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Performance monitoring by the supplementary eye field

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Intelligent behaviour requires self-control based on the consequences of actions. The countermanding task is designed to study self-control; it requires subjects to withhold planned movements in response to an imperative stop signal, which they can do with varying success. In humans, the medial frontal cortex has been implicated in the supervisory control of action[1–3]. In monkeys, the supplementary eye field in the dorsomedial frontal cortex is involved in producing eye movements, but its precise function has not been clarified[4]. To investigate the role of the supplementary eye field in the control of eye movements, we recorded neural activity in macaque monkeys trained to perform an eye movement countermanding task. Distinct groups of neurons were active after errors, after successful withholding of a partially prepared movement, or in association with reinforcement. These three forms of activation could not be explained by sensory or motor factors. Our results lead us to put forward the hypothesis that the supplementary eye field contributes to monitoring the context and consequences of eye movements.

To evaluate the hypothesis that neurons in the supplementary eye field (SEF) register the consequences of actions, we collected behavioural and neurophysiological data from two macaque monkeys performing an eye movement countermanding task that manipulated their ability to withhold planned movements[5,6]. On trials with no stop signal, the monkeys received positive reinforcement following a saccade to the target. On trials with a stop signal, the monkeys earned reinforcement when the partially prepared saccade to the target was cancelled and fixation was maintained. The task is described in detail in Fig. 1 of Supplementary Information. The delay of the stop signal relative to the target was adjusted such that monkeys failed to cancel the saccade in half of the trials. We analysed the distribution of reaction times and the probability of cancelling the movement to determine the time needed to cancel the planned movement—the stop-signal reaction time[5,6].

In the two monkeys, 175 neurons (monkey A, 58; H, 117) recorded in the SEF provided sufficient data during the countermanding task for us to analyse. Figure 2 of Supplementary Information shows the location of the recordings. Neurons were classified by the presence of visual, movement and postsaccadic activity. The hypothesis was tested by comparing the activity between stop-signal trials with cancelled or non-cancelled movements and the activity observed in trials with no stop signal. Here we focus on three types of neurons. Neurons of the first type (26/175; 15%) were modulated specifically when monkeys failed to cancel the planned movement (Fig. 1). Neurons of the second type (23/175; 13%) were modulated specifically when monkeys successfully cancelled planned movements (Fig. 2). Neurons of the third type (39/175; 22%) were active before and during the delivery of reinforcement (see below).

Could this neural activation in the SEF be explained by sensory or motor factors? The modulation during countermanding trials was compared to the presence of visual, movement or postsaccadic activity during memory-guided saccades, but none of the three types of neurons could be uniquely identified with a previously described cell type in the SEF. Table 1 in Supplementary Information gives the incidence of visual and saccade-related activity for these types of neurons.

Several observations indicate that the first type of neural modulation is not exclusively of sensory origin even though different patterns of visual stimulation occurred in non-cancelled trials and in trials without the stop signal (Fig. 1). First, if the modulation were a visual off-response, then these neurons should respond to the disappearance of the fixation spot in trials with no stop signal or to the disappearance of the target in memory-guided saccade trials, but they did not. Second, if the modulation were a visual on-response to the stop signal, it should occur during successfully cancelled trials, but it did not. Finally, in additional testing of a subset of neurons of this type ($n = 12$), the modulation was observed even if the visual stimulation after the non-cancelled saccade was identical to that in trials with no stop signal. Other observations indicate that modulation of the first type was not responsible for producing movements and is distinct from the postsaccadic activity in the frontal eye field (FEF). First, the modulation was not observed after movements in trials without a stop signal even though the metrics and dynamics of non-cancelled saccades are not different from saccades in trials without a stop signal[6]. Second, the modulation occurred after both contraversive and ipsiversive saccades whereas SEF neurons have mainly contralateral movement fields[7]. Third, the modulation had no relation to the gaze behaviour after the error, occurring with equal magnitude whether monkeys continued fixating the target or shifted gaze to the location of the fixation spot or elsewhere. The inability to explain this modulation in terms of retinal stimulation or eye movements allows the possibility that it signals the occurrence of an error. Evidence supporting this interpretation is the observation that the putative error-related activity in the SEF occupied the same interval as error-related potentials originating in medial frontal cortex[8–13] (Fig. 1c).

Several observations lead to a different interpretation of the second type of modulation (Fig. 2). It cannot be a visual response to the stop signal because it did not happen in non-cancelled trials. The activation could not contribute to cancelling the movement because it occurred after the stop-signal reaction time (Fig. 3a). To determine how this modulation related to performance, its magnitude was

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quantified as a function of both the stop-signal delay and the probability of not cancelling the movement. The strength of this modulation did not vary with stop-signal delay. However, for a given stop-signal delay the probability of cancelling the movement varied across sessions. The magnitude of the modulation increased significantly with the probability of failing to cancel the planned movement in the trials during which each neuron was recorded ($r^2 = 0.24$; t = 5.6; d.f. = 101; $P < 0.001$) (Fig. 3b). Thus, the strength of the neural signal in the SEF associated with successful cancelling of planned movements was related not to the external variable of stop-signal delay but instead to an internal variable related to performance.

During the countermanding task, gaze-shifting and gaze-holding neurons are activated concurrently when movements are cancelled[14]. Because they are mutually incompatible, co-activation of the gaze-holding and gaze-shifting systems engenders a conflict in processing that is proportional to the magnitude of co-activation[15,16]. The probability of cancelling a planned eye movement is dictated by the balance of activation of gaze-holding and gaze-shifting neurons because movements are cancelled 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 (Fig. 3b) corresponds to this measure of conflict.

Trials in which movements are not cancelled despite the stop signal provide a critical test of this interpretation. Under the particular conditions of this eye movement countermanding task, when planned movements were not cancelled, gaze-holding

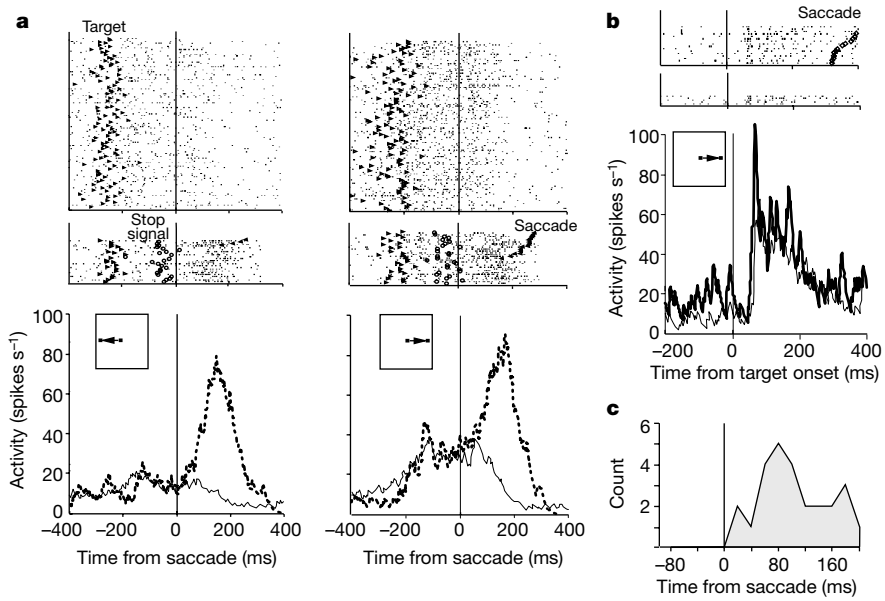

Figure 1 Putative error signal. **a**, Neural activity in no-stop-signal (top) and non-cancelled stop-signal (middle) trials, aligned on initiation of leftward and rightward eye movements with times of target, stop signal, and occasional gaze shift away from the target. Bottom, average discharge rate in no-stop-signal (solid lines) and non-cancelled (dotted lines) trials. **b**, Activity in no-stop-signal (top) and cancelled stop-signal trials (middle) aligned on presentation of target with times of eye movement in no-stop-signal trials. Bottom, average discharge rate in no-stop-signal (thin solid lines) and cancelled (thick lines) trials. **c**, Latencies of modulation after errors.

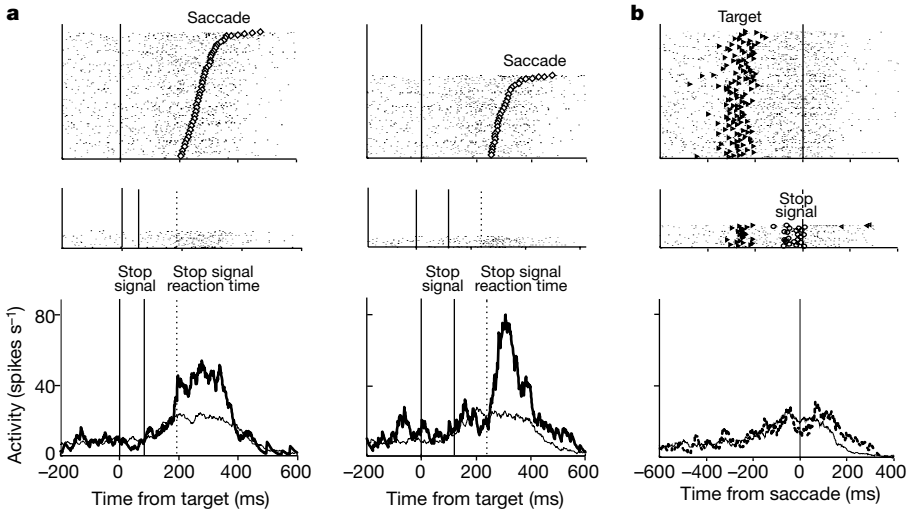

Figure 2 Putative conflict signal. **a**, Activity in no-stop-signal (top) and cancelled stop-signal (middle) trials with stop-signal delays of 93 ms (left) and 144 ms (right)—yielding 3% and 27% non-cancelled errors—with times of stop signal, stop-signal reaction time and eye movement indicated. Bottom: average discharge rate in no-stop-signal (thin lines) and cancelled (thick lines) trials. **b**, Activity in no-stop-signal (top) and non-cancelled stop-signal (middle) trials with times of target presentation, stop signal and gaze shift. Bottom: average discharge rate in no-stop-signal (thin line) and non-cancelled (thick line) trials.

neurons were not activated[14]. Hence, by definition there is no conflict of processing in non-cancelled trials. If the second type of neural modulation in SEF represents conflict in processing, then it should not occur on non-cancelled trials. To test this prediction, the magnitude of modulation in cancelled and non-cancelled trials was quantified for each neuron. Neurons that exhibited modulation in cancelled trials most commonly were not modulated in non-cancelled trials and vice versa ($\chi^2 = 762.64$; d.f. = 20; $P < 0.0001$; Fig. 3 in Supplementary Information). Thus, the data support the hypothesis that the second type of neuron in the SEF signals processing conflict.

The third type of activity in the SEF required another interpretation (Fig. 4). The countermanding task dissociates behaviour from reinforcement. Identical actions (saccades to the target) yield different outcomes (successful no-stop-signal trials or unsuccessful non-cancelled 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 behavioural response from those related to the reinforcement of that response. Although we do not have definitive data, orofacial movements provide an unsatisfactory explanation of the third type of modulation for several reasons. First, inspection of the monkeys during recordings revealed no association between the activity of these neurons and movements of the mouth. Second, the time course and level of activation was the same for trials that earned the primary reinforcer plus the secondary reinforcer as it was for trials that earned only the secondary reinforcer. Third, other investigators have reported reward-related activity in the SEF that could be dissociated from activity related to mouth movements[17]. Finally, the reinforcement-related signal in the SEF resembles neural activity associated with the receipt of reward recorded in other structures connected with the SEF[18]. Thus, neurons of the third type were the functional complement of the putative error-related neurons, signalling the expectation and receipt of reinforcement.

Whereas neural activity in the FEF was sufficient to cancel motor planning[14] or to initiate saccades[19], the present findings indicate markedly different neural modulation in the SEF, despite numerous parallels between the areas[4]. In fact, the SEF is not necessary for producing accurate visually guided saccades[20]. These observations suggest a new framework for understanding SEF function. While performing the countermanding task, subjects adjust performance across trials, increasing response time following trials with stop signals, for example[21]. Such self-adjustments have inspired the concept of a supervisory control system that monitors and controls the perception and production systems during decision making, error correction, production of responses that are not well-learned and in overcoming habitual responses[22,23]. The present results indicate that when monkeys must exert control over the initiation of an eye movement, neurons in the SEF may signal the production of an error, the anticipation of reinforcement or the presence of processing conflict. Indeed, modulated SEF activity is observed in other tasks that require suppressing prepotent responses to produce arbitrary conditional responses[24–26]. What role might the SEF play in the countermanding task? The likelihood of cancelling a movement if the stop signal happens is increased if the reaction time is

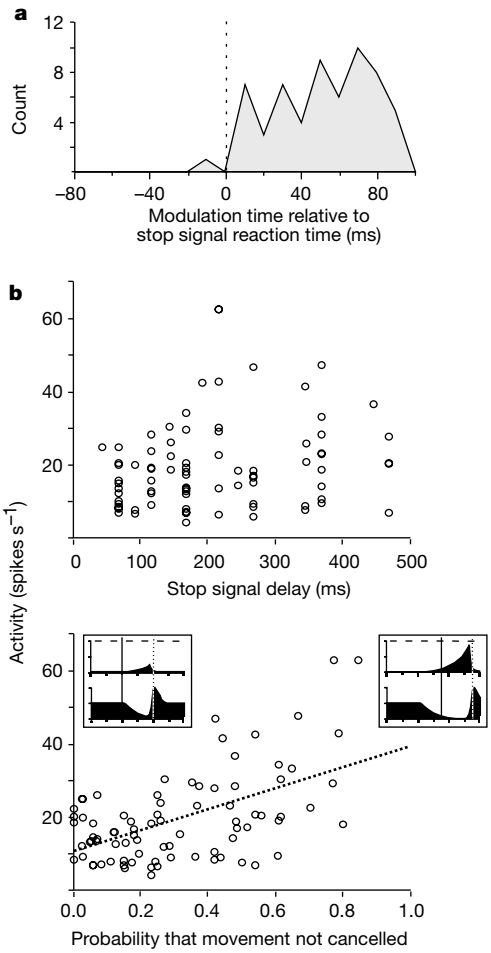

Figure 3 Population data of putative conflict signal. **a**, Latencies of modulation after cancelled movements in relation to stop-signal reaction time. **b**, Magnitude of modulation in cancelled trials plotted against stop-signal delay (top) and failure probability (bottom). Each neuron contributed a point for each stop-signal delay with sufficient data. Dotted line plots regression. Inset panels illustrate state of activation of gaze-shifting neurons (top) and gaze-holding neurons (bottom). Conflict corresponds to the magnitude of co-activation of mutually incompatible processes. On trials with low failure probability (left inset), gaze-shifting activation increases only slightly before the gaze-holding activation cancels movement preparation. Thus, the co-activation of the opposing processes is smaller. On trials with higher failure probability (right inset), gaze-shifting activation increases more before gaze-holding activity cancels movement preparation. Consequently, the co-activation of the opposing processes is greater.

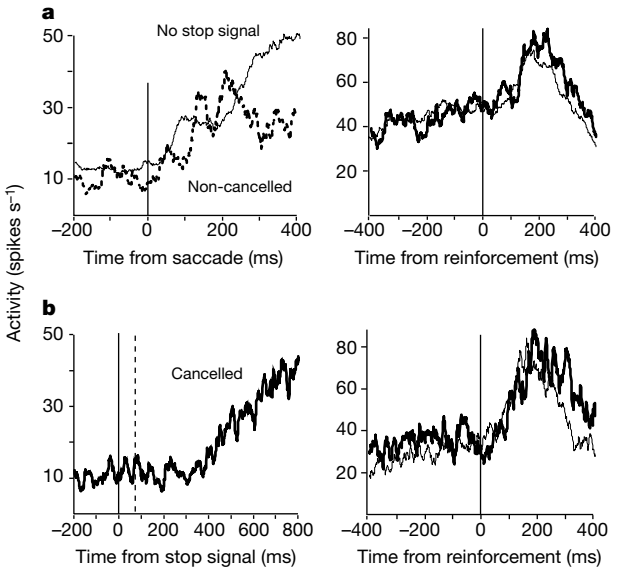

Figure 4 Putative reinforcement signal. **a**, Left, activation grew after successful no-stop-signal trials (thin line) but was reduced in non-cancelled trials (thick dotted line). Right, activation was increased while the monkey awaited reinforcement, and peaked after delivery of primary plus secondary (thick line) or only secondary (thin line) reinforcement. **b**, In cancelled trials, activation grew after the stop-signal reaction time (left) and showed the same increase before reinforcement and the same peak after delivery of primary plus secondary reinforcement (thick line) or only secondary reinforcement (thin line).

longer. Recent findings indicate that activation of the SEF can influence the excitability of gaze centres; when monkeys suppress a reflexive saccade to produce an antisaccade, neurons in the SEF show increased activity[24] while neurons in FEF[27] exhibit reduced activity. Also, electrical stimulation of the SEF inhibits neuronal activity in the FEF[28] and can delay movements[29,30]. Thus, diverse observations about SEF function might be accommodated by the hypothesis that the SEF functions as a node in the brain's supervisory control system. □

Methods

Two male macaque monkeys (*Macaca mulatta, Macaca radiata*) were prepared for training and physiological recording using aseptic procedures under isofluorane anaesthesia. The experimental protocol conformed to United States Public Health Service guidelines and was approved by the Vanderbilt Animal Care Committee. A PDP-11/83 presented stimuli and collected eye position, spike and event data.

The application of the eye movement countermanding task in neurophysiological experiments has been described[14]. After a central spot was fixated, it disappeared at the same time as a visual target was presented either in the most sensitive zone of a neuron's response field or in the opposite hemifield at the same eccentricity. On a fraction of trials after a delay, referred to as the stop-signal delay, the fixation spot reappeared, instructing monkeys to withhold the movement ('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 ('cancelled trials'). If the monkeys generated a saccade to the peripheral target during stop-signal trials ('non-cancelled trials'), no reward was given. On correct trials juice reward was given on a variable ratio schedule coupled with an acoustic secondary reinforcer given on every trial.

Performance in the countermanding task is probabilistic because of the variability in reaction times across trials. The probability of not cancelling the movement increases as the delay between the signal to initiate the movement and the signal to inhibit the movement ('stop-signal delay') increases. Stop-signal delays were varied according to the monkeys' performance, so that at the shortest (longest) stop-signal delay monkeys generally inhibited the movement on more than 85% (less than 15%) of the stop-signal trials. Movements generated with a short latency tend to be initiated before the stop-signal can influence the system. Conversely, movements generated with long latencies tend to be inhibited because there is enough time for the stop signal to influence the system. The time needed to cancel the movement, known as 'stop-signal reaction time', can be estimated from a simple race model; this model determines the response time on no-signal trials that corresponds to the probability of cancelling a movement at each stop-signal delay. The mean stop-signal reaction time calculated from the behavioural data collected while recording from SEF neurons was 100 ms (A, 104 ms; H, 95 ms).

Neural activity was compared between different types of trials using average activation functions constructed by convolving spike trains with a combination of growth and decay exponential functions that resembled a postsynaptic potential. Criteria for a significant difference in activity between either cancelled or non-cancelled trials and the appropriate latency-matched no-signal trials was that the difference in average firing rate exceed by 2 standard deviations (s.d.) the mean difference in activity during the 600-ms interval before target presentation, provided that the difference reached 6 s.d. and remained above the 2 s.d. threshold for 50 ms. The time interval between the beginning of differential activity and the stop signal reaction time was then determined. The magnitude of modulation in cancelled trials was measured as the time-averaged difference in discharge rate between the activity on cancelled and latency-matched no signal trials.

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High constitutive activity of native H_3 receptors regulates histamine neurons in brain

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Some G-protein-coupled receptors display 'constitutive activity', that is, spontaneous activity in the absence of agonist[1–4]. This means that a proportion of the receptor population spontaneously undergoes an allosteric transition, leading to a conformation that can bind G proteins[3]. The process has been shown to occur with recombinant receptors expressed at high density, and/or mutated, but also non-mutated recombinant receptors expressed at physiological concentrations[5–7]. Transgenic mice that express a constitutively active mutant of the β_2-adrenergic receptor display