Switching from automatic to controlled behavior: cortico-basal ganglia mechanisms

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Abstract

Although we carry out most daily tasks nearly automatically, it is occasionally necessary to change a routine if something changes in our environment and the behavior becomes inappropriate. Such behavioral switching can occur either retroactively based on error feedback or proactively by detecting a contextual cue. Recent imaging and electrophysiological data in humans and monkeys have suggested that the frontal cortical areas play executive roles in behavioral switching. The anterior cingulate cortex acts retroactively and the pre-supplementary motor area acts proactively to enable behavioral switching. The lateral prefrontal cortex reconfigures cognitive processes constituting the switched behavior. The subthalamic nucleus and the striatum in the basal ganglia mediate these cortical signals to achieve behavioral switching. We discuss how breaking a routine to allow more adaptive behavior requires a fine-tuned recruitment of the frontal cortical-basal ganglia neural network.

Breaking a routine: difficult but crucial

Driving to one's workplace is an easy task: a task that most of us do on a daily basis for several years. One sees the same houses, the same trees, and the same traffic lights. One may not even be aware how the car accelerates and slows down, despite being the driver. If on one day there is unexpected congestion in the main road ahead, one may make up one's mind quickly and turn into a side-road, successfully avoiding the traffic jam. But if the decision is late even by only a second, the chance to turn and avoid the congestion may be missed. This example illustrates that most daily behaviors are composed of well-learned routines–only occasionally, an important decision is made to switch from a routine behavior to an alternative, more appropriate given the context, behavior.

Naturally, behavioral switching has been an important question in experimental psychology [1], and there has been a recent surge of interest among neuroscientists in this issue. Several recent studies with human subjects using neuroimaging methods and transcranial magnetic stimulation as well as with patients with prefrontal lesions suggest that several regions in the frontal cortex play different roles in behavioral switching [2–5].

However, how the brain actually executes behavioral switching is not fully understood from the human data alone. The switching-associated reconfiguration of cognitive processes suggested by the psychological studies is likely composed of serial and parallel neuronal activity changes which occur within a short period before the decision to switch. However, the spatiotemporal resolution of the imaging data may not be sufficient for elucidating such fast changes in neuronal activity. To this end, single unit recording experiments using trained animals provide important complementary data.

In this article, we synthesize the insights provided by human neuroimaging data and animal single neuron data and put forward a framework that specifies the neural circuits involved in the execution of behavioral switching.

Two modes of behavioral switching

In order to understand the neural mechanisms of behavioral switching, it is important to understand what triggers such switching. Let us consider a situation in which procedure A is the appropriate behavior in order to obtain a reward in context α, while procedure B is the appropriate behavior in context β (Fig. 1), and a motivated subject has already learned these associations. Suppose the context changes from α to β. If the subject is unaware that the context has changed, s/he will perform procedure A and will therefore receive no or little reward (Fig. 1, left). This negative feedback signal triggers behavioral switching on the next trial. On the other hand, if the subject is aware of the context change, s/he will perform procedure B instead of A and will obtain a reward (Fig. 1, right). We term these two modes of switching 'retroactive switching' and 'proactive switching' respectively.

Note that this classification is different from the proposal by Braver and colleagues on proactive and reactive control of cognitive function [6]. Proactive control in their framework refers to a sustained process before the onset of an imperative stimulus, whereas reactive control refers to a transient process after the onset of an imperative stimulus. There is no particular emphasis in their hypothesis on how behavior may switch when the context changes. Instead, our main goal is to understand the switching process where, we believe, the retroactive-proactive distinction is useful.

In retroactive switching (Fig. 1, left), the subject's behavior is bound to fail on switch trials. This is costly in a dangerous world where one-time failure could be fatal. However, a change in context may be indicated in advance by a change in sensory inputs, which is often called a cue. Detecting the cue enables proactive switching in which the behavior may continue to be optimal even on switch trials. In a social context, the cue may be a change in facial expression or gaze direction of one's partner or manager [7]. It should be emphasized that the subject has to discover the cue from his/her experience. The discovery depends on learning, specifically learning of statistical relationships between the cues and the outcomes (e.g., rewarded or punishing).

A main proposal in this article is that retroactive switching and proactive switching are controlled by different regions in the medial frontal cortex, anterior cingulate cortex (ACC) and the pre-supplementary motor area (pre-SMA).

## The anterior cingulate cortex and retroactive switching

The brain region that enables retroactive switching needs to be sensitive to negative feedback (e.g., reduced reward or punishment). It also needs to have access to the brain regions that implement alternative learned procedures. The ACC seems to fulfill both of these requirements.

First, many neurons in the monkey ACC are excited by negative feedback. In experiments using monkeys, the monkeys are trained to perform a task in order to obtain a certain amount of reward. If the reward is absent (e.g., due to poor performance) or reduced in amount experimentally, some ACC neurons are excited [8–11,12]. Task-selectivity of ACC neurons is strongest after switching and declines thereafter, consistent with their role in retroactive switching [13]. Neuronal activity in the ACC after negative feedback may continue if and until the monkey switches procedures [9] (Box 1). Further, switching is impaired by inactivation of the ACC [9].

Box. 1

Retroactive switching by ACC neurons

There is empirical evidence that errors result in adjustments of behavior in several ways. First, subjects can correct their action slips resulting from premature responses immediately after they have committed an error [62]. Second, subjects slow down on subsequent trials after errors, a phenomenon known as post-error slowing [62]. As long as the correct action remains unchanged, such cautious responding is adaptive to attain the intended goal on the next trial. The ACC is implicated in both error detection [79, 80] and post-error adjustments [81]. Third, once subjects realize on the basis of feedback (such as reduced reward) that the previously correct action becomes no longer valid, they switch behavior or learn a correct action (retroactive switching).

In a pioneering study designed to explore the role of the ACC in retroactive switching [9], monkeys were trained to perform one of two different arm movements, either pushing or turning a handle, in response to a movement trigger signal. Choosing a correct movement was rewarded and the correct movement remained unchanged in a block of trials, so that monkeys kept selecting the same movement. After a variable number of constant-reward trials, the amount of the reward decreased by 30% for each subsequent correct trial. At this stage monkeys were free to switch to the alternate movement. Once they did, the alternate movement was defined as the correct movement, and the reward reverted to the full amount. Thus, monkeys voluntarily selected one of the two movements based on the reduced amount of reward. An analysis of ACC neurons revealed that neuronal activity increased during the interval between the receipt of reduced reward and the switch to the alternate movement (Figure 1, middle). Notably, no such activation was observed when the monkey was given the full amount of reward in constant-reward trials (Figure 1, top) or when the reward was reduced but the monkey failed to switch to the alternate movement (Figure 1, bottom). Most importantly, chemical inactivation of the ACC impaired switching of movements based on the reduced amount of reward. These data indicate a crucial role for the ACC in retroactive behavioral switching. Similar activity properties were later found in the human ACC [82].

Ordinary reward

Reduced reward → Movement alteration

Reduced reward → Failure to change movements

1 s
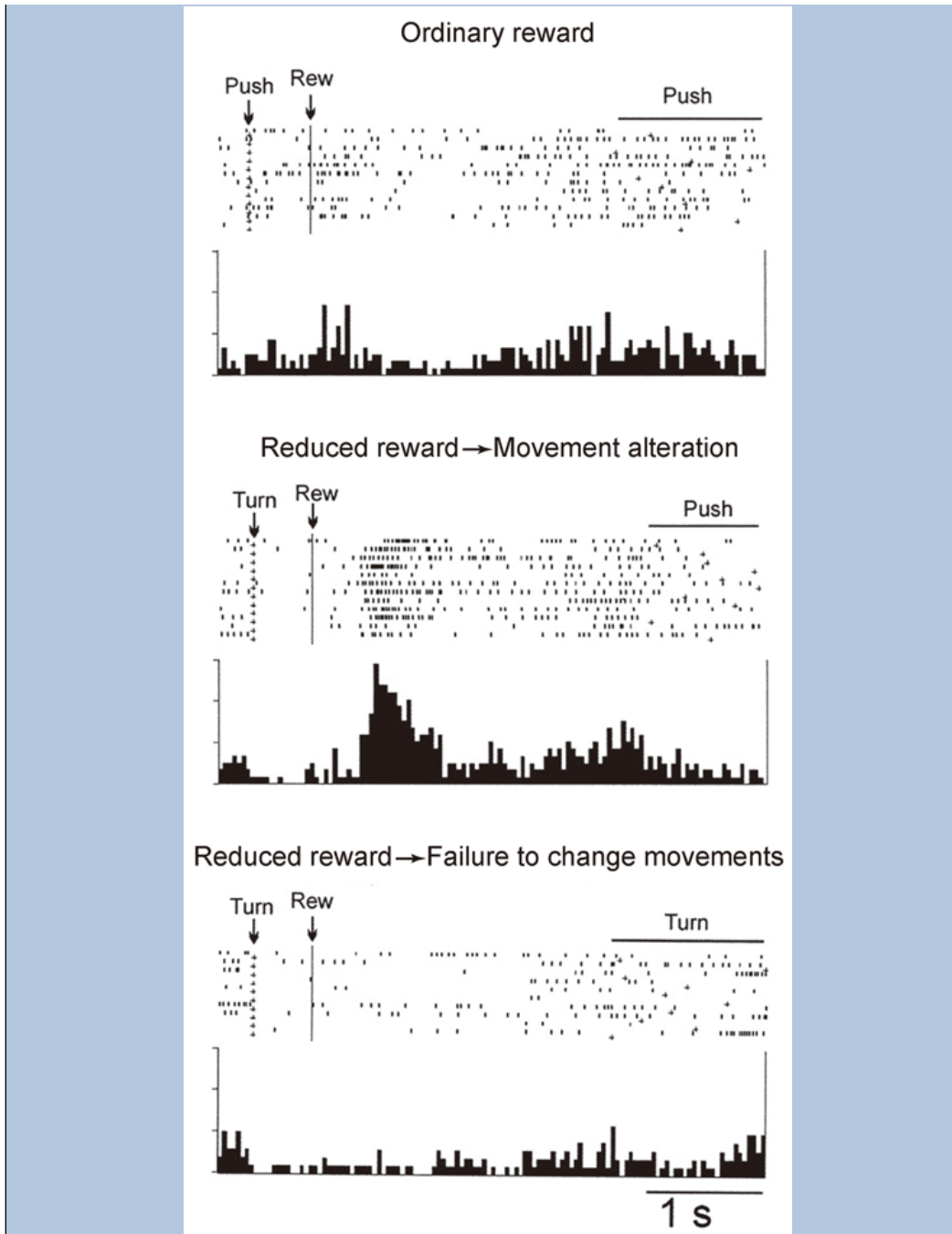
Figure for Box. 1. Retroactive switching by ACC neurons
Activity of a representative ACC neuron recorded while the monkey selected one of two
movements (pushing or turning a handle) based on reduced reward. Top: The neuron was
not very active after ordinary reward and the monkey continued to select the same
movement. Middle: The same neuron increased discharges after the receipt of reduced
reward and before the initiation of the alternate movement. Bottom: The neuron remained
inactive when the monkey did not switch to the alternate movement despite a reduction of
reward.

Second, the switching function of the ACC may be mediated by its connections to the lateral prefrontal cortex (LPFC) [14], [15], which is thought to play an executive role in procedure implementation. An alternative pathway may be the connections to the striatum [16], which is equipped with mechanisms for behavioral selection [17]. The role of the ACC-striatum connection is perhaps supported by the finding that striatal neurons show rapid changes in activity after retroactive switching in associative learning [18].

Neuroimaging studies with human subjects support the above conclusion. fMRI studies have indicated that the ACC is activated when the subject fails to perform a trial correctly (e.g., by failing to stop a button press) [19–24]. Human EEG studies have revealed error-related potentials just after the erroneous motor response or after the error feedback, which are thought to be generated in the ACC [2]. Similar error-related potentials are generated within the monkey ACC [25–27], which may be associated with the error-induced burst firing of ACC neurons described above.

The sensitivity of ACC neurons to negative feedback suggests that it may be related to motivational decision-making in general. In fact, some ACC neurons are excited by positive feedback (i.e., reward), but only when the reward is unexpected (i.e., immediately after the correct choice is discovered) [12], [28]. These results suggest that the ACC enhances cognitive processes not only before switching (based on an unexpected error) but also after switching (based on an unexpected reward). Indeed, lesions of the ACC may cause general impairments in decision-making based on the history of actions and outcomes [29], [30].

The pre-SMA and proactive switching

A conflict in information processing characteristically occurs in proactive switching. The subject's performance on switch trials is much worse (high error rate and longer reaction time) than when the same context is repeated (non-switch trial), a phenomenon called 'switch cost' [1]. This is thought to occur because multiple cognitive operations are executed in response to the switch cue, which may include (1) suppression of the old procedure and (2) facilitation of the new procedure. The switch cost is particularly high if the old procedure has been repeated and therefore has become habitual or automatic.

Various lines of research suggest that the pre-SMA [31] is essential for proactive switching. Functional MRI studies have shown that the pre-SMA is consistently activated when human subjects switch between two tasks proactively in response to a cue [32], [33]. Repetitive transcranial magnetic stimulation over the pre-SMA disrupts subjects' performance in switch trials, but not in non-switch trials [33].

Such pre-SMA activation may be related to the cognitive operations described above. First, the pre-SMA seems to have a powerful mechanism to suppress body movements. For example, electrical stimulation of the pre-SMA suppresses ongoing or impending body movements in humans [34] and monkeys [35]. The pre-SMA is activated consistently when the human subject tries to stop an impending movement [36], [19], [37]. Such inhibitory control is impaired in patients with lesions including the pre-SMA [38] and in normal subjects when transcranial magnetic stimulation is applied over the pre-SMA [39]. Second, the human pre-SMA is activated when two procedures compete with each other [19], [22], [37]. Thus, the conflict associated with proactive switching (i.e., conflict between the old and new procedures) is likely to be processed in the pre-SMA [40], [41].

The fact that transcranial magnetic stimulation over the pre-SMA disrupts performance only on switch trials [33] suggests that the pre-SMA generates switch-related signals transiently at the time of switching. This is in contrast to the ACC, where neural processing continues after an erroneous choice [42] and even after a correct choice [12], [28]. The hypothesized difference is

supported by a recent finding that the pre-SMA and the ACC show transient and sustained responses, respectively, to incentive cues [43].

Another indication that the pre-SMA may be related to behavioral switching comes from studies with trained monkeys. Many pre-SMA neurons are activated before the monkey switches button presses from one target to the other in response to a sensory cue [44]. They are also active when the monkey switches from one learned sequential procedure to another learned procedure, but only on the first trial [45]. However, it is unclear from these experiments whether the pre-SMA can act rapidly enough to enable proactive switching under the time constraint described above. It is also unclear how the pre-SMA might enable switching.

In a recent study using an oculomotor switching task Isoda & Hikosaka presented evidence that the pre-SMA competes with automatic processes to enable behavioral switching (Box 2) [46]. Confirming the above prediction, switch-related pre-SMA neurons are activated transiently at the time of switching. It was also shown that pre-SMA neurons, as a population, perform the two operations hypothesized above: (1) suppression of the old procedure and (2) facilitation of the new procedure. Switching is successful if the activation of pre-SMA neurons precedes the initiation of the automatic process; switching fails if the initiation of the automatic process precedes the activation of pre-SMA neurons.
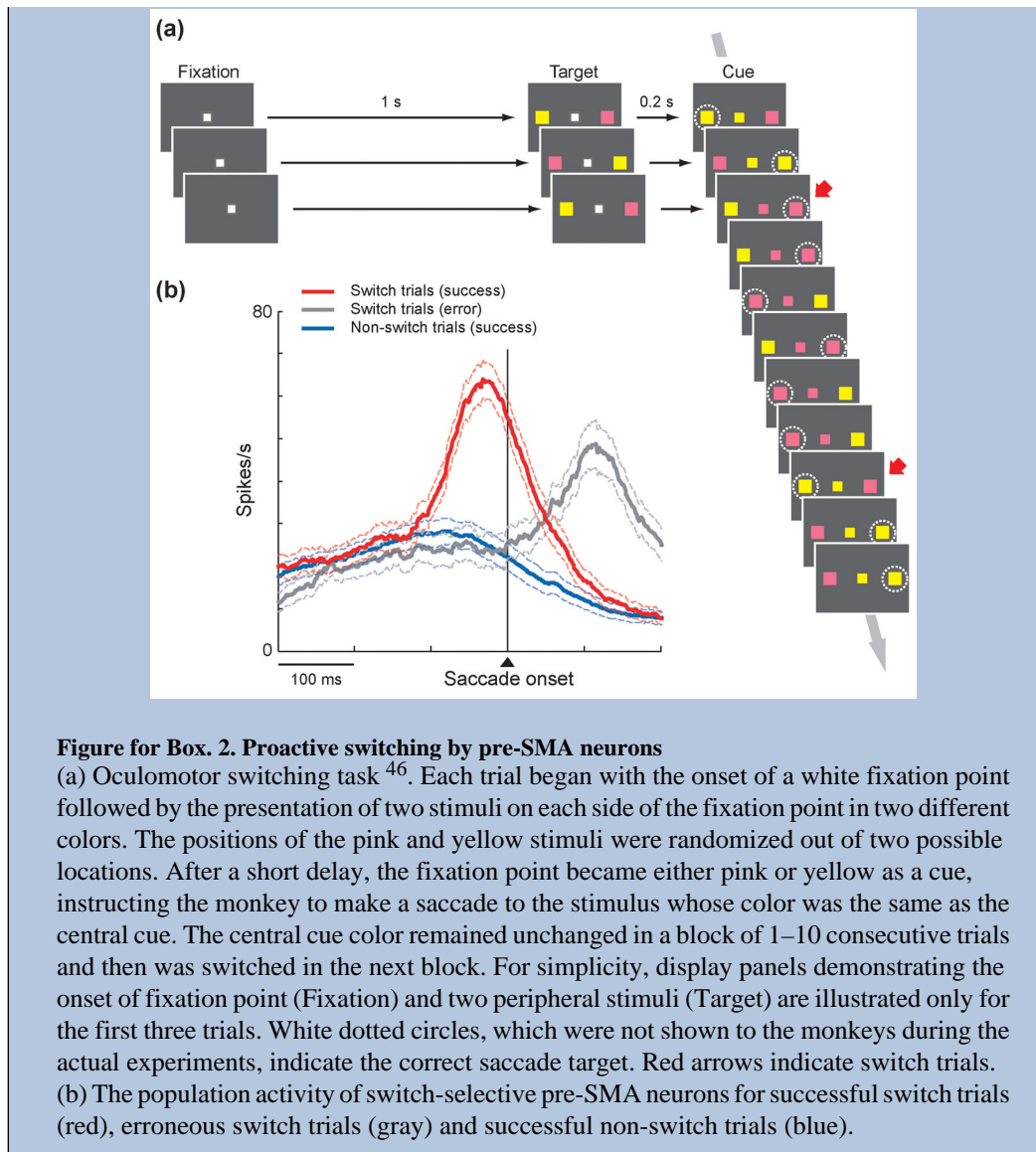

Box. 2

Electrophysiological evidence for the role of the pre-SMA in proactive switching

To study the neural mechanisms of proactive switching, Isoda and Hikosaka devised an oculomotor switching task [46]. The task can be viewed as a change-signal task in which, just before the subject is about to perform the prepotent response based on the previous cue, a different cue is presented [44]. Unlike most of the change-signal tasks, the prepotency is created internally by repeating the same response. This is the hallmark of automaticity or habit formation. Further, there is no special cue for switching.

In the oculomotor switching task the monkeys developed automaticity and showed a clear switch cost which was expressed as an increased rate of errors and increased reaction times [46]. On switch trials they tended to make a prepotent but wrong saccade especially when the saccade occurred earlier than a latency which we called 'behavioral differentiation time'. Many pre-SMA neurons were activated on switch trials, but not non-switch trials. Importantly, the onset of the switch-selective activity preceded the behavioral differentiation time when switching occurred correctly. When the monkey failed to switch, the pre-SMA neurons did become active, but after the wrong saccade. When the pre-SMA neuronal activity was boosted with electrical stimulation before the behavioral differentiation time, the success rate of switching increased.

Figure for Box. 2. Proactive switching by pre-SMA neurons
(a) Oculomotor switching task [46]. Each trial began with the onset of a white fixation point
followed by the presentation of two stimuli on each side of the fixation point in two different
colors. The positions of the pink and yellow stimuli were randomized out of two possible
locations. After a short delay, the fixation point became either pink or yellow as a cue,
instructing the monkey to make a saccade to the stimulus whose color was the same as the
central cue. The central cue color remained unchanged in a block of 1–10 consecutive trials
and then was switched in the next block. For simplicity, display panels demonstrating the
onset of fixation point (Fixation) and two peripheral stimuli (Target) are illustrated only for
the first three trials. White dotted circles, which were not shown to the monkeys during the
actual experiments, indicate the correct saccade target. Red arrows indicate switch trials.
(b) The population activity of switch-selective pre-SMA neurons for successful switch trials
(red), erroneous switch trials (gray) and successful non-switch trials (blue).

The lateral prefrontal cortex and rule implementation

Another cortical area that is thought to be essential for behavioral switching is the LPFC [47].
Patients with prefrontal lesions show impairments in switching behaviors [48–50] or in inhibiting
prepotent responses [51, 52]. Similarly to the pre-SMA, the LPFC is activated when response
inhibition is required [36, 53]. Other studies suggest that the LPFC is predominantly active when
relevant rules are retrieved, maintained, and implemented [13, 54]. Strong activation of the LPFC
occurs when the rules are complex and require changes in stimulus-response relationships in
multiple dimensions, as typically seen in the Wisconsin Card Sorting Task (WCST) [55, 56].
Rule-selective activity is also found in single neurons in the monkey LPFC [57]. Switching
between complex tasks requires reconfiguration of cognitive processes, and this may be done
by changes in functional connectivity among frontal cortical areas [58, 59, 5].

The task rules, which are presumably represented in different regions in the LPFC, need to be
executed as motor outputs. Each sub-region in the LPFC may select a correct motor response
by inhibiting an incorrect response, since neurons specialized for a particular dimension (e.g.,

color), which are clustered in the LPFC, respond to WCST stimuli selectively when no-go responses are required [60]. Part of the LPFC is characterized as a negative motor area (i.e., a cortical area stimulation of which suppresses voluntary movements), the other one around the pre-SMA [34]. Thus, it is possible that the LPFC has a mechanism to inhibit motor behavior, but in a selective manner to choose the right behavior. The selection-related inhibition may constitute the LPFC activation during response inhibition described above. Connections to the striatum might mediate such selective inhibitions as well as disinhibitions [61].

Cortico-basal ganglia mechanisms and behavioral switching

The outcome of behavioral switching is a change in motor behavior. A crucial aspect of behavioral switching, as we have suggested above, is the suppression of prepotent body movements. This is particularly clear for proactive switching, but is also true for retroactive switching in which performance often becomes slower after an erroneous trial [62, 63].

One possibility may be that the switch-related cortical signals are mediated by an area that has a powerful capacity to inhibit motor areas. A candidate is the basal ganglia whose final outputs are exclusively inhibitory and are directed to a wide variety of motor structures including the cerebral cortex through the thalamus [64]. The basal ganglia contain parallel circuits which are capable of removing inhibition (direct pathway) or enhancing inhibition (indirect and hyperdirect pathway) [65]. Most cortical areas, including the pre-SMA, ACC, and LPFC, project to the striatum and STN, both being input zones of the basal ganglia [66]. These anatomical features suggest that the basal ganglia are instrumental for selecting appropriate motor behaviors [17].

The function of the basal ganglia is heavily dependent on dopamine, as evidenced in Parkinson's disease. It has been shown that patients with Parkinson's disease have difficulty in changing motor or cognitive behaviors [67] and that dopaminergic medication remediates impairments in switching between tasks [68]. The contribution of the basal ganglia in behavioral switching is also shown in human subjects without dopamine deficits. Subjects performing switching tasks show activations in the striatum [69–71] and the STN [36, 72], or both [73]. There is a tendency for switching that is based on abstract rules to be associated with striatal activations, whereas switching relying on suppression of a prepotent response is associated with STN activations [73]. Using a stop-signal task, Aron and colleagues found that stopping a prepotent motor response activated the inferior frontal cortex (IFC), pre-SMA, and STN [36], which were shown to be connected with each other using diffusion-weighted imaging tractography [72]. Recent studies by Li and colleagues suggest that the IFC is involved in orienting attention to a salient event (i.e., stop process), whereas the pre-SMA is more specialized for mediating response inhibition via the STN and caudate nucleus [74, 75].

When monkeys perform the oculomotor switching task, a group of STN neurons show a switch-selective activity change (mostly an increase in activity) [76]. The activity is similar to that seen in pre-SMA neurons, but occurs slightly later, consistent with the hypothesis that STN neurons receive the switch-related signal from the pre-SMA. The monkeys' actions, assessed with the go-nogo task, are usually suppressive, suggesting that the STN works mainly to suppress the old no-longer-valid procedure. This conclusion is consistent with a study on patients with Parkinson's disease. Electrical stimulation of the STN in these patients improved their motor symptoms, but the stimulation interfered with the normal ability to slow down when faced with decision conflict [77].

Since the STN has excitatory connections to the final output neurons in the basal ganglia located in the substantia nigra pars reticulata (SNr) or the globus pallidus internal segment (GPi) (Fig. 2) [65], their phasic activation will lead to a phasic inhibition of motor-related neurons in the basal ganglia-recipient thalamus and subcortical motor-related neurons including those in the

superior colliculus (SC). Since signal transmission through the hyperdirect pathway is fast [65], the activity of pre-SMA neurons will be translated into an actual stopping action rapidly. These features fulfill one of the two mechanisms requisite to proactive switching: suppression of the old procedure.

On the other hand, the striatum (caudate or putamen) may also be involved in the execution of behavioral switching. Its output via the direct pathway may be used for the facilitation (disinhibition) of the new procedure (Fig. 2). This could serve as the other mechanism for proactive switching, facilitation of the new procedure, such as the saccade to a different colored target [46] or the antisaccade [71, 78]. On the contrary, the output of the striatum via the indirect pathway may be used for the suppression of the old procedure or the task rule-related inhibition of motor outputs.

Concluding remarks

When the circumstances necessitate it, we make the important decision to change our behavior by breaking a routine. Recent studies with human and non-human primate subjects have begun to elucidate the neural mechanisms underlying such behavioral switching. These studies suggest that different areas in the medial and lateral frontal cortices play executive roles in behavioral switching and do so using different algorithms.

What triggers behavioral switching represents one aspect of the switching algorithm. Switching may occur retroactively based on error feedback indicating that the current behavior is no longer appropriate. A critical structure for this retroactive switching is the ACC. In many cases, however, there is a sensory cue that predicts a change in the context. The subject can use the cue to switch behaviors proactively so that failure can be avoided. Such proactive switching is mainly governed by the pre-SMA. Importantly, the subject may not be aware of the presence of the cue initially, but may learn the meaning of the cue with experience.

Another aspect of the switching algorithm arises if the task rule changes before and after switching. In this case, cognitive processes need to be reconfigured to accommodate the rule change. Such cognitive reconfiguration seems to be performed by changes in functional connectivity among frontal cortical areas, including the LPFC. Even if the ACC or pre-SMA sends signals for switching, the switching would not be accomplished if the new rule has not been implemented (e.g., due to malfunction of the LPFC).

However, it is debatable whether each of the ACC, pre-SMA, and LPFC performs an exclusive function described above and is thus requisite for a certain type of behavioral switching. In fact, a lesion in each area may not lead to an impairment in switching. Instead, these prefrontal cortical regions may constitute a large network in which different switching algorithms are computed differentially but in an overlapping manner.

These switching algorithms need to be executed by selecting an appropriate motor behavior. The basal ganglia are considered to be a major mediator of the switch execution signals. In particular, the STN receives the switch-related signal from the pre-SMA and suppresses the ongoing but no-longer-valid behavior so that the new behavior can be executed. The striatum may also contribute to switching based on its input from the frontal cortical areas. Underlying these neural operations may be parallel neural circuits in the basal ganglia (direct, indirect, and hyperdirect pathways) by which a valid behavior can be selected while invalid behaviors can be suppressed.

However, behavioral switching is only part of what animals would do to adapt to changing worlds. Changing behavior gradually, based on reward outcome, is another important type of behavioral adaptation. It is still unclear, however, whether rapid adaptation (i.e., switching)

and slow adaptation (i.e., reward-based changes) are controlled by the same or different brain networks (see also Box 3).

Box. 3

Outstanding questions

Is the ACC necessary for retroactive switching?

We have proposed that the ACC is essential for retroactive switching. However, unlike a reversible inactivation study [9], recent lesion studies indicate that retroactive switching per se is impaired neither by ACC lesions [29] nor by lesions in different parts of the LPFC or the orbitofrontal cortex [30]. This raises the possibility that, although the ACC is necessary for retroactive switching in the intact animal, other brain areas take over after ACC lesion and enable switching.

What are the roles of neuromodulators in behavioral switching?

The brain areas related to behavioral switching, especially the ACC and pre-SMA, receive substantial dopaminergic inputs from the ventral tegmental area and the substantia nigra [83]. Since some dopamine neurons carry reward-related value signals [84, 85], it is plausible that dopamine in the medial frontal cortex is essential for behavioral switching [2]. Experimental evidence in support of this hypothesis is currently lacking, however. These medial frontal cortical areas are also mutually connected with the locus coeruleus, which is a major source of noradrenergic signals. Since the locus coeruleus is thought to regulate the balance between exploration and exploitation [86], it may also be related to behavioral switching.

How is behavioral switching related to reward-based learning?

A dominant theory proposes that reward-based learning is based on plasticity in corticostriatal synapses which is conditioned by dopaminergic inputs [87]. However, as the animal experiences two alternating task conditions repeatedly, reward-based changes in behavior tend to become faster [88]. It is thus likely that any reward-based change in behavior involves both striatum-based plasticity and medial frontal cortex-based switching. The transition of the dopamine neuron's response from the reward outcome to a predictive cue [84] might be related to the hypothetical transition from retroactive switching to proactive switching.

How important is behavioral switching in social contexts?

Behavioral switching may be particularly important in social contexts. An animal (or human) is surrounded by many animals (or humans) which have different behavioral traits. It is then crucial to switch behaviors in anticipation of (rather than in response to) the other individual's behavior. Facial expressions, gestures, vocalization, and gaze direction can provide many cues for switching, which the animal may need to learn in order to enable proactive switching [7].

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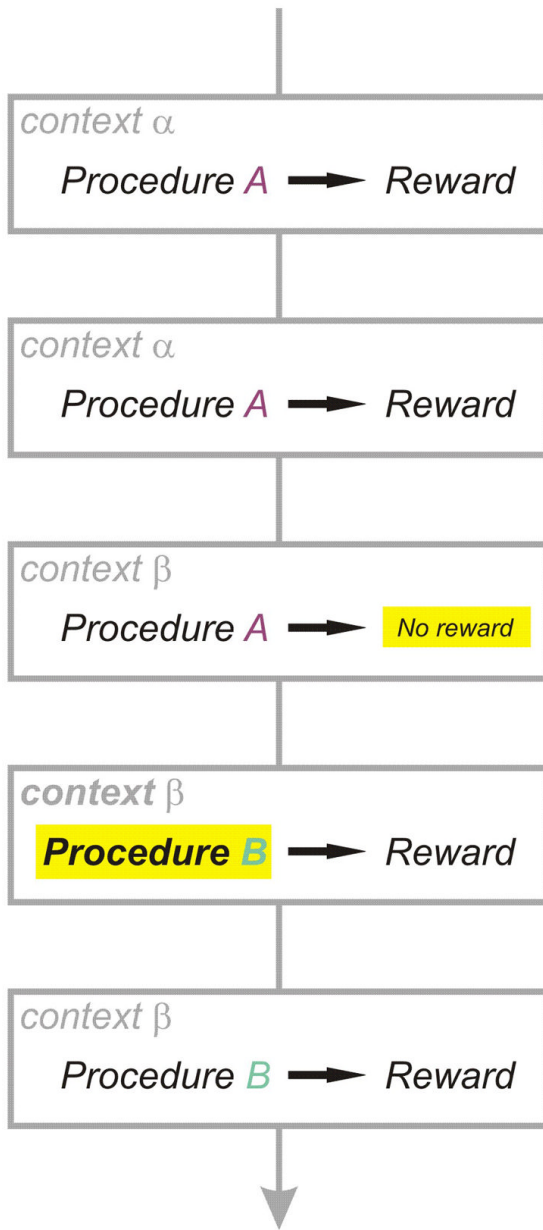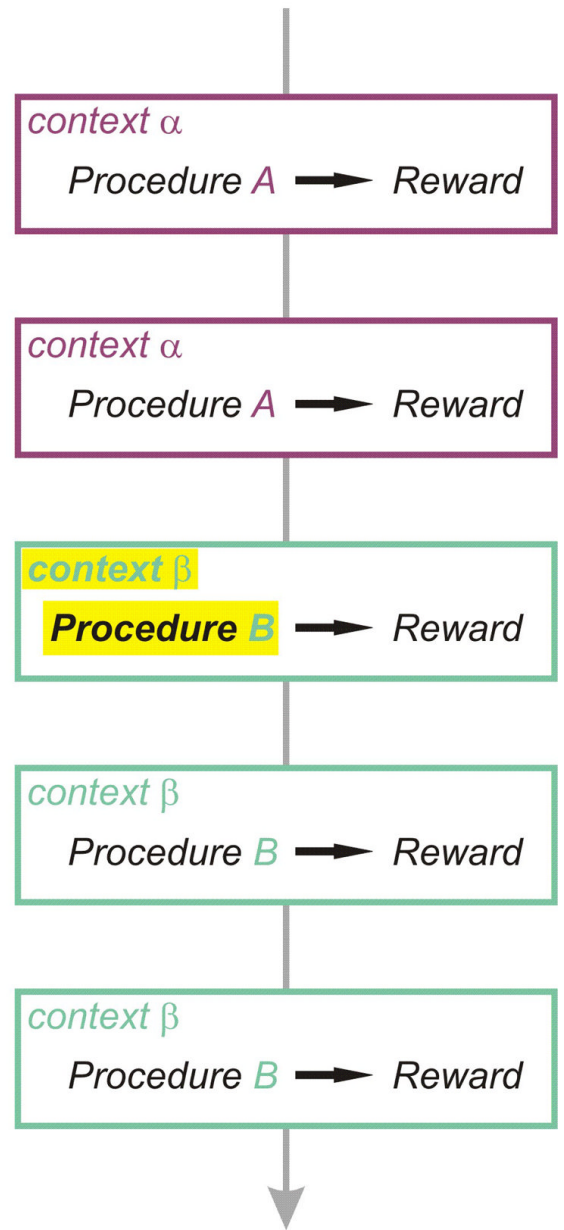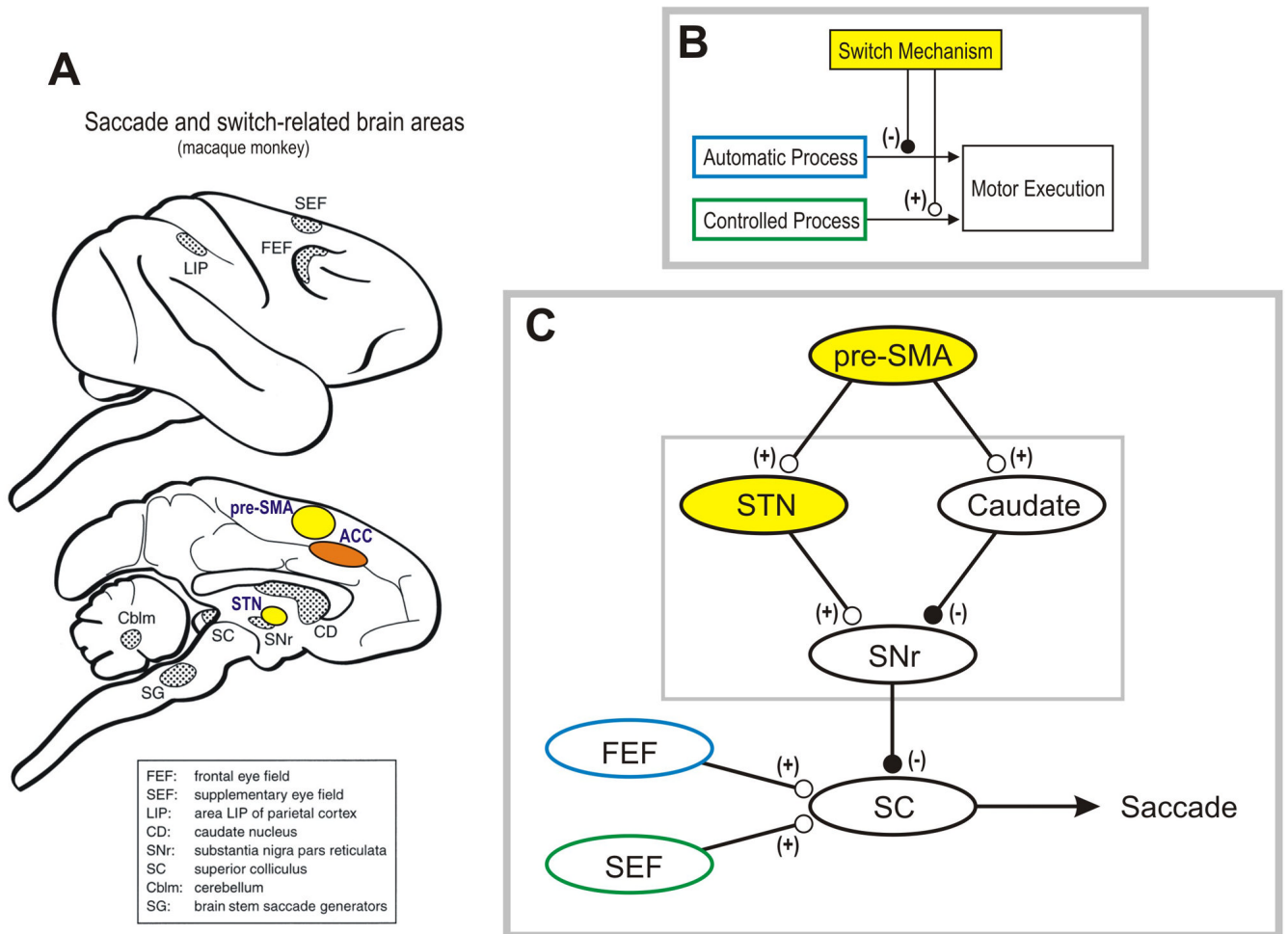
Figure 1. Retroactive and proactive switching

Retroactive switching (left) is triggered by a failure (decreased reward value or an error). In this case the context cue is either absent or unknown to the animal (indicated by gray rectangles). Proactive switching (right) is triggered by a cue signaling a context change so that the subject will not experience the failure. This is possible, however, only after the subject has learned the meaning of the cue (indicated by purple and green rectangles). Highlighted in yellow are triggers of behavioral switching and switched procedures.

Figure 2. Neural mechanism of proactive switching in oculomotor behavior

A neural mechanism of behavioral switching must be able to (1) detect a change in the context, (2) suppress the prepotent, automatic process, and (3) facilitate the alternative, controlled process (conceptual scheme). The suppression must occur quickly because the automatic process emits a motor signal quickly; the facilitation can occur thereafter because the controlled process is slow. Recent studies have suggested that the pre-SMA, together with other frontal cortical areas, acts as a switch mechanism and the basal ganglia may mediate the switch-related signal from the cortical areas. In our study using saccadic eye movement, many neurons in the pre-SMA became active selectively and proactively on switch trials (Box 2). It was also shown, using a go-nogo task, that some pre-SMA neurons suppress the prepotent saccade, others facilitate the alternative saccade, and the rest have both functions. The suppressive pre-SMA neurons tended to be active earlier than the facilitatory pre-SMA neurons, consistent with the conceptual scheme. In the basal ganglia, the STN may serve to suppress the automatic saccade by enhancing the inhibitory output of the basal ganglia (SNr) on the SC or the thalamo-cortical network. The caudate nucleus might serve to facilitate the controlled saccade by disinhibiting the target of the basal ganglia. We speculate that the signals for the automatic and controlled saccades are carried mainly by the frontal eye field (FEF) and the supplementary eye field (SEF) respectively. In the possible neural network, excitatory and inhibitory connections are indicated by (+) and (−) respectively.