

Representation of Immediate and Final Behavioral Goals in the Monkey Prefrontal Cortex during an Instructed Delay Period

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We examined neuronal activity in the lateral prefrontal cortex of monkeys performing a path-planning task in a maze that required the planning of actions in multiple steps. The animals received an instruction that prompted them to prepare to move a cursor in the maze stepwise from a starting position to a goal position by operating manipulanda with either arm. During a delay period in which the animal prepared to start the first of three cursor movements to approach the pre-instructed goal, we identified two types of neuronal activity: the first type reflected the position within the maze to which the animal intended to move the cursor as an initial step (an immediate goal) and the second type reflected the position within the maze that was to be captured as a final goal. Neither type reflected motor responses. We propose that these two types of neuronal activity are neuronal correlates that represent immediate and ultimate behavioral goals. This finding implicates the prefrontal cortex in governing goal-oriented sequential behavior rather than sensorimotor transformation.

Keywords: action planning, behavioral goals, maze, monkey, problem solving, single-cell recording

Introduction

It is generally agreed that the lateral part of the prefrontal cortex (PFC) of primates is involved in the cognitive control of behavior and that the PFC reacts to signals that dictate forthcoming actions (Goldman-Rakic, 1987; Passingham, 1993; Petrides, 1994; Fuster, 1997; Miller and Cohen, 2001; Tanji and Hoshi, 2001). Neurons in the PFC exhibit short-lived changes in activity in response to instructional cues, followed by long-lasting activity that persists throughout instructed delay periods that precede the initiation of a predetermined behavior. It has been established that activity during an instructed delay period reflects both the sensory information contained in the instruction cue (Fuster and Alexander, 1971; Funahashi *et al.*, 1989; Wilson *et al.*, 1993; Rao *et al.*, 1997; Constantinidis *et al.*, 2001) and the properties of behavioral responses that are planned in accordance with an instruction (Quintana *et al.*, 1988; Hasegawa *et al.*, 1998; Quintana and Fuster, 1999). Although the neuronal activity observed in the latter studies was thought to signify a planned action or prepared motor behavior, the exact nature of such neuronal activity has remained unclear. Specifically, it is not known to what extent such activity represents the motor attributes of prepared responses or cognitive processes that reflect planning during the instructed delay period. To address this issue, we designed a behavioral task to examine the extent to which neuronal activity in the PFC reflects behavioral goals, as opposed to motor responses, while instructions are received. For this purpose, we devised a path-planning task in which monkeys were required

to plan multiple actions to acquire a spatial goal according to instructions given during an instructed delay period (Mushiaki *et al.*, 2001, 2002). We found that activity in the vast majority of PFC neurons reflected cognitive processes that generate information used for the attainment of immediate and final behavioral goals. A preliminary account of this study appeared elsewhere (Saito *et al.*, 2001, 2004).

Materials and Methods

Subjects and Apparatus

Two male Japanese monkeys (*Macaca fuscata*), weighing 6.8 and 7.5 kg, were used in this study. The care and treatment of the animals were in accordance with National Institutes of Health guidelines and the Guidelines for Animal Care and Use published by our institute. Each animal was seated in a primate chair. The animal's head was restrained, and it faced a 15" color monitor that was positioned at a distance of 43 cm from its eyes. Two manipulanda in the chair could be operated by supination and pronation of either forearm with one degree of freedom. A computer system controlled the behavioral task. Eye position was monitored using an infrared eye camera system (R21-C-AC; RMS, Hiroasaki, Japan) with a 250 Hz sampling rate.

Behavioral task

The monkeys were trained to perform a path-planning task that required the planning of multiple movements of a cursor to reach a goal within a maze (Fig. 1A). A checkerboard-like maze and a 1.5° cursor were displayed on the monitor. The movement of the cursor was linked to the movement of the manipulanda.

To begin the trial, the animal was required to hold the two manipulanda in a neutral position for 1 s (initial hold). Subsequently, a cursor was presented at the center of the maze to indicate the starting position (start display). One second later, a goal cursor position was presented for 1 s (goal display). After a delay (delay 1 or delay 2), the color of the cursor was changed from green to yellow, which served as an initiation signal (first GO). The animal was required to move the cursor within 1 s by supination or pronation of either forearm. The cursor moved in the direction specified by the animal to a position that was defined as the immediate goal. After a hold period of 1 s (second hold), the next GO signal was presented (second GO). The animal was required to move the cursor stepwise to reach the goal that had been presented during the goal display. While moving the cursor stepwise, no visual cues were provided to indicate the direction in which the cursor was to be moved. Thus, the monkey selected the direction of each cursor movement without the aid of visual cues, but based solely on the memorized position of the final goal. When the cursor reached the position of the final goal, the animal received a reward (fruit juice).

To dissociate the movements of the arms and cursor, we trained the monkeys to perform the task described above with three different arm-cursor assignments (Fig. 1B). The assignment was changed every 48 trials, and the monkeys were required to adapt to new assignments without further instruction. Both monkeys required relatively few trials to become accustomed to each new arm-cursor assignment. Data collected during these transitional behavioral states were excluded from the analysis.

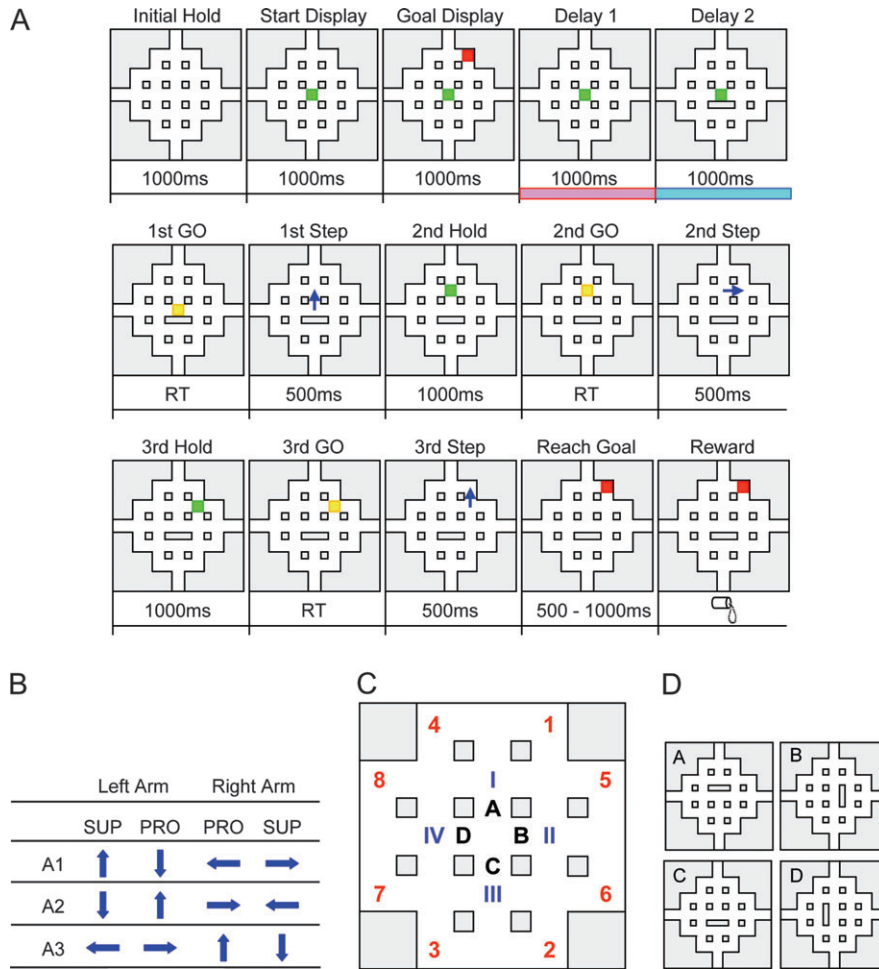


Figure 1. The path-planning behavioral task. (A) Temporal sequence of events in the task used in the present study. The behavioral sequence is depicted from the top left to the bottom right. Each panel represents a maze that was displayed on a monitor. Green squares denote current cursor positions and red squares indicate the position of the final goal. Yellow squares represent movement initiation (GO) signals. Blue arrows delineate cursor movements. Light red and blue bars at the bottom of the upper panels indicate the task periods that were defined as delay 1 and delay 2, respectively. RT, response time (<1 s). (B) Directions of cursor movements assigned to supination (SUP) or pronation (PRO) of either arm. Arm movements were assigned to each cursor movement in three different ways. A1–A3 represent arm–cursor assignments 1–3. (C) Goal and path-block positions within the maze. The final goal in each trial corresponded to one of the eight positions indicated by the red numbers (1–8). During the recordings of neuronal activity, we used either positions 1–4 or 5–8 as a set of goals. Four positions (blue, I–IV) were defined as immediate goals. One of four paths adjacent to the central starting position (black, A–D) was randomly removed (referred to as a path-block), as illustrated in (D). (D) Each panel shows the location of a path-block that obscured a path at the top, right, left, or bottom of the start position.

We used one of two sets of final goals for each recording session (either set 1–4 or 5–8, represented in red in Fig. 1C). To force the monkeys to select more than one immediate goal to reach a final goal, one of four possible paths (A–D, black in Fig. 1C) was removed randomly during delay 2, 1 s after the beginning of delay 1, as illustrated in Figure 1D. The removal of a path was referred to as a path-block and was scheduled in such a way that four final goals and four positions of the path-block were selected equally and randomly within each trial, which prevented a one-to-one association between the position of the path-blocks and the immediate goals. If the animal attempted to move the cursor in the direction in which the path had been blocked, the cursor movement was blocked and an error signal was given, which required the monkey to restart the trial. In the present study, we analyzed only data collected while an animal moved the cursor from the start position to the final goal by moving the cursor in three steps.

Surgery and Data Acquisition

After completing the behavioral training, an area of the skull (20 × 25 mm) over the right principal sulcus was removed and an acrylic recording chamber (25 × 30 mm) was mounted on the skull over the cavity. All surgical procedures were performed under aseptic conditions using pentobarbital sodium anesthesia (30 mg/kg i.m.)

with ketamine hydrochloride (10 mg/kg i.m.) and atropine sulfate. Antibiotics and analgesics were administered to prevent postsurgical infection and pain.

Following surgery, cortical sulci were identified using a magnetic resonance imaging (MRI) scanner (OPART 3D-System; TOSHIBA, Tokyo, Japan). Prior to recording neuronal activity within the PFC, we first defined the frontal eye field (FEF) using intracortical microstimulation (ICMS; Bruce *et al.*, 1985). The recording sites covered the expanse of the PFC extending 14 mm rostrocaudally in sites at which ICMS with currents of <80 μ A did not evoke saccades. We sampled neuronal activity rostral to the FEF, including the banks of the principal sulcus and the adjacent cortical convexity.

Neuronal activity was recorded extracellularly using glass-insulated Elgiloy microelectrodes (1.0–2.5 M Ω at 333 Hz), which were inserted through the dura while the monkeys were performing the behavioral task. The electrodes were manipulated with an electrode positioning system (EPS; Alpha-Omega, Nazareth, Israel). Single-unit potentials were amplified with a multi-channel processor and were discriminated using a multi-spike detector (MCP plus 8, MSD; Alpha-Omega). We advanced the electrodes into the cortex until discriminable action potentials were obtained, after which we recorded the activity of all cells without preselection. Behavioral events and neuronal activity were displayed

online on computer screens and oscilloscopes and were stored for offline analysis.

Data Analysis

Behavioral Performance

To evaluate the behavioral performance of each monkey, we measured success rates and response times (RT). The RT was defined as the time that elapsed between the appearance of the first GO signal and the execution of a required movement. We determined whether the RT was influenced by the arm-cursor assignment (Tukey-Kramer multiple comparison test, $\alpha = 0.01$) or by the location of the path-block (*t*-test, $\alpha = 0.01$). To examine the effect of the path-block, we compared the RT between two types of trials, namely effective and ineffective path-block trials (trials in which the path-block did and did not interrupt a direct path to the final goal, respectively). For example, for final goal 1 or 5 as depicted in Figure 1C, a path-block that interrupted A or B was defined as an effective path-block, while a path-block that interrupted C or D was ineffective.

Statistical Analysis of Neuronal Activity

Our database included neurons from which activity was recorded during more than two blocks of trials for each arm-cursor assignment. In this report, we analyzed neuronal activity during the delay 1 and delay 2 periods that preceded the first GO signal. If neuronal activity (discharge rate) during either of the two delay periods (0–1000 ms in each period) was significantly different (Wilcoxon signed-ranks test, $\alpha = 0.05$) from that during a control period (500 ms in the initial hold period, starting 300 ms after its onset), we defined the activity as delay-related.

Initially, to examine whether delay-related activity reflected motor responses, we performed simple linear regression analysis using the following formula

$$\text{Firing rate} = \beta_0 + \beta_1 \times (\text{arm movement}) \quad (1)$$

where β_0 is the intercept and β_1 is the coefficient. The categorical factor was the type of the arm movement with four levels that were left pronation, left supination, right pronation and right supination. We calculated the probability (*P* value) that the coefficient equaled zero. If the $P < 0.01$, we judged that the activity reflected the motor response. Subsequently, for neurons in which activity was found to be unrelated to motor variables, we analyzed how delay-related activity reflected three behavioral factors: the position of the goal displayed during the goal display period (final goal), the position of the cursor in the first step (immediate goal) and the location of the blockade path (path-block). We could not apply a three-way ANOVA with the three behavioral factors, because our experimental design did not allow for a balanced ANOVA table. We therefore performed multiple linear regression analysis for neuronal activity by using the following formula

$$\begin{aligned} \text{Firing rate} = & \beta_0 + \beta_1 \times (\text{final goal}) + \beta_2 \times (\text{immediate goal}) + \beta_3 \times (\text{path-block}) \\ & + \beta_4 \times (\text{FG} \times \text{IG}) + \beta_5 \times (\text{FG} \times \text{PB}) + \beta_6 \times (\text{IG} \times \text{PB}) \end{aligned} \quad (2)$$

In this formula, β_0 is the intercept, and β_1 , β_2 , β_3 , β_4 , β_5 , and β_6 are coefficients. The regressors indicated in the parentheses were entered into the analysis as dummy variables. The categorical factors for the final goal were the four positions of the goal that was instructed during the goal display period. The categorical factors for the immediate goal were the four positions to be reached with the first movement of the cursor. The categorical factors for the path-block were the four locations of the path-block that corresponded to A–D in Figure 1C. The categorical factors for the combination of the final and immediate goals (FG \times IG), the final goal and path-block (FG \times PB), or the immediate goal and path-block (IG \times PB) were the possible combinations of the positions of each behavioral factor. We calculated the probability (*P* value) that the coefficient equaled zero using a commercial software (MATLAB 6.5, MathWorks, Natick, MA). We took $P < 0.01$ to be statistically significant. First, based on the analysis of probability with formula 2, we classified the delay-related activity as ‘path-block selective’ if $P_{\beta_3 = 0} < 0.01$ or $P_{(\beta_5 = 0 \text{ or } \beta_6 = 0)} < 0.01$. Ninety-seven neurons were found to be path-block selective with this analysis. We excluded these neurons for

further analysis. Next, the delay-related activity was classified as ‘behavioral goal-selective’ if it significantly reflected at least one of the factors for the final goal, immediate goal, and its combination. We classified such ‘behavioral goal-selective’ neurons into three subgroups: ‘final goal-selective’ ($P_{\beta_1 = 0} < 0.01$, $P_{\beta_2 = 0} \geq 0.01$, and $P_{\beta_4 = 0} \geq 0.01$ in formula 2), ‘immediate goal-selective’ ($P_{\beta_1 = 0} \geq 0.01$, $P_{\beta_2 = 0} < 0.01$, and $P_{\beta_4 = 0} \geq 0.01$), or ‘final and immediate goal-selective’ ($P_{\beta_1 = 0} < 0.01$ and $P_{\beta_2 = 0} < 0.01$, or $P_{\beta_4 = 0} < 0.01$). Furthermore, we calculated the variance inflation factors (VIFs) to examine the possible existence of multi-collinearity for the two factors: final and immediate goals. We did this analysis to check the possibility that the behavioral strategies adopted by the monkeys led to a bias in the number of times the combinations of the factors occur together (Draper and Smith, 1998). We confirmed that the VIF was small enough (< 2) to rule out the behavioral bias concerned.

A separate analysis was performed for neuronal activity during the goal display period. In the same way as the two delay periods, we performed a multiple regression analysis to examine the effect of the positions of the final goal on neuronal activity.

Quantification of Selectivity for Final and Immediate Goals

In the next step of the analysis, we calculated the selectivity index (SI) of behavioral goal-selective neurons to quantify the selectivity of such neurons for the final and immediate goals. The SI was defined as $(V_f - V_i) / (V_f + V_i)$, where V_f was the *F*-value for the final goal and V_i was the *F*-value for the immediate goal that were derived from the regression analysis using formula 2. Positive values reflected selectivity for the final goal, whereas negative values reflected selectivity for the immediate goal.

Statistical Analysis for Eye Movements

Although the monkeys were not required to control their gaze while performing the task, we nevertheless analyzed eye position and movement extensively. First, we calculated the average horizontal and vertical eye positions in 10 ms bins for each trial and performed multiple linear regression analysis to examine relationship between eye positions and locations of the final and immediate goals by using the following formula

$$\text{Eye position} = \beta_0 + \beta_1 \times (\text{final goal}) + \beta_2 \times (\text{immediate goal}) + \beta_3 \times (\text{combination}) \quad (3)$$

In this formula, β_0 is the intercept, and β_1 , β_2 and β_3 are coefficients. The categorical factors for the final goal, immediate goal, and its combination were the same as in formula 2. Furthermore, we used multiple regression analysis to estimate how behavioral goal-selective neuronal activity related to eye position or saccade. We calculated the mean firing rates and the mean eye positions in 50 ms bins for each trial. We also computed vertical and horizontal components of saccades that fell on 50 ms bins. We used the following linear models to express neuronal activity

$$\text{Firing rate} = \beta_0 + \beta_1 \times (\text{horizontal EP}) + \beta_2 \times (\text{vertical EP}) \quad (4)$$

$$\text{Firing rate} = \beta_0 + \beta_1 \times (\text{h-SV}) + \beta_2 \times (\text{v-SV}) \quad (5)$$

In these formulas, β_0 is the intercept, and β_1 and β_2 are coefficients. EP represents eye position, and h-SV and v-SV mean horizontal and vertical components of saccade vector, respectively. To evaluate relationships between neuronal activity and each factor, we calculated regression coefficient, *R*, for each formula by using corresponding bin-by-bin data for neuronal activity and eye position/saccade metrics.

Results

Task Performance

Both monkeys moved the cursor stepwise from a start position to reach to a briefly cued goal. Although during training the start and goal positions were specified at various positions within the maze, the start position was always at the center of the maze in trials during which neuronal activity was measured. The animals

performed the task at a success rate of >95%. In >94% of successful trials, the animals reached the remembered goal with three movements of the cursor and avoided the path-blocks (Table 1). Performance errors resulted mainly from premature initiation of supination/pronation during the hold period, except for a transitional period during which the arm-cursor assignment was altered and during which the animals committed the error of approaching the path-block with the cursor. The RT varied with the type of arm movement, but was independent of the position of the immediate goal (Tukey-Kramer multiple comparison test, $P > 0.05$). The RT was not influenced by the arm-cursor assignment (Table 2). We also examined whether the RT differed according to the location of the path-block and found no significant differences for the RT of effective and ineffective path-block trials (t -test, $P > 0.1$; Table 3).

Behavioral-goal Selective Neuronal Activity

A total of 1311 PFC neurons (898 and 413 from monkeys 1 and 2, respectively) exhibited significant changes in activity during delay 1, delay 2 or both delay periods (Wilcoxon signed-ranks test, $P < 0.05$). We first performed a linear regression analysis for 1096 neurons that were active during delay 1 and for 1136 neurons that were active during delay 2 to determine whether delay-related activity reflected arm movements ($\alpha = 0.01$). Surprisingly, we found that only 1.3% (14 of 1,096) and 2.9% (33 of 1,136) of the delay-related neurons reflected the prepared arm movements during delay 1 and delay 2, respectively (see Table 4). An example of PFC neurons that exhibited properties that reflected non-motor attributes is shown in Figure 2. In this

example, neuronal activity appeared to be initiated exclusively during delay 2, the period during which the animal prepared to move the cursor by supinating the left arm in arm-cursor assignment A1 (top panels in Fig. 2). However, in assignment A2, the same neuron was active only when the animal prepared to respond by pronating the left arm (middle panels in Fig. 2). In assignment A3, the same neuron appeared to be active while the animal prepared to respond by pronating the right arm (bottom panels). What were common factors that led to the activation of this neuron? As illustrated in Figure 2, neuronal activity commenced each time the animal prepared to move the cursor upward to attain the first immediate goal, which was the first step in the task.

In light of the aforementioned finding, we analyzed the extent to which delay-related activity was related to behavioral factors other than the forthcoming arm movement. We first analyzed activity during delay 2 by examining the possible relationship of neuronal activity to three behavioral factors, namely the location of the path-block, the position of the remembered final goal and the position of the planned immediate goal. We found that the activity of 8.5% (97) of neurons was related significantly to the location of the path-block, including the interaction between the two other factors (multiple regression analysis, $P < 0.01$). A representative neuron that exhibited such activity is shown in Figure 3A. This neuron was more active when the path-block was located at position D. In this report, we focused on neural activity that was significantly related to either the final or immediate goal (including the interaction between them). We found that the activity of 23.6% (268) of neurons that were active during delay 2 were selective for the behavioral goals (multiple regression analysis, $P < 0.01$). We confirmed that the activity of these neurons was not influenced by the location of the path-block that appeared during delay 2 period, as exemplified by the activity of the neuron shown in Figure 3B.

We classified behavioral goal-selective activity into three subgroups, which were termed immediate goal-selective (IG), final goal-selective (FG), and final and immediate goal-selective (FG \times IG). The activity of IG neurons was significantly related only to the position of the immediate goal ($P < 0.01$), whereas the activity of FG neurons was significantly related only to the position of the final goal. The activity of FG \times IG neurons was significantly related to both factors. An example of activity in a neuron that is representative of IG neurons is shown in Figure 4. This neuron discharged markedly during delay 2 only when the animal prepared to move the cursor upward towards immediate

Table 1
Task performance

	Successful trials	
	Goal attained	Goal attained in three steps
Monkey 1	96.8 (5594/5778)	91.1 (94.1 ^a) [5262/5778 (5594 ^b)]
Monkey 2	96.5 (5902/6118)	90.6 (94.0 ^a) [5545/6118 (5902 ^b)]
Total	96.6 (11496/11896)	90.8 (94.0 ^a) [10807/11896 (11496 ^b)]

Values are for the rate of successful trials (percentage). Values in parentheses below the success rates indicate the numbers of successful trials/the total number of trials. The task performance was calculated for all trials completed during a one-week-long neuronal recording session.

^aPercentage of trials in which the goal was attained with three movements of the cursor.

^bNumber of trials in which the goal was attained.

Table 2
Reaction times

	Immediate goal	Arm movement				Average
		Left		Right		
		SUP	PRO	SUP	PRO	
Monkey 1	1	281.1 \pm 51.6	283.6 \pm 34.5	270.4 \pm 42.5	-	278.4 \pm 43.3
	2	-	285.9 \pm 39.4	273.3 \pm 37.6	266.2 \pm 42.6	275.1 \pm 40.3
	3	264.8 \pm 42.3	281.7 \pm 32.4	-	255.6 \pm 32.4	267.4 \pm 37.2
	4	271.4 \pm 43.0	-	268.8 \pm 37.6	255.4 \pm 36.5	265.2 \pm 39.4
	Average	272.4 \pm 45.5	283.7 \pm 35.0	270.8 \pm 38.7	259.1 \pm 37.1	271.5 \pm 40.3
Monkey 2	1	319.2 \pm 51.6	322.4 \pm 56.9	345.6 \pm 50.7	-	328.0 \pm 54.4
	2	-	343.7 \pm 56.0	331.4 \pm 61.2	338.3 \pm 58.3	337.9 \pm 58.7
	3	339.3 \pm 56.5	325.2 \pm 56.9	-	343.3 \pm 62.3	334.8 \pm 59.3
	4	322.6 \pm 56.5	-	329.3 \pm 55.9	351.2 \pm 57.4	334.1 \pm 57.9
	Average	326.6 \pm 55.9	329.8 \pm 57.4	335.6 \pm 56.5	344.2 \pm 59.5	333.5 \pm 57.6

Values are the means \pm SD response time in ms. SUP, supination; PRO, pronation.

Table 3
Reaction times for different types of path-block

	Related path-block	Unrelated path-block	Total
Monkey 1	271.3 ± 40.6	271.6 ± 40.1	271.5 ± 40.3
Monkey 2	336.7 ± 58.3	332.0 ± 57.2	333.5 ± 57.6

Values are the means ± SD response time in ms.

Table 4
Classification of prefrontal cortex neuronal activity during delay 1 and delay 2

		Related to arm movement	Related to path-block	Related to goals	Related to delay
Delay 1 activity	Monkey 1	12 (1.6)	-	144 (19.6)	734 (100)
	Monkey 2	2 (0.6)	-	69 (19.1)	362 (100)
	Total	14 (1.3)	-	213 (19.4)	1096 (100)
Delay 2 activity	Monkey 1	27 (3.5)	83 (10.6)	173 (22.1)	782 (100)
	Monkey 2	6 (1.7)	14 (4.0)	95 (26.8)	354 (100)
	Total	33 (2.9)	97 (8.5)	268 (23.6)	1136 (100)

Values are the numbers of neurons. Values in parentheses are the percentages of the total.

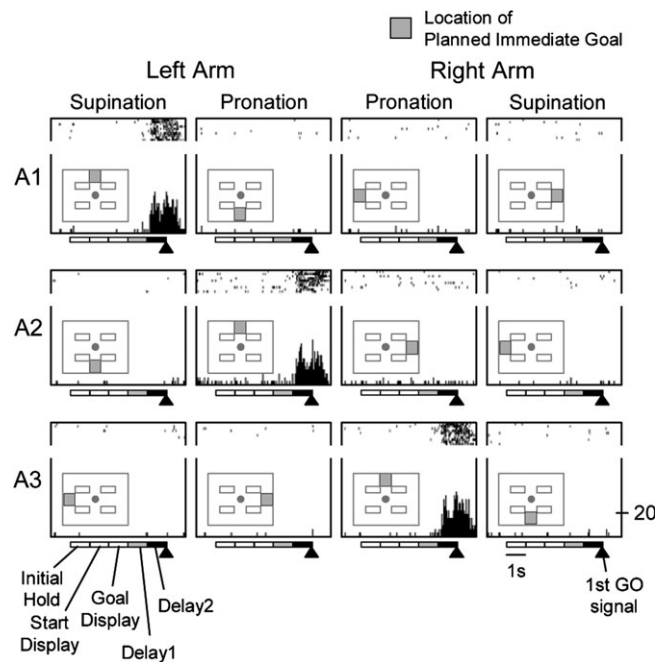


Figure 2. Activity of a prefrontal cortex (PFC) neuron that was selective for the intended position of the cursor, but not for arm movement. Each panel displays a raster display (above) and a peri-event histogram (50 ms bins; below) sorted according to the first movement of the arm. In the raster displays, each row represents a trial, while dots represent discharges from the neuron. The raster displays and histograms are aligned to the appearance of the first GO signal (filled triangles). Gray squares indicate the position to which the animal intended to move the cursor as a first movement (immediate goal). The immediate goal was not cued by any visual signals, but had to be determined by the monkey. Each bar at the bottom of each panel indicates the task period denoted at the bottom left. A1–A3 correspond to the arm–cursor assignments shown in Figure 1*B*. Ordinate scale is 20 spikes/s.

goal I, irrespective of the location of the final goal (top panels in Fig. 4). By contrast, in the representative FG neuron shown in Figure 5, activity was selective for the final goal, which appeared at position 3, rather than for any of the immediate goals. It is important to note that the neuronal response was not a simple

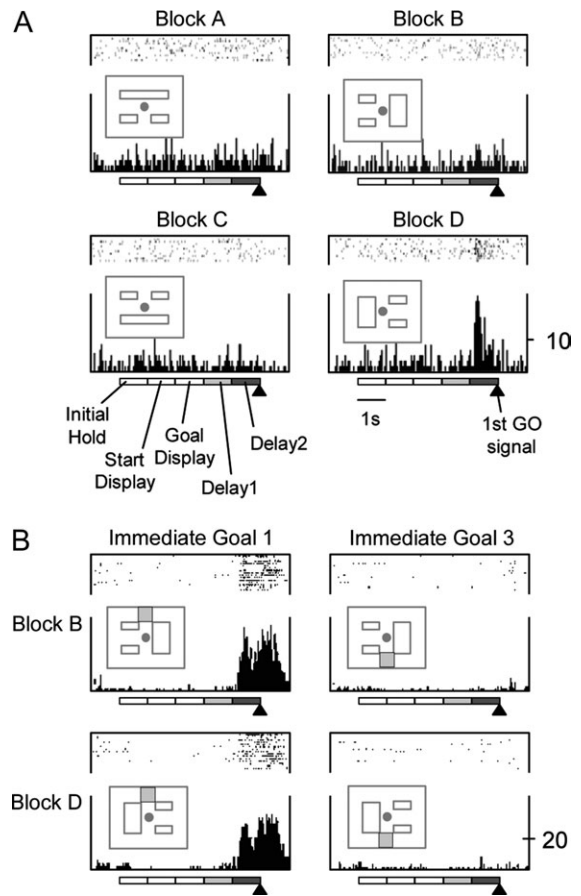


Figure 3. Examples of a path-block-selective PFC neuron and of an immediate goal-selective PFC neuron that was not affected by the position of the path-block. (A) Discharges of a PFC neuron that responded selectively to a path-block at the left of the start position. The location of each path-block is shown by the large rectangle inside an enlarged view of the central part of the maze in each panel. (B) Discharges of a PFC neuron that responded selectively to an immediate goal and for which activity was not influenced by the location of the path-block. This is the same neuron for which activity is shown in Figure 2. Each bar at the bottom of each panel indicates the task period. The raster displays and histograms are aligned to the appearance of the first GO signal (filled triangles).

visual response, because the final goal remained invisible during the delay periods and the path-block that was presented during this period indicated neither the subsequent position to which the cursor should have been moved nor the position of the final goal. Furthermore, we found that 45.5% (122) of behavioral goal-selective neurons exhibited activity that was selective for the combination of the immediate and final goals during delay 2. A representative FG × IG neuron is shown in Figure 6. This neuron was active only when the animal prepared to move the cursor downward toward the immediate goal (position III) as a first step in reaching the final goal at position 3 (bottom left panel in Fig. 6), but not when the final goal was at position 2 (bottom right).

With respect to activity during delay 1, we found that 61.0% (130) of neurons were selective for the final goal and 35.7% (76) of neurons were selective for both the final and immediate goals. However, neurons that were selective exclusively for the immediate goal were observed infrequently (7 neurons, 3.3%). The distribution of goal selectivity is summarized in Table 5.

To quantitatively compare the distribution of activity related to the final and immediate goal during delay 1 and delay 2, we calculated the SI for each neuron as described in the Materials

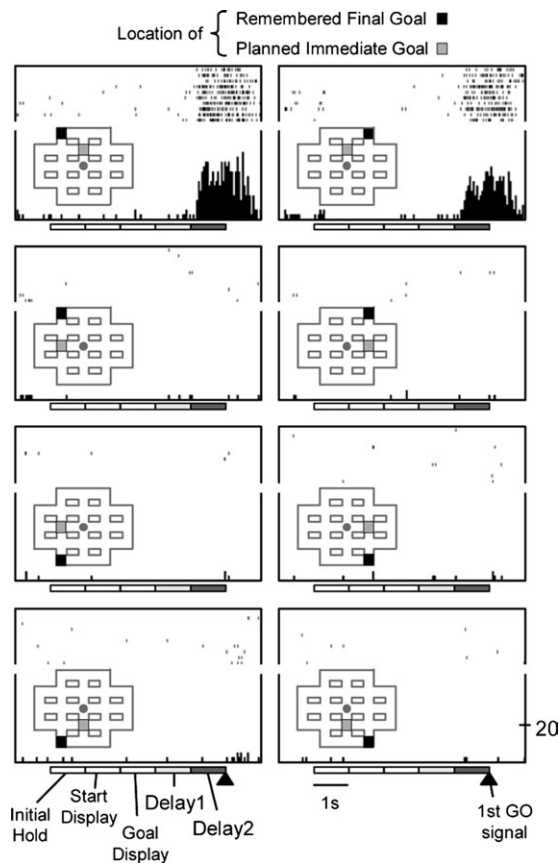


Figure 4. Example of immediate goal-selective neural activity. This PFC neuron showed marked activity during the period (delay 2) in which the animal intended to move the cursor to an immediate goal I, irrespective of the position of the final goal. Display formats are as in Figure 2, except that activity was sorted according to selectivity for the behavioral goal. The black and gray squares in the maze in each panel indicate the positions of the final and immediate goals, respectively.

and Methods. As shown in Figure 7, the distribution of positive SI values was predominant during delay 1, which reflected the preferential final goal representation. By contrast, during delay 2, the immediate goal was represented in a sizeable population of neurons, while the final goal was represented in a separate population of neurons. The distribution of the SI during delay 1 differed significantly from that during delay 2 (χ^2 test, $P < 0.001$), with the median of 0.38 for delay 1 and 0.24 for delay 2.

Time Course of Neuronal Activity that Reflected the Final Goal

As noted above, activity that reflected the position of the final goal was observed during both delay 1 and delay 2. This begged the question: did individual neurons exhibit continuous activity across both periods, or were neurons active during only one of the two delay periods? In addition, we sought to determine whether final goal-selective activity during the delay periods was a continuation of activity that had commenced in response to the presentation of the visual signal indicating the position of the final goal. To this end, we explored the distribution of final goal-selective neurons that were active during the three task periods (the goal display period, delay 1 and delay 2). For individual neurons, we examined the presence or absence of final goal selectivity in each of the three periods using the regression analysis described in the Material and Methods, and

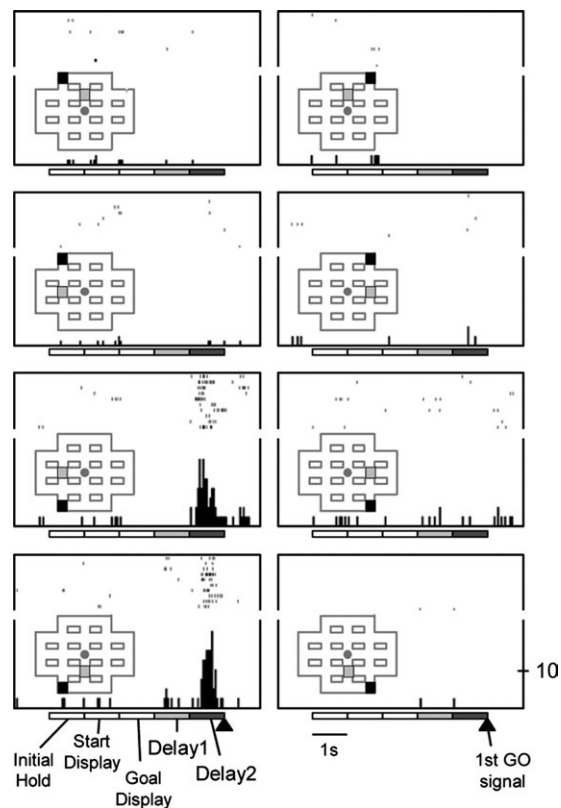


Figure 5. Example of final goal-selective neural activity. This PFC neuron exhibited final goal selectivity during delay 2, irrespective of the position of the immediate goal.

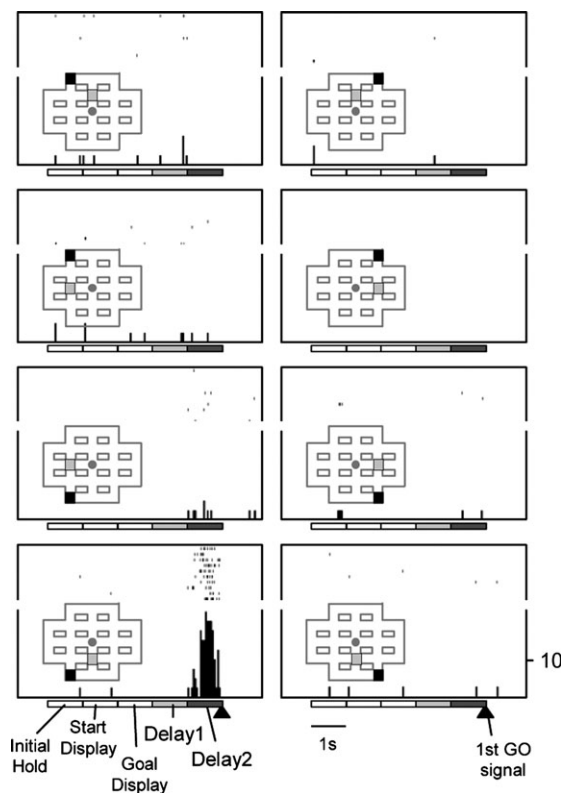


Figure 6. Example of final and immediate goal-selective neural activity. This PFC neuron discharged during delay 2 only when the animal intended to move the cursor to immediate goal III to reach final goal 3. Conventions are as in Figure 4.

Table 5

Classification of goal-related prefrontal cortex neuronal activity during delay 1 and delay 2

		FG	FG × IG	IG	Total
Delay 1 activity	Monkey 1	85 (59.0)	54 (37.5)	5 (3.5)	144 (100)
	Monkey 2	45 (65.2)	22 (31.9)	2 (2.9)	69 (100)
	Total	130 (61.0)	76 (35.7)	7 (3.3)	213 (100)
Delay 2 activity	Monkey 1	62 (35.8)	81 (46.8)	30 (17.3)	173 (100)
	Monkey 2	47 (49.5)	41 (43.2)	7 (7.4)	95 (100)
	Total	109 (40.7)	122 (45.5)	37 (13.8)	268 (100)

Values are the numbers of neurons. Values in parentheses are the percentages of the total. FG, final goal-selective; IG, immediate goal-selective; FG × IG, final and immediate goal-selective.

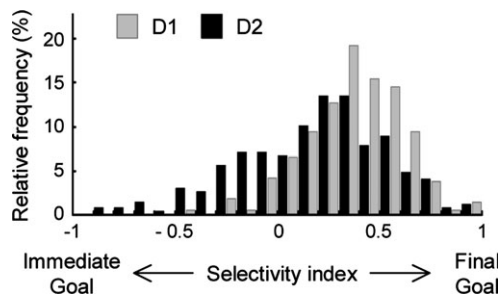


Figure 7. Comparison of behavioral goal selectivity during the delay periods. The frequency of occurrence of neurons that were either final or immediate goal-selective is depicted. The selectivity index (SI) was calculated as described in Materials and Methods. Positive SI values indicate final goal selectivity, and negative values indicate immediate goal selectivity. Each histogram depicts the relative frequency of neurons with SI values grouped in bins of 0.1. Data are for neurons that were active during either delay 1 (D1; 213 neurons, median for SI = 0.38) or delay 2 (D2; 268 neurons, median for SI = 0.24).

we subsequently classified each neuron into one of seven groups according to the period(s) during which final goal selectivity was detectable, as illustrated by the Venn diagram in Figure 8. We found that few neurons (9.2% or 42 of 456 final goal-selective neurons) were continuously active throughout the three periods, as exemplified in Figure 9C. Similarly, few neurons were active throughout delay 1 and delay 2 (12.1%, or 55/456). The distribution of neurons categorized according to the seven categories (bottom panel in Fig. 8) revealed that the majority (63.8%, or 291/456) was active during only one of the three task periods. Typically, final goal-selective activity during the goal display period decreased during the subsequent delay periods (Fig. 9A). A substantial proportion of neurons exhibited final goal selectivity that appeared *de novo* either during delay 1 (14.9%, or 68/456; Fig. 9B) or delay 2 (23.5%, or 107/456; Fig. 5).

Cortical Distribution of Recording Sites

Cortical sites of electrode entry (Fig. 10B) were reconstructed based on the results of the MRI, which revealed the location of the recording chamber with reference to the cortical sulci. Although the exact localization of neurons from which we obtained recordings awaits detailed histological study, three points are worth reporting at this stage. First, delay-related neurons that reflected behavioral goals were located within the lateral PFC, dorsal and ventral to the principal sulcus with a possible predominance in the dorsal area (Fig. 10C). Second, neurons that responded to the visual cue with goal-selective activity during the goal display period were located primarily ventral to the principal sulcus (Fig. 10D). The distribution of delay-related, behavioral goal-selective neurons was significantly

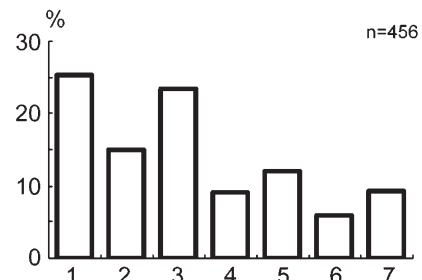
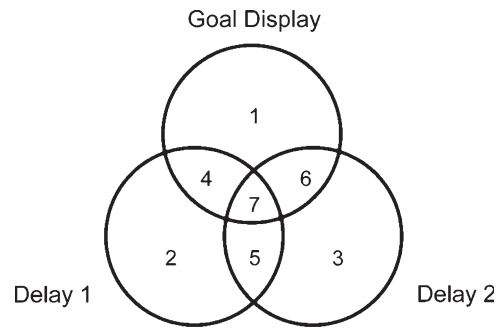


Figure 8. Distribution of final goal-selective neurons according to the stage of the behavioral task. Final goal-selective neurons were classified into seven categories according to the presence or absence of selective activity during each of the three task phases (goal display, delay 1, and delay 2). Each category is shown in the Venn diagram. The bar graph shows the distribution of neurons in each category (expressed as a percentage of the total number of neurons).

different from that of neurons that responded to the visual cue (χ^2 test, $P < 0.001$), which indicated that the former were located more dorsal to the latter. Finally, neurons that exhibited selective responses to the path-block were located primarily ventral to the principal sulcus (Fig. 10E). The distribution of goal-selective neuron was studied based on the number of selective neurons per recording site. We also performed the aforementioned statistical analysis using the proportion of selective neurons per total sample of neurons at a given site, and found results pointing to the same regional differences.

Relation to Eye Positions and Movements

We examined whether there was any relationship between eye positions and the location of the final or immediate goal. For this purpose, we calculated the average horizontal and vertical eye positions in 10 ms bins for each trial, and then obtained eight sets of quantified data for eye positions that were sorted according to locations of the final and immediate goals (Fig. 11). We then performed regression analysis on these data using the location of either the final or immediate goal as a factor. We found that the locations of neither the final goal nor the immediate goal significantly influenced the eye positions throughout the task periods preceding the first GO signal, as shown with sequential P -value displays at the bottom of Figure 11 ($P > 0.05$). In the next step of the analysis, we investigated whether neuronal activity that was found related to the location of behavioral goals, as described above, had any relation to either eye positions or eye movements during any task phases. For this purpose, we performed multiple regression analysis using three sets of regressors: vertical and horizontal eye positions, vertical and horizontal components of saccade vector, as well as the locations of final and immediate goals. Results of this analysis are shown in

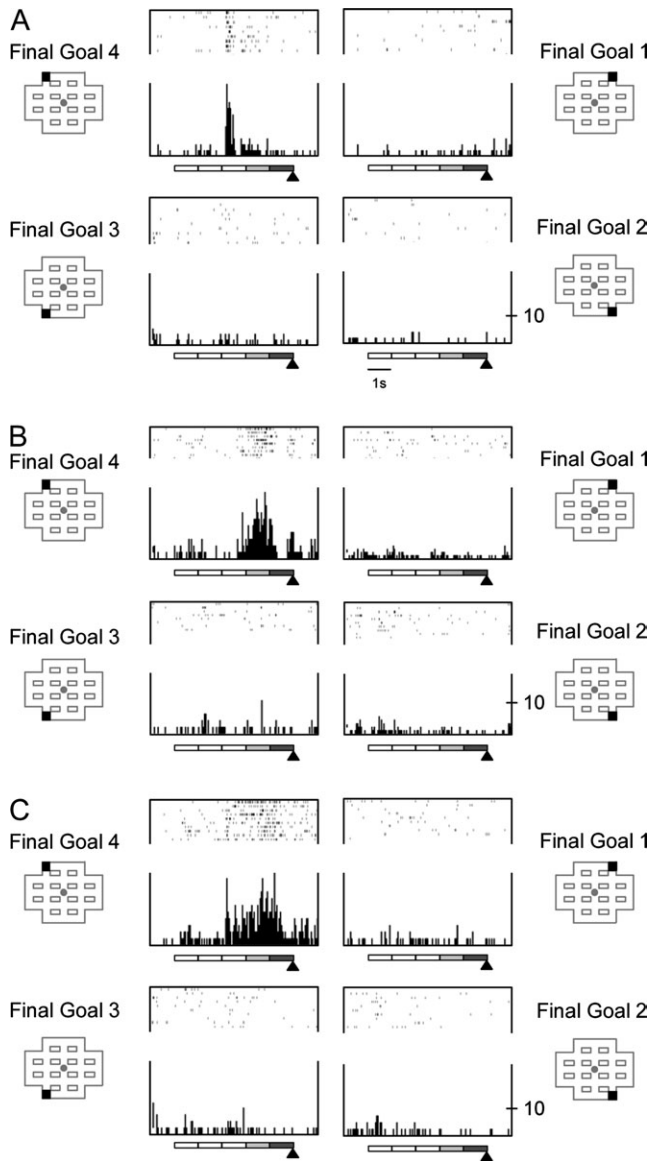


Figure 9. Examples of final goal-selective neural activity during three different stages of the task. (A) Discharges of a PFC neuron that responded phasically to the appearance of the goal at position 4. The selective activity of this neuron decreased during delay 1 and delay 2. This neuron was classified as category 1 in Figure 8. (B) Final goal-selective activity that occurred prominently during delay 1. This neuron was classified as category 2 in Figure 8. (C) Final goal-selective activity that occurred continuously during the goal display, delay 1 and delay 2 periods. This neuron was classified as category 7 in Figure 8. The activity of this neuron increased after the appearance of the goal at position 4, and this activity was maintained throughout delay 1 and delay 2. Display formats are as in Figure 2, except that activity was sorted according to final goal selectivity. The black square in each maze indicates the position of the remembered final goal.

Figure 12 that displays sequential plots of coefficients of determination (R^2) for examples of six PFC cells. As typically shown in Figure 12, none of PFC neurons tested revealed apparent relation to eye positions or movements.

Retinocentric Goal Representation?

We examined a possibility that the aforementioned behavioral goal-selective neurons could code the position of goals relative to a retinocentric frame of reference. To examine this possibil-

ity, neuronal activity was regressed on to the horizontal and vertical positions of the goal specified in the retinal coordinates. For this purpose, the retinal locations of the final and immediate goals were reconstructed based on their positions in the maze and the position of the eyes. We then applied four independent variables (horizontal and vertical eye position of final and immediate goals in retinal coordinates) to a regression model. This analysis revealed that the regression coefficients never reached a significant level ($P > 0.05$).

Discussion

We studied neuronal activity in the lateral PFC in monkeys as they performed a path-planning task. The task required the animals to navigate a maze stepwise to reach a remembered goal position in a maze by operating manipulanda with either forearm. We determined which behavioral factors influenced neuronal activity during the period in which the animals were planning to initiate the first movement of the cursor toward the goal. We found that few PFC neurons reflected motor attributes of the subsequent behavioral task. More importantly, we found that two major factors influenced neuronal activity during this period. The first factor was the position in the maze to which the animal intended to move the cursor as an initial step (referred to as the immediate goal). The second factor was the position in the maze to which the cursor would ultimately be moved as a result of at least three movements of the cursor (referred to as the final goal). The activity of a majority of PFC neurons reflected the combination of both factors.

Paucity of Activity Reflecting Motor Responses

We found that only a small minority of PFC neurons (1.3 and 2.9% during delays 1 and 2, respectively) reflected forthcoming motor responses. This finding is at variance with previous reports on PFC activity during planning or an instructed delay period. Although it was reported that PFC neuronal activity reflected primarily the visuospatial information that was provided as a visual cue rather than the direction of intended motion (Niki and Watanabe, 1976; Boussaoud and Wise, 1993; Funahashi *et al.*, 1993), the proportion of the population of task-related neurons that reflected an instructed action ranged from one-third to one-fifth. The discrepancy between our data and those of previous studies might be explained (at least in part) by the fact that we dissociated the direction of the animal's movements and the direction of the movement of visual objects that were acted upon in the present study. It is conceivable that the apparent correlation between PFC activity and direction of motion that was described in previous reports might have included neuronal activity reflecting the motion of visual objects that were produced as an outcome of intended action.

Neural representation of the target of visually guided arm movements has been reported before in several motor areas by Alexander and colleagues (Alexander and Crutcher, 1990a,b; Crutcher and Alexander, 1990; Shen and Alexander, 1997a,b). They found that neurons in cortical motor areas and in the putamen responded during a motor planning period as a function of the direction in which a visual cursor would move in response to a forthcoming arm movement. However, as compared with the PFC, these motor areas contained a higher proportion of neurons reflecting the direction of limb movement itself rather than the spatial target of movements.

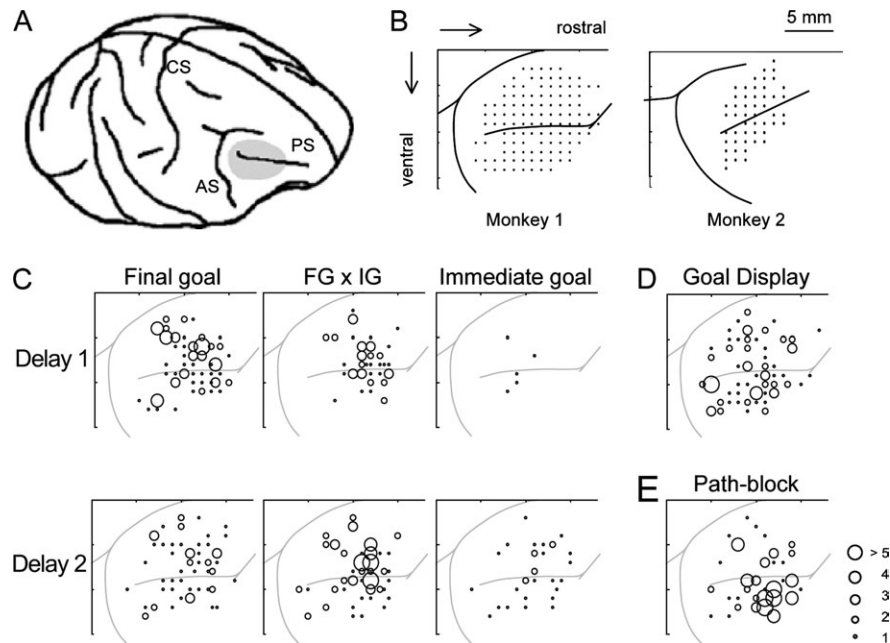


Figure 10. Cortical surface maps of recording sites. (A) Schematic drawing of a monkey brain. The shaded area corresponds to the approximate location of the recording sites shown in (B). AS, arcuate sulcus; CS, central sulcus; PS, principal sulcus. (B) Cortical surface map showing the points at which electrodes entered the brain relative to the cortical sulci, based on magnetic resonance imaging (MRI). (C) Recording sites corresponding to the locations of neurons that exhibited selectivity for the behavioral goals during delay 1 (top) and delay 2 (bottom). The number of delay-related neurons that was selective for each behavioral goal was plotted separately at each penetration site. The size of the circle is proportional to the number of neurons selective for the final goal (FG), the immediate goal (IG), or both the final and immediate goals (FG × IG). (D) Recording sites corresponding to the locations of goal-selective neurons that were active during the goal display period. (E) Recording sites corresponding to the locations of neurons that exhibited selectivity for the path-block during delay 2. C–E show data from monkey 1 (corresponding to left panel in B).

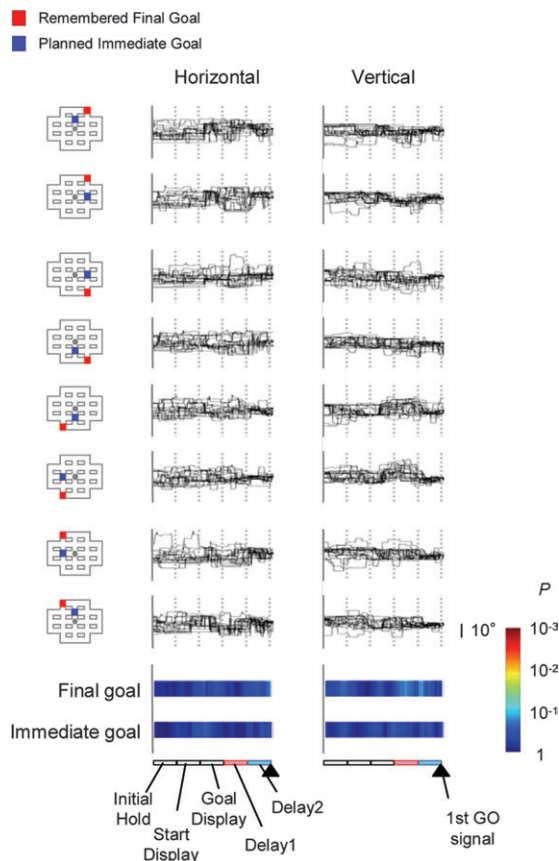


Figure 11. Eye position and movement during performance of the path-planning task. Traces of horizontal and vertical eye positions for 20 trials are displayed. Data were

This suggests that there may be a gradient in coding movement goals to movement metrics in moving from the PFC to motor areas, although absolute boundaries in the types of information coded in these areas may not exist.

Neuronal Activity Reflecting the Immediate Goal

During the delay periods that preceded the first GO signal, monkeys were required to select a position to which the cursor was to be moved (an immediate goal) or the direction of the first of three cursor movements necessary to reach the position of the final goal. This information was not provided by cues, because neither the presentation of the goal nor the path-block provided a visual cue that would indicate the direction of the first cursor movement. Thus, the animals were required to generate the information for the first movement without the aid of cues. Consequently, neuronal activity that reflected the immediate goal did not reflect currently available or remembered visual signals. We propose that the neuronal activity that was observed to be selective for the immediate goal reflected PFC activity that represented an immediate behavioral goal generated during planning. The immediate goal-selective activity was most prominent during

sorted according to the position of the final goal (red) and immediate goal (blue). The traces are aligned to the appearance of the first GO signal (filled triangles). Icons to the left indicate the positions of the final and immediate goals for each panel of eye movements. The two color scales at the bottom of each panel indicate time-varying plots of statistical *P*-values (regression analysis looking for relation of bin-by-bin eye positions to goals) in successive 10 ms bins. The color scale bar at the bottom right indicates the magnitude of the *P*-values. The two bars at the bottom indicate task periods.

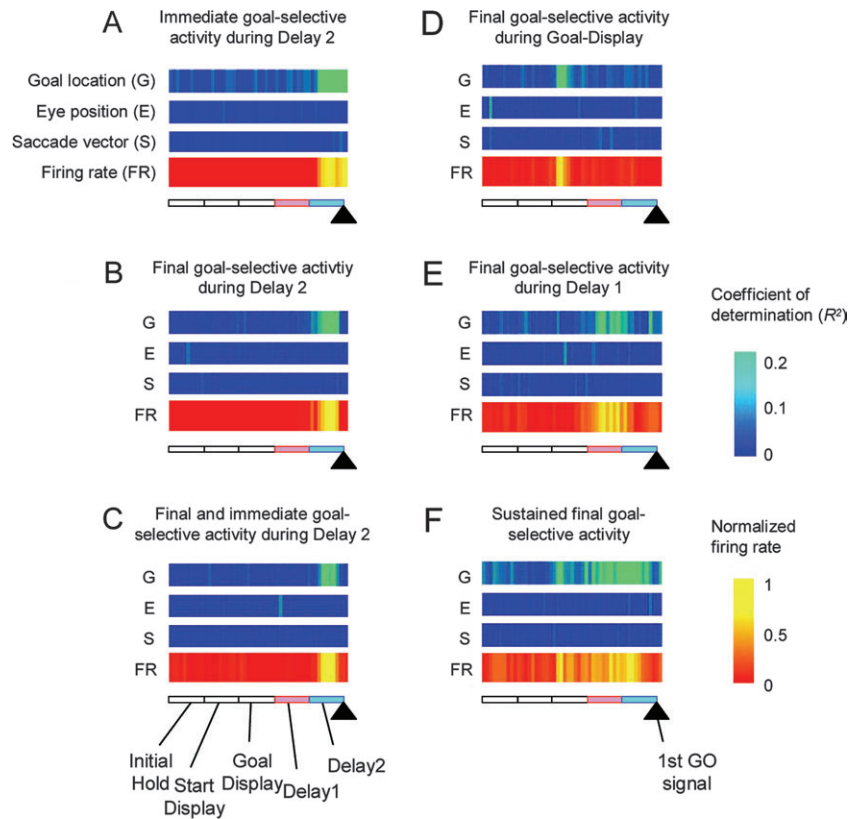


Figure 12. Regression analysis for six PFC neurons looking into correlation of neuronal activity with behavioral goal, eye position, and eye movement. Each panel shows time-varying plots of statistical R^2 -values for three regressors (goal location, eye position and saccade vector), where neuronal activity was regressed with the location of immediate or final goal, horizontal and vertical eye position, and horizontal and vertical components of saccade vector in successive 50 ms bins (displayed with three blue–green scales). Time-varying firing rate of each PFC neuron, in a 50 ms bin, is also shown in a red–yellow scale (FR). The FR indicates neuronal activity in trials for a preferred goal. Each example in A–F shows results of analysis for neurons that were also described in previous figures: (A) immediate goal-selective neuron shown in Figure 4; (B) immediate and final goal-selective neuron in Figure 5; and (C) final goal-selective neuron in Figure 6. (D–F) final goal-selective neurons that were active during the goal display (shown in Fig. 9A), during delay 1 (shown in Fig. 9B), and during the goal display, delay 1 and delay 2 (sustained type shown in Fig. 9C). Color-scale bars at the bottom right indicate the magnitude of the R^2 or normalized firing rate (FR).

delay 2. A small fraction of the activity during delay 1, however, also reflected the immediate goal, which suggested that the monkeys had already initiated the planning of the first cursor movement during delay 1. Nevertheless, because the PFC is involved in monitoring (Petrides, 1995) and anticipating future events (Sakagami and Niki, 1994; Watanabe, 1996; Rainer *et al.*, 1999), an alternative interpretation of the findings is that internal monitoring or expectation of the cursor motion (or the outcome of the forthcoming action) produced the immediate goal-selective activity.

Neuronal Activity Reflecting the Final Goal

We found that the activity of a large proportion of PFC neurons reflected the position of the final goal (61 and 41% during delays 1 and 2, respectively). To interpret this finding, we should first consider the possibility that this activity might reflect the visual cue that was presented during the goal display, because previous studies have established that PFC neurons maintain sensory information provided by visual cues during an instructed delay period (Goldman-Rakic, 1987). This explanation is plausible for activity that persisted during the delay periods after being initiated during the goal display period. However, we found that for half of the final goal-selective neurons, activity during the delay period commenced only after the disappearance of the visual cue. This finding is in line with previous reports that prefrontal neurons build up cue-instructed activity throughout

a delay period, in the absence of apparent cue-evoked activity (Kojima and Goldman-Rakic, 1982; Chafee and Goldman-Rakic, 1998). On the other hand, for 24% of final-goal selective neurons, activity started *de novo* during delay 2; for these neurons, activity may be generated in neural networks, including the PFC. Furthermore, final goal-selective activity coded the location of the goal in a spatial reference frame defined in the maze, rather than in a retinocentric reference frame. These observations suggest that information about the final goal would appear to be provided internally through the activity of neuronal networks that involve the PFC. Such information is likely to be an expression of the prospective memory of the achievement of the final goal, rather than the reflection of the retrospective memory of the visual signal. This view is supported by our finding in the present study that the final goal-selective activity during the delay periods was attributable to neurons that were distributed dorsal to the principal sulcus, whereas activity that reflected sensory responses to the presentation of the goal during the goal display was attributable to neurons that were distributed ventral to the principal sulcus in the lateral PFC (Petrides, 1991, 1995; Owen *et al.*, 1996; Hoshi and Tanji, 2004).

Interpretation of the Present Findings with Reference to Previous Reports

In previous reports on PFC activity during an instructed delay period, the properties of PFC neurons were described as being

representative of either the visual information that was provided with an instruction cue or the direction of forthcoming motion (Fuster and Alexander, 1971; Fuster, 1973; Kojima and Goldman-Rakic, 1982, 1984; Funahashi *et al.*, 1989; Wilson *et al.*, 1993; Miller *et al.*, 1996; Rao *et al.*, 1997; Rainer *et al.*, 1998). In the present study, we report a novel aspect of information representation by PFC neurons, namely behavioral goal representation. Our findings indicate that neuronal activity related to the immediate goal was neither a sensory nor a motor representation but instead represented the objective of the forthcoming behavior. It is important to note that, in the paradigm used in the present study, the animals were required to create information that specified an immediate goal. In view of the gradual shift of information from that representing the final goal to that representing the immediate goal, which occurred during the transition from delay 1 to delay 2, it is likely that the information related to the immediate goal was transformed from the final goal-related information during the process of behavioral planning. This process of transformation resembles the transformation process observed by Fukushima *et al.* (2004), who reported that the representation of an updated target was generated internally according to a nonspatial instruction.

Recent studies have revealed that the activity of PFC neurons during an instructed delay period represents a variety of behavioral factors that are more abstract in nature than the sensorial representation of instruction signals or the direction of future movements. Such behavioral factors include task conditions or rules (Hoshi *et al.*, 1998; White and Wise, 1999; Wallis *et al.*, 2001), behavioral monitoring (Petrides, 2000), multiple motor planning (Averbeck *et al.*, 2002) and the coding of abstract information (Freedman *et al.*, 2001; Nieder *et al.*, 2002; Ninokura *et al.*, 2003). The results of the present study suggest that an additional factor, namely behavioral goals (specifically, a planned immediate goal and a prospective final goal), should be considered to be part of the repertoire of PFC representations during an instructed delay period.

Notes

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