

Brain mechanisms for switching from automatic to controlled eye movements

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Abstract: Human behaviour is mostly composed of habitual actions that require little conscious control. Such actions may become invalid if the environment changes, at which point we need to switch behaviour by overcoming habitual actions that are otherwise triggered automatically. It is unclear how the brain controls this type of behavioural 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. This was demonstrated using colour-matching saccade tasks performed by rhesus monkeys. We found that a group of pre-SMA neurons was selectively activated when subjects successfully switched from a habitual saccade to a controlled alternative saccade. Electrical stimulation in the pre-SMA replaced automatic incorrect saccades with slower correct saccades. A further test suggested that the pre-SMA enabled switching by first suppressing an automatic unwanted saccade and then boosting a controlled desired saccade. Our data suggest that the pre-SMA resolves response conflict so that the desired action can be selected. Possible neuronal circuits through which the pre-SMA might exert its switching functions will be discussed.

Keywords: presupplementary motor area; medial frontal cortex; subthalamic nucleus; substantia nigra pars reticulata; basal ganglia; monkeys; saccadic eye movement; habitual action; conscious control; decision-making

Parallel neural network for controlling behaviour

Our daily behaviour consists mostly of habitual actions. You get up in the morning, take a shower, eat breakfast, drive your car to workplace, and start your computer to check emails. You may pay little attention to each of these steps and may not remember where you parked your car. One day, however, you may find that your usual parking lot

is under construction. Then, you decide not to go into the parking lot and think hard where to go.

Habitual actions make our life efficient and easy. They can be performed smoothly and quickly with little mental efforts (owing to learning based on everyday practice) (Anderson, 1982). This is because, as previous research suggests (Hikosaka et al., 1999), such learned procedures or habits are controlled by the motor part of the brain (such as the motor cortex, anterior part of the cerebellum, posterior part of the basal ganglia) whereas the cognitive part of the brain (such as the prefrontal and parietal association cortices, posterior part of the cerebellum, anterior part of the basal ganglia) is at rest.

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However, such habitual actions may suddenly become inappropriate if something changes in our environment (Monsell, 2003). Then, the ongoing routine processes in the motor part of the brain must be stopped and instead the cognitive part of the brain must kick in swiftly. This is an important moment of decision-making.

Several lines of research have suggested the presupplementary motor area (pre-SMA) plays a key role in such a behavioural switching process (Shima et al., 1996; Nakamura et al., 1998; Ullsperger and von Cramon, 2001; Rushworth et al., 2002; Nachev et al., 2005; Crone et al., 2006; Woodward et al., 2006). However, the underlying mechanism is still unclear.

Switching from automatic to controlled behaviour

Suppose, in context alpha, action A is appropriate (Fig. 1A). By repeating action A in this context, it becomes habitual or automatic. At some point the context may change, say, to beta, and action A is no longer appropriate and instead action B becomes appropriate. In other words, you have to switch from action A to action B. To enable the switching, you have to do two things: (1) suppress action A which has been automatic or habitual, and (2) boost action B which has been suppressed.

An important step in our research was to create this sort of switching in a behavioural task for monkeys. After many attempts we came up with

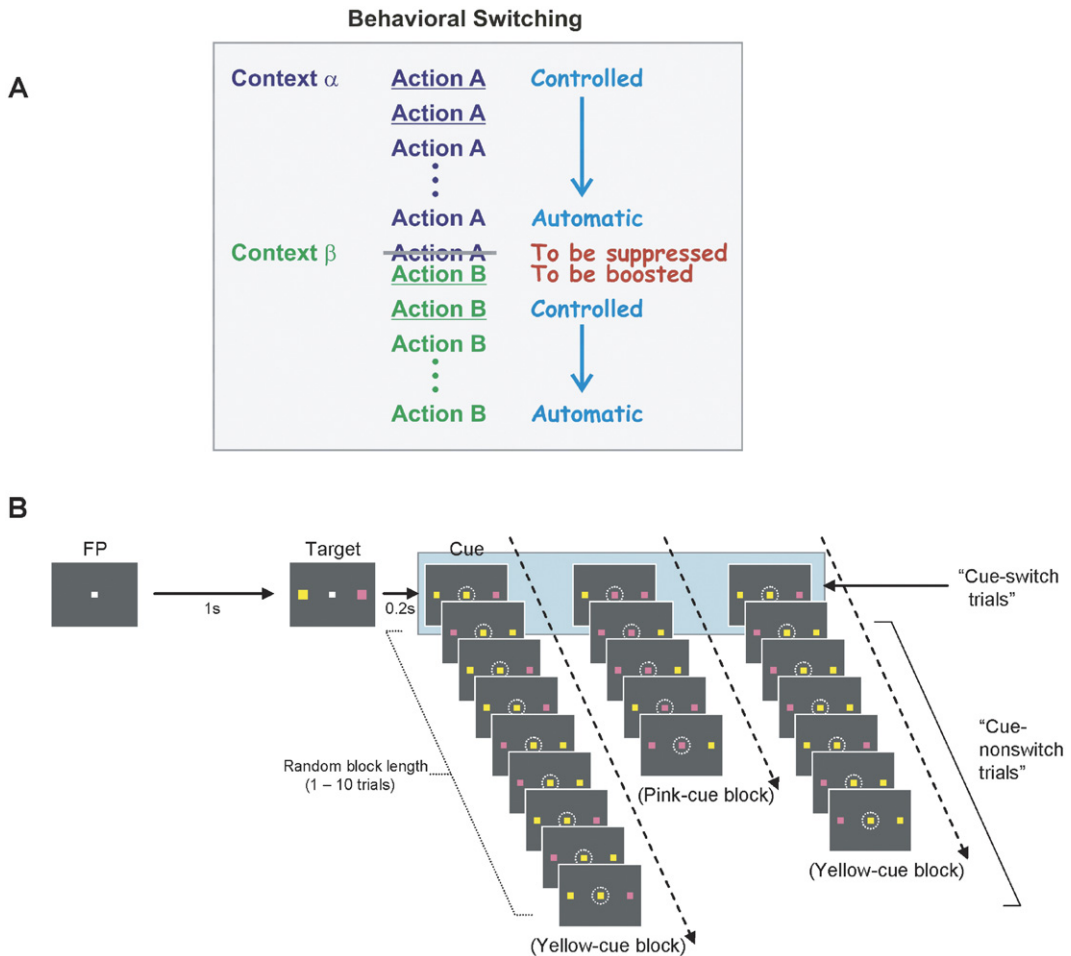


Fig. 1. (A) Scheme of switching from automatic to controlled action. (B) Saccade overriding task — a behavioural task to examine switch-selective neuronal activity. (See Color Plate 5.1.1 in color plate section.)

a task which we call ‘saccade overriding task’ (Fig. 1B) (Isoda and Hikosaka, 2007). It is basically a colour-matching task. First, a central fixation point appeared and the monkey had to fixate it. After 1 s, two stimuli appeared on the left and right in two different colours, for example, pink and yellow. The positions of the pink and yellow stimuli were randomized. After a short period, the fixation point turned its colour to either pink or yellow as a cue. The monkey’s task was to make a saccade to the stimulus whose colour was the same as the central cue.

A critical feature of this task is that the cue colour remained the same in a block of 1–10 trials. It is thus likely that the colour of the upcoming cue will be the same as that in the preceding trial, and it seems natural for the monkey to start preparing for a saccade to the same colour stimulus by assuming that the cue colour will not change.

However, our main interest was in the trial when the cue colour changed. Let’s call it ‘switch trial,’ as opposed to ‘nonswitch trial.’ In this switch trial, the habitual action is to make a saccade to the stimulus with the same colour, but it would lead to an error. Therefore, the monkey has to suppress the habitual action and instead make a saccade following the cue instruction. Indeed, the monkey’s saccade behaviour was different between the switch trials and the nonswitch trials. The saccade

reaction times (RTs), measured from the change in the colour of the fixation point, were much longer and the error rate was higher in the switch trial than in the nonswitch trials. In the switch trials, most errors occurred when the saccade RTs were too short; later saccades were usually successful (Fig. 3D). This is because the saccades with short RTs were based on the preceding colour rule and therefore quick, and therefore were bound to be wrong in the current colour rule. In the nonswitch trials, habitual saccades with short RTs were correct because the colour rule remained the same.

We obtained another important piece of information from the RT data in the switch trials. The monkey’s performance became above the chance level at 213 ms from cue onset or later (Fig. 3C, D). We call it *behavioural differentiation time*. Suppose there are neurons somewhere in the brain that enable the switch. Their activity must be differentiated between the switch and nonswitch trials before the behavioural differentiation time.

Switch-selective neurons in the pre-SMA

Figure 2 shows the macaque brain (left) and the human brain (right), viewed from the mesial side (Picard and Strick, 2001). The pre-SMA is located in the medial frontal cortex anterior to the SMA (supplementary motor area). The pre-SMA

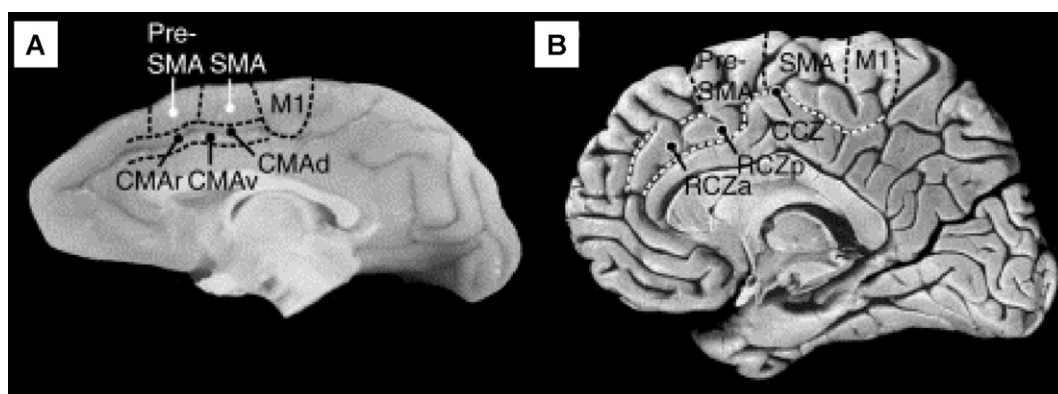


Fig. 2. The brains of the macaque monkey (A) and the human (B) viewed from the mesial side. CCZ: caudal cingulate zone, CMAr: dorsal cingulate motor area, CMAv: ventral cingulate motor area, M1: primary motor cortex, Pre-SMA: pre-supplementary motor area, RCZ: rostral cingulate zone, RCZa: anterior rostral cingulate zone, RCZp: posterior rostral cingulate zone, SMA: supplementary motor area. Adapted with permission from Picard and Strick (2001).

was originally characterized and localized in the macaque monkey (Matelli et al., 1991; Matsuzaka et al., 1992), but human brain imaging studies have supported the existence of the pre-SMA in the human brain as well (Picard and Strick, 2001). Human brain imaging studies have shown that the pre-SMA is activated in many cognitive tasks rather than motor tasks (Picard and Strick, 1996).

We found many neurons in the pre-SMA that became active selectively in switch trials in the saccade overriding task. Interestingly, the switch-

selective activity was usually direction-selective. Some ($n=26$) were active only when the saccade was switched to the contralateral side. The others ($n=15$) were active only when the saccade was switched to the ipsilateral side. A smaller number of neurons ($n=9$) were active in either direction of switch.

Let's consider the switch from the yellow block to the pink block (Fig. 3A, B). It means that the yellow stimulus has been the target to choose in the last several trials. Therefore, when the two

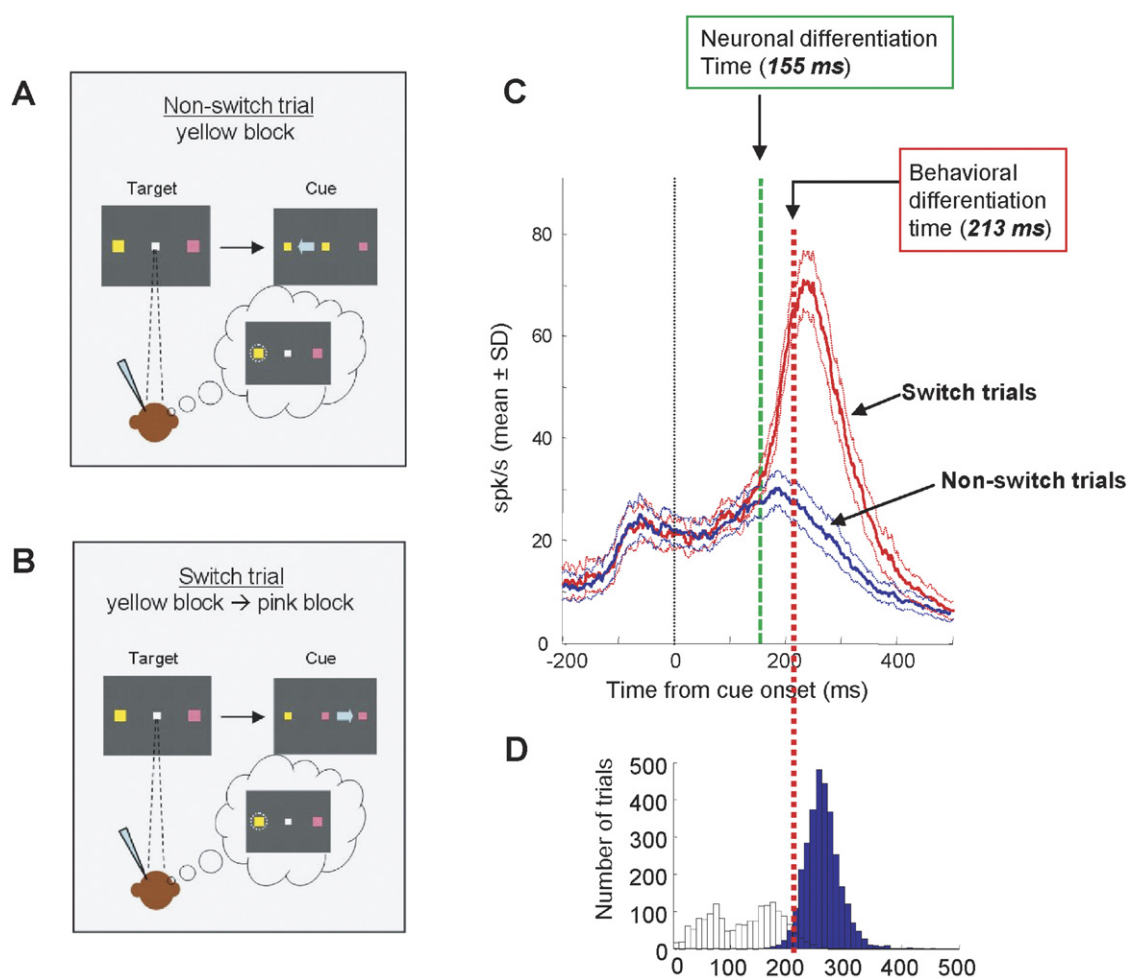


Fig. 3. Switch-selective neuronal activity in the monkey pre-SMA. (A–B) In the saccade overriding task the monkey prepares for a habitual saccade to the stimulus whose colour is the same as the target colour in preceding trials (i.e., yellow). This preparation is valid in nonswitch trials (A), but not in switch trials (B). (C) The population activity of switch-selective pre-SMA neurons for nonswitch trials (blue) and switch trials (red). (D) The distribution of saccade reaction times in switch trials, shown separately for incorrect saccades (light blue) and correct saccades (dark blue). (See Color Plate 5.1.3 in color plate section.)

stimuli come on, the monkey is likely to attend to the yellow stimulus and may start preparing for a saccade to the stimulus. The saccade will be successful in no-switch trials (Fig. 3A). In the switch trial, however, the fixation point turns into pink, and the saccade must be made to the pink stimulus (Fig. 3B). This is the time when pre-SMA neurons fire. Is the firing early enough?

In Fig. 3C we align the population activity of switch-selective pre-SMA neurons on the time of cue onset, and compared their activity between the nonswitch and switch trials. The two sets of activity, which were almost identical initially, diverged at 155 ms after the cue onset. We call it *neuronal differentiation time*. Importantly, the *neuronal differentiation time* was significantly earlier than the *behavioural differentiation time*, 213 ms (Fig. 3D). To summarize, the switch-selective activity of pre-SMA neurons appears to be early enough to enable the switch.

To test whether the pre-SMA activity is actually used for the switch, we applied electrical stimulation in the pre-SMA only in half of the switch trials, and compared the monkey's performance between the switch trials without stimulation and the switch trials with stimulation. We found that the correct rate increased considerably with pre-SMA stimulation. This was true for both contralateral and ipsilateral switches, indicating that the stimulation effect was not due to directional bias. As we indicated before, the erroneous saccades occurred too early based on the previous cue colour. One effect of pre-SMA stimulation was to eliminate such premature and habitual saccades.

Mechanisms of pre-SMA-induced behavioural switching

The above findings may be interpreted in two different ways: (1) the pre-SMA suppresses the unwanted saccade that is triggered by the habitual process, or (2) the pre-SMA facilitates the desired saccade based on the controlled process. To examine these possibilities, we characterized the activity of the switch-selective pre-SMA neurons using a saccade-Go/Nogo task. The saccade-Go/Nogo task was similar to the saccade overriding

task. A critical difference was that there was only one target. It appeared on the left or right randomly, and in yellow or pink randomly. If the cue colour was the same as the target colour, the monkey had to make a saccade to the target. If their colours were different, the monkey had to withhold a saccade and continue to fixate. If a neuron becomes active in Go trials, its action is likely to facilitate the saccade. If the neuron becomes active in Nogo trials, its action is likely to suppress the saccade. Furthermore, we should be able to tell whether the neuron influences leftward saccades or rightward saccades.

Let's consider a neuron in the left pre-SMA that becomes active only when the saccade is switched from left to right (as in Fig. 3B). Since the cue colour has been yellow in the preceding trials, the monkey is ready for a saccade to the yellow target on the left side, which was ipsilateral to the pre-SMA neuron. In the switch trial, the cue colour turns out to be pink, and the monkey has to make a saccade to the pink target on the right side, contralateral to the neuron. This is the time when the neuron is selectively active. This switch requires two actions. First, the habitual saccade to the ipsilateral side must be suppressed. Second, the saccade to the contralateral side must be boosted. Does this pre-SMA neuron perform such actions? If so, which action does it perform?

Using the Go-Nogo task, we found that there are three groups of switch-selective neurons in the pre-SMA: suppression only, facilitation only, and both suppression and facilitation. Importantly, these actions were usually consistent with the direction of switching. For example, the switch-selective neuron considered in relation to Fig. 3B may be active only in left Nogo trials suggesting that it suppresses leftward (ipsilateral) saccades, or may be active in right Go trials suggesting that it facilitates rightward (contralateral) saccades, or may be active in both cases. We also found that the Nogo-type neurons tended to be active earlier than the Go-type neurons.

In conclusion, the pre-SMA enables switching from a habitual action to an alternative action, first by suppressing the habitual action and then boosting the alternative action.

Discussion

At the beginning of this article, we presented a scheme of behavioural switching (Fig. 1). In Fig. 4A, we present a circuit diagram that would realize these operations. There are an automatic or habitual process and a controlled process, either of which can trigger a motor execution mechanism. For an appropriate behavioural switch, we need a

switch mechanism. This mechanism must be able to suppress the automatic process (or its output) and boost the output of the controlled process. The switch mechanism should be deployed only when the context is changed.

Our study has suggested that the pre-SMA contains such a switch mechanism. Switch-selective pre-SMA neurons are usually not active, but become active when the environment or context

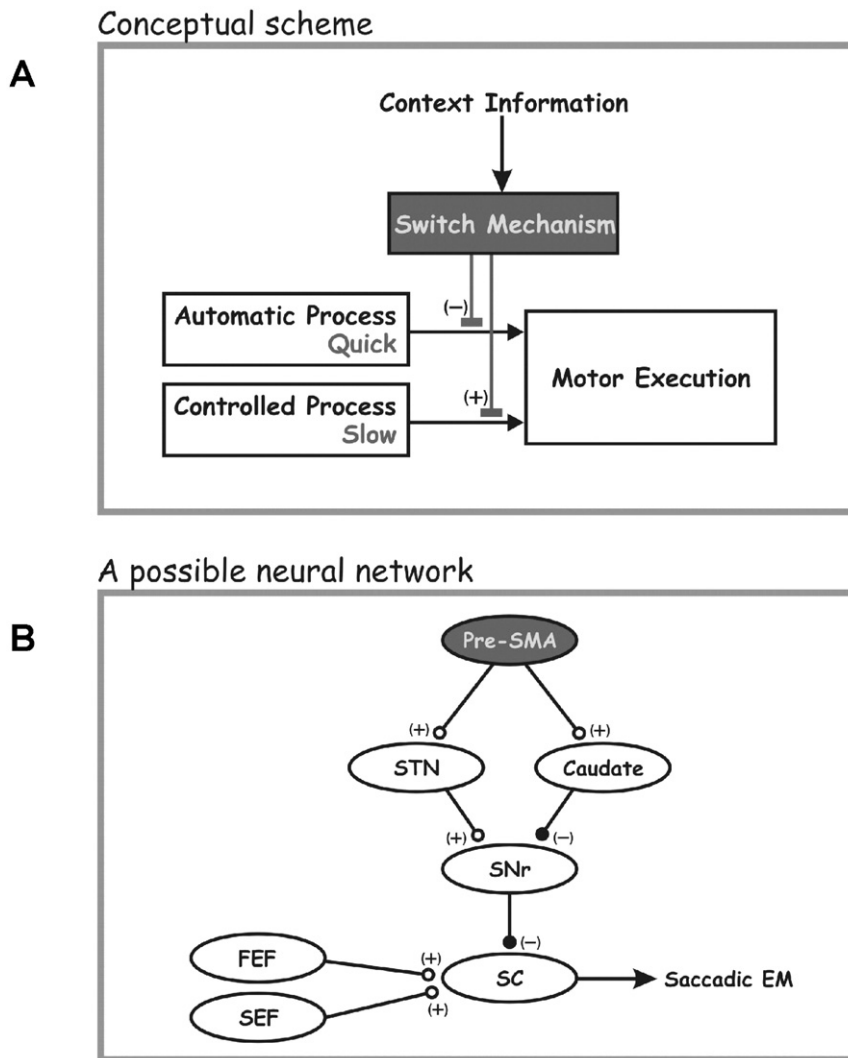


Fig. 4. Hypothetical schemes for switching from automatic to controlled action. (A) Conceptual scheme. (B) Neural network scheme for switching of saccadic eye movements. FEF: frontal eye field, SC: superior colliculus, SEF: supplementary eye field, STN: subthalamic nucleus. (+) and (-) indicate excitatory and inhibitory connections, respectively.

changes. The switch-selective activation occurs well before the monkey switches saccade behaviour. Electrical stimulation of the pre-SMA increases the likelihood of successful switches.

We also showed that the switch-selective activity starts at different timings depending on the neuron's action. It is well known that automatic or habitual actions are very quick while cognitively controlled actions are slow. In other words, the automatic process produces outputs more quickly than the controlled process. Therefore, in order for the switch mechanism to work efficiently, the inhibition of the automatic process should occur first to prevent the execution of the habitual response. The facilitation of the controlled process may occur later. This is actually what we have seen in the pre-SMA: The switch neurons with Nogo action become active earlier than those with Go action.

The next question is: How does the pre-SMA exert its Nogo and Go effect on saccade outputs? Figure 4B shows our hypothesis. The main circuit for saccade initiation is the excitatory pathways from the cortical eye fields to the superior colliculus. The Nogo action requires a powerful inhibition, which we assigned to the inhibition from the substantia nigra pars reticulata (SNr). The pre-SMA, among other frontal cortical area, is known to project to the subthalamic nucleus (STN) (Inase et al., 1999) which in turn project to the SNr (Kita and Kitai, 1987). Since these connections are excitatory, the output of pre-SMA neurons would lead to an inhibition of saccadic neurons in the superior colliculus. This might represent the Nogo or inhibitory action of the switch mechanism. The Go action may be accomplished with the signal originating from the pre-SMA going through the caudate nucleus (Inase et al., 1999). Since the caudate nucleus has direct inhibitory connections to the SNr, the net effect of the pre-SMA signal would be facilitatory (Hikosaka et al., 2000).

We have performed similar experiments on STN neurons, and found similar switch-selective neurons. Importantly, their switch-selective activity of STN neurons starts slightly later, on the average, than that of pre-SMA neurons, but before the behavioural differentiation time. This result is consistent with the hypothetical circuit diagram

in Fig. 3B. Human brain imaging studies have also shown the role of the STN in behavioural switching (Aron and Poldrack, 2006; Monchi et al., 2006). Unexpectedly, however, we found not only Nogo neurons (expected from the diagram) but also Go neurons in the STN. One way to explain this result may be to postulate indirect connections from the STN to the SNr through the globus pallidus external segment (GPe). Since GPe neurons are known to be inhibitory, the net effect of the STN output would be reversed from Nogo to Go. This suggests that there are many combinations of neural connectivity between the STN and the GPe (Nambu et al., 2000), which may allow STN-projecting cortical areas to control body movements in many different ways.

Currently we have no data on the possible Go mechanism involving the caudate nucleus. There is some evidence from human brain imaging studies indicating that the caudate nucleus becomes active in switch trials (Monchi et al., 2006). One small problem of this pathway is that the conduction time of caudate neurons is quite long (almost 20 ms) (Hikosaka et al., 1993), so that it may not be suitable for quick switching actions. It may still be functional, however, since the Go action can be delayed compared with the Nogo action. Although not shown in this diagram, cortico-cortical connections from the pre-SMA to the prefrontal areas including the supplementary eye field may serve as the Go mechanism (Husain et al., 2003; Nachev et al., 2005; Stuphorn and Schall, 2006). These possibilities are testable using our experimental paradigm.

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