Representation of Behavioral Tactics and Tactics-Action Transformation in the Primate Medial Prefrontal Cortex

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To expedite the selection of action under a structured behavioral context, we develop an expedient to promote its efficiency: tactics for action selection. Setting up a behavioral condition for subhuman primates (*Macaca fuscata*) that induced the development of a behavioral tactics, we explored neuronal representation of tactics in the medial frontal cortex. Here we show that neurons in the posterior medial prefrontal cortex, but not much in the medial premotor cortex, exhibit activity representing the behavioral tactics, in advance of action-selective activity. Such activity appeared during behavioral epochs of its retrieval from instruction cues, maintenance in short-term memory, and its implementation for the achievement of action selection. At a population level, posterior medial prefrontal cortex neurons take part in transforming the tactics information into the information representing action selection. The tactics representation revealed an aspect of neural mechanisms for an adaptive behavioral control, taking place in the medial prefrontal cortex.

Key words: action; decision making; medial prefrontal cortex; monkey; neuron; tactics

Significance Statement

We studied behavioral significance of neuronal activity in the posterior medial prefrontal cortex (pmPFC) and found the representation of behavioral tactics defined as specific and efficient ways to achieve objectives of actions. Neuronal activity appeared during behavioral epochs of its retrieval from instruction cues, maintenance in short-term memory, and its use preceding the achievement of action selection. We found further that pmPFC neurons take part in transforming the tactics information into the information representing action selection. A majority of individual neurons was recruited during a limited period in each behavioral epoch, constituting, as a whole, a temporal cascade of activity. Such dynamics found in behavioral-tactics specific activity characterize the participation of pmPFC neurons in executive control of purposeful behavior.

Introduction

When confronted with a frequent need to select actions immediately in response to a prompt, we often develop an expedient for promoting an efficient selection (Desrochers et al., 2010) (i.e., tactics for action selection). In a previous study, we found that monkeys develop a behavioral tactics to expedite the selection of action: when required repetitively to respond promptly to the appearance of a visual cue and select an action of reaching to a spatial target that were either concordant or discordant to the spatial location of cues, they used the tactics of selecting either an

illuminated or nonilluminated target (Matsuzaka et al., 2012, 2013). The requirement to select the valid tactics, not the action per se, turned out to be a behavioral condition that specifically called for cellular activity in a posterior portion of the medial prefrontal cortex (pmPFC). The activity, however, was observed during the response period when a number of behavioral factors conjointly took their part. This finding led us to explore the cellular representation of tactics selection in isolation when the tactics is formulated in accordance with instructions. In the present study, we indeed discovered cellular activity representing the behavioral tactics, independent of action selection, during behavioral epochs for retrieving, maintaining in short memory, and for implementing the tactics. We found further that such activity, abundant in the pmPFC but infrequent in the medial premotor cortex, was actively involved in transforming the tactics information into the information representing action selection.

Recent accumulation of studies concerning the lateral part of the prefrontal cortex (IPFC) has established multiple aspects of its role in integrative control of behavior (Miller and Cohen, 2001; Fuster, 2008; Tanji and Hoshi, 2008; Passingham and Wise, 2014). In contrast to the wealth of knowledge on the participation

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A tactics-only cued trials **B fully cued trials** **C reactive-selection trials**

Figure 1. Behavioral task performed by the animals under three behavioral conditions, illustrated schematically in *A–C*. **A**, An instruction cue (cyan or blue) indicates whether the animals should select the tactics of responding to a forthcoming response signal that will appear after a delay period: reaching either to (pro-reach) or away (anti-reach) from an illuminated target. Under this condition, the selection of action is possible only after the appearance of the response signal. **B**, Animals follow two sets of instructions in accordance with two different behavioral rules. Under the spatial-inference rule, a cyan cue indicates that the forthcoming response to a Go signal is to reach to the cued target. A blue cue requires a forthcoming reach to a target away from the cued target. Thus, both information for the selection of tactics and action are cued. Under the color-conditional rule, a red cue means a future reach to the right and a green cue indicates a reach to the left, giving rise to a reach toward or away from a cued target. **C**, Animals wait for the appearance of a response signal, presented simultaneously with a Go signal, to promptly select an action according to the spatial-inference rule or the color-conditional rule.

Figure 2. *A*, A representative example of a pmPFC neuron that exhibited tactics-selective activity during the cue period of tactics-only cued trials. Neuronal activity recorded during all of the correctly performed trials was sorted by the reaching direction (left or right) and cue (pro-reach, anti-reach). Tick marks indicate the occurrence of spikes aligned with the onset of the Cue and Go signal (cyan vertical lines), and the averaged activity is plotted as the spike density function (SDF, $\sigma = 20$ ms). The height of the frame for the SDF corresponds to 30 impulses per second. The green squares, crosses, circles, and triangles represent the cue onset, Go signal onset, hold button release, and target button press, respectively. The bin width = 10 ms. The visual cue signaling the tactics-evoked marked response in the anti-reach but not the pro-reach trials. *B*, Cortical areas explored in the present study. Left, Dorsal view of the left cerebral hemisphere and the locations of the pmPFC and the SMA. Right, Spatial distribution of task-related neurons in Monkey H whose brain was sectioned for histological verification of recording sites. Histology was not available from the other animal. However, physiological properties of the analyzed areas were in accordance with the previous reports (Matsuzaka et al., 2012, 2013), and the distribution of behavioral-task related neurons was comparable between the two animals. Purple rectangles represent the pmPFC. Orange rectangles represent the SMA. Broken line indicates the midline. The number of neurons recorded in each electrode track is denoted by the size of the circle. Crosses represent that no task-related neuron activity was recorded. Numbers on the left are the anterior–posterior levels in Horsley–Clarke coordinates.

of the IPFC in specific aspects of perception/attention-based (Romo et al., 1999; Lebedev et al., 2004; Crowe et al., 2013), rule-based (White and Wise, 1999; Wallis et al., 2001; Genovesio et al., 2005), category-based (Freedman et al., 2001; Shima et al., 2007; Cromer et al., 2010), or goal-oriented control of motor behavior (Genovesio et al., 2006; Mushiaki et al., 2006; Yamagata et al., 2012), little is known about the behavioral role of its medial counterpart. The present findings of tactics representation revealed an aspect of proficiency-oriented neural mechanisms for an adaptive behavioral control, providing an initial step of understanding the workings of the pmPFC in higher-order aspects of behavioral control.

Materials and Methods

Animals and experimental setup. We used two monkeys (*Macaca fuscata*; a male weighing 9.5 kg and a female weighing 5.5 kg) cared for in accordance with the National Institutes of Health guidelines and the guidelines of our institute. During experimental sessions, the monkeys were seated in a primate chair equipped with a hold button in its arm rest, facing a panel. The panel was equipped with a central fixation target (a white light emitting diode [LED]) and two buttons, one on the right and one on the left, each back-illuminated with a full-colored LED. Each trial of the present behavioral task began when the animals pressed the hold button for 1 s. The monkeys were trained to gaze at the center fixation point throughout the task performance in

Figure 3. Time-dependent plots of neuronal selectivity for the tactics and action under the three behavioral conditions (data are for the same neuron shown in Fig. 2A). The time courses of tactics (green) and action (red) selectivity were computed consecutively as the CPD using a moving time window (width = 200 ms, step = 20 ms; for details of the calculation, see Materials and Methods). Solid lines indicate that the tactics or action had significant effects on neuronal activity ($p < 0.01$) in a multiple regression model that uses the tactics and action as regressors. Dotted lines indicate nonsignificant data. **A**, Neuronal selectivity for the tactics and action computed from 103 tactics-only cued trials. On the left, the trials are aligned with the Cue onset (left vertical line), whereas on the right, the trials are aligned with the Go signal onset (right vertical line). This neuron exhibited enhanced selectivity for the tactics transiently after the cue onset. **B**, Neuronal selectivity for the tactics and action during the fully cued trials (128 trials). The conventions are the same as in **A**. **C**, Selectivity for the tactics and action during the reactive selection trials (123 trials). The trials are aligned with the Go signal onset only.

each trial, until a reward was delivered (0.5 s after the correct button was pushed).

Behavioral task. The monkeys were trained to perform a two choice arm-reaching task of reaching to and press either the left or right button on the panel. Three different behavioral conditions were given to the animals to inform them how to respond to subsequent signals (instructing the response tactics) or which target to reach (instructing the selection of action). First, visual cues (0.5 s) instructed behavioral tactics to respond to forthcoming choice signals for selecting a correct action (see Fig. 1A, tactics-only cued trials). One cue (light cyan) meant a preparation to reach toward an illuminated portion of a pair of targets, whereas the other cue (blue) indicated readiness to reach away from the illuminated target. After a delay period (1–1.5 s), either the right or left of the reach targets was illuminated with a white LED. It was only after the appearance of the choice signals (a pair of illuminated and nonillumi-

nated target) when the monkeys were able to select actions (of right or left reach) to obtain a reward. Under the second behavioral condition (see Fig. 1B, fully cued trials), a different set of instruction cues indicated both the behavioral tactics and future actions. An instruction cue illuminated one of the spatial target pair. If illuminated with cyan, it meant a future reach toward the illuminated target. If blue, it instructed a future reach away from the illumination. Thus, the visual cues instructed both the tactics to cope with the target pairs and the future actions to be selected. After a delay period (1–1.5 s), the animals responded to a Go signal (1 kHz tone) to initiate a target reach. To examine a possibility that medial frontal cortex neurons may also represent a behavioral rule of selecting an action target based on a target inference or color-conditional rule, we added a control task in which a green illumination instructed a future action to reach left and a red illumination meant a cue for preparing a right reach. The locations of color cues were either concordant or discordant to the reach target. Under the third condition, there was no instruction cue. Monkeys waited (1–1.5 s) for the appearance of a choice cue with cyan or blue illumination, or green or red illumination. They had to respond promptly to the choice cue, in accordance with either the target inference or color conditional rule, to initiate a correct reach (see Fig. 1C, reactive selection trials). Each of the three behavioral conditions was given consecutively in a block of 40 trials where the tactics and actions were pseudo-randomly determined. Under all conditions, a trial was cancelled if the monkeys released the hold button before Go signal or failed to keep gazing at the fixation point before delivery of the reward.

Neuron recording. While the monkeys were performing the behavioral task, we recorded neuronal activity from the bilateral medial frontal cortex, including the pmPFC and the supplementary motor area (SMA). In both monkeys, the two cortical areas were identified based on the anatomical and physiological criteria described previously (Matsuzaka et al., 2012). Spike activity of neurons was recorded with glass-coated Elgiloy electrodes (impedance, 0.8–1.2 M Ω at 1 kHz), amplified, band-pass filtered at 300–3.3 kHz, and sorted using a multispikes detector (Alpha-Omega). Eye positions were continuously monitored with an infrared corneal reflection system. The behavioral task and data sampling were controlled

using Visual TEMPO (Reflective Computing). Task-related neurons were searched for while advancing the microelectrodes by hydraulic micromanipulators (Narishige, MO-81) during the monkeys' task performance. When we found one, to ensure that the same neuron was recorded across the three behavioral conditions, we presented at least one behavioral condition twice separated by blocks of the other behavioral conditions. If the activity was inconsistent between the blocks of same the same behavioral conditions, or if the spike's waveform changed, we discarded such data from the analysis. Before examining neuronal activity during performance of the task, sensory responses of the neurons were tested at each electrode site by presenting objects in the monkey's visual field, touching the monkey's body surface, and manipulating the monkey's joints. To examine evoked movements, we also used intracortical microstimulation (cathodal current, 10–80 μ A; pulse width, 300 μ s;

interval, 3 ms; 12–80 pulses). Within the medial frontal cortex spanning A15–A30 in Horsley–Clarke's coordinate, we identified the pmPFC and the SMA according to the physiological and anatomical criteria described in previous studies (see Fig. 2).

Sampling of spiking activity. We sampled 229 neurons in the pmPFC and 114 neurons in the SMA of the two monkeys, as they were recorded during performance of sufficient number of trials (at least 15 correct trials for each combination of trial type, target, and tactics) for subsequent statistical analyses under the three behavioral conditions. For analyzing neuronal activity, we dealt with correctly performed trials only and excluded erroneous trials and corrective trials in which a correct response was made after having pressed a wrong target. We defined the task-related neuronal activity as follows.

Cue period activity. We took 500 ms time interval following the cue onset as the cue period. If the firing rate in that period was significantly greater ($p < 0.01$ by Mann–Whitney test) than in the control period (500 ms preceding the cue onset), we defined such activity as cue-responsive.

Delay period activity. We calculated the firing rate of neurons during the 500 ms time interval preceding the Go signal onset. If the firing rate in that period was significantly greater ($p < 0.01$ by Mann–Whitney test) than in the control period (500 ms preceding the instruction cue onset), we defined such activity as delay period activity.

Response period activity. Neuronal activity occurring after the appearance of Go signal may be time locked to the Go signal, monkey's hold button release, or target button press. We therefore divided the response period into three epochs of 300 ms: epoch 1 following the cue onset, epoch 2 beginning 150 ms before and ending 150 ms after the hold release, and epoch 3 preceding the target hit. In this report, we did not go into details of analysis in each epoch. Instead, we selected the epoch that gave the highest firing rate for each neuron. If the firing rate in that epoch was significantly greater ($p < 0.01$ by Mann–Whitney test) than in the control period (500 ms time interval preceding the Go signal), neuronal activity was defined as having response period activity. The response period activity selected as such was separately examined during performance of tactics-only cued, fully cued, and reactive-selection tasks.

Analysis of neuronal selectivity for behavioral factors. To examine the extent to which individual neurons exhibited selectivity for the tactics (reach to vs away from the illuminated target) or for the action (reach to left vs right target), we used a multiple regression analysis based on the following model:

$$\text{Firing rate} = a1 \times \text{Action} + a2 \times \text{Tactics} + b + \varepsilon$$

where *Tactics* is the spatial concordance between the cue and the target (reach to vs away from the cue), *Action* is the direction of the subject's arm reach, *a1* and *a2* are regression coefficients, *b* is the intercept, and ε is the residual error. We performed this analysis under the tactics-only cued condition. Neurons that showed significant effects ($p < 0.05$) of action or tactics during the cue, delay, or response periods were regarded as selective for these factors.

Time-dependent analysis of behavioral selectivity found in individual neurons. We examined quantitatively the time course of behavioral selec-

Figure 4. *A–C*, Tactics-selective activity of a pmPFC neuron preferentially observed during the delay and response period of tactics-only cued trials. Data plots and display formats are the same as in Figure 3. CPD was calculated from the neuronal activity during 68 tactics-only cued trials (*A*), 100 fully cued trials (*B*), and 103 reactive selection trials (*C*).

tivity exhibited by individual neurons during the progress of behavioral epochs of cue, delay, and response periods. For this purpose, we analyzed the instantaneous selectivity for the tactics and action of individual neurons by computing the coefficient of partial determination (CPD) defined below. We first calculated instantaneous neuronal firing rate using a moving time window (width = 200 ms, step = 20 ms) in each trial. For the analysis of precue and postcue period activity, the window was shifted in the period beginning 200 ms before and ending 1000 ms after the cue onset in tactics-only cued trials. For the analysis of late delay and response period, the time window was shifted in the period beginning 1000 ms before and ending 1000 ms after the onset of the Go signal.

In each time window, we counted the instantaneous firing rate of neurons on a trial-by-trial basis, then analyzed its dependence on the action and the tactics by multiple regression analysis. We used a multiple regression analysis based on the following model:

$$\text{IFR}(t) = a1 \times \text{Action} + a2 \times \text{Tactics} + b + \varepsilon$$

where *IFR*(*t*) is the instantaneous firing rate at time *t*, *Action* is the direction of the subject's arm reach (left vs right), *Tactics* is the spatial concordance between the cue and the target (reach to vs away from the cue), *a1* and *a2* are regression coefficients, *b* is the intercept, and ε is the residual error. This model was used for the analysis of the activity in tactics-only cued, fully cued, and the reactive selection trials (see Figs.

Figure 5. Venn diagrams showing the relationships among tactics-selective pmPFC neurons that appeared under the three different behavioral conditions. Numbers indicate the result of multiple regression analyses of the effects of behavioral tactics and action ($p < 0.05$; see Materials and Methods). **A**, Numbers of tactics-selective neurons during the cue period. **B**, Numbers of tactics-selective neurons during the delay period. **C**, Numbers of tactics-selective neurons during the response period.

3, 4, 6, 8, 10, 11, 12). When analyzing neuronal data under the fully cued behavioral condition, we also considered the effects of behavioral rules on neuronal activity by incorporating a control study (addition of color conditional rule). In that case, we used the following model:

$$IFR(t) = a1 \times Action + a2 \times Tactics + a3 \times Rule + b + \epsilon$$

where *Rule* is the behavioral rule (target inference or color conditional) and $a3$ is the third regression coefficient. This model was used for the combined analysis of neuronal selectivity for the tactics, action, and rule (see Fig. 7).

In each regression model, we defined the neuronal selectivity for each of the behavioral factors (i.e., action, tactics, and rule) as CPD. The CPD for factor X at time t was defined by the following:

$$CPD(X, t) = [SSE_{partial} - SSE_{full}] / SSE_{partial}$$

where $SSE_{partial}$ is the sum of the squared errors in a regression model that lacks the factor X , and SSE_{full} is the sum of the squared errors in a regression model that has all the factors.

For the analysis of the temporal variance of neuronal population's selectivity for tactics and action, we calculated the mean CPD by averaging individual neurons' CPD over the neuronal population as follows:

$$CPD_{mean}(X, t) = \frac{\sum_{i=1}^n CPD_i(X, t)}{n}$$

where the $CPD_i(X, t)$ is CPD of neuron i for factor X at time t , and n is the number of the neurons in the population. We then calculated the deviation of the CPD_{mean} (ΔCPD_{mean}) from the baseline period. Mean CPD during the 1000 ms period following the trial onset was computed using the moving time window; then it was subtracted from the CPD_{mean} during the pre-cue and post-cue, and pre-go and post-go periods. Therefore,

$$\Delta CPD_{mean}(X, t) = CPD_{mean}(X, t) - CPD_{base}(X)$$

$$CPD_{base}(X) = \frac{\sum_{i=1}^n \sum_{j=1}^T CPD_i(X, t_j)}{n \times T}$$

where T is the number of the time windows in the baseline period and t_j is the j th time window.

A permutation test was performed to evaluate the significance of the ΔCPD_{mean} . The null hypothesis for this test is that the CPD values in the time window t and the baseline period belonged to the common group. Thus, to generate the null distribution of ΔCPD_{mean} , for each time window at time t , we randomly swapped the CPD values of individual neurons $CPD_i(X, t)$ with those in the baseline period to generate the surrogate groups of CPD: one for the baseline period and the other for the time window in question. Then, we used the surrogate data to calculate the difference in the mean CPD between the baseline period and time t , $\Delta'CPD_{mean}(X, t)$.

We generated 10,000 surrogate data by repeating this random swapping of the CPD values. If the null hypothesis is correct, ΔCPD_{mean} would be within the chance level distribution of $\Delta'CPD_{mean}(X, t)$. We defined the chance level distribution of $\Delta'CPD_{mean}(X, t)$ as its 99% confidence range. The $\Delta CPD_{mean}(X, t)$ was defined as significant if it exceeded the limit of the confidence range.

Results

Two monkeys were trained to perform a two choice arm-reaching task under three different behavioral conditions. First, visual cues instructed behavioral tactics to respond to forthcoming choice signals for selecting a correct action (Fig. 1A, tactics-only cued trials). One cue (light cyan) meant a preparation to reach toward an illuminated portion of a pair of targets, whereas the other cue (blue) indicated readiness to reach away from the illuminated target. After a delay period (1–1.5 s), either the right or left of the reach targets was back-illuminated with a white LED. It was only after the appearance of the choice signals (a pair of illuminated and nonilluminated target) when the monkeys were able to select actions (of right or left reach) to obtain a reward. Under the second behavioral condition (Fig. 1B, fully cued trials), a different set of instruction cues indicated both the behavioral tactics and future actions. An instruction cue illuminated one of the spatial target pair. If illuminated with cyan, it meant a future reach toward the illuminated target. If blue, it instructed a future reach away from the illumination. Thus, the visual cues instructed both the tactics to cope with the target pairs and the future actions to be selected. After a delay period, the animals responded to a Go signal (1 kHz tone) to initiate a target reach. To examine a possibility that medial frontal cortex neurons may also represent a behavioral rule of selecting an action target based on a target inference or color-

Figure 6. Population analysis of the time course of tactics-selective activity and comparison of neuronal tactics selectivity under different behavioral conditions. **A**, Time-dependent plots of tactics selectivity calculated for the neuronal population in the pmPFC (purple traces, top) and SMA (orange traces, bottom) under the three behavioral conditions. The tactics selectivity was calculated consecutively as the CPD values characterizing individual neurons' activity, using a moving time window (width = 200 ms, step = 20 ms; for the details of the calculation, see Materials and Methods), then averaged across 153 neurons in the pmPFC and 73 neurons in the SMA. The CPD values are plotted as relative values by subtracting the reference values calculated during a baseline period (1000 ms preceding the Cue onset or the Go signal). The plots are aligned with the onset of a Cue signal or Go signal. Thin lines indicate the limits of the 99% confidence level of the CPD values deviating from the reference values (calculated with a permutation test; see Materials and Methods). **B–D**, Scatter plots presenting the distribution of the tactics selectivity of individual pmPFC neurons under the tactics-only cued (ordinate) versus fully cued (abscissa) task conditions. The tactics selectivity was calculated as CPD values during the cue (**B**), delay (**C**), and response periods (**D**). The mean CPD was significantly greater under the tactics-only cued than the fully cued condition during the cue ($n = 72$, $p < 0.005$, Kolmogorov–Smirnov test), delay ($n = 112$, $p < 0.001$), and response periods ($n = 118$, $p < 0.001$). **E**, Scatter plot of the distribution of the tactics selectivity of individual pmPFC neurons during response periods under the tactics-only cued (ordinate) versus reactive selection (abscissa) task conditions ($n = 118$, $p < 0.038$).

conditional rule, we added a control task in which a green illumination instructed a future action to reach left and a red illumination meant a cue for preparing a right reach. The locations of color cues were either concordant or discordant to the reach target. Under the

third condition, there was no instruction cue. Monkeys awaited the appearance of a choice cue with cyan or blue illumination, or green or red illumination. They had to respond promptly to the choice cue, in accordance with either the target inference or color-conditional

Figure 7. Time courses of neuronal activity selective for the behavioral factors of tactics, action, and rule, examined during the performance of fully cued trials. **A**, Example of analysis of a pmPFC neuron. The instantaneous firing rate was calculated on a trial-by-trial basis, using a moving time window (width = 200 ms, step = 20 ms); its dependence on the tactics, action, and behavioral rule was then analyzed consecutively with multiple regression analysis. The selectivity for each variable was computed as the CPD (explained in Materials and Methods), and color-plotted in a time-dependent manner. **B**, Analysis of neuronal population activity. The selectivity computed for each neuron (i.e., the CPD values) along the consecutive time window was averaged and then expressed as relative values deviating from the mean values during the baseline period. Separate displays are constructed for time-dependent plots of action, tactics, and rule selectivity (thick traces). Thin lines indicate the upper and lower limits of the 99% confidence range.

rule, to initiate a correct reach (Fig. 1C, reactive selection trials). Each of the three behavioral conditions was given consecutively in a block of 40 trials where the tactics and actions were pseudo-randomly determined.

Tactics-selective neuronal activity

Upon the presentation of instruction cues for the behavioral tactics, we found neuronal activity in the pmPFC that was selective

to either one of the two tactics. In the example of a pmPFC neuron (shown in Fig. 2A), the activity appeared selectively when the cue instructed anti-reach. This activity was not a simple response to the color of the instruction cue because the cue-selective response of this neuron was not observed under the fully cued condition (Fig. 3B).

To compare the neuronal selectivity to behavioral factors under the three behavioral conditions, we quantified the selectivity to the tactics and action (left vs right reach) in a time-dependent manner (for the detail of calculation, see Materials and Methods). The selectivity appeared strikingly different depending on the behavioral condition. As typically found in the pmPFC, the tactics-selective activity of the pmPFC neuron appeared predominantly during performance of the tactics-only cued condition (Fig. 3A) but not under the fully cued condition (Fig. 3B). In another example of pmPFC neuron, the tactics-selective activity appeared during the delay period following the cue (Fig. 4), only under the tactics-only cued condition. The analysis also revealed that the tactics selectivity appeared independently of the selectivity for the action.

We sampled neuronal activity that was found to be modulated during the cue, delay, or response period from cortical areas defined as pmPFC ($n = 153$) and SMA ($n = 73$) by the anatomical and physiological criteria described previously (Fig. 2B) (Matsuzaka et al., 2012, 2013). Multiple regression analysis (see Materials and Methods) revealed that 74 (48%) pmPFC and 21 (29%) SMA neurons exhibited significant selectivity for the tactics. As for the pmPFC, 28 neurons showed the selectivity during the postcue period, and for 35 neurons the selectivity appeared during the delay period. For another 36 pmPFC neurons, the tactics selectivity appeared during the epoch of response period (Fig. 5). In contrast, the occurrences of tactics-selective SMA neurons were much fewer during the postcue ($n = 4$) or delay ($n = 8$) periods, although 13 SMA neurons were tactics selective during the response period. We therefore focused our analysis primarily on the instruction-cue induced activity in the pmPFC.

We found that the strength of tactics selectivity apparent during the tactics-only cued trials was often weakened considerably when the cue directly instructed the action (Figs. 3, 4). A population analysis revealed that the tactics selectivity (expressed as the CPD value; see Materials and Methods) appeared significantly greater during performance of tactics-only cued than fully cued trials (Fig. 6A). The differences were significant during the cue period, delay period, and the response period (Fig. 6B–D; $p < 0.005$ by Kolmogorov–

Figure 8. Time-dependent appearance of the tactics-selective activity in individual pmPFC neurons during tactics-only cued trials. Each row represents the color-coded CPD value representing the tactics of a single neuron. The time windows where the CPD value is significantly greater ($p < 0.05$ by permutation test) than that of the baseline period (1000 ms from trial onset) are coded according to a color scale inset to the left of the display, whereas insignificant windows are coded in green, corresponding to the 10th scale from the top. Only the neurons that showed significant elevation of CPD value in at least three consecutive bins are included ($N = 125$) in this color plot display. Neurons are sorted by the time of appearance of the peak value of their CPD (earliest neuron is on the top). The trials are aligned with the onset of the Cue (left) and Go signal (right).

rov-Smirnov test). The tactics selectivity during the response period was also greater in tactics-only cued than in reactive selection trials, but the difference was only marginally significant (Fig. 6E).

Finally, we looked into the possibility that pmPFC neurons may represent behavioral rules for selecting forthcoming actions. For this purpose, we used the data obtained during the control experiment examining the effects of behavioral rules (color-conditional vs spatial inference) under the behavioral condition of fully cued trials. The selectivity for the tactics, action, and the rule were computed as the time series of CPD values (see Materials and Methods). When examined for individual pmPFC neurons, the rule had little effect on neuronal activity in contrast to tactics and action (Fig. 7A). Similarly, at the population level, the selectivity for the rule during the cue, delay, and response periods remained insignificant from the precue baseline period (Fig. 7B). In contrast, the selectivity for the forthcoming action after the cue exhibited persistent elevation until the response period, whereas the selectivity for the tactics was only modestly enhanced, transiently after the cue. Thus, these data indicate that pmPFC neurons contribute little in representing behavioral rules, at least for the selection of color versus spatial rules as examined in the present context.

Tactics-selective activity of individual neurons appearing in a time-dependent cascade

Under the tactics-only cued condition, the monkeys had to retrieve the tactics information from the instruction cue, hold it in memory during the delay period, and use the information to select actions during the response period. To examine how individual neurons take part in each of these processes, we analyzed the time course of the strength of tactics-selective activity appearing in any of the behavioral epochs for each neuron. Neuronal firing rate was measured using a moving time window (width = 200 ms, step = 20 ms); then the magnitude of the tactics selectivity was computed (as CPD value) consecutively in a time-dependent manner (as exemplified in Figs. 3, 4). We found first that a majority of the pmPFC neurons exhibited significant tactics-selective activity only during a limited portion of the be-

Figure 9. **A**, Occurrences of tactics-selective activity during the behavioral epochs of cue, delay, and response periods of tactics-only cued trials. Data from the pmPFC (left) and the SMA (right) are shown. Numbers are derived from multiple regression analysis of the effects of behavioral tactics and action ($p < 0.05$). **B**, Occurrences of action-selective activity in the pmPFC (left) and the SMA (right) during the behavioral epochs of cue, delay, and response periods of fully cued trials. Numbers are derived from multiple regression analysis of the effects of behavioral tactics and action ($p < 0.05$).

havioral epochs (Fig. 8), forming, as a whole, a temporal cascade of selective activity covering the information encoding-decoding period in the behavioral sequence. Second, most neurons represented tactics during either the cue or delay, or response period but few did so during multiple task periods. To quantitatively assess the distribution of tactics-selective neurons during the cue, delay, and response periods, we performed multiple regression analysis; neuronal firing rate during each epoch was accounted for by the tactics (pro- and anti-reach) and the action (reach to left or right). The analysis revealed that, among 55 pmPFC neurons that exhibited tactics-selective activity in either cue or delay period, only 8 had such activity in both periods. Among 54 neurons that were found to be selective during either the cue or response period, only a small minority (10 of 54) exhibited the selectivity during both periods. And finally, 11 of 60 neurons (having the selectivity during the delay or response period) exhibited the selectivity continuously overlapping the two periods (Fig. 9A). Among the 21 pmPFC neurons that exhibited tactics-selective activity during multiple task periods, the preferred tactics in each period was consistent (either pro-reach or anti-reach) for the majority of neurons ($19/21 = 90.4\%$).

Transition from tactics to action representation

In accordance with previous studies (Matsuzaka et al., 2012, 2013), the pmPFC had an abundance of neurons whose activity was significantly dependent on the monkeys' action. When

Figure 10. Three examples of neuronal activity selective for tactics and action, differentially appearing during each epoch in the behavioral task. Only the activity during the tactics-only cued trials is presented. Conventions for the display are the same as in Figure 3. **A**, A pmPFC neuron that exhibited a tactics-selective response to the cue, and action-selective activity during the response period. This neuron exhibited transient activation in response to the cue signal that instructed the tactics of the forthcoming reach. The tactics selectivity was statistically significant during the 680 ms period following cue onset ($p < 0.01$, anti-reach > pro-reach), then declined to an insignificant level during the delay period. During the response period, activity was significantly selective for the action (left > right reach) but not for the tactics. **B**, A pmPFC neuron that initially exhibited tactics-selective delay-period activity and action-selective activity thereafter. This neuron exhibited preferential activation throughout the delay period of pro-reach trials. The tactics selectivity during this period was statistically significant ($p < 0.01$). During the response period, the selectivity for action (left > right reach) was significant ($p < 0.01$), but the selectivity for tactics was insignificant. **C**, A pmPFC neuron that exhibited selective activity for the tactics (anti-reach > pro-reach) and the direction of reach during the response period (right-reach > left-reach) during the response period ($p < 0.01$).

the forthcoming action was fully cued along with the tactics, the action selectivity appeared during the cue, delay, or response period (as shown in Fig. 9B). What was new was the finding that a number of pmPFC neurons individually exhibited the selectivity for both the tactics and action. We found further that the tactics selectivity initially found in response to the tactics cue may later turn into the action selectivity within each of single neurons. To examine, in detail, the time of appearance of neuronal tactics and action selectivity, we analyzed the time course of each selectivity by calculating instantaneous values representing each of selectivity (calculated as

CPD values; see Materials and Methods) consecutively throughout the performance of tactics-only cued trials encompassing the cue, delay, and response periods.

We found three types of selectivity distribution among pmPFC neurons. The first type was tactics selectivity during the cue or early delay period, followed by action selectivity during the response period (as exemplified by the time-dependent plot of neuronal selectivity shown in Fig. 10A). The second type was the tactics selectivity appearing continuously during the delay period, followed by action selectivity during the response period (Fig. 10B). The last type was the selectivity to both tactics and action during the response period (Fig. 10C).

To examine how each of all sampled neurons takes part in representing the tactics and action selectivity, the time course of neuronal selectivity for both was simultaneously analyzed as the 2D, time-dependent changes in selectivity, individually calculated as CPD values (giving rise to displays in Fig. 11). As clearly indicated in the 2D color-coded displays, the tactics selectivity during the cue period (observed among the first group of neurons; Fig. 11A) or the delay period (the second group of neurons; Fig. 11B) was replaced with action selectivity during the response period (see also Fig. 12A,B). Thus, together with the third group of neurons (Figs. 11C, 12C) that were both tactics- and action-selective during the response period, these pmPFC neurons, as a population, appear to take part in the transition of information representing the tactics to action.

Finally, quantitative assessment was made to determine how many of pmPFC neurons were selective to both tactics and action (dual coding) or selective to one of either. We performed a multiple regression analysis to examine the effect of tactics and action on neuronal activity during the cue, delay, and response periods (Table 1). The multiple regression analysis found that, during the cue period, 28 pmPFC neurons had significant tactics-selective activity. Of these 28, 9 neurons also had significant action-selective activity during the response period. During the delay period, 35 neurons were selective for the tactics, 11 of which were also action-selective during the response period. During the response period, 36 neurons were selective for the tactics, and 15 of them were also action-selective.

Discussion

In the present study, we found that neurons in the pmPFC exhibit activity selective to behavioral tactics in response to instruction

signals. Such selectivity was scarcely observed when a forthcoming action was informed together with the tactics to select the action, suggesting its instructional role in facilitating the choice of action at the time of responding to a Go signal. The tactics-selective activity of each neuron appeared for only a fraction of the task period spanning from the instruction cue appearance to response initiation, as if information moves from one neuronal population to another across time in the task. We found further that the tactics selectivity of individual neurons was later replaced with the selectivity to action, and appeared to take part in transforming the tactics information to action-specifying information. The tactics selectivity induced by the instruction cue characterized neuronal activity in the pmPFC, which was found to a far less extent in the posterior medial motor area (the SMA).

pmPFC neurons represent behavioral tactics independently of action selection

In a previous report, we found that pmPFC neurons were active predominantly when animals underwent the development of tactics to select actions (Matsuzaka et al., 2012). The activity, however, appeared at the time of motor response when multiple behavioral processes come into play. Therefore, to identify the representation of tactics, it was necessary to set up a behavioral condition where the tactics is determined in isolation of other variables. This was achieved in this study by giving instructions solely as to the tactics of whether to respond to illuminated or nonilluminated target, to be used later when selecting actions of capturing right or left target. Importantly, the tactics-selective activity disappeared or was much reduced when motor action was informed together with the tactics (i.e., when the tactics is no longer necessary for selecting a correct action).

Temporal properties of tactics representation in individual neurons

We found that the tactics-selective activity appeared shortly in response to a visual instruction cue, during the delay period when either tactics had to be remembered, and also at the time of responding to a Go signal that prompted the selection of action. These findings point to the role of pmPFC neurons in retrieving the tactics information, in retaining that information as a short memory, and in the use of tactics to select actions. Interestingly, individual neurons mostly took part in any

Figure 11. Temporal distributions of tactics and action selectivity of pmPFC neurons shown in Figure 8 ($n = 125$) during tactics-only cued trials. The CPD values of the tactics and action were calculated simultaneously from each neuron's activity using a moving time window and are color coded: red represents pure action selectivity; green represents pure tactics selectivity. The compound strength of the selectivity, calculated as the square root of the sum of their squares, is coded by brightness. Neurons are classified into three groups according to the time of appearance of peak values of CPD for tactics. **A**, pmPFC neurons that exhibited peak CPD value for the tactics within 1000 ms following cue onset ($n = 50$). Top, Temporal distribution of CPD for the tactics and action illustrated as a color-coded matrix. Neurons are sorted by the timing of the peak value of their CPD (earliest neuron is on the top). The trials are aligned with the onset of the Cue (left) and the Go signal (right), indicated by red vertical lines. Bottom, The mean value of the CPD regarding the tactics (green) and action (red). **B**, pmPFC neurons that exhibited peak CPD values for the tactics during the delay period (within 1000 ms preceding the Go signal, $n = 29$). **C**, pmPFC neurons that exhibited peak CPD values for the tactics during the response period ($n = 46$).

Figure 12. Scatter-plot diagrams comparing magnitudes of tactics (abscissa) versus action (ordinate) selectivity during the task epochs of cue (left), delay (middle), and response (right) periods under the tactics-only cued behavioral condition. Magnitudes of selectivity are expressed as the CPD values averaged over the period of respective behavioral epochs. **A–C**, Data from the pmPFC neurons that exhibited highest selectivity for the tactics during cue period (**A**), delay period (**B**), and response period (**C**). The same neurons as in Figures 8 and 11. **A**, The three red dots represent the data for the neuron whose tactics selectivity is plotted time-dependently in Figure 10*A*. **B**, The red dots correspond to data plotted in Figure 10*B*.

Table 1. Number of pmPFC neurons that exhibited significantly selective activity for the tactics during the cue, delay, and the response periods^a

Task period	No. of neurons: tactics-selective (dual coding)
Cue	28 (9)
Delay	35 (11)
Response	36 (15)
Any	74 (24)

^aNumbers in parentheses indicate the number of dual-coding neurons, which had tactics-selective activity during the respective task period and action-selective activity during the response period.

one of these processes but not two, indicating behavioral-stage specific participation of each neuron. Furthermore, the tactics-selective neuronal activity lasted for a short duration, covering only a fraction of each epoch of the behavioral periods, giving rise to a temporal cascade of activity spanning the strategic time period that covers retrieval, retention, and use of tactics

information. This finding suggests the existence of cortical neural-circuit mechanisms incorporating sequential activation of dynamically formulated neuronal assembly (Constantinidis et al., 2002), such as proposed in the mPFC (Fujisawa et al., 2008) or parietal cortex of rodents (Harvey et al., 2012), or in the IPFC (Cromer et al., 2011; Lara and Wallis, 2014) and medial premotor cortex (Crowe et al., 2014; Merchant et al., 2015) of monkeys.

Representation of tactics converted to action representation

Under the tactics-only cued condition, the monkeys extracted the tactics from the color cue based on the trained associative rule (cyan for pro-reach and blue for anti-reach), kept it in the working memory throughout the delay period for the subsequent decision of the direction of reaching movement. During this period, neuronal activity in the pmPFC, as a whole, prominently reflected the cued tactics (Fig. 6*A*). The tactics representation gave way to the action representation shortly in response to the Go signal. Indeed, examined at individual-neuron basis, the tactics selectivity among a sizeable number of neurons shifted to the action selectivity (Figs. 11, 12). This representational shift within each neuron, in addition to the transition of tactics-to action-representation at a population level, appears to indicate the participation of pmPFC neurons in the transformation of information-specifying tactics to information-determining action. These findings also suggest the dynamic and multiplexed nature of representation taken place by prefrontal neurons. Such multiplexed or “high dimensional selectivity” for information appears to be an essential property of prefrontal neurons (Yamagata et al., 2012). Computational studies found that neuronal population-containing mixed selectivity

within individual components is capable of encoding a larger amount of information with fewer neurons than the population-containing neurons individually selective for single items (Rigotti et al., 2013). Such neurons seem to endow the neural network with richer context-dependent capability of information coding, thus facilitating sophisticated performance of complex behavioral tasks (Rigotti et al., 2010).

Functional properties of medial prefrontal compared with other prefrontal areas

Accumulation of studies examining neuronal activity in the IPFC of behavioral-task performing monkeys have produced a list of its behavioral roles, including preparatory set (Fuster, 1990), predictive coding (Rainer et al., 1999), attentional control (Lebedev et al., 2004; Buschman and Miller, 2007), or attentional selection (Rowe and Passingham, 2001), the detection and generation of event sequences across time (Fuster, 1990; Averbeck et al., 2002;

Quintana and Fuster, 1999; Fujii and Graybiel, 2003; Hoshi and Tanji, 2004), and categorization (Freedman et al., 2002; Shima et al., 2007; Merchant et al., 2011, 2014). Each of these cognitive operations contributes to a crucial aspect of executive control of behavior, culminating in the selection and implementation of abstract response strategies. Indeed, neurophysiological studies of the primate prefrontal cortex indicate its role in either strategies or rules, at varying levels of abstractions (White and Wise, 1999; Asaad et al., 2000; Hoshi et al., 2000; Wallis and Miller, 2003; Barraclough et al., 2004).

Although a lesion study suggested the role of the dorsomedial part of the PFC in action monitoring (Petrides, 1996), functional studies on the mPFC of subhuman primates have been scarce. An early study reported the presence of neurons related to monkeys' eye and ear movements (Bon and Lucchetti, 1994). Compared with the wealth of knowledge obtained in the LPFC, not much of functional properties of medial prefrontal neurons has been reported in relation to the guidance of voluntary actions, except for those of neurons in the dorsal bank of the anterior cingulate sulcus; cingulate neurons have been characterized as being involved in goal-based action selection (Matsumoto et al., 2003) or in encoding of action-value based prediction errors (Matsumoto et al., 2007). The present report is the first, to our knowledge, to describe the cue-induced tactics representation and its transformation into action in the dorsal crown part of the medial PFC, confined to its posterior part, including areas 9 and 8B (Petrides and Pandya, 1999). We found that pmPFC neurons hardly exhibited selective activity depending on behavioral rules defined in this study: action selection according to a target-inference rule or a color-conditional rule (Fig. 7). This finding stands in contrast to previous reports on the lateral prefrontal cortex where neuronal activity exhibited prominent selectivity for various rules (White and Wise, 1999; Wallis et al., 2001; Wallis and Miller, 2003). We, however, do not intend to negate or disregard the role of pmPFC in encoding behavioral rules in general. Rather, we propose to emphasize preferential participation of multiple areas in the prefrontal cortex in different aspects of rule-based behavior. The diversity of afferent and efferent connections reported on lateral and medial portions of the prefrontal cortex (Petrides and Pandya, 1999, 2006) seems to substantiate this view.

Two recent studies are of particular relevance to this issue. Tsujimoto et al. (2011, 2012) reported that neurons in the dorsolateral prefrontal and orbitofrontal cortex encoded the response selection rule or cued strategy of whether to stay with or shift from the previously performed action. In contrast, neurons in the frontopolar cortex did not show such activity. In another study, monkeys were trained on a Wisconsin Card Sorting Test analog that required the maintenance and updating of rules of stimulus selection (Buckley et al., 2009). Performance on this task profoundly deteriorated after the aspiration of the cortex lining the principal sulcus, the anterior cingulate sulcus, and the orbitofrontal cortex. In contrast, ablation of the superior dorsolateral prefrontal cortex (including the pmPFC) failed to cause any noticeable impairment. These findings suggest that the guidance of behavior based on response rules, or relying on strategies or tactics require participation of largely separate regions in the prefrontal cortex.

The present study indicates that pmPFC neurons take part in representing behavioral tactics that determine the specific ways to achieve objectives of actions. Compared with the selection of behavioral strategies or rules, commonly defined as a prescribed guide for conduct or action, the tactics selection may constitute adaptive cognition of lower order. Behavioral tactics, however, is

of abstract nature beyond the level of sensory perception or motor execution, requiring knowledge of past events, behavioral context, and objectives of future actions. Anatomical connections with area 46, cingulate areas, upper bank of STS, and retrosplenial areas (Barbas et al., 1999; Petrides and Pandya, 1999, 2006) seem to provide information to formulate the representation of behavioral tactics in this part of medial PFC. In future studies, on the other hand, involvement of mPFC neurons in other aspects of behavioral control is likely to be revealed, in view of brain-imaging studies on human subjects indicating the involvement of the medial PFC in diverse aspects of higher-order cognitive functions (Duncan and Owen, 2000; Raichle et al., 2001; Amodio and Frith, 2006; Rushworth et al., 2007).

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