (Schultz, Apicella & Ljungberg, 1993). Thus, anatomical connections exist that might explain the differential modulation of activity in SEF as compared to FEF we have observed.

In summary, the new data from the countermanding paradigm suggest a function for SEF that distinguishes it from FEF. Whereas FEF generates signals sufficient to select targets and control the production of eye movements, SEF may serve to monitor performance, registering whether the actions that are produced lead to the desired consequences. Such monitoring seems vital for a self-controlled system that can adapt to changing circumstances.

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