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Switching from automatic to controlled action by monkey medial frontal cortex

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Human behavior is mostly composed of habitual actions that require little conscious control. Such actions may become invalid if the environment changes, at which point individuals need to switch behavior by overcoming habitual actions that are otherwise triggered automatically. It is unknown how the brain controls this type of behavioral switching. Here we show that the presupplementary motor area (pre-SMA) in the medial frontal cortex has a function in switching from automatic to volitionally controlled action in rhesus macaque monkeys. We found that a group of pre-SMA neurons was selectively activated when subjects successfully switched to a controlled alternative action. Electrical stimulation in the pre-SMA replaced automatic incorrect responses with slower correct responses. A further test suggested that the pre-SMA enabled switching by first suppressing an automatic unwanted action and then boosting a controlled desired action. Our data suggest that the pre-SMA resolves response conflict so that the desired action can be selected.

Most of our everyday actions are automatic, or have automatic components, for good reasons: they are fast, demand less effort and thus occur efficiently (for example, driving home from work through a familiar route or generating a prepotent response to accelerate upon seeing a green light). The action will continue automatically unless a new or surprising situation arises in the external environment. In such novel encounters (for example, with road work or a child on a crosswalk), the automatic action must be replaced with a deliberately controlled action (for example, making a detour through unfamiliar routes or stepping on the brake instead of automatically accelerating)[1,2]. This ability to switch actions under volitional control is the hallmark of executive functions. It allows individuals to flexibly adjust behavior to a changing environment in favor of new solutions at the cost of performance speed[3]. Although the distinction between automatic and controlled processing for human cognition has long been an important theme in the psychology literature[1,2,4,5], neural substrates for the dual processing mechanism are largely unknown. This study probes a neural account for the control process whereby automatic responses are overcome and an alternative desired response is issued.

It is known that the medial frontal cortex (MFC) is important in diverse aspects of higher motor control[6–15]. Among the areas that constitute the MFC, we are particularly interested in the pre-SMA[6,8,16,17], because previous studies suggest a function for the pre-SMA in changing action plans or task sets[18–21]. Critical aspects related to the activation of the pre-SMA are unclear, however, partly because the tasks used in earlier experiments were not aimed at elucidating the nature of the neural substrates and partly because the temporal resolution of the technique used had limitations. Furthermore, the fundamental question of how the pre-SMA switches action remains unsolved. Here, using an action-switching paradigm, we have studied single-neuron activity to test our hypothesis that the pre-SMA is important in switching from automatic to controlled action when automatic processing is no longer valid. We show that the pre-SMA achieves this type of behavioral switching well within the critical time window available for influencing behavior. Our findings also indicate that the pre-SMA enables switching by first suppressing an automatic inappropriate action and then facilitating a controlled desirable action. We discuss our findings in relation to the the conflict-monitoring hypothesis, which has been advocated on the function of the MFC.

RESULTS

Two rhesus monkeys (*Macaca mulatta*), T and S, were trained to perform a saccade-overriding task (**Fig. 1a**). In each trial, after central fixation on a white spot of light (fixation point) for 1 s, two colored stimuli (pink and yellow) appeared in the periphery, which were randomly positioned in one of two possible locations. After a brief delay (200 ms for monkey T; 100 ms for monkey S), a cue (either pink or yellow) was presented over the fixation point. The monkeys were then required to make a saccade to one of the peripheral stimuli, whose color was the same as the cue. Notably, the color of the cue remained unchanged during a block consisting of a varying number of trials ('cue-nonswitch trial') and was then switched in the next block ('cue-switch trial'). Because of this, the monkeys were able to anticipate the correct saccade target in the cue-nonswitch trials. Indeed, saccadic reaction times (SRTs) were significantly shorter and error rates were consistently lower in the consecutive cue-nonswitch trials (**Fig. 1b**,**c**; *post hoc* Tukey's least-significant-difference test, $P < 10^{-15}$), indicating that the selection of action was more automatic. This automatic action

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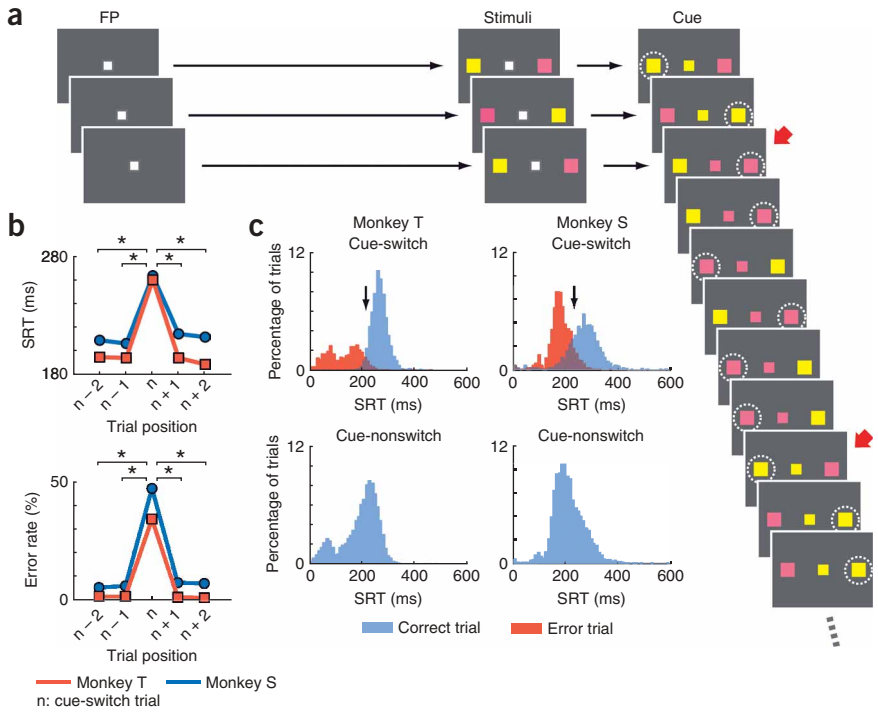

Figure 1 Behavioral task and animal performance. (**a**) The sequence of events in the saccade-overriding task. For simplicity, display panels demonstrating the onset of the fixation point (FP) and two peripheral stimuli (Stimuli) are illustrated only for the first three trials. White dotted circles (not shown to the monkeys) indicate saccade targets; red arrows represent the cue-switch trials. (**b**) Average SRTs (top) and average error rates (bottom) as a function of the trial position in blocks (n represents the cue-switch trials). *, statistically significant difference ($P < 10^{-15}$, *post-hoc* Tukey's least–significant-difference test). (**c**) Distribution of SRTs for the cue-switch trials (top) and cue-nonswitch trials (bottom). Black arrows indicate the BDT.

became unfavorable, however, in the cue-switch trials, leading to a substantial switch cost[3]; that is, higher error rates and longer saccade latencies (**Fig. 1b**,**c**). To make a correct switch better than the chance level, monkeys T and S required 213 ms and 238 ms, respectively (arrows in **Fig. 1c**; $P < 0.05$, binomial test), which will be referred to as the behavioral differentiation times (BDTs) hereafter.

Pre-SMA neural activity related to successful switching

We recorded the activity of 181 single neurons in the pre-SMA while the monkeys were performing the task. Of these, the activity of 55 neurons differed substantially in the successful cue-switch trials ('switch neurons'; see Methods). **Figure 2a** shows the responses of a single switch neuron. The trials were sorted according to their positions in each block relative to the cue-switch trials (n represents the cue-switch trial). This neuron showed a strong response before saccade initiation in the correctly performed cue-switch trials but only when the saccade target was ipsilateral. The clear laterality of the responses made it unlikely that the switch-related activation reflected an increase in arousal or task difficulty or a genuine response to conflict (response competition). We refer to this neuron as an ipsi-switch neuron, as the monkey successfully switched the saccade from the primed contralateral nontarget to the nonprimed ipsilateral target in those trials. Similarly, most switch neurons showed an increase in activity upon cue switching (increase type, $n = 50$; **Table 1**). Out of these, 26 were contra-switch neurons, 15 were ipsi-switch neurons and 9 were bilateral-switch neurons (**Table 1**). The ensemble average activity showed a clear enhancement in the correct cue-switch trials (**Fig. 2b**). Notably, when the monkeys failed to switch the saccade, the activity did not increase before saccade initiation (**Fig. 2a**,**b**). Instead, the switch neurons showed a delayed increase in activity (**Fig. 2a**,**b**). The delayed activity cannot represent a signal related to the commission of errors (error signal) because it occurred well before the error feedback signals (beep tone and the extinction of visual stimuli) and because the activity showed directional selectivity. Instead, the delayed activation on switch-error trials seems to reflect a switch signal that was unable to accomplish successful switching.

To see how the activity of the switch neurons evolved in response to the cue switch, we aligned the ensemble activity for all of the increase-type switch neurons with the cue onset (**Fig. 2c**) for the cue-switch trials (red) and cue-nonswitch trials (blue). Here the direction of the saccade target in the cue-switch trials was opposite that in the cue-nonswitch trials. For the cue-switch trials, the saccade target was in the direction for which switch neurons showed switch-related responses (for example, contralateral target for contra-switch neurons; 'sw-dir') and for the cue-nonswitch trials the saccade target was in the opposite direction (for example, ipsilateral target for contra-switch neurons; 'opp-sw-dir'). We compared these kinds of trials because they were indistinguishable for the monkeys until cue onset. In both cases the monkeys were primed for the stimulus that had been the target in the cue-nonswitch trials (but would become the nontarget in the cue-switch trials, 'opp-sw-dir'). As expected, the activity of the switch neurons was initially similar between the cue-nonswitch and cue-switch trials. The instruction to switch was given by the central cue and then the switch-related activity evolved and diverged from the activity observed in the cue-nonswitch trials 158 ms after the cue onset (neuronal differentiation time, NDT; see Methods). Notably, the NDT was shorter than the BDT, even if the pre-SMA efferent conduction delay (the conduction time needed for the pre-SMA activity to influence eye movement; 28 ms for monkey T and 35 ms for monkey S; see Methods; **Supplementary Fig. 1** online) was subtracted from the BDT (213 ms for monkey T and 238 ms for monkey S). This result indicates that the switch-related activity was early enough to cause the switching. In contrast, the NDT for switch-error trials was 220 ms (**Fig. 2c**, gray), which was later than the BDT if the pre-SMA efferent delay was subtracted. Therefore, the timing of the switch-related activity was critical for successful switching because its delay resulted in switch errors (**Fig. 2c**, gray).

Pre-SMA microstimulation improves behavioral switching

Because most of the switch neurons increased their firing on the successful cue-switch trials, it was tempting to see whether artificial activation of the pre-SMA could improve performance on those trials. For this purpose, a train of electrical pulses (60 cathodal pulses of 0.2-ms duration at 200 Hz, 60–80 μA) was delivered through the electrodes in half of the cue-switch trials, the onset of which was timed to coincide with cue onset so that stimulation simulated the switch-related activity in a slightly enhanced manner. We found that in 65%

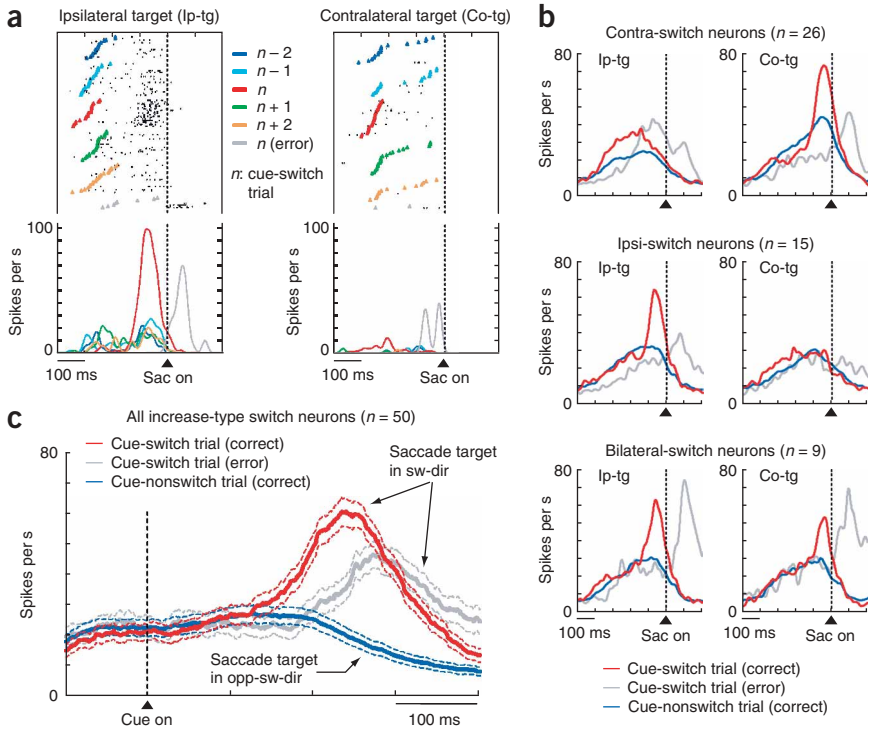

Figure 2 Switch-selective activity of pre-SMA neurons. (**a**) Activity of a single ipsi-switch neuron. Rastergrams and spike density functions (SDFs) are sorted according to the trial position in each block (n represents the cue-switch trials) and aligned with saccade onset. In rastergrams, black dots indicate the time of individual action potentials and colored triangles indicate the time of cue onset; trials are arranged in order of SRTs. Activity in switch-error trials is shown in gray. (**b**) Ensemble average SDFs for contra-switch neurons (top), ipsi-switch neurons (middle) and bilateral-switch neurons (bottom) are shown separately for the correct cue-switch trials (red), correct cue-nonswitch trials (blue) and switch error trials (gray). All SDFs are aligned with saccade onset. (**c**) Ensemble SDFs (mean ± s.d.) for all increase-type switch neurons. SDFs are aligned with cue onset. Note that the direction of the saccade target for the cue-switch trials is opposite that for the cue-nonswitch trials.

(48/74) of sessions, the percentage of correct saccades significantly increased, at least for one target position ($P < 0.05$, χ^2 test; **Fig. 3a**). The increase in the percentage of correct saccades was accompanied by delayed responses (**Fig. 3b**,**c**), implying that the monkeys' fast responses, which would have led to switch errors (**Fig. 3b**, top), were suppressed and the correct slower responses were increased instead (**Fig. 3b**, bottom). The improvement of performance was, on the whole, not due to the stimulation biasing the saccade to one spatial direction, because improvement in one direction and deterioration in the other direction was observed only in one session (**Fig. 3a**). In fact, the monkeys' performance improved bilaterally in 13 sessions (**Fig. 3a**).

We also considered the possibility that the monkeys sensed electrical stimulation and learned to use this percept to switch saccades. To test this possibility, we conducted a control experiment in which stimulation was delivered on a fraction of cue-nonswitch trials, in addition to one-half of the cue-switch trials ($n = 13$ sessions; see Methods). If the monkeys switched saccades simply on the basis of the percept of the stimulation, the percentage correct in the cue-nonswitch trials should decrease while the percentage correct in the cue-switch trials increases. We found that the stimulation in the cue-nonswitch trials did not decrease the percentage correct in any of the 13 session ($P > 0.05$), whereas the percentage correct increased in the cue-switch trials significantly in 11 sessions. Note, however, that the stimulation on the cue-nonswitch trials delayed saccade onset ($P < 10^{-9}$, Mann-Whitney U-test), similarly to the effect on the cue-switch trials.

Neural mechanisms of behavioral switching

It has been considered that behavioral switching requires two control processes: suppression of a primed (but no longer valid) behavior and facilitation of an alternative behavior[3]. To examine which action individual pre-SMA neurons may perform, we introduced a saccade go or no-go task (**Fig. 4a**). In this task, after central fixation on the fixation point for 1 s, a peripheral colored stimulus (yellow or pink) appeared randomly at one of two possible locations. After a short delay

Table 1 Classification of switch neurons

	Increase-type			Decrease-type		Mixed type
	Contralateral-switch (n = 26)	Ipsilateral-switch (n = 15)	Bilateral-switch (n = 9)	Contralateral-switch (n = 2)	Ipsilateral-switch (n = 2)	Contra-switch (increase) & ipsi-switch (decrease) (n = 1)
Contra go	4	0	1	0	0	0
Ipsi no-go	4	0	0	0	1	0
Contra go & ipsi no-go (dual)	9	0	0	0	0	0
Ipsi go	0	0	1	0	0	0
Contra no-go	0	1	0	0	0	0
Ipsi go & contra no-go (dual)	0	2	0	1	0	0
Bilateral go	0	0	1	1	0	0
Bilateral no-go	2	1	0	0	0	0
Non-selective	3	7	3	0	0	1
Not tested	4	4	3	0	1	0

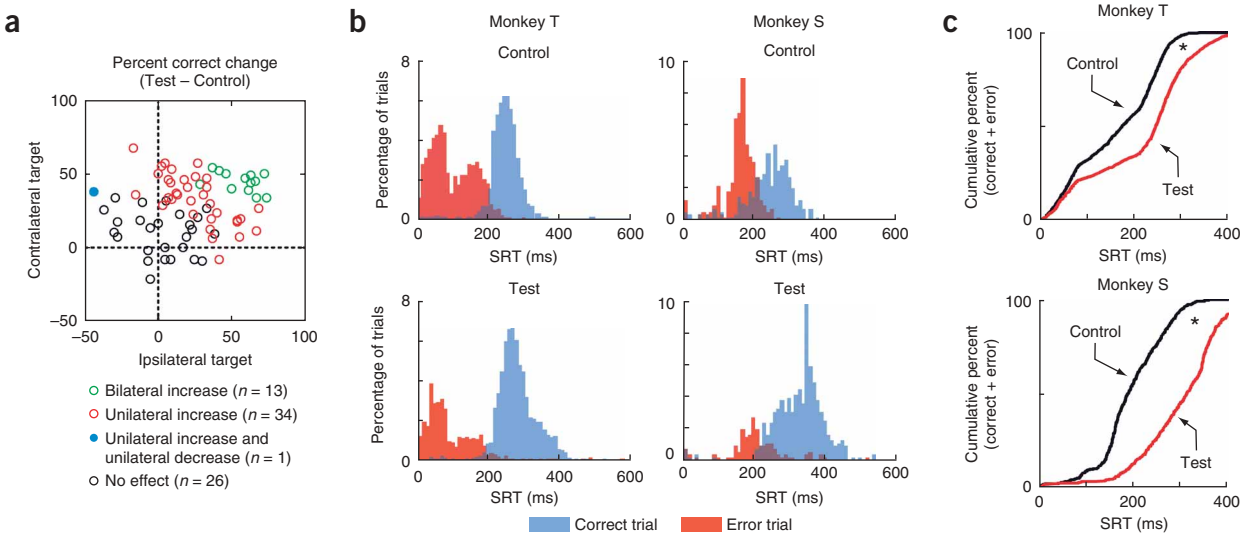

Figure 3 Effects of electrical stimulation in the pre-SMA on performance of the cue-switch trials. (**a**) Changes in the percentage correct when the saccade target was contralateral (ordinate) plotted against changes in the percentage correct when the saccade target was ipsilateral (abscissa). Positive values indicate improvement of performance, whereas negative values indicate deterioration. Cue-switch trials with stimulation were referred to as test trials and those without stimulation as control trials. Each circle represents the data from a single session (total $n = 74$). Statistically significant effects are shown by colored circles (see inset). (**b**) The distribution of SRTs in the cue-switch trials for the control (top) and test (bottom) trials. The SRTs for the correct trials were significantly longer in test trials than in control trials ($P < 10^{-51}$ for both monkeys, Mann-Whitney *U*-test). (**c**) Cumulative percentage of SRTs for the control (black) and test (red) trials, in which correct and error trials are combined. *, statistically significant difference ($P < 10^{-63}$ for both monkeys, Kolmogorov-Smirnov test).

(200 ms for monkey T, 50 ms for monkey S), the color of the fixation point changed to one of the two stimulus colors. If the colors of the fixation point and the stimulus were the same (50–70% of all trials), the monkeys had to make a saccade to the stimulus (go trial). If different, the monkeys had to withhold saccade initiation (no-go trial). **Figure 4b** shows the responses of the same switch neuron as is shown in **Figure 2a**. When a peripheral visual stimulus was presented ipsilaterally (**Fig. 4b**, left), the neuron initially responded to the stimulus non-differentially. After the onset of the cue, however, the neuron showed a stronger response in the go trials than in the no-go trials ($P < 0.05$, re-sampling). By contrast, when the stimulus was presented contralaterally (**Fig. 4b**, right), the neuron showed a stronger response in the no-go trials than in the go trials ($P < 0.05$, re-sampling). These results suggest that this switch neuron facilitated ipsilateral saccades and inhibited contralateral saccades (dual type). Note that the combination of these neuronal actions was totally congruent with the requirement for this neuron to switch ipsilaterally (**Fig. 2a**), supporting the view that the switch-related activity represents the control signal for saccade switching. Out of 43 switch neurons that were tested in the saccade go or no-go task, 9 neurons were classified as pure no-go type, 12 neurons were dual type, 8 neurons were pure go type and 14 neurons were nonselective type (**Table 1**). None of the switch neurons showed a totally incompatible pattern in terms of directional selectivity between the saccade-overriding task and the saccade go or no-go task (for example, an ipsi-switch neuron showing ipsilateral no-go activity).

As mentioned, it was crucial for the switch neurons to generate switch-related activity early enough to achieve saccade switching (**Fig. 2c**). We thus measured the NDT for individual switch neurons: that is, the time when the switch-related activity in the cue-switch trials started to diverge from the activity in the cue-nonswitch trials. We found that the NDT for no-go and dual-type neurons was significantly earlier than that for go type neurons (**Fig. 4c**; $P < 0.01$, *post-hoc* Tukey's least-significant-difference test) and that most of their NDT preceded the BDT (**Fig. 4c**, left). Notably, in 57% (12/21) of neurons that were either no-go or dual type, the NDT preceded the BDT by more than, or equal to, the pre-SMA efferent delay. This suggests that the switch neurons with inhibitory functions are important in successful saccade switching. Although the NDT of go-type neurons was significantly later and often followed the BDT (**Fig. 4c**, left), it still preceded the average SRT (**Fig. 4c**, right), suggesting that go-type switch neurons were also capable of contributing to saccade switching, especially on trials with the delayed initiation of saccades.

DISCUSSION

We have shown that a group of neurons in the pre-SMA was activated selectively and phasically before the monkeys successfully switched to a desired alternative saccade by overriding an automatic invalid saccade. These neurons also fired on switch-error trials, but the onset of their activation was too late to successfully override the automatic saccade. These findings are relevant to a conflict-monitoring hypothesis which has been advocated on the function of the MFC[12], because the cue-switch trial in the saccade-overriding task invokes a conflict between the correct saccade to the nonprimed target and the incorrect saccade to the primed target.

The conflict-monitoring hypothesis assumes that certain brain regions detect and signal the occurrence of conflict, thereby triggering strategic adjustments in cognitive control in subsequent performance. Although the conflict-monitoring function is generally ascribed to the anterior cingulated cortex (ACC)[12], some recent studies have suggested that the relevant function may instead lie within the pre-SMA[15,22–24] or the adjacent supplementary eye field (SEF)[25]. Moreover, one model predicts that the conflict tends to precede the overt response on correct trials, but tends to follow the response on error trials[26]. We observed this in switch neurons in the pre-SMA. This parallel raises the possibility that the activity of the pre-SMA switch neurons reflects the monitoring of conflict.

Our experiments, however, suggest that the pre-SMA acts to resolve response conflict. First, when the switching was successful in the

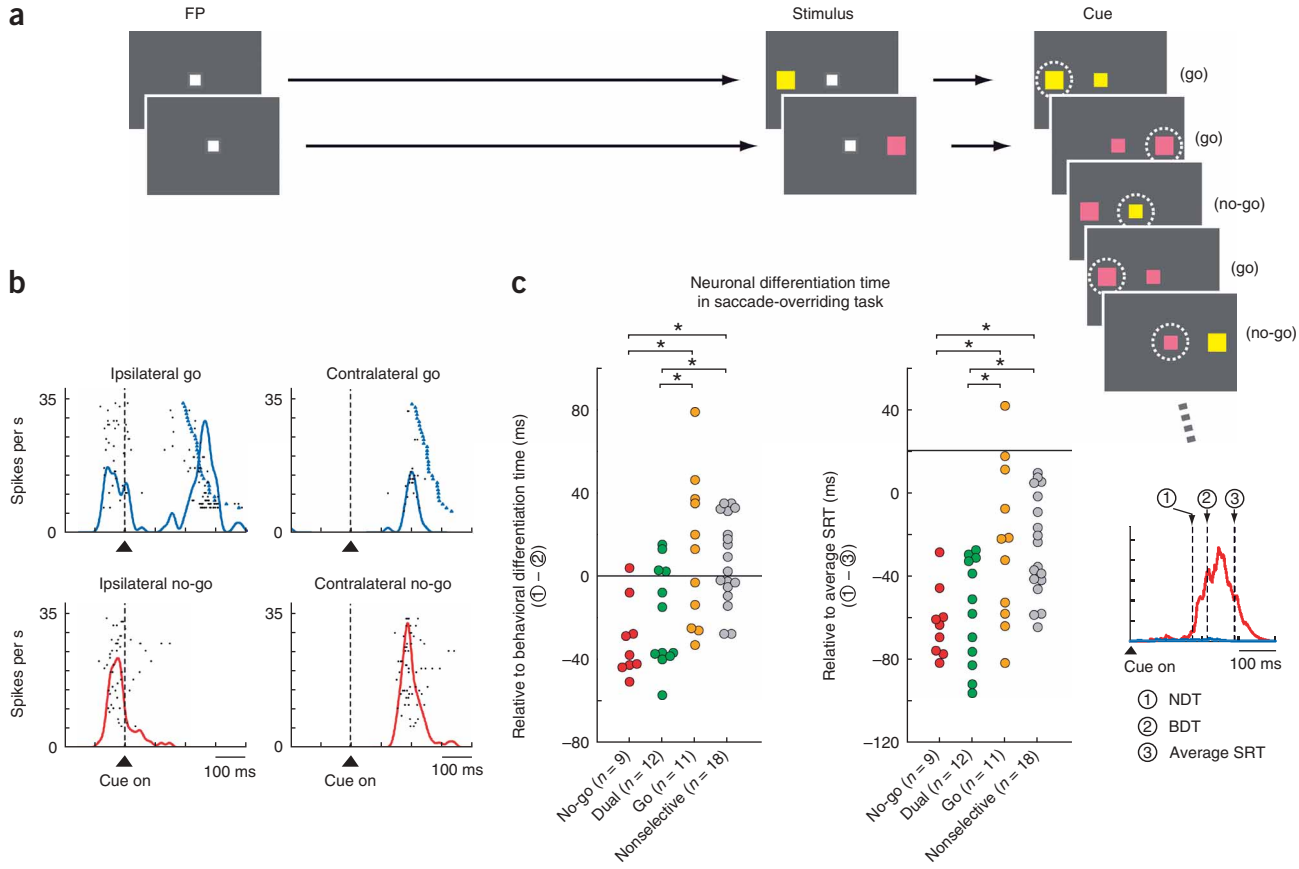

Figure 4 Characterization of pre-SMA switch neurons using the saccade go or no-go task. (**a**) The sequence of trial events. For simplicity, display panels demonstrating the onset of the fixation point (FP) and a peripheral stimulus (Stimulus) are illustrated only for the first two trials. White dotted circles indicate the direction of gaze required for a correct response. (**b**) The responses of the same switch neuron as shown in **Figure 2a**. Rastergrams and SDFs are aligned with cue onset. In the top panels (go trials), trials are arranged in order of SRTs; blue triangles indicate the time of saccade onset. (**c**) The NDT for individual switch neurons relative to the BDT (left) and relative to the average SRT (right). Negative values indicate that the NDT preceded the BDT (left) or average SRT (right). Switch neurons are grouped according to their functional subtypes in the saccade go or no-go task. Bilateral-switch neurons yielded two data points. *, statistically significant difference ($P < 0.01$, *post-hoc* Tukey's least significant difference test). Inset shows how to compute these time values for the neuron shown in **Figure 2a** as an example; activity for the cue-switch trials is indicated in red and activity for the cue-nonswitch trials in blue.

saccade-overriding task, the onset of the pre-SMA switch-related activity was earlier than the onset of reliable behavioral switching judged as the transition from premature incorrect saccades to correctly switched saccades. This indicates that the pre-SMA switch-related activity is early enough to initiate the switch before a primed, but incorrect, saccade is triggered. By contrast, when the onset of the pre-SMA switch-related activity started later, the switching was unsuccessful. These findings strongly suggest that the pre-SMA is necessary for behavioral switching and its early activation is crucial for successful switching. Second, the fact that the majority of the switch neurons showed directional selectivity also supports an executive function, rather than a monitoring function, for the pre-SMA. Third, the examination of the switch-related pre-SMA neurons in the saccade go or no-go task suggests that they are capable of inhibiting saccades in one direction and facilitating saccades in the other direction. In most cases, these motor effects (for example, contra go and ipsi no-go) were consistent with the requirements for the particular type of switching (for example, ipsi-to-contra switching; **Table 1**). Finally, artificial activation of the pre-SMA by electrical microstimulation increased the percentage of correct saccades on the cue-switch trials.

Several functional neuroimaging studies in humans have recently revealed that the blood oxygen level–dependent (BOLD) signal increase seen in the pre-SMA is positively related to the level of response conflict[22–24]. Based on this, the authors speculate that the pre-SMA may resolve response conflict rather than signal the conflict *per se*. Our findings provide strong evidence in favor of this hypothesis, suggesting that the pre-SMA indeed acts to resolve response conflict between incompatible motor plans so that the desired action can be selected. It should be emphasized that examining the neural activity in fine time resolution in relation to switching behavior and examining the motor effects of single neurons were crucial for drawing the above conclusion from our experiments, neither of which could be done in human imaging studies. On the other hand, it is difficult to train animals to perform complex switching tasks, which allow us to disentangle the cognitive factors involved in behavioral switching. In this sense, human and animal experiments have complemented each other to allow researchers to reach a functional concept of the pre-SMA.

Our data, together with a report on human subjects[21], suggest that the pre-SMA is involved in executive control over behavior. However, the neighboring areas, including the SEF and ACC, might perform a

function similar to that of the pre-SMA. A recent stimulation experiment in monkeys shows that the SEF has an executive influence on action[27] separate from its monitoring function[10,25]. Another line of study in monkeys shows that rostral cingulate motor area neurons are crucial in the voluntary shift of movement based on reward[28]. These studies suggest that the MFC participates in top-down control over behavior, in addition to evaluative control. Further studies are necessary to determine the unique functions of these cortical areas in executive motor control.

It is well known that automatic or habitual actions are fast whereas cognitively controlled actions are slow[2]. In other words, the automatic process produces output more quickly than the controlled process. Thus, for the switch mechanism to work efficiently, the inhibition of the automatic process should occur first to prevent the execution of a habitual response. By contrast, the facilitation of the controlled process may occur later. In support of this idea, the switch neurons with a no-go action became active earlier than those with a go action. The inhibitory effect of electrical stimulation in the pre-SMA shown in this study and a previous study[29] may also indicate that the switch neurons with a no-go action are important in switching. Our data thus suggest that the pre-SMA enables behavioral switching in a behaviorally efficient manner.

It would be useful to discuss the possible neural pathways whereby the pre-SMA is capable of suppressing undesirable saccades. There are two major areas to which the pre-SMA projects directly: the prefrontal or premotor cortex and the basal ganglia[30,31]. Considering cortical structures, it is known that the frontal eye field (FEF)[32–34] and the SEF (S.J. Heinen & A.N. Anbar, *Soc. Neurosci. Abstr.* 451.19, 1998) can suppress the initiation of saccades. The pre-SMA, however, does not project to the FEF[35–37]. Moreover, the projection from the pre-SMA to the SEF remains controversial[30,38], though this possibility cannot be ruled out entirely. In contrast, the basal ganglia are equipped with long-range inhibitory connections that could contribute to the selection of appropriate behavior[39]. Particularly important for saccadic eye movement is the inhibitory connection from the substantia nigra pars reticulata (SNr) to the superior colliculus (SC)[40]. The pre-SMA could enhance the SNr-induced inhibition of SC neurons via two routes: the so-called 'hyperdirect pathway' from the frontal cortex to the SNr through the subthalamic nucleus (STN)[41] and the so-called 'indirect pathway' from the caudate nucleus (CD) to the SNr through the external segment of the globus pallidus[42]. Between them, the former appears to take precedence because its conduction time is much shorter[43,44]. Indeed, a recent human neuroimaging study pointed out the importance of the STN in response inhibition[45]. Altogether, the pathway from the pre-SMA to the SNr through the STN seems to be a good candidate for the anatomical substrate for the suppression of unwanted saccades, which must be accomplished quickly. On the other hand, the facilitation of saccades by the pre-SMA could be ascribed to the so-called 'direct pathway' from the CD directly to the SNr, which subserves disinhibition of the target neurons in the SC[40]. Further studies are necessary to test the basal ganglia hypothesis in relation to behavioral switching.

In summary, the present study shows that neurons in the pre-SMA become active when subjects are successful in switching from an automatic unwanted action to a controlled desired action. Notably, the time of the neuronal activation was early enough for the pre-SMA to ensure successful switching. Modeling published in the psychology literature has indicated that a certain system intervenes in nonroutine situations when routine actions or habits have to be altered or inhibited in favor of a novel behavioral demand[1]. Our data seem to provide anatomical and physiological accounts for the controlled process under which the organisms dynamically switch actions in a constantly changing environment.

METHODS

General. Two rhesus monkeys, T and S, were used as subjects in this study. All animal care and experimental procedures were approved by the National Eye Institute. Institute Animal Care and Use Committee and complied with the Public Health Service Policy on the humane care and use of laboratory animals. During experimental sessions, the monkeys were seated in a primate chair and placed in a sound-attenuated room. Visual stimuli were rear-projected by an active-matrix liquid crystal display projector onto a frontoparallel screen 33 cm from the monkey's eyes. Eye movement was monitored using a scleral search coil system with 1-ms resolution. For single-neuron recordings, we used conventional electrophysiological techniques described previously[46].

Behavioral tasks. The monkeys were trained to perform the following three tasks by operant conditioning with positive reinforcement: a memory-guided saccade task, a saccade-overriding task and a saccade go or no-go task. All trials started with the presentation of a white spot of light (fixation point) at the center of a screen, which the monkeys had to fixate on.

In the memory-guided saccade task, a peripheral cue came on for 100 ms after the monkeys had fixated on the fixation point for 800 ms. The monkeys were required to remember the cued location while maintaining central fixation on the fixation point for another 800–1,200 ms. The fixation point then disappeared and the monkeys had to make a saccade to the cued location. A reward was given for the correct saccade. This task was used to estimate the response field of a cell under study.

In the saccade-overriding task, after the monkeys had fixated on the fixation point for 1 s, two colored stimuli (yellow and pink) were presented in the periphery. The positions of the stimuli were randomly determined out of two possible locations: one in the cell's response field and the other in the diametrically opposite position if a cell under study had a clear response field; otherwise the stimuli were presented to the right and to the left of center (10–20° in eccentricity). After a short delay (200 ms for monkey T, 100 ms for monkey S), the color of the fixation point was changed to one of the two stimulus colors ('cue'). The monkeys were then required to make a saccade within 1 s to the stimulus whose color was the same as the cue (target stimulus). A reward was given after the monkeys captured the correct target and maintained the fixation for another 300 ms. A saccade to the other stimulus—the stimulus whose color was different from that of the cue (nontarget stimulus)—was treated as an error and was not rewarded. In those switch-error trials, a tone signal was given for 200 ms as a feedback as soon as the eye entered an electronic window centered at the wrong target ($\sim$35 ms after saccade onset), which was followed by the extinction of visual stimuli. Importantly, the color of the cue remained unchanged during a block of trials (the number of trials per block varied randomly: 1–10 for monkey T, 1–8 for monkey S) and then was switched in the next block. We refer to the first trial of individual blocks as cue-switch trials and the remaining trials as cue-nonswitch trials. The interval between the stimulus onset and cue onset for monkey S was shorter (100 ms) than that for monkey T (200 ms) because monkey S was unable to succeed in the cue-switch trials if the interval was equal to, or longer than, 150 ms (percent error, 93.1%) due to very fast responses in the cue-nonswitch trials (mean SRT, 116.6 ms; median SRT, 98.0 ms).

In the saccade go or no-go task, after the monkeys fixated on the fixation point for 1 s, a peripheral colored stimulus (either yellow or pink, unpredictable to the monkeys) appeared randomly at one of two possible locations: if a cell under study had a clear response field, this location was either in the cell's response field or in the position diametrically opposite to it; otherwise, the stimulus was presented to the right or to the left of center (10–20° in eccentricity). After a short delay (200 ms for monkey T, 50 ms for monkey S), the color of the fixation point changed. If the colors of the fixation point and the stimulus were the same (50–70% of all trials), the monkey had to make a saccade to the stimulus (go trial). If these were different, the monkey had to withhold saccade initiation and continue central fixation (no-go trials). A reward was given after each correct go or no-go response.

Cortical localization. Neuronal recordings were made in three hemispheres of the pre-SMA. The pre-SMA is involved in motor control in an effector-nonselective manner[8,47,48]. The pre-SMA was defined in accordance with physiological criteria established previously[17]. For this, we first physiologically mapped the SMA by observing somatosensory responses and bodily movements elicited by intracortical microstimulation, ICMS (a train of 12–22 cathodal pulses of 0.2-ms duration at 330 Hz). The pre-SMA was then identified rostrally to the face representation of the SMA, in which ample visual responses were observed and forelimb movements were elicited by ICMS with relatively high currents (30–80 μA) and with more pulses (40–50 pulses), usually when the monkeys were executing natural arm movements[7,16,17,29]. In the identified pre-SMA, eye movements were not evoked *de novo* with currents up to 80 μA, confirming that the recording sites did not include the supplementary eye field. The location of neuronal recording and electrical stimulation in the pre-SMA is shown in **Supplementary Figure 2** online.

Electrical stimulation during the saccade-overriding task. To see the effects of electrical stimulation on the percentage correct and SRTs in the cue-switch trials, we delivered ICMS in the pre-SMA in half of the cue-switch trials (test trials). In the remaining half, we did not deliver stimulation (control trials). The ICMS delivered was a 300-ms train of cathodal pulses (pulse width, 0.2 ms) at 200 Hz and its onset was timed at the cue onset so that ICMS could simulate and enhance the firing of the switch neurons (**Fig. 2c**). The stimulus current was typically set at 80 μA (60–80 μA) based on a previous report[29].

To rule out the possibility that the monkeys might have used the delivery of ICMS *per se* as a cue to switch the saccade, we employed 13 control experimental sessions. For the control sessions, in addition to one-half of the cue-switch trials, ICMS was applied either on one-half of the second trials in each block (that is, '$n+1$' cue-nonswitch trials; $n = 3$ sessions) or on randomly chosen cue-nonswitch trials ($n = 10$ sessions). If ICMS, in fact, cued the monkeys to switch the saccade, then the effects of ICMS should be equally expected on the cue-switch trials and cue-nonswitch trials. Specifically, the percentage correct of the cue-switch trials should increase whereas that of the cue-nonswitch trials should decrease.

Statistical analysis. To define a switch neuron, we compared the firing frequency during a presaccadic interval in the saccade-overriding task among the following three conditions: case 1, correct cue-switch trials in which the saccade was made to the target in one direction; case 2, correct cue-nonswitch trials in which the saccade was made to the same target as in case 1; case 3, correct cue-nonswitch trials in which the saccade was made to the target opposite to case 1.

A neuron was then accepted as a switch neuron if the firing frequency during the presaccadic interval (see below) in case 1 was significantly larger (for increase-type) or smaller (for decrease-type) than that in both case 2 and case 3 (one-way ANOVA, $P < 0.05$; followed by Tukey's least-significant-difference test, $P < 0.05$). We performed this procedure separately for the contralateral and ipsilateral targets. To determine the presaccadic interval for the above comparison, we first analyzed all of the data using time windows ranging from 50- to 100-ms duration before saccade initiation with a 5-ms step. We then chose an 85-ms window as the presaccadic interval because it maximized the number of switch neurons; we wanted to collect and further characterize as many potentially interesting neurons as possible. Our choice was justified by the fact that the ensemble activity aligned with saccade onset for the cue-switch trials significantly diverged from that for the cue-nonswitch trials 88 ms before saccade initiation (data not shown).

We included case 3 in the above comparison to rule out a spurious effect derived from the difference in the monkeys' 'set' in the initial phase of the cue-switch trials. Suppose that a neuron simply displays direction-selective activity before contralateral saccades without any additional switch-related activity. This neuron would not fire before ipsilateral saccades in the cue-nonswitch trials (case 2). When the target is presented ipsilaterally on the cue-switch trial (case 1), this neuron would initially fire because the monkey has been primed for the contralateral nontarget (because it has been the target). Even though the monkey eventually switches correctly to an ipsilateral saccade, the neuronal activity driven by the primed set may remain until the onset of the correct ipsilateral saccade. The comparison between case 1 and case 2 alone would characterize this neuron as switch related. The neuron, however, would fire before contralateral saccades in the cue-nonswitch trials (case 3), as well as in case 1. The inclusion of case 3 would thus eliminate such direction-selective activity.

Continuous neuronal activation functions (spike density functions, SDFs) were generated by convolving each spike with a Gaussian kernel (s.d. = 10 ms). Ensemble averaged SDFs were then constructed by averaging individual SDFs with weights depending on the number of trials for each neuron.

To measure the BDT in the saccade-overriding task (**Fig. 1c**), the frequency distribution of SRTs was constructed for both correct switch trials and switch error trials (bin width, 5 ms). The binomial test ($P < 0.05$) was then applied to each bin to test whether the occurrence of correct trials was significantly larger than chance. The BDT was finally determined as the center of the first bin from which a significant difference continued for at least ten bins (that is, 50 ms).

To classify the neuronal type in the saccade go or no-go task, we adopted the following logic: if a neuron is related to a saccade-generation process (go type), then the peak activity of that neuron during the presaccadic interval in the correct go trials must exceed its peak activity in the correct no-go trials. In contrast, if a neuron is related to a saccade-suppression process (no-go type), then its peak activity in the correct no-go trials must exceed its peak activity during the presaccadic interval in the correct go trials. To assess this, we compared the peak values of SDF in the following time windows between go and no-go trials. For go trials, we aligned the neuronal activity with saccade onset and set an 85-ms window before saccade onset (we used the same duration of time window as in the saccade-overriding task). For no-go trials, we aligned the neuronal activity with cue onset and set an 85-ms window whose center was at the BDT for the saccade go or no-go task (see below). The latter choice was based on the assumption that, in order for the monkeys to reliably cancel the saccade in no-go trials, the required neuronal process must have been completed by the BDT. To determine the statistical significance of difference in the peak activity between go and no-go trials, we used a re-sampling procedure[49] ($n = 1{,}000$) to estimate a 95% confidence interval of the activity difference.

The BDT in the saccade go or no-go task was computed in a manner similar to that in the saccade-overriding task. In short, the frequency distribution of SRTs was constructed for the correct no-go and incorrect no-go (that is, noncancellation error) trials (bin width, 5 ms). The binomial test ($P < 0.05$) was then applied to each bin to test whether the occurrence of correct trials was significantly larger than chance. The BDT was finally determined as the center of the first bin from which a significant difference continued consecutively for at least 10 bins (that is, 50 ms), which was 187.5 ms for monkey T and 222.5 ms for monkey S.

The NDT for individual switch neurons (**Fig. 4c**) was estimated by a re-sampling procedure[49]. Suppose that we had 15 correct cue-switch trials and 20 correct cue-nonswitch trials for a particular neuron. For this neuron, we drew 15 trials with replacement at random from the cue-switch trials and constructed SDF aligned on cue onset. Likewise, we drew 20 trials with replacement at random from the cue-nonswitch trials and constructed SDF aligned on cue onset. We then sought the time when the two SDFs started to diverge. For this purpose, we first searched the time bin (bin width, 1 ms) where the difference in the two SDFs was maximum, during an interval delimited by cue onset and the longest SRT obtained in that session. We then sought backward in time for the first bin where the two SDFs first crossed (intersection time). To estimate the confidence limits for the intersection time, we repeated this procedure 1,000 times and took the 97.5 percentile point as the NDT for the neuron. In the comparison of SDFs between the two trial groups, the saccade target in the cue-switch trials was in the opposite direction from the saccade target in the cue-nonswitch trials. For the cue-switch trials the saccade target was in the direction in which switch neurons showed switch-related responses (for example, the contralateral target for contra-switch neurons) and for the cue-nonswitch trials the saccade target was in the opposite direction (for example, the ipsilateral target for contra-switch neurons). The rationale for this comparison is as follows: the monkeys' set before target onset should be the same between these cases (for example, primed for the ipsilateral target) and any switch-related response must appear as a divergence of activity in the cue-switch trials from activity in the cue-nonswitch trials. In estimating the NDT described above, we adopted two conservative procedures. First, we chose

the cue-nonswitch trials whose SRTs were longer than the BDT in the saccade-overriding task ($\geq$213 ms for monkey T; $\geq$238 ms for monkey S). Because the SRTs in the cue-nonswitch trials were consistently shorter (**Fig. 1b**,**c**), inclusion of all cue-nonswitch trials would make the NDT unfairly shorter. Second, we used an asymmetric kernel with a combination of growth and decay exponential functions that resembled a postsynaptic potential to construct SDFs for the precise time-course analysis[50]. Our motivation using of this asymmetric kernel was that with this kernel, each spike exerts influence only forward in time, whereas with the Gaussian kernel, spikes exert influence backward in time as well. Indeed, the use of the Gaussian kernel with a 10-ms s.d. yielded systematically earlier NDT than was obtained with the asymmetric kernel, by an average of 21.0 ms.

The NDT for a population of the switch neurons (**Fig. 2c**) was also estimated using re-sampling. As described in the Results, we recorded from 50 increase-type switch neurons. This means that we had 50 pairs of SDFs (constructed with the asymmetric kernel) for cue-switch and cue-nonswitch trials, with each pair being derived from individual switch neurons. From these, we drew 50 pairs with replacement at random and constructed the ensemble average activity for cue-switch and cue-nonswitch trials. We then sought the time when the two average activities started to diverge. For this purpose, we first searched the time bin (bin width, 1 ms) where the difference in the two activities was at a maximum, during an interval delimited by cue onset and the longest SRT. We then sought backward in time for the intersection time. To estimate the confidence limits for the intersection time, we repeated this procedure 1,000 times and took the 97.5 percentile point as the NDT for a population of neurons.

To estimate the pre-SMA efferent conduction delay for monkey T, we used the difference in SRT distribution between control and test trials that was induced by electrical stimulation during the saccade-overriding task (**Fig. 3c**, top). As shown, the electrical stimulation shifted the cumulative percentage distribution to the right (**Fig. 3c**, top, red line), but this occurred only after some time period following the stimulation onset. In other words, the cumulative percentage for the control and test trials first overlapped and then diverged. This point of divergence should correspond to the efferent delay (that is, the conduction time needed for the pre-SMA activity to influence eye movement). To this end, we first constructed an average cumulative percentage distribution (aCPD) separately for the control and test trial using sessions in which stimulation significantly improved performance. Next, we searched the time bin (bin width, 1 ms) where the difference in the two aCPDs was maximum. We then sought backward in time for the intersection time. We estimated a 95% confidence interval of the intersection time using re-sampling ($n = 1{,}000$). The efferent conduction delay was finally defined as a time point corresponding to a 97.5 percentile of the intersection time (**Supplementary Fig. 1**).

We were unable to employ the same procedure to estimate the pre-SMA efferent conduction delay for monkey S because of a lack of SRTs shorter than 100 ms (**Fig. 3b**, right). Instead, we used the same procedure as reported previously[29]. For this purpose, monkey S was trained to perform a delayed visually guided saccade task. In short, after the central fixation on the fixation point for 800 ms, a peripheral target stimulus came on either to the right or to the left of center (15° eccentricity), but the monkey was required to maintain central fixation for another 800–1,200 ms. The fixation point then disappeared, which signaled the monkey to make a saccade to the visible target. During performance of this task, electrical stimulation was delivered in half of the trials. The ICMS delivered was a 150-ms train of cathodal pulses (pulse width, 0.2 ms) at 330 Hz with current intensity at 80 μA, and its onset was timed so that roughly half of the stimulation trials were affected[29]. Specifically, the onset of stimulation was timed at 180–240 ms after the GO signal (disappearance of the fixation point). As reported[29], this stimulation procedure delayed saccade initiation, particularly for ipsiversive saccades. To estimate the efferent conduction delay for monkey S, we first constructed the aCPD aligned with stimulation onset separately for the control and test trials by using sessions in which stimulation significantly affected SRTs (Kolmogorov-Smirnov test, $P < 0.05$). Next, we searched the time bin (bin width, 1 ms) where the difference in the two aCPDs was maximum. We then sought backward in time for the intersection time. A 95% confidence interval of the intersection time was estimated by re-sampling ($n = 1{,}000$). The efferent conduction delay was finally defined as a time point corresponding to a 97.5 percentile of the intersection time (**Supplementary Fig. 1**).

All the statistical procedures were assessed by two-tailed tests and carried out using commercial software (MATLAB 7.0, MathWorks).

Note: Supplementary information is available on the Nature Neuroscience website.

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AUTHOR CONTRIBUTIONS

M.I. and O.H. jointly designed the study, performed the experiments, conducted the data analyses and wrote the manuscript.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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