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The role of the medial prefrontal cortex in achieving goals

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Achieving goals in changing environments requires the course of action to be selected on the basis of goal expectation and memory of action–outcome contingency. It is often also essential to evaluate action on the basis of immediate outcomes and the discrimination of early action steps from the final step towards the goal. Recently, in single-cell recordings in monkeys, the neuronal activity that appears to underlie these processes has been noted in the medial part of the prefrontal cortex. Medial prefrontal cells were also active when the subjects extracted the rules of a task in a novel environment. The processes described above might play important roles in rule learning.

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Abbreviations
DOE differential outcomes effect
ERN error-related negativity
PFC prefrontal cortex

Introduction

Achieving goals in changing environments requires a set of cognitive functions. In such environments, fixed stimulus–response mappings rarely provide the appropriate action to achieve a goal. Selection of an action should be based on an internal representation of the goal and the recent experience of action–outcome contingency [1]. Thus, a representation of the goal and of the action–outcome contingency are essential in achieving goals in changing environments. In some cases, the memory of action–outcome contingency might have only limited reliability, thereafter the organism has to attempt multiple actions one after another to achieve the goal. A quick evaluation of an action outcome is required in this situation. Moreover, it is often the case that a sequence of actions is required to achieve the goal. Early preparatory action steps are conducted to set up a condition in which the final action step achieves the goal. Because it is more difficult to motivate the organism to conduct such early action steps, as they do not immediately lead to the goal, they should be discriminated from the final step and supported by a specific mechanism. Neuropsychological findings and model studies suggest the importance of evaluating the outcome of individual action steps in such multi-step behavior [2,3]. Thus, three processes are important in achieving goals in changing environments: first, action selection based on goal expectation and memory of action–outcome contingency; second, action evaluation based on immediate outcome; and third, discrimination of the early steps from the final step towards the goal. Here, we discuss the important roles that the medial part of the prefrontal cortex (medial PFC) plays in these three processes. In this review, we refer to the medial PFC as an area including the dorsal and ventral banks of the anterior part of the cingulate sulcus. This area includes the cingulate motor area, but does not include the pre-supplementary motor area. Some authors refer to this same extent of cortex as the anterior cingulate cortex (ACC), but others exclude the dorsal bank of the very anterior part of the cingulate sulcus from their definition of the ACC.

The ability to quickly form stimulus–reward associations is also essential in achieving goals in changing environments. We do not discuss it in this review, because the medial PFC does not appear to be associated with this function, and also because it has recently been discussed elsewhere [4,5••].

Action selection based on goal expectation

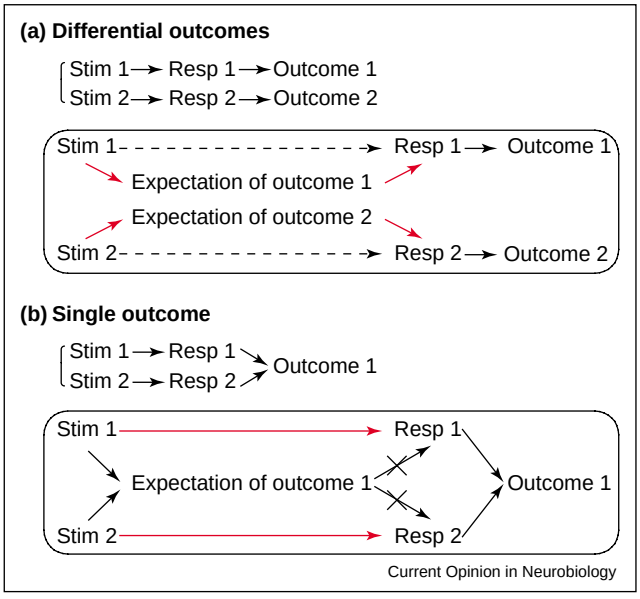
Goals for animals are usually primary rewards, such as water, food, and sexual contact. Neuronal mechanisms by which reward expectation influences action selection have been examined in animals using liquid and food rewards [6–12,13•,14]. However, in some of these studies, the experimenters found that action selection was independent of the manipulated reward expectation. In other studies, the manipulated reward expectation was associated with the position of the action target; therefore, the action–reward association could not be distinguished from stimulus–reward association. Only Shima and Tanji [8] and Matsumoto *et al.* [14] noted experimental situations in which an action was selected on the basis of reward information.

In a study by Shima and Tanji [8], the monkey was required to either push or turn a handle to obtain a reward. After the monkey repeated an identical movement (e.g. push) a few times, the amount of reward began to decrease (by 30% in each successive trial). Thereafter, if the monkey shifted to another movement (e.g. from

push to turn), they could get the full amount of reward. Otherwise, the reward amount would decrease further. When the monkey shifted the movement, during the time period from the acquisition of reduced reward to the initiation of action in the next trial, many cells in the rostral cingulate motor area (CMAr) located in the depth of cingulate sulcus exhibited discharges. The activity was selective for the direction of movement shift: some cells fired in the shift from push to turn, whereas others fired in the shift in the opposite direction. Furthermore, a reversible blockade of CMAr by muscimol injection impaired the response shift that was based on the reward, whereas the monkey's response shift that was based on an auditory cue was not degraded. The contribution of the medial PFC to action selection based on reward information has also been noted in a lesion study of monkeys [15••] and in a human imaging study by Bush *et al.* [16] with a task similar to that of Shima and Tanji. Thus, we now know that the medial PFC is crucial for reward-based action selection. However, in all these studies, it was not determined whether the animals selected the action on the basis of the reward experienced in the previous trial (the reduction in reward in Shima and Tanji [8]) or on the basis of the expected reward at the end of the current trial (the full amount of reward in Shima and Tanji [8]).

In order to study the neuronal processes underlying the representation of action–outcome contingency, distinctly distinguishable different outcomes should be combined with different actions. Moreover, to make the action selection in individual trials independent from events in previous trials, it is required that actions are preceded by discriminative stimuli. However, a problem arises. Once discriminative stimuli are introduced, there is a possibility that the animal uses stimulus–response mapping or basic associations (i.e. habit) in action selection. In the field of animal psychology of learning it has been demonstrated, however, that parallel learning of two stimulus–response contingencies is facilitated when two different types of reward follow the correct performance of the two responses [17–19]. This effect is illustrated in Figure 1. Assume that there are two stimuli (Stim 1 and Stim 2), two motor responses (Resp 1 and Resp 2), and two types of reward (Outcome 1 and Outcome 2). The learning of Stim 1–Resp 1 and Stim 2–Resp 2 was faster when they were followed by two types of reward (i.e. Stim 1–Resp 1–Outcome 1 and Stim 2–Resp 2–Outcome 2) than when the same stimuli and responses were followed by the same type of reward (i.e. Stim 1–Resp 1–Outcome 1 and Stim 2–Resp 2–Outcome 1). This effect is called the differential outcomes effect (DOE). The DOE occurs even when one of the reward conditions is no reward, and it cannot be explained by the effect of intermittent reinforcement [20]. The DOE indicates that learning of action selection based on stimulus–reward and action–reward associations is quicker than that of action selection based on stimulus–response associations, thereby suggesting that learning goal-based action selection is more advantageous than habit formation in changing environments.

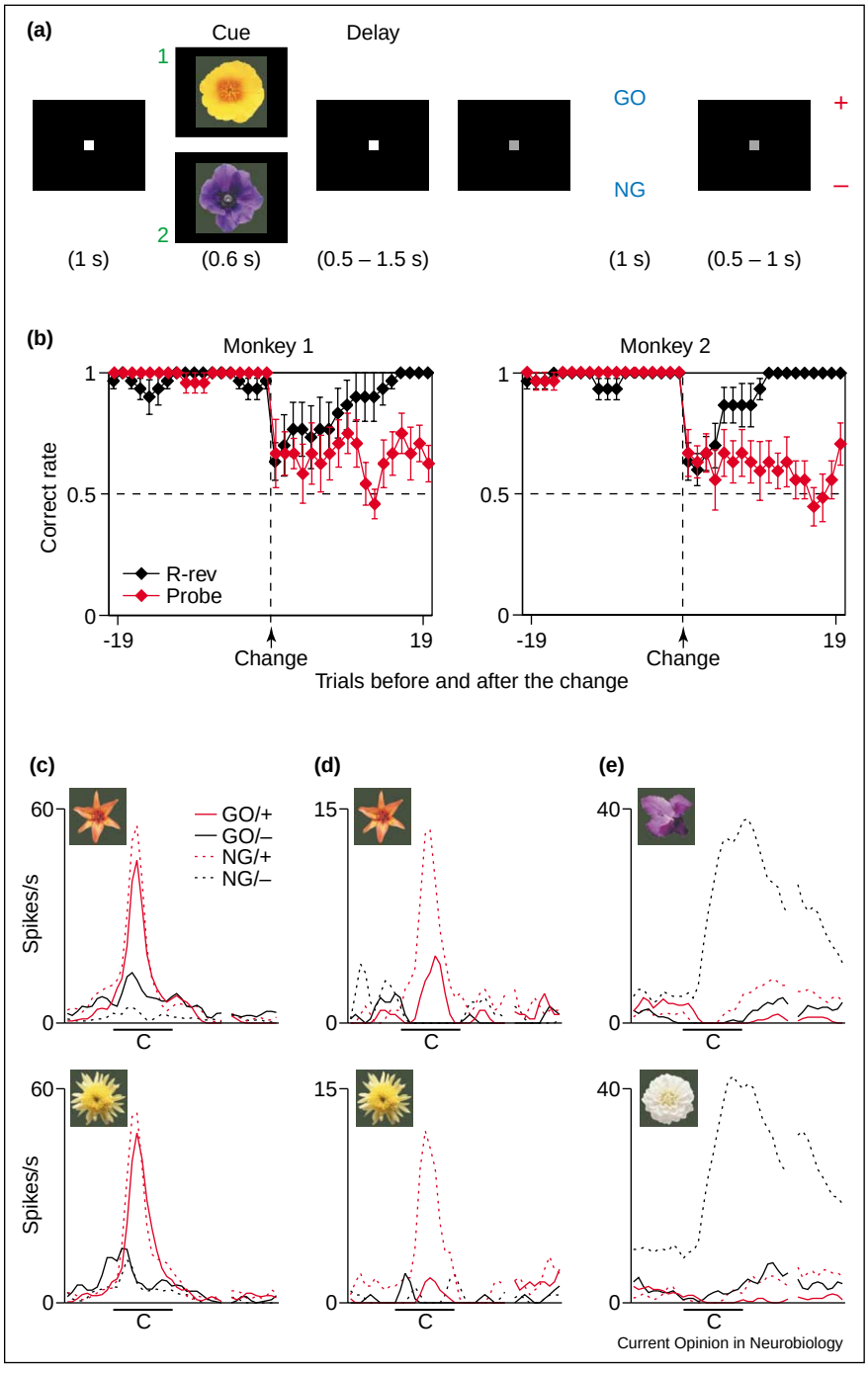
Figure 1



Schematic view of the differential outcomes effect (DOE). In procedures with both **(a)** differential outcomes and **(b)** a single outcome, animals learned mappings of two responses (Resp 1, Resp 2) to two stimuli (Stim 1, Stim 2). (a) Two types of outcome (Outcome 1, Outcome 2) follow correct performance of the two responses in the differential outcomes procedure, (b) whereas an identical outcome (Outcome 1) is provided to the correct performance of both responses in the single outcome procedure. The assumed psychological processes underlying action selections are shown in the boxes. Red arrows indicate the processes that mainly contribute to action selections.

Matsumoto *et al.* [14] utilized the DOE to examine the neuronal mechanisms that underlie goal-based action selection. They trained monkeys in a visually cued, asymmetrically rewarded GO/NO-GO task (Figure 2a). The relations among visual cues, motor actions, and reward conditions were changed every 40–60 trials, so that the monkeys had to repeatedly learn the visual–motor mapping in new conditions. Within a block of 40–60 trials, however, the relations among these variables were fixed. There were four possible types of trial block (Table 1). While the monkeys fixated their gaze at the center of the monitor screen, one of the two visual cues was presented and after a delay the monkeys performed either a GO response (pulling the joystick and then returning it to the initial position) or a NO-GO response (holding the joystick with no movement), depending on the cue. After another delay, a liquid reward was provided (Reward +) after correct GO responses and the monkeys received no reward (Reward −) after correct NO-GO responses (Blocks I and III in Table 1), or a liquid reward was provided after correct NO-GO responses and no

Figure 2



Medial PFC activity representing action–goal combinations while actions are selected based on current goals (reward conditions). **(a)** The sequence of events in the task. The small white or gray square with black background indicates the fixation point at the center of the monitor. The blue GO and NG indicates the GO response and NO-GO responses, respectively. The red + and − on the right indicates reward and no reward after correct response, respectively. **(b)** The ratio of trials with correct responses before and after the introduction of symmetrical reward schedule in a probe test (red lines) and the reward reversal (black lines). **(c)** A medial PFC cell with discharges that appeared immediately after the onset of visual cues but represented anticipated reward. The bar accompanied by C under each histogram indicates the cue presentation for 0.6 s. The colors and styles of lines indicate the reward condition and the required motor response, respectively (red, reward +; black, reward −; solid, GO; dashed, NO-GO). **(d)** Another medial PFC cell with transient discharges that appeared only under a specific action-goal combination (NO-GO and reward). **(e)** Activity of a third medial PFC cell. In this cell, discharges specific to an action–outcome combination (NO-GO and no reward) persisted throughout the delay period. Adapted with permission from [14].

Table 1

Visual-motor-reward contingencies.

Block	Visual cue	Motor action	Reward condition
I	Cue 1	GO	Reward +
	Cue 2	NO-GO	Reward −
II	Cue 1	NO-GO	Reward +
	Cue 2	GO	Reward −
III	Cue 1	NO-GO	Reward −
	Cue 2	GO	Reward +
IV	Cue 1	GO	Reward −
	Cue 2	NO-GO	Reward +

The eight combinations of visual cues, motor actions, and reward conditions in four blocks used in Matsumoto *et al*. [14]. Two combinations were included in each block. The order of blocks was changed pseudo-randomly.

reward was provided after correct GO responses (Blocks II and IV). A sound was presented following correct responses in unrewarded trials, so that the monkeys could distinguish incorrect responses (errors) from correctly performed unrewarded responses. Gaze fixation was required throughout the trial. Even in unrewarded trials, the monkeys had to perform correctly to advance to later rewarded trials, because the same condition was repeated until the monkeys performed correctly.

The task did not require the monkeys to anticipate the reward condition, and the task could correctly be performed only on the basis of stimulus–motor mapping. However, considering the DOE, it was expected that the frequent reversal pushed the monkeys to use the strategy of goal-based action selection. Two lines of behavioral evidence supported this theory. First, the break in gaze fixation was more frequent in unrewarded trials than in rewarded trials, suggesting that the monkeys correctly anticipated the reward condition. Secondly, in a probe test, in which both correct GO and correct NO-GO responses were rewarded, the monkeys' performance considerably deteriorated and remained at a low level (Figure 2b). Under the symmetrical reward schedule used in the probe test, the anticipated reward condition could not specify an action because one reward condition was combined with both actions, whereas the stimulus-motor association continued to be relevant (Figure 1b). Therefore, the results suggest that the monkeys selected an appropriate motor response depending on the anticipation of the reward condition and the memory of motor–reward contingency. In summary, the behavioral findings show that the monkeys had the representation of the goal and knowledge of the causal relationship between action and goal. These are the conditions that Dickinson and Balleine [21] proposed for defining goal-directed behavior.

Matsumoto *et al*. [14] recorded the activity of single PFC cells using all eight combinations of two visual cues, two actions (GO/NO-GO), and two reward conditions (reward/no reward) in four blocks of trials. By doing so, they distinguished the effects of each of the three variables (visual cues, action types, and reward conditions) on neuronal activity. They noted two types of neuronal activity in the medial PFC during the cue presentation. Some cells fired only when a particular reward condition was anticipated, independent of the identity of the visual cue and of the motor action (goal-representing cells, Figure 2c). Other cells fired only in association with a particular combination of action and reward condition, independent of the identity of the visual cue (action-goal-representing cells, Figure 2d and e). Because the time of cue presentation was the earliest possible time to select an action that would be executed after 1.1–2.1 s, it was suggested that the sequential activation from the goal-representing cells to the action-goal-representing cells in the medial PFC is the neuronal correlate of the goal-based action selection. It is unlikely that the representation of anticipated reward condition was induced by the visual cue within the medial PFC, because there were few medial PFC cells that represented visual cues or combinations of visual cues and reward conditions. The possible sites at which anticipation of the reward condition was induced by the cue include the amygdala, orbitofrontal cortex, and dopamine neurons in the midbrain.

Walton *et al*. [22••] conducted a lesion study that has relevance to this topic by testing rats with a T-maze. One arm of the maze was flat and there was a small amount of food at the end, by contrast the other arm of the maze had a steep barrier and a large amount of food was placed at its end. Intact rats selected the arm with a barrier, whereas rats with bilateral lesions in the medial PFC selected the flat arm. The representation of anticipated reward amount was intact in lesioned rats, because they selected arms with a large amount of reward when steep barriers were placed in both arms. It is possible that the lesioned rats did not make the effort to climb over the barrier because such efforts were not associated with a large amount of reward. This deficit could be related to the action–outcome contingency representation. However, we should be cautious in interpreting the corresponding results between the findings in monkeys and this finding in rats. The part of the monkey medial PFC in which Matsumoto *et al*. [14] recorded might correspond to the prelimbic cortex in the rat brain, but rats with a lesion in the prelimbic cortex climbed over the barrier to obtain a large amount of reward as did normal rats [23].

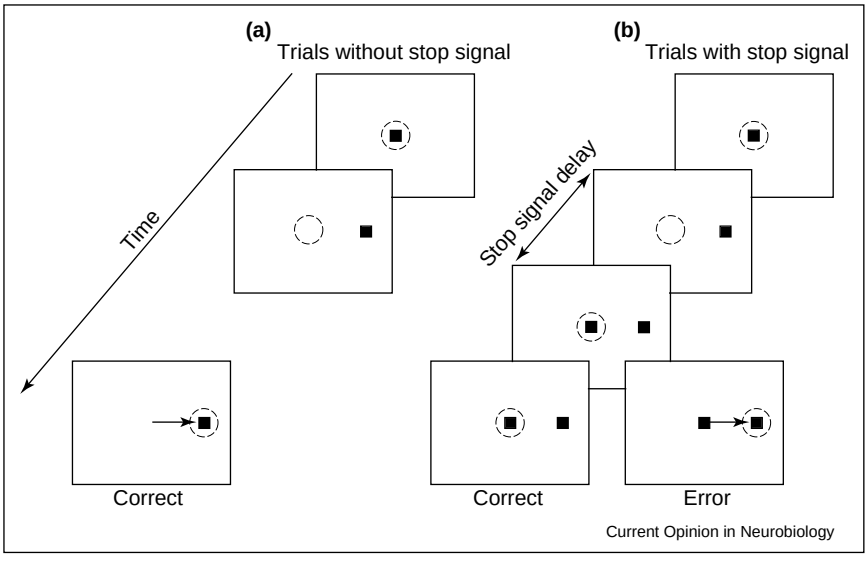
Action evaluation based on immediate outcome

Both human imaging studies and single cell recordings in monkeys have demonstrated the activation of many areas in the brain at the time when subjects received or missed rewards or goals, such as the medial, lateral, and orbital parts of PFC [24,25,26••,27–29], the amygdala [30], the

dorsal and ventral striatum [31–33], the subthalamic nucleus [34], and the midbrain dopamine cells [35,36]. However, these reward- and error-related activities are not necessarily involved in action evaluation, because rewards are related to a variety of psychological functions [37]. A potential site for the evaluation of action based on the actions' immediate outcome is the medial PFC, because error-related negativity (ERN) has been revealed here [38]. ERN is an electroencephalographic potential that was originally observed in the frontal cortex when subjects made an erroneous motor response in reaction time tasks. Because subjects were instructed to respond as soon as possible in reaction time tasks, they tended to make premature responses, in which they often noticed that the response was wrong at the moment of responding. The ERN was time-locked to the motor response (its onset is around 80 ms after the onset of activity on the electromyograph), and so it was presumed that neural processes for the execution of motor response (including corollary discharges) were a component of the ERN source. It was later noted that ERN also occurred when negative feedback was provided after the motor response had been completed. It was also observed, in the learning procedure of a task that the ERN at the time of feedback decreased with increased learning, whereas the ERN at the time of the motor response execution increased as learning did. It was thus concluded that the ERN occurs generally when the system first detects that the consequence of an action is worse than expected. The experimenters found the ERN to be localized in the medial PFC around the anterior part of the cingulate sulcus.

Ito *et al.* [39] reported that cells in the monkey medial PFC were activated when an action was evaluated by its consequence. They trained monkeys with a countermanding saccade task (Figure 3). A target appeared when a fixation spot disappeared and the monkeys made a saccade to the target (Figure 3a). In some trials, a stop signal appeared at the location of the fixation spot some time after the onset of the target but before the onset of saccade (Figure 3b). In this case, the monkey had to stop the saccade and continue fixating its gaze at the center fixation position. Correct saccades in trials with no stop signal and correct cancellation of saccades in trials with a stop signal were rewarded with juice 400 ms after the onset of the target. The monkey always succeeded or always failed in cancelling saccade when the delay from the onset of target to the onset of stop signal was very short or very long, respectively. However, when tested with a range of delays from the onset of the target to the onset of the stop signal, the monkey succeeded in canceling saccade in some trials but failed in canceling and made a saccade in other trials. When the monkey failed in canceling, some medial PFC cells fired immediately after the onset of saccade but before the time when the reward would have been delivered if the monkey had succeeded in canceling. Many of the same cells also fired at the time of reward delivery when the reward was

Figure 3



A countermanding saccade task used to examine medial PFC activity associated with evaluation of action. **(a)** In this task the monkey had to fixate on a spot until a target came into view, which it should then make a saccade to. **(b)** A stop signal (identical to the fixation spot) appeared in some trials at the fixation spot with a delay (the stop signal was presented after a delay after onset of the target but before the onset of a saccade). The monkey had to cancel the saccade in these trials. Neuronal activity in the medial PFC was compared between trials in which a stop signal was presented but the monkey made a saccade (not canceled saccades, marked by 'error' in [b]) and those in which no stop signal was presented and the monkey simply made a saccade (a). Dotted circle indicates the position of gaze.

omitted after performing correct responses. It appears that medial PFC activity generally represented a mismatch between expected and experienced consequences. The cells were sensitive to both a mismatch in visual environment and a mismatch in reward delivery. Cells in the supplementary eye field also fired in the not cancelled trials, but they were not tested with the omission of reward delivery [40].

Discrimination of early steps from the final step

Shidara and Richmond [41••] trained monkeys to perform a reaction time task with a multi-trial reward schedule while they recorded activity of single cells from the medial PFC, more specifically in the ventral bank of the anterior cingulate sulcus. In each trial, the monkey had to detect a color change of a fixation spot (from red to green) and respond by removing their hand from a bar. If the response was conducted within 1 s after the color change, the color of the spot turned blue to indicate a success. The number of successful trials the monkeys were required to perform before a juice reward was provided was chosen randomly at the beginning of each schedule. Across trials within a schedule, the rectangle became brighter, thereby signaling the distance from juice reward delivery. The activity of many medial PFC cells was dependent on the position of the current trial in the reward schedule. Two types of activity are particularly relevant to the discussion here. Some medial PFC cells exhibited activity that gradually increased during unrewarded early steps but diminished at the final step. Another group of cells were activated only in the final rewarded trial. The activity of the first group of cells could support the execution of actions in the early steps, which are not supported by immediate reward expectation. The functional significance of the gradual increase in activity during the early steps is more difficult to discuss.

Interaction between the medial and the lateral prefrontal cortex

On the basis of the neuropsychological examination of prefrontal damaged patients and imaging studies of normal human subjects [42], the lateral PFC has also been considered to be crucial in goal-directed behavior, planning, and problem solving. Because the medial PFC and the lateral PFC have reciprocal dense connections [43–48], these two prefrontal areas are likely to interact to support cognitive functions. On the basis of human imaging data, it has been proposed that the anterior medial PFC is involved in carrying out endogenous plans, whereas the anterior lateral PFC is involved in carrying out exogenous plans, and the frontal tip is involved in mediating the interaction between them [49]. In line with this hypothesis, it has been noted that neurons in the monkey lateral PFC extract categorical information from sensory inputs [50,51], maintain the working memory of spatial location and object information [52–54], maintain sequences of action targets [55], maintain attention to space [56] and sensory dimension [57], and maintain more general task rules [58–60]. In one study [60], monkeys were required to employ either a matching- or a non-matching-to-sample rule, as instructed by a cue appearing at the beginning of the trial. The activity in the lateral PFC that represented matching rules started immediately after presentation of the cue that indicates the rule to be used on that trial and continued until the time of action selection [60]. Although matching rules were also represented by some medial PFC cells [61], the activity was limited to a short period immediately before the action was selected. Circuitry in the lateral PFC might contribute to action selection and execution by maintaining the relevant information extracted from external cues, whereas the medial PFC contributes to selection by mediating the interaction with internal evaluation.

When the rule for guiding action selection is unclear to subjects, they have to select their actions depending on a temporarily hypothesized rule to achieve the goal. In the study by Matsumoto *et al*. [14], which is described above, medial PFC cells exhibited greater activity when new action–outcome contingencies were being learned after reversals. A greater activity of cells in the medial PFC was also reported by Procyk *et al*. [62] during learning of new sequences of sequential touches on three targets. Goal-based action selection with hypothesized rules might guide rule learning. Evaluation of action is also important for the extraction of rules. A human positron emission tomography study showed the activation of the medial PFC during efforts to extract rules for mapping the relationship between spatial pattern configurations and action directions [63]. If the correct rule requires a sequence of actions, the discrimination of early steps from the final step will be important to avoid an immediate rejection of a hypothetically formed rule. Thus, the medial PFC could contribute to the formation of new rules on the basis of the three functions discussed above: goal-based action selection, outcome-based action evaluation, and discrimination of early from final steps leading towards a goal. Because the rules themselves are probably represented in the lateral PFC once they are formed, the medial PFC mainly works during the learning process. The actual mechanisms underlying this interaction between medial PFC and lateral PFC remain to be elucidated. The pre-supplementary motor area, which is connected to both the medial PFC and the lateral PFC [64,65], might mediate the interaction, because cells in this area were specifically activated when sequential actions were being learned [66].

Conclusions

The medial PFC contributes to goal achievement by three processes, namely, goal-based action selection, rapid action evaluation by immediate outcome, and discrimination of the early steps from the final step towards

the goal. The interaction of the medial PFC with the lateral PFC in forming new rules should be further studied. By studying how the medial PFC helps the lateral PFC to learn new rules, we will be able to uncover the brain mechanisms of cognitive development on the basis of an individual's motivation to achieve.

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