Prefrontal Task-Related Activity Representing Visual Cue Location or Saccade Direction in Spatial Working Memory Tasks

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Takeda, Kazuyoshi and Shintaro Funahashi: Prefrontal task-related activity representing visual cue location or saccade direction in spatial working memory tasks. J Neurophysiol 87: 567–588, 2002; 10.1152/jn.00249.2001. To examine what kind of information task-related activity encodes during spatial working memory processes, we analyzed single-neuron activity in the prefrontal cortex while two monkeys performed two different oculomotor delayed-response (ODR) tasks. In the standard ODR task, monkeys were required to make a saccade to the cue location after a 3-s delay, whereas in the rotary ODR (R-ODR) task, they were required to make a saccade 90° clockwise from the cue location after the 3-s delay. By comparing the same task-related activities in these two tasks, we could determine whether such activities encoded the location of the visual cue or the direction of the saccade. One hundred twenty one neurons exhibited task-related activity in relation to at least one task event in both tasks. Among them, 41 neurons exhibited directional cue-period activity, most of which encoded the location of the visual cue. Among 56 neurons with directional delay-period activity, 86% encoded the location of the visual cue, whereas 13% encoded the direction of the saccade. Among 57 neurons with directional response-period activity, 58% encoded the direction of the saccade, whereas 35% encoded the location of the visual cue. Most neurons whose response-period activity encoded the location of the visual cue also exhibited directional delay-period activity that encoded the location of the visual cue as well. The best directions of these two activities were identical, and most of these response-period activities were postsaccadic. Therefore this postsaccadic activity can be considered a signal to terminate unnecessary delay-period activity. Population histograms encoding the location of the visual cue showed tonic sustained activation during the delay period. However, population histograms encoding the direction of the saccade showed a gradual increase in activation during the delay period. These results indicate that the transformation from visual input to motor output occurs in the dorsolateral prefrontal cortex. The analysis using population histograms suggests that this transformation occurs gradually during the delay period.

INTRODUCTION

Neurophysiological studies using spatial working memory tasks have revealed that many neurons in the prefrontal cortex exhibit tonic activation during the delay period (delay-period activity) (Funahashi et al. 1989, 1993; Fuster 1973; Fuster and Alexander 1971; Kojima and Goldman-Rakic 1982, 1984; Kubota and Funahashi 1982; Kubota et al. 1974; Niki 1974; Niki and Watanabe 1976; Rainer et al. 1998; Rao et al. 1997; Wilson et al. 1993). Most of this delay-period activity has been shown to have directional selectivity, such that delay-period activity was observed only when visual cues were presented at a particular location in the visual field (Funahashi et al. 1989, 1993; Niki 1974; Niki and Watanabe 1976; Rainer et al. 1998; Rao et al. 1997; Wilson et al. 1993). In addition, delay-period activity was observed only when the monkey performed correctly in the task. When the monkey made an error, delay-period activity either was not observed or was observed but truncated (Funahashi et al. 1989, 1997; Fuster 1973; Niki and Watanabe 1976). Based on these observations, delay-period activity has been considered a neuronal correlate of temporary active storage mechanisms in working memory processes (Funahashi and Kubota 1994; Fuster 1997; Goldman-Rakic 1987, 1995, 1996).

A few studies have analyzed the information encoded by delay-period activity (Funahashi et al. 1993; Niki and Watanabe 1976). Niki and Watanabe (1976) examined the same neuron’s delay-period activity while monkeys performed two-choice manual versions of the delayed-response tasks and a two-choice conditional-position task. In the delayed-response tasks, the monkey selected either a right or left or an upper or lower response key after the delay depending on the position where the cue was presented, whereas in the conditional-position task, the monkey selected either a right or left key after the delay depending on whether the cue was presented in an upward or downward position. They found that 78% of delay-period activity encoded the location of the visual cue, whereas the remaining 22% encoded the direction of the response (right or left). Funahashi et al. (1993) also examined delay-period activity while monkeys performed a delayed pro-saccade task and a delayed anti-saccade task. In these tasks, visual cues were presented at the same location. However, the direction of the saccade in the delayed anti-saccade task was opposite the direction in the pro-saccade task. They also found that 70% of delay-period activity encoded the location of the visual cue and the remaining 30% encoded the direction of the saccade. These results indicate that delay-period activity acts as a mechanism for the temporary storage of visual and motor information in working memory processes and that most delay-period activity encodes sensory information.

Working memory is a mechanism for the temporary active...
storage of information. However, working memory can also be considered a dynamic system that includes mechanisms for processing and integrating information (Baddeley 1986; Funahashi and Kubota 1994; Miyake and Shah 1999). Understanding how information is processed and integrated is essential for understanding neuronal mechanisms in working memory. The finding that about 70% of delay-period activity encodes the location of the visual cue, whereas about 30% encodes the direction of the saccade suggests that processing and integrating information to produce motor output occur in the prefrontal cortex. To elucidate the mechanism for processing and integrating information, it is crucial to identify what kind of information is encoded by each task-related activity. Most previous studies have described the “differential” nature of task-related activity, depending on differences in stimuli or motor responses (Funahashi et al. 1989, 1993; Niki 1974; Niki and Watanabe 1976; Quintana et al. 1988; Rainer et al. 1998; Rao et al. 1997; Wilson et al. 1993). However, the type of information that is encoded by each task-related activity has not been considered. Therefore in the present experiment, we analyzed single-neuron activity in the prefrontal cortex while two monkeys performed two types of oculomotor delayed-response tasks. In the standard oculomotor-delayed response (ODR) task, monkeys were required to make a saccade to the cue location after a 3-s delay, whereas in the rotatory ODR (R-ODR) task, they were required to make a saccade 90° clockwise from the cue location after the 3-s delay. In the latter task, monkeys were required to transform visual input to motor output to perform correct eye movement. In addition, by comparing task-related activity between these two tasks, we can identify whether task-related activity encodes the location of the visual cue or the direction of the saccade. Therefore we can discuss how the prefrontal cortex participates in transformation processes from visual input to motor output.

A preliminary report of this study has been published in abstract form (Takeda et al. 1999a,b). This experiment was conducted as part of the Cooperation Research Program of the Primate Research Institute, Kyoto University (1998–2000).

**METHODS**

**Subjects and apparatus**

Two rhesus monkeys (monkey M, 3.6 kg; monkey N, 3.8 kg) were used in this study. Each monkey was housed individually in a home cage. Monkeys were deprived of water in their home cages but could obtain their daily requirement of water in the laboratory as a reward. To ensure each monkey’s condition, body weight and water intake were measured daily. All experiments were conducted according to the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. This experiment was approved by the Animal Research Committee of the Faculty of Integrated Human Studies, Kyoto University.

During training and recording sessions, the monkey sat in a primate chair in a dark room. The monkey’s head was fixed by a head-restraining instrument. The monkey faced a 21-in color monitor (E77F, NANA0) on which a fixation point and visual cues were presented. The monitor was placed 30 cm away from the monkey’s face. The monkey’s eye positions were monitored by the magnetic search coil technique (Robinson 1963). Two laboratory computers (PC-386GE and PC-486HX, Epson) controlled the monkey’s behavior, presented visual stimuli on the monitor, recorded neuronal activities, and monitored eye movements.

**Behavioral tasks**

In the present study, we used two types of ODR tasks; an ODR task and a rotatory oculomotor delayed-response (R-ODR) task. By analyzing neuronal activity in both tasks, we could identify whether task-related activity encoded the location of the visual cue or the direction of the saccade.

**ODR TASK.** In this task, the monkey was required to make a saccade to the location where the cue had been presented after a 3-s delay. The temporal sequence of this task is illustrated in Fig. 1A (top). After a 5-s intertrial interval (ITI), a fixation point (FP; white circle, 0.5° in visual angle) was presented at the center of the monitor. If the monkey continued to look at the FP for 1 s, a visual cue (white circle, 1° in visual angle) was presented for 0.5 s at one of eight predetermined locations around the FP. The monkey was required to maintain fixation on the FP throughout the 0.5-s cue period and subsequent 3-s delay period. At the end of the delay period, the FP was extinguished. This was the go signal for the monkey to make a saccade within 0.35 s.

**R-ODR task.** In this task, the monkey was required to make a saccade to 90° clockwise from the location where the visual cue had been presented. Bot- tom: a rotatory ODR (R-ODR) task. The monkey was required to make a saccade to 90° clockwise from the location where the visual cue had been presented. **FIG. 1.** Diagrams of 2 types of oculomotor-delayed response (ODR) tasks and cue locations. A: temporal sequences of task events. Top: a standard ODR task. The monkey was required to make a saccade to the location where the visual cue had been presented. Bottom: a rotatory ODR (R-ODR) task. The monkey was required to make a saccade to 90° clockwise from the location where the visual cue had been presented. **B:** locations of the visual cue in each task. FP, fixation point. The eccentricity of cue locations was 17°.
The location of the visual cue was randomized over trials. If the monkey performed the correct eye movement, it was rewarded by a drop (about 0.2 ml) of water. To estimate whether the monkey’s eye movement was correct or not, we set a square window (4–6° in visual angle) around the target location and considered that the monkey performed a correct saccade if its eye position fell within this window. If the monkey broke fixation during the cue or delay period, if the monkey failed to perform a saccade within the 0.35-s response period, or if the eye movement didn’t fall within the correct window, the trial was aborted immediately without reward and the next trial began. The visual cue was presented at one of eight predetermined peripheral locations (Fig. 1B, top). Its eccentricity was 17°. The location of the visual cue was randomized over trials.

R-ODR TASK. In this task, the monkey was required to make a saccade 90° clockwise from the location where the visual cue had been presented. The temporal sequence of this task is illustrated in Fig. 1A (bottom). After a 5-s ITI, the FP (a white cross, 0.5° in visual angle) was presented at the center of the monitor. If the monkey continued to look at the FP for 1 s, the visual cue (white circle, 1° in visual angle) was presented for 0.5 s at one of four predetermined locations around the FP. The monkey was required to maintain fixation on the FP throughout the 0.5-s cue period and subsequent 3-s delay period. At the end of the delay period, the FP was extinguished. This was the go signal for the monkey to make a saccade within 0.35 s (the response period) in a direction 90° clockwise from the location where the visual cue had been presented. If the monkey performed the correct eye movement, it was rewarded by a drop (about 0.2 ml) of water. We used the same square window around the target location and the same criterion to determine correct saccades as was used in the ODR task. If the monkey broke fixation during the cue or delay period, if the monkey failed to perform a saccade within the 0.35-s response period, or if its eye movement didn’t fall within the correct window, the trial was aborted immediately without reward and the next trial began. The visual cue was presented at one of four predetermined peripheral locations (Fig. 1B, bottom). Its eccentricity was 17°. The location of the visual cue was randomized over trials.

Surgical procedure

We first performed surgery under aseptic conditions to implant an eye coil to monitor eye movements and a stainless steel device to restrain the monkey’s head during the experiments. The monkey was first immobilized by injecting ketamine intramuscularly and then anesthetized by intravenous injection of pentobarbital sodium (25 mg/kg). Using the technique described by Judge et al. (1980), the eye coil was implanted under the conjunctiva in one eye. To restrain the monkey’s head during the experiment, a head-restraining device made of stainless steel was implanted on the skull. To reinforce the implantation of the head-restraining device, stainless steel bolts were implanted on the skull. The connector for the eye coil, the head-restraining device, and the stainless steel bolts were fixed to the skull with dental acrylic.

After we finished the monkey’s training, we performed a second surgery. In this surgery, we implanted a stainless steel cylinder to record neuronal activities from the prefrontal cortex. The monkey was first immobilized by injecting ketamine intramuscularly and then anesthetized by intravenous injection of pentobarbital sodium (25 mg/kg). We fixed the monkey’s head in the stereotaxic apparatus and exposed a part of the skull. We made a small hole (20 mm in diameter) using a trephine in the skull at the area corresponding to the principal sulcus as estimated by stereotaxic coordinates (30.0 mm anterior from the interaural plane and 15.0 mm lateral from the midline) and attached the stainless steel cylinder with one of the implanted stainless steel bolts. After each surgery, the monkey was administered antibiotics (Cephalosporin, FUJISAWA) for a few days to prevent infection. The monkey was given a full amount of food and water during the recovery period.

Recording single-neuron activity

After the monkey fully recovered from the second surgery, we started recording single-neuron activity from the cortex within and surrounding the principal sulcus while the monkey performed both tasks. In the recording sessions, the monkey performed each task in blocks of 100–150 trials. After we isolated single-neuron activity, we usually recorded the neuron’s activity while the monkey performed the R-ODR task and then recorded its activity while the monkey performed the ODR task. Single-neuron activity was recorded by glass-coated egigy1 microelectrodes (0.5–1.5 MΩ at 1 kHz). Raw neuron activity was amplified using an amplifier (DAM80, World Precision Instruments) and monitored using an oscilloscope (SS-7802, Iwatsu Electronics). At the same time, we isolated single-neuron activity using a window discriminator (DIS-1, BAK Electronics) and monitored its output using an oscilloscope. The output of the window discriminator was input to the computer (PC-386GE, Epson) and stored together with task events on magnetic media. We also stored raw neuron activities, task events, and horizontal and vertical eye movements on magnetic tapes using a data recorder (PC-108 M, Sony Precision Technology).

Data analysis

To examine whether the recorded neuron exhibited task-related activity (cue-period activity, delay-period activity, or response-period activity), we made rasters and histograms triggered at three alignment points (the onset of the cue period, the end of the delay period, and the onset of reward delivery) for each cue condition in both tasks. Using these rasters and histograms, we first visually inspected whether or not the neuron had task-related activity. Then we performed statistical analysis to identify characteristics of task-related activity.

First, to estimate the neuron’s baseline discharge rate, we calculated the mean discharge rate during the 1-s fixation period for each cue condition. For cue-period activity, we calculated the mean discharge rate during the 300-ms period (from 100 to 400 ms after the onset of the visual cue) for each cue condition. If the mean discharge rate during the cue period differed significantly from the mean discharge rate during the fixation period by the Mann-Whitney U test (P < 0.05), we considered that this neuron exhibited cue-period activity. Similarly, for delay- and response-period activity, we calculated either the mean discharge rate during the 3-s delay period for each cue condition or the mean discharge rate during the 300-ms response period (150 ms before and after the period when the peak activity was observed) for each cue condition. If the mean discharge rate during either the delay period or the response period differed significantly from the mean discharge rate during the 1-s fixation period by the Mann-Whitney U test (P < 0.05), we considered that the neuron exhibited delay-period activity or response-period activity, respectively. In addition, we classified response-period activity into two groups (pre- and postsaccadic activity) based on whether the initiation of response-period activity preceded the initiation of saccadic eye movements. These statistical tests were run independently for each task-related activity.

Previous studies have shown that most neurons with cue-period activity, delay-period activity, or response-period activity exhibit directional selectivity during the ODR task (Funahashi et al. 1989–1991). Therefore we also examined directional selectivity for task-related activity. In the present study, we first examined the difference in the mean discharge rates among all cue conditions for each task-related activity by one-way ANOVA. We considered that the task-related activity had directional selectivity if this difference was significant (P < 0.05). To estimate the best direction of task-related activity, we made a tuning curve for each task-related activity. The
tuning curve was made from the mean discharge rate under each cue condition based on its best fit to the Gaussian function

$$f(d) = B + R \times \exp(-0.5[(d - D)/Td]^2)$$

where \(f(d)\) is the discharge rate as a function of the visual cue location \(d\). The constants can be interpreted as follows: \(B\) indicates the discharge rate during the fixation period, \(R\) indicates the discharge rate at the best direction, \(D\) indicates the direction associated with the maximum discharge rate, and \(Td\) is an index of the tuning width. We considered \(D\) to be the best direction for task-related activity. We used \(D_{ODR}\) for the best direction in the ODR task and \(D_{R-ODR}\) for the best direction in the R-ODR task.

To identify whether task-related activity encodes the location of the visual cue or the direction of the saccade, we compared the cue conditions under which the maximum task-related activity was observed in the ODR and R-ODR tasks for the same neuron. Since the location of the visual cue and the direction of the saccade are different in the R-ODR task, we use the term “cue condition” to describe trial conditions in the ODR and R-ODR tasks. Thus the 0° cue condition indicates that the visual cue was presented at the 0° location in both tasks, while the direction of the saccade was 0° in the ODR task but 270° in the R-ODR task. We also use the term “max cue condition” to describe the cue condition under which the maximum task-related activity was observed. We determined the max cue condition of task-related activity in the ODR task and the max cue condition of the same task-related activity in the R-ODR task. We then compared the max cue conditions in the two tasks. In the ODR task, the location of the visual cue and the direction of the saccade were the same, whereas in the R-ODR task, the direction of the saccade was 90° clockwise from the location of the visual cue. Therefore if the max cue conditions of task-related activity were the same in the two tasks, this task-related activity would be considered to encode the location of the visual cue. On the other hand, if the max cue condition in the R-ODR task was 90° counterclockwise from that in the ODR task, this task-related activity would be considered to encode the direction of the saccade. In the present experiment, eight cue locations were used in the ODR task, whereas only four cue locations were used in the R-ODR task. Therefore if the max cue condition in the ODR task was 90° clockwise from the max cue condition in the ODR task, this activity would be considered to encode the direction of the saccade. Similarly, if the max cue condition in the R-ODR task was 135° counterclockwise from the max cue condition in the ODR task, this activity would be considered to encode the direction of the saccade. If the max cue condition in the R-ODR task was 45° counterclockwise from the max cue condition in the ODR task, it would be difficult to determine whether the task-related activity encoded the location of the visual cue or the direction of the saccade. Therefore we compared the best directions of tuning curves for this task-related activity in the two tasks. If the difference between the best directions in the two tasks was less than 45°, we considered that this task-related activity encoded the location of the visual cue. On the other hand, if the difference between the best directions in the two tasks was more than 45°, we considered that this task-related activity encoded the direction of the saccade.

In some neurons, the max cue condition of task-related activity in the R-ODR task was more than 135° counterclockwise from the max cue condition in the ODR task. For these neurons, we could not determine whether this task-related activity encoded the location of the visual cue or the direction of the saccade. Therefore we excluded these neurons from this analysis.

**Histological examinations**

At the end of the experiment, we made electrolytic lesions by passing a positive current through the elgiloy microelectrode at the four corners of the recording area to identify the recording site during histological examinations. Monkeys were deeply anesthetized by injecting an overdose of pentobarbital sodium (45–50 mg/kg) intravenously. The brain was first perfused by saline, and then by 10% formalin solution with 2% potassium ferrocyanide. The brain was removed from the skull and stored in 10% formalin solution with 30% sucrose. The brain was cut into 100-μm-thick coronal sections, and each section was stained with cresyl violet.
RESULTS

Behavioral performance

In the present experiment, the two monkeys performed both the ODR and R-ODR tasks at a correct performance rate of more than 85% throughout the recording sessions. Figure 2 shows distributions of end points of saccades in two tasks for the two monkeys. In the ODR task, the end points of saccades made distinct clusters close to each of the eight targets (Fig. 2, A and C). Similarly, in the R-ODR task, the end points of saccades also made distinct clusters close to each of the four targets (Fig. 2, B and D). Since monkeys performed memory-guided saccades during the response period, end points of saccades were often displaced a little from the actual target location. To quantify saccade accuracies in each task condition for each monkey, we calculated means of distances between saccade ends and target locations. For monkey M, the average displacement from the target location was 3.3° in ODR task and 5.5° in R-ODR task. For monkey N, the average displacement from the target location was 3.8° in ODR task and 4.7° in R-ODR task. There was no significant difference in the accuracy of saccades during each task between two monkeys. In addition, the saccade latencies showed no difference in two task conditions (monkey M, 289.9 ± 20.0 (SD) ms in ODR task and 284.1 ± 22.2 ms in R-ODR task; monkey N, 294.5 ± 17.0 ms in ODR task and 281.9 ± 18.9 ms in R-ODR task).

Database

We recorded the activities of 304 neurons (monkey M, n = 96; monkey N, n = 208) from the cortex within and surrounding the principal sulcus and arcuate sulcus.

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**TABLE 1. Number of neurons that exhibited task-related activity in both tasks**

<table>
<thead>
<tr>
<th>Task-Related Activity</th>
<th>ODR</th>
<th>R-ODR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cue-period activity</td>
<td>62</td>
<td>57</td>
</tr>
<tr>
<td>Directional</td>
<td>59</td>
<td>54</td>
</tr>
<tr>
<td>Omni-directional</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Delay-period activity</td>
<td>76</td>
<td>88</td>
</tr>
<tr>
<td>Directional</td>
<td>71</td>
<td>83</td>
</tr>
<tr>
<td>Omni-directional</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Response-period activity</td>
<td>99</td>
<td>110</td>
</tr>
<tr>
<td>Pre-saccadic</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Directional</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Omni-directional</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Post-saccadic</td>
<td>84</td>
<td>87</td>
</tr>
<tr>
<td>Directional</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>Omni-directional</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>Pre- and Post-saccadic</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Directional</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Omni-directional</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fixation-related activity</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Reward-related activity</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Non task-related</td>
<td>89</td>
<td>95</td>
</tr>
<tr>
<td>Total</td>
<td>251</td>
<td>269</td>
</tr>
</tbody>
</table>

Since many neurons exhibited task-related activity for more than one task event, the sum of the numbers for each task-related activity exceeds the total number of neurons.

**TABLE 2. Classification of task-related activity**

<table>
<thead>
<tr>
<th>No. of Neurons</th>
<th>Monkey M</th>
<th>Monkey N</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixation-related activity</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cue-period activity</td>
<td>21</td>
<td>22</td>
<td>43</td>
</tr>
<tr>
<td>Delay-period activity</td>
<td>21</td>
<td>39</td>
<td>60</td>
</tr>
<tr>
<td>Response-period activity</td>
<td>23</td>
<td>47</td>
<td>70</td>
</tr>
<tr>
<td>Pre-saccadic</td>
<td>1</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Post-saccadic</td>
<td>22</td>
<td>37</td>
<td>59</td>
</tr>
<tr>
<td>Pre- and Post-saccadic</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Neurons that exhibited the same task-related activity during both the ODR and R-ODR tasks

In the present study, we tried to understand what kind of information each task-related activity encoded. Therefore, we compared the max cue conditions for the same task-related activity between the ODR and R-ODR tasks in the same neuron. Of the 216 neurons recorded in both tasks, we analyzed 121 neurons that exhibited task-related activity for at least one task event during the performance of both tasks in detail. Among these 121 neurons, 43, 60, 70, and 2 exhibited cue-period activity, delay-period activity, response-period activity, and fixation-related activity, respectively (Table 2). Fixation-related activity is a phasic response to the appearance of the fixation point.

We first examined whether or not the task difference affected spontaneous background discharge rates since White and Wise (1999) found rule-dependent neuronal activity in the prefrontal cortex. We selected mean discharge rates during the fixation period as background discharge rates because the monkey’s behavior was exactly the same in the two tasks. In 121 neurons, we calculated the mean discharge rates during the 1-s fixation period in both the ODR and R-ODR tasks, respectively, and compared these rates between the two tasks. Figure 4 shows a scattergram of mean discharge rates in the fixation period. The correlation coefficient calculated from this scattergram is 0.737. The mean discharge rates during the ODR task and R-ODR task were 9.21 ± 6.76 spikes/s (n = 121, mean ± SD) and 9.27 ± 7.47 spikes/s (n = 121), respectively. Background activity during the ODR task was not significantly different from that during the R-ODR task (Wilcoxon signed-rank test, P = 0.94). Therefore these results indicate that there was no task-dependent difference in background discharge rates in the present experiment.

Cue-period activity

Of 43 neurons exhibited cue-period activity in both tasks, 41 (95%) exhibited directional cue-period activity and 2 exhibited omni-directional cue-period activity (Table 3). Figure 5 shows an example of a neuron with directional cue-period activity. In the ODR task, this neuron showed significant cue-period activity whenever visual cues were presented on the left side of the visual field (Fig. 5A). The maximum (max) cue condition of cue-period activity was 225° in the ODR task. In the R-ODR task, significant cue-period activity was also observed when the visual cues were presented at the 90° and 180° locations (Fig. 5B). The max cue condition of cue-period activity was 180° in the R-ODR task. For this neuron’s cue-period activity, the max cue conditions were 225° in the ODR task and 180° in the R-ODR task. Therefore this neuron’s directional cue-period activity was considered to encode the location of the visual cue. In addition, the best directions of cue-period activity based on the tuning curves were 177.2° in the ODR task and 155.9° in the R-ODR task. The best directions of cue-period activity were almost identical in the two tasks. This result confirms that this neuron’s directional cue-period activity encodes the location of the visual cue.

Figure 6 shows two other examples of neurons in which the best directions of cue-period activity were almost iden-

![Figure 4](http://jn.physiology.org/issue/FIGURES/0187/0121/FIG4.jpg)
tical in the two tasks. In neuron m101 (Fig. 6A), the best directions were 347° in the ODR task and 343.4° in the R-ODR task. In neuron m080 (Fig. 6B), the best directions of cue-period activity were 100.7° in the ODR task and 120.1° in the R-ODR task. These results indicate that the maximum cue-period activity of these neurons was observed with the same cue condition in both tasks, regardless of the direction of saccades. Therefore we could conclude that the directional cue-period activity of these neurons encodes the location of the visual cue.

We compared the best directions (D) of cue-period activity between the two tasks for all neurons that exhibited directional cue-period activity. Figure 7A shows the distributions of the differences between the best directions (D_{R-ODR} - D_{ODR}) in the two tasks. With regard to 90% of cue-period activity, the differences between the best directions in the two tasks were
distributed between $-45^\circ$ and $45^\circ$. The mean difference between the best directions in the two tasks was $7.9 \pm 28.0^\circ$. These results support the notion that cue-period activity encodes the location of the visual cue.

To examine whether or not the magnitude of cue-period activity was task-dependent, we compared the peak discharge rates during the cue period in the two tasks for 26 neurons that exhibited good Gaussian fitting. Figure 7B shows a scattergram of peak discharge rates of cue-period activity in the two tasks. The mean peak discharge rates were $27.22 \pm 17.46$ spikes/s ($n = 26$) in the ODR task and $25.54 \pm 14.13$ spikes/s ($n = 26$) in the R-ODR task. The mean peak discharge rates were not significantly different between the two tasks (Wilcoxon signed-rank test, $P = 0.55$). Therefore this result indicates that the magnitude of cue-period activity was similar between the two tasks for most of the neurons.

**Delay-period activity**

Of 60 neurons exhibited delay-period activity in both tasks, 56 (93%) exhibited directional delay-period activity and 4 (7%) exhibited omni-directional delay-period activity (Table 3). For neurons with directional delay-period activity, we compared the max cue conditions of delay-period activity and the best directions calculated from tuning curves of delay-period activity in the two tasks. As a result, directional delay-period activity was classified mainly into two groups. In one group, delay-period activity encoded the location of the visual cue, whereas in the other group, delay-period activity encoded the direction of the saccade. In one neuron, the max cue condition of delay-period activity in the R-ODR task was more than $135^\circ$ counterclockwise from the max cue condition in the ODR task, and we could not determine whether task-related activity encoded the location of the visual cue or the direction of the saccade for this neuron.

**Delay-period activity encoding the location of the visual cue**

In 48 (86%) of 56 neurons with directional delay-period activity, delay-period activity encoded the location of the visual cue. Figure 8 shows an example of directional delay-period activity that encoded the location of the visual cue. In the ODR task, this neuron exhibited significant delay-period activity when visual cues were presented at the $270^\circ$ and $315^\circ$ locations (Fig. 8A). The max cue condition of delay-period activity was $315^\circ$ in the ODR task. In the R-ODR task, significant delay-period activity was observed when the visual cue was presented at the $270^\circ$ location (Fig. 8B). The max cue condition of delay-period activity was $270^\circ$ in the ODR task. Therefore this neuron’s directional delay-period activity appears to encode the location of the visual cue. In addition, the best direction of delay-period activity based on the tuning curve was $297.0^\circ$ in the ODR task and $269.7^\circ$ in the R-ODR task. The best directions of delay-period activity were almost identical in the two tasks. Because the directions of saccades that were performed for the same cue condition were different in the two tasks, this result also supports the notion that this neuron’s directional delay-period activity encodes the location of the visual cue rather than the direction of the saccade.

The directional tuning of delay-period activity in the ODR and R-ODR tasks is compared in Fig. 9. Two examples show tuning curves of delay-period activity in which the best directions in the two tasks were almost identical. For neuron m090, the best directions were $57.7^\circ$ in the ODR task and $56.6^\circ$ in the R-ODR task. For neuron m134, the best directions were $19.4^\circ$ in the ODR task and $38.6^\circ$ in the R-ODR task. In these neurons, either the best directions of delay-period activity in the two tasks were almost identical or the difference between the best directions in the two tasks was less than $45^\circ$. Figure 10A shows the distributions of the difference between the best directions in the two tasks ($D_{R-ODR} - D_{ODR}$) for all directional delay-period activity. In 86% of neurons with directional delay-period activity, the differences between the best directions in the two tasks were between $-45^\circ$ and $45^\circ$. Therefore these findings indicate that the directional delay-period activity of these neurons apparently encodes the location of the visual cue.

**Delay-period activity encoding the direction of the saccade**

In 7 (13%) of 56 neurons with directional delay-period activity, delay-period activity encoded the direction of saccadic eye movement. Figure 11 shows an example of directional delay-period activity that encoded the direction of the saccade.
In the ODR task, this neuron exhibited significant delay-period activity when the visual cues were presented at the 0° and 90° locations (Fig. 11A). The max cue condition of delay-period activity was 0° in the ODR task. In the R-ODR task, significant delay-period activity was observed when the visual cue was presented at the 90° location (Fig. 11B). The max cue condition of delay-period activity was 90° in the R-ODR task. The max cue conditions were 0° in the ODR task and 90° in the R-ODR task. In the ODR task, the location of the visual cue and the direction of the saccade were the same, whereas in the R-ODR task, the direction of the saccade was 90° clockwise from the location of the visual cue. Therefore this neuron’s directional delay-period activity was considered to encode the direction of the saccade. In addition, the best direction of delay-period activity based on the tuning curve was −1.7° in the ODR task and 68.7° in the R-ODR task, for a difference of about 70°. This result also supports the notion that the directional delay-period activity of this neuron encodes the direction of the saccade.

Figure 10A shows distributions of the difference between the best directions in the two tasks for all directional delay-period activity. In only seven neurons (13%), the differences between the best directions in the two tasks (\(D_{\text{ODR}} - D_{\text{ODR}}\)) were distributed between 45° and 135°. The mean difference between the best directions was 95.9° ± 35.5° (n = 7). Thus these neurons exhibited maximum delay-period activity when the monkey performed saccades to a certain direction, regardless of where the visual cues were presented. Therefore the directional delay-period activity of these neurons is considered to encode the direction of the saccade.

**Comparison of peak activity in the ODR and R-ODR tasks**

To examine whether or not the magnitude of delay-period activity was task-dependent, we compared the peak discharge rates of delay-period activity between the two tasks for 32 neurons that exhibited good Gaussian fitting. Figure 10B is a scattergram of peak discharge rates of delay-period activity in the two tasks. The mean peak discharge rates were 13.41 ± 8.79 spikes/s (n = 32) in the ODR task and 14.03 ± 8.61 spikes/s (n = 32) in the R-ODR task, and this difference was not significant (Wilcoxon signed-rank test, \(P = 0.25\)). Therefore, this result indicates that the magnitude of delay-period activity was not task dependent.

**Response-period activity**

Of 70 neurons exhibited response-period activity in both tasks, 59 exhibited postsaccadic activity, 10 exhibited presaccadic activity, and 1 exhibited both activities (Table 3). Seventy-eight percent of the neurons with postsaccadic activity ( \(n = 47\) ) showed directional selectivity and the remaining 22% ( \(n = 13\) ) showed omni-directional activity. All of the neurons (11/11) with presaccadic activity showed directional selectivity (Table 3). For neurons that exhibited directional response-period activity, we compared the max cue conditions and the best directions calculated from tuning curves for response-period activity in the ODR and R-ODR tasks. As a result, directional response-period activity was classified into four groups. In the first group ( \(n = 33\) ), response-period activity encoded the direction of the saccade. In the second group ( \(n = 20\) ), response-period activity encoded the location of the visual cue. In the third group ( \(n = 2\) ), directional response-period activity was observed in the ODR task, but omni-directional activity was observed in the R-ODR task. In the fourth group ( \(n = 3\) ), we could determine the max cue conditions and best directions for response-period activity in both tasks. However, the max cue condition for response-period activity in the R-ODR task was more than 135° counterclockwise from the max cue condition in the ODR task.

**Response-period activity encoding the direction of the saccade**

Among the 57 neurons that exhibited directional response-period activity, 33 (58%) showed activity that en-
A ODR task

B R-ODR task

C Post-saccadic activity
coded the direction of the saccade. Of 33 neurons, 88% (n = 29) exhibited postsaccadic activity and the remaining 12% (n = 4) exhibited presaccadic activity. Figure 8 shows an example of postsaccadic activity that encoded the direction of the saccade. In the ODR task, this neuron exhibited significant postsaccadic activity in trials in which the visual cues were presented at the 135° location (Fig. 8A). The max cue condition for postsaccadic activity was 135° in the ODR task. In the R-ODR task, significant postsaccadic activity was observed when the visual cues were presented at the 270° location (Fig. 8B). The max cue condition for postsaccadic activity was 270° in the R-ODR task. In the ODR task, the location of the visual cue and the direction of the saccade were the same, whereas in the R-ODR task, the direction of the saccade was 90° clockwise from the location of the visual cue. In this example, the max cue condition was 135° in the ODR task and 270° in the R-ODR task. Therefore, this neuron’s directional postsaccadic activity is considered to encode the direction of the saccade. The best directions for postsaccadic activity calculated from the tuning curve were 134.9° in the ODR task and 242.7° in the R-ODR task. The difference between the best directions in the two tasks was 107.8°, which is close to 90°. This result confirms that this neuron’s directional postsaccadic activity encodes the direction of the saccade.

Figure 12 shows other examples of presaccadic activity (n171) and postsaccadic activity (m070). The best directions were 78.6° in the ODR task and 164.7° in the R-ODR task for neuron n171 and 134.9° in the ODR task and 242.7° in the R-ODR task for neuron m070. In these neurons, the differences between the best directions in the two tasks were approximately 90° (86.1° for neuron n171 and 107.8° for neuron m070). Therefore the directional activity of these neurons is thought to encode the direction of the saccade.

Figure 13A show distributions of the difference between the best directions in the two tasks (D_{ODR-ODR}^\text{R-ODR}) for all directional response-period activity. In 58% of these neurons (33/57), the differences between the best directions in the two tasks (D_{ODR-ODR}^\text{R-ODR}) were distributed between 45° and 135°. For these neurons, the mean difference between the best directions in the two tasks was 94.8 ± 22.5° in postsaccadic activity (n = 4) and 99.8 ± 33.5° in presaccadic activity (n = 29).

**Response-period activity encoding the location of the visual cue**

Among the 57 neurons that exhibited directional response-period activity, 20 (35%) showed activity that encoded the location of the visual cue. Of these 20 neurons, 15 (75%) exhibited postsaccadic activity and 5 (25%) exhibited presaccadic activity. Figure 14 shows an example of presaccadic activity that encoded the location of the visual cue. In the ODR task, this neuron exhibited significant presaccadic activity when the visual cues were presented at the 0°, 45°, 225°, and 270° locations (Fig. 14A). The max cue condition for presaccadic activity was 270° in the ODR task. In the R-ODR task, significant presaccadic activity was observed when the visual cues were presented at the 270° location (Fig. 14B). The max cue condition for presaccadic activity was 270° in both the R-ODR and ODR tasks, indicating that the directional presaccadic activity of this neuron encodes the location of the visual cue. The best directions for presaccadic activity...
Sixty-five percent of the neurons (13/20) whose response-period activity encoded the location of the visual cue also had cue-period activity and/or delay-period activity in both tasks. Among these, 11 neurons (85%) exhibited both directional delay-period activity and directional response-period activity in both tasks. An example of these neurons is shown in Fig. 14. In the ODR task, this neuron exhibited significant delay-period activity when the visual cues were presented at the 225°, 270°, and 315° locations (Fig. 14A). The max cue condition of delay-period activity was 270° in the ODR task. In the R-ODR task, significant delay-period activity was also observed when the visual cues were presented at the 90° and 270° locations (Fig. 14B). The max cue condition of delay-period activity was 270° in the R-ODR task. The max cue conditions of delay-period activity were the same in the two tasks. Therefore this neuron’s directional delay-period activity is considered to encode the location of the visual cue. As shown previously, this neuron also exhibited directional presaccadic activity in both tasks. The max cue condition for presaccadic activity was 270° in both tasks. These results indicate that the max cue conditions were the same for both delay-period activity and presaccadic activity in both tasks and therefore that both activities encode the location of the visual cue.

Figure 15 shows other examples of the neuron with both delay-period and presaccadic activities (n110) and the neuron with both delay-period and post-saccadic activities (n123). In these examples, the max cue conditions for delay-period and response-period activities were the same (270°) in both tasks, regardless of the directions of the saccades. Therefore both delay-period and response-period activities are thought to encode the location of the visual cue. Of 11 neurons with both delay-period and response-period activities, 10 showed identical max cue conditions for both delay-period and response-period activities, and both activities encoded the location of the visual cue. Among these 10 neurons, 5 exhibited post-saccadic activity and 5 exhibited presaccadic activity.

Comparison of peak activity in the ODR and R-ODR tasks

To examine whether or not the magnitude of pre- or post-saccadic activity is task-dependent, we compared the peak discharge rates of pre- or post-saccadic activity in the two tasks for 27 neurons that exhibited good Gaussian fitting. Figure 13B is a scattergram of peak discharge rates of pre- or post-saccadic activity in both tasks. The mean peak discharge rate of presaccadic activity was 27.91 ± 7.09 spikes/s (n = 6) in the ODR task and 31.22 ± 12.91 spikes/s (n = 6) in the R-ODR task. The mean peak discharge rate of post-saccadic activity was 22.98 ± 6.95 spikes/s (n = 21) in the ODR task and 23.29 ± 8.94 spikes/s (n = 21) in the R-ODR task. There was no significant difference between the peak discharge rates of post-saccadic activity (Wilcoxon signed-rank test, P = 0.60) or post-saccadic activity (Wilcoxon signed-rank test, P = 0.99).

Population analysis of delay-period activity encoding the location of the visual cue and the direction of the saccade

We examined what type of information each task-related activity encoded during spatial working memory processes. As a result, we found that directional cue-period activity encoded
the location of the visual cue. For directional delay-period activity, 86% encoded the location of the visual cue, whereas 13% encoded the direction of the saccade. For directional response-period activity, 58% encoded the direction of the saccade, whereas 35% encoded the location of the visual cue. In addition, as is seen in Figs. 7A, 10A, and 13A, the means of the difference between the best directions ($D_{R-ODR} - D_{ODR}$) in two tasks was 7.9° in cue-period activity, 18.9° in delay-period activity, and 67.1° in response-period activity. The mean of these distributions was shifted progressively farther to 90°. These results suggest that the transformation of information from visual input to motor output occurs during the delay period in the prefrontal cortex.

To elucidate the process of information transformation from visual input to motor output, we made population histograms (population average of delay-period activity) using neuronal activities at the max cue conditions for all neurons with delay-period activity that encoded the location of the visual cue and the direction of the saccade, respectively. Using directional delay-period activity that encoded the location of the visual cue ($n = 48$), we made two population histograms; one histogram ($ODRcue$) using activities at the max cue condition in the ODR task and another ($R-ODRcue$) using activities at the max cue condition in the R-ODR task. Similarly, using directional delay-period activity that encoded the direction of the saccade ($n = 7$), we made two other population histograms; one histogram ($ODRsac$) using activities at the max cue condition in the ODR task and another ($R-ODRsac$) using activities at the max cue condition in the R-ODR task.

As shown in Fig. 16A, $ODRcue$ exhibited tonic excitation during the delay period. Throughout the delay period, the discharge rate of delay-period activity was maintained at around 14 spikes/s. Similarly, $R-ODRcue$ also exhibited tonic excitation during the delay period (Fig. 16B), although the discharge rate of delay-period activity increased slightly from the beginning of the delay period (13 spikes/s) to the end of the delay period (15 spikes/s). These results indicate that delay-period activity encoding the location of the visual cue shows tonic excitation during the 3-s delay period and that the discharge rate of delay-period activity maintains at a similar rate throughout the delay period in both tasks. Among 48 neurons with directional delay-period activity that encoded the location of the visual cue, 31 exhibited tonic excitation, 8 exhibited gradual increase of activity, 3 exhibited gradual decrease of activity, and 6 showed tonic inhibition during the delay period.

On the other hand, $ODRsac$ shows a gradual increase of activity during the delay period, and reached 18 spikes/s at the end of the delay period (Fig. 16A). Similarly, $R-ODRsac$ shows more rapid increase of activity after the onset of the delay period until the end of the delay period and reached 20 spikes/s at the end of the delay period (Fig. 16B). Among seven neurons with directional delay-period activity that encoded the direction of the saccade, three exhibited tonic excitation and four exhibited gradual increase of activity during the delay period.

Comparing the temporal patterns of activation between $ODRcue$ and $ODRsac$ (Fig. 16A), during the early phase of the delay period, the discharge rates of $ODRcue$ and $ODRsac$ were almost the same. However, the discharge rate of $ODRsac$ became higher than $ODRcue$ during the late phase of the delay period. Similarly, comparing the temporal patterns of activation between $R-ODRcue$ and $R-ODRsac$ (Fig. 16B), the discharge rates of $R-ODRcue$ and $R-ODRsac$ were almost the same at the early phase of the delay period. However, the discharge rate of $R-ODRsac$ increased rapidly during the late phase of the delay period. These results indicate that, at the population level, neuronal activity encoding motor outputs gradually develops during the delay period, whereas neuronal activity encoding visual inputs maintains at a constant level during the delay period, suggesting that the transformation of information from visual input to saccade output occurs during the delay period.

**DISCUSSION**

In the present experiment, we examined what kind of information each task-related activity encodes by using two different oculomotor delayed-response tasks (ODR and R-ODR tasks). As a result, most of the neurons with directional cue-period activity encoded the location of the visual cue. Among the neurons with directional delay-period activity, 86% encoded the location of the visual cue, whereas 13% encoded the direction of the saccade. Among the neurons with directional response-period activity, 58% encoded the direction of the saccade, whereas 35% encoded the location of the visual cue. We used two monkeys ($M$ and $N$) for this experiment. In monkey $M$, 95% of directional delay-period activity encoded the location of the visual cue and the remaining 5% encoded the direction of the saccade. And 78% of directional response-period activity encoded the direction of the saccade and the remaining 22% encoded the location of the visual cue. Similarly in monkey $N$, 81% of directional delay-period activity encoded the location of the visual cue and 16% encoded the direction of the saccade. And 49% of directional response-period activity encoded the direction of the saccade and 22% encoded the location of the visual cue. These results show that the proportions of neurons encoded the location of the visual cue and neurons encoded the direction of the saccade are similar in two monkeys, indicating that both monkeys used similar strategies to perform two tasks. An analysis using population histograms of delay-period activity showed that information encoding the location of the visual cue was maintained during the delay period, while the magnitude of activity encoding the direction of the saccade gradually increased during the delay period. These results indicate that the transformation of information from visual input to motor output occurs in the dorsolateral prefrontal cortex and that this transformation occurs gradually during the delay period.

**Cue-period activity encodes the location of the visual cue**

Among the 43 neurons that exhibited cue-period activity in both tasks, 95% exhibited directional cue-period activity. For most of the neurons with directional cue-period activity, the max cue condition was observed with the same cue condition in both tasks. Therefore the directional cue-period activity of these neurons is considered to encode the location of the visual cue.

Cue-period activity has been reported by many authors using various behavioral paradigms such as delayed-response tasks (Funahashi et al. 1990; Fuster 1973; Niki 1974), delayed matching-to-sample tasks (O'Scalaidhe et al. 1999; Rainer et al. 1998), delayed paired associate tasks (Asaad et al. 1998, ...
A  ODR task

(135° → 135°) C D R

(90° → 90°) C D R

(45° → 45°) C D R

(180° → 180°) C D R

(225° → 225°) C D R

(270° → 270°) C D R

(315° → 315°) C D R

B  R-ODR task

(90° → 0°) C D R

(180° → 90°) C D R

(0° → 270°) C D R

(270° → 180°) C D R
2000; Rainer et al. 1999), and go/no-go discrimination tasks (Sakagami and Niki 1994; Sakagami and Tsutsui 1999; Watanabe 1986). For example, Rainer et al. (1998) examined neuronal activity during the sample period while monkeys performed a delayed matching-to-sample task using an array of three objects. In this task, only one of these objects was relevant for task performance. The monkey needed to find the target object and remember its location. They found that 68% of prefrontal neurons modulated their activities during the sample period depending on the target location despite the physically identical array of objects.

Most of the research done in the prefrontal cortex has shown that most cue-period activity is “differential,” such that cue-period activity is observed only when a stimulus with a particular shape or color is presented or when the visual cue is presented at a particular location. Therefore cue-period activity is considered to reflect visual inputs. Funahashi et al. (1990) examined the same neuron’s cue-period activity while monkeys performed the ODR task and the visual probe (VP) task. In the VP task, monkeys were simply required to maintain gaze at a fixation target to obtain a reward regardless of where the visual stimuli appeared. They found that the magnitudes of responses to visual stimuli were the same in both tasks and that the directional tuning of these responses was also the same in the two tasks. Therefore they concluded that the responses to visual cues in both tasks reflected the same underlying visual responsivity and visual receptive field of the neuron and suggested that cue-period activity is a neuronal correlate of registered visual information. The present results also indicate that cue-period activity reflects visual inputs.

Delay-period activity reflecting the temporary storage of information

Neurophysiological studies using spatial working memory tasks have revealed that many neurons in the prefrontal cortex exhibit tonic activation during the delay period (delay-period activity) (Funahashi et al. 1989, 1993; Fuster 1973; Fuster and Alexander 1971; Kojima and Goldman-Rakic 1982, 1984; Kubota and Funahashi 1982; Kubota et al. 1974; Niki 1974; Niki and Watanabe 1976; Rainer et al. 1998; Rao et al. 1997; Wilson et al. 1993). Most delay-period activity has been shown to have directional selectivity, such that delay-period activity is observed only when visual cues are presented at a particular location in the visual field (Funahashi et al. 1989, 1993; Niki 1974; Niki and Watanabe 1976; Rainer et al. 1998; Rao et al. 1997; Wilson et al. 1993). In addition, delay-period activity was observed only when the monkey performed correctly in the task. When the monkey made an error, delay-period activity either was not observed or was observed but truncated (Funahashi et al. 1989, 1997; Fuster 1973; Niki and Watanabe 1976). In addition, previous studies using nonspatial working memory tasks such as delayed matching-to-sample tasks and delayed conditional tasks have indicated that delay-period activity also reflects mechanisms for the temporary active storage of nonspatial information, such as faces (O’Scalaidhe et al. 1997, 1999; Wilson et al. 1993) and object shapes, patterns, or colors (Miller et al. 1996; Quintana et al. 1988; Rainer et al. 1998; Rao et al. 1997; Sakagami and Niki 1994; Watanabe 1990, 1992; Yajeya et al. 1988). Therefore delay-period activity can be considered a neuronal correlate of temporary active storage mechanisms in working memory processes (Funahashi and Kubota 1994; Fuster 1997; Goldman-Rakic 1987, 1995, 1996). The present results confirm the notion that delay-period activity is a neuronal correlate of temporary active storage mechanisms of information. In addition, the present results show that delay-period activity represents information for motor outputs as well as information for sensory inputs. Similar results have been reported by Niki and Watanabe (1976) and Funahashi et al. (1993).
Delay-period activity encodes either the location of the visual cue or the direction of the saccade

Among 60 neurons that exhibited delay-period activity in both tasks, 93% exhibited directional delay-period activity. By comparing the directional selectivity of delay-period activity between ODR and R-ODR tasks, directional delay-period activity was classified into two groups. In one group (86%), directional delay-period activity is considered to encode the location of the visual cue. In the other group (13%), directional delay-period activity is thought to encode the direction of the saccade. Thus the present results show that delay-period activity encodes either the location of the visual cue or the direction of the saccade and that while most delay-period activity encodes the location of the visual cue, some encodes the direction of the saccade.

Similar results have been observed for prefrontal activity. Niki and Watanabe (1976) examined the same neuron’s delay-period activity while monkeys performed two different spatial delayed-response tasks and a conditional position discrimination task with a delay. In the spatial delayed-response tasks, the monkeys were required to respond on either the right or the left response key (right-left DR task) or on either the upward or the downward response key (up-down DR task) depending on where the visual cue was presented. In the conditional position discrimination task, the monkeys were required to press the right response key or the left response key when the visual cue was presented at the upper position or the downward position, respectively. They found that 78% (25/32) of “differential” delay-period activity encoded the location of the visual cue, whereas the remaining 22% (7/32) encoded the direction of the response. Similarly Funahashi et al. (1993) examined the characteristics of the same neuron’s directional delay-period activity while monkeys performed a delayed pro-saccade task and a delayed anti-saccade task. In these tasks, visual cues were presented at the same location. However, in the delayed pro-saccade task, monkeys were required to make saccades to where the visual cues were presented, whereas in the anti-saccade task, monkeys were required to make saccades opposite to where the visual cues were presented. They found that 70% (30/43) of directional delay-period activity encoded the location of the visual cue and the remaining 30% (13/43) encoded the direction of the saccade. In addition, Boussaoud and Wise (1993) and Di Pellegrino and Wise (1993) reported that there were more neurons that showed activity reflecting the significance of stimuli in the prefrontal cortex than in the premotor cortex. Recently, Hoshi et al. (2000) found neuronal

FIG. 13. A: distribution of differences between the best directions in response-period activity in the 2 tasks. The differences between the best directions \((D_{\text{ODR}}-D_{\text{ODR}})\) were distributed from \(-90^\circ\) to \(202.5^\circ\). The mean difference between best directions was \(12.4 \pm 26.5^\circ\) (presaccadic activity, \(n = 5\)) and \(3.84 \pm 34.9^\circ\) (postsaccadic activity, \(n = 15\)) for neurons encoding the location of the visual cue, and \(94.8 \pm 22.5^\circ\) (presaccadic activity, \(n = 4\)) and \(99.8 \pm 33.5^\circ\) (postsaccadic activity, \(n = 29\)) for neurons encoding the direction of the saccade. B: comparison of peak discharge rates of response-period activity in the 2 tasks. The correlation coefficients were 0.546 for presaccadic activity and 0.66 for postsaccadic activity. There were no significant differences between the peak discharge rates of either pre- or postsaccadic activity in the 2 tasks (presaccadic activity, Wilcoxon signed-rank test, \(P = 0.66, n = 6\); postsaccadic activity, Wilcoxon signed-rank test, \(P = 0.99, n = 21\)).
activity in the prefrontal cortex that reflected the result of motor selection while monkeys performed behavioral tasks in which responses to different positions were required based on two behavior rules. In these tasks, after a sample cue (triangle or circle) appeared at one of three locations (top, left, or right), one of two types of choice cue appeared after the delay. The type of the choice cue indicated the condition for the task (location match or shape match). In the location-matching condition, either three circles or three triangles were presented as choice cues and the monkeys were required to press a target where the same shape as the sample cue was presented. In the shape-matching condition, one circle and one triangle were presented as choice cues, and the monkeys were required to press a target where either a circle or triangle had been presented as a sample cue. They found three types of neuronal activity during the choice cue period. One type of neuronal activity encoded the past sensory information, another type encoded the configuration of the current choice cues, and the third type encoded the properties of future targets.

These results indicate that directional delay-period activity and other types of activity in the prefrontal cortex encode the location of the visual cue or the direction of motor action. Since delay-period activity representing the location of the visual cue encodes information regarding the past event and since delay-period activity representing the direction of the saccade encodes information regarding future events, prefrontal neurons appear to encode both retrospective and prospective information. Although most directional delay-period activity encodes retrospective information such as the location where the visual cue was presented, about one-third of delay-period activity encodes prospective information such as the direction of the forthcoming saccade, indicating that the transformation from retrospective information to prospective information occurs within the prefrontal cortex.

Response-period activity encoding the direction of the saccade

Among the 70 neurons that exhibited response-period activity in both tasks, 57 (81%) exhibited directional selectivity. For 58% of the neurons with directional response-period activity, the maximum response-period activity in the ODR task was observed at 90° clockwise from the max cue condition in the R-ODR task. Because, in the R-ODR task, the direction of the saccade was 90° clockwise from the location of the visual cue, the directional response-period activity of these neurons is considered to encode the direction of the saccade. Most of these neurons (n = 29) exhibited postsaccadic activity, whereas a few (n = 4) exhibited presaccadic activity.

It has been reported that neurons in the dorsolateral prefrontal cortex show presaccadic activity, although the percentage of these neurons was small (Boch and Goldberg 1989; Funahashi et al. 1991). The characteristics (e.g., temporal patterns of responses, response latencies, directional tunings) of presaccadic activity observed in the prefrontal cortex were similar to those observed in the frontal eye field (Bruce and Goldberg 1985) and the superior colliculus (Mays and Sparks 1980; Munoz and Wurtz 1995; Wurtz and Goldberg 1972). The dorsolateral prefrontal cortex projects to the frontal eye field (Barbas and Mesulam 1981) and many neurons in the frontal eye field activate before saccades (Bruce and Goldberg 1985).

It has also been reported that dorsolateral prefrontal neurons project to the superior colliculus (Goldman-Rakic and Nauta 1976) and the caudate nucleus (Arikuni and Kubota 1986; Selemon and Goldman-Rakic 1985), where presaccadic activity was observed in many neurons (Hikosaka et al. 1989; Mays and Sparks 1980; Munoz and Wurtz 1995; Wurtz and Goldberg 1972). The present results show that presaccadic activity encoding the direction of the saccade is present in the prefrontal cortex. Therefore although only small numbers of prefrontal neurons encoded the direction of the saccade by presaccadic activity, this activity could affect neuronal activity in brain areas related to oculomotor controls.

On the other hand, it has been shown that most saccade-related activity observed in the prefrontal cortex is postsaccadic (Funahashi et al. 1991). However, almost all postsaccadic activities were directionally selective. Postsaccadic activity had basically the same response characteristics as presaccadic activity except that postsaccadic activity began after the initiation of the saccade. Therefore this activity is considered to be a feedback signal from oculomotor centers (Funahashi et al. 1991). The present results reveal that most of the neurons whose response-period activity encoded the direction of the saccade were postsaccadic and that the postsaccadic activity of these neurons was directionally selective. These results confirm that postsaccadic activity observed in the prefrontal cortex is a feedback signal from brain areas that are related to oculomotor controls.

Response-period activity encoding the location of the visual cue

For 35% of the neurons with directional response-period activity (n = 20), the maximum response-period activity was observed with the same cue condition in both tasks. Therefore the directional response-period activity of these neurons is thought to encode the location of the visual cue. Among these, 75% (n = 15) exhibited postsaccadic activity and 25% (n = 5) exhibited presaccadic activity.

Response-period activity has been frequently observed in prefrontal neurons. Differential responses during the response period have been observed during a spatial delayed alternation task (Kubota and Niki 1971), during spatial delayed-response tasks (Fuster 1973; Kubota and Funahashi 1982; Kubota et al. 1974; Niki 1974; Niki and Watanabe 1976), during delayed matching-to-sample tasks (Quintana et al. 1988; Rosenkilde et al. 1981), during a conditional go/no-go task (Watanabe 1986), and during visually guided lever-pressing behaviors (Sakai 1974). Because response-period activity was generated differentially depending on the response direction (e.g., left or right) or type of response (e.g., go or no-go), such activity has been considered to encode information regarding motor performance and to act as a trigger signal to initiate a behavioral response (Kubota 1978). This notion was confirmed by the observation that response-period activity was always initiated before movement (Kubota et al. 1974; Sakai 1974). However, anatomical findings have shown that there is no direct anatomical connection between the prefrontal cortex and the primary skeletonmotor and oculomotor areas (e.g., Fuster 1997). An experiment using oculomotor tasks revealed that the great majority of saccade-related activities were postsaccadic, such that phasic and directionally selective saccade-
A  ODR task

B  R-ODR task
related activity was initiated after the initiation of saccadic eye movements (Funahashi et al. 1991). Postsaccadic activity had response characteristics that were basically similar to those of presaccadic activity. Therefore this activity is considered to be a feedback signal from oculomotor centers (Funahashi et al. 1991). Goldman-Rakic et al. (1990) suggested that postsaccadic activity could act as a signal to terminate unnecessarily prolonged delay-period activity because the timing of the termination of delay-period activity coincided with the initiation of postsaccadic activity.

In the present experiment, one-third of response-period activity observed in the prefrontal cortex encoded the location of the visual cue and not the direction of the saccade. The present results show that even presaccadic activity encoded the location of the visual cue. This result suggests that not only postsaccadic activity but also presaccadic activity can act as a signal to modulate task-related activities in the prefrontal cortex. In addition, response-period activity encoding the location of the visual cue was often accompanied by directional delay-period activity encoding the location of the visual cue. The best directions for these two activities were almost identical. These results also support the notion that response-period activity may act as a signal to terminate unnecessary delay-period activity in the prefrontal cortex. Signals that are input from other cortical and subcortical structures and to modulate prefrontal activities have been considered to be crucial for explaining neuronal mechanisms of working memory processes (Funahashi 2001; Funahashi and Kubota 1994). The present
results indicate that even presaccadic activity can act as such a signal.

Population analysis of delay-period activity

The present results reveal that directional delay-period activity represents either retrospective or prospective information. Most directional delay-period activity encodes retrospective information, such as the location where the visual cue had been presented, whereas about one-third of delay-period activity encodes prospective information, such as the direction of the forthcoming saccade. These results indicate that the transformation from retrospective information (visual input) to prospective information (motor output) occurs in the prefrontal cortex during the delay period. Third, R-ODRsac activity showed more rapid increase than ODRsac activity during the delay period. Because the location of the visual cue and the direction of the saccade were the same in the ODR task, whereas the direction of the saccade was 90° clockwise from the location of the visual cue in the R-ODR task, information transformation from visual input to motor output was more crucial for correct performance in the R-ODR task than in the ODR task. Therefore the rapid development of R-ODRsac activity during the delay period might reflect the neuronal process of information transformation from visual input to motor output.

Similar temporal changes in neuronal discharge or population activity have been reported by several groups. For example, Quintana and Fuster (1999) examined prefrontal activity while monkeys performed a delayed matching-to-color task and a delayed conditional task and reported that the discharge of neurons that attuned to the cue color tended to diminish in the course of the delay, whereas the discharge of those that attuned to response directions tended to be accelerated in the course of the delay. A similar result has been reported very recently by Constantinidis et al. (2001). Although they did not examine what kind of information each delay-period activity encoded, the temporal pattern of neuronal firing that attuned to response directions was similar to the population histograms encoding the directions of saccades (ODRsac and R-ODRsac). Further, some studies using delayed matching-to-sample tasks have revealed that information represented by task-related activities in the prefrontal cortex was modulated during the time course of the tasks (Asaad et al. 2000; Hasegawa et al. 1998; Miller 1999, 2000; Rainer et al. 1999; Sawaguchi and Yamane 1999). For example, Rainer et al. (1999) examined prefrontal activity while monkeys performed delayed paired-associate tasks and showed that the neuronal activity in the prefrontal cortex primarily reflected information regarding the sample stimulus during and shortly after sample presentation. However, prefrontal neuronal activity began to reflect information regarding the anticipated target (prospective coding) toward the end of the delay. Sawaguchi and Yamane (1999) also showed similar temporal modulation of information represented by a population of prefrontal neurons.
These results indicate that although recent studies by Schlag-Rey et al. (1997) and Zhang and Barash (2000) show that the supplementary eye field and the posterior parietal area participate in sensory-motor transformation, the transformation of information from visual input to motor output occurs in the prefrontal cortex as well. The present results suggest that at the population level, neuronal activity encoding motor output gradually develops during the delay period, whereas neuronal activity encoding visual input was maintained throughout the delay period. Therefore we conclude that the transformation of information from visual input to saccade output occurs gradually in the prefrontal cortex during the delay period.

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