Neuronal Activity Throughout the Primate Mediodorsal Nucleus of the Thalamus During Oculomotor Delayed-Responses. II. Activity Encoding Visual Versus Motor Signal

Yumiko Watanabe and Shintaro Funahashi
Department of Cognitive and Behavioral Sciences, Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-8501, Japan

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Watanabe, Yumiko and Shintaro Funahashi. Neuronal activity throughout the primate mediodorsal nucleus of the thalamus during oculomotor delayed-responses. II. Activity encoding visual versus motor signal. J Neurophysiol 92: 1756–1769, 2004. First published May 12, 2004; 10.1152/jn.00995.2003. We collected single-neuron activity from the mediodorsal (MD) nucleus of the thalamus, examined the information that was represented by task-related activity during performance of a spatial working memory task, and compared the present results with those obtained in the dorsolateral prefrontal cortex (DLPFC). We used two oculomotor delayed-response (ODR) tasks. In the ordinary ODR task, monkeys were required to make a memory-guided saccade to the location where a visual cue had been presented 3 s previously, whereas in the rotary ODR task, they were required to make a memory-guided saccade 90° clockwise from the cue direction. By comparing the best directions of the same task-related activity between the two tasks, we could determine whether this activity represented the cue location or the saccade direction. All cue-period activity represented the cue location. In contrast, 56% of delay-period activity represented the cue location and 41% represented the saccade direction. Almost all response-period activity represented the saccade direction. These results indicate that task-related MD activity represents either visual or motor information, suggesting that the MD participates in sensory-to-motor information processing. However, a greater proportion of delay- and response-period activities represented the saccade direction in the MD than in the DLPFC, indicating that more MD neurons participate in prospective information processing than DLPFC neurons. These results suggest that although functional interactions between the MD and DLPFC are crucial to cognitive functions such as working memory, there is a difference in how the MD and DLPFC participate in these functions.

INTRODUCTION

The thalamic mediodorsal nucleus (MD) has close anatomical connections with the dorsolateral prefrontal cortex (DLPFC) (Giguere and Goldman-Rakic 1988; Goldman-Rakic and Porrino 1985; Kievit and Kuypers 1977; Ray and Price 1993). Damage to the medial thalamus, including the MD, often causes “prefrontal” syndromes in humans, such as deficits in the Wisconsin Card Sorting test, verbal or nonverbal fluency tests, and the Stroop test (Van der Werf et al. 2000). Lesions to the MD in monkeys produce severe deficits in the performance of memory tasks such as a delayed-response task, a delayed alternation task, and a delayed matching-to-sample task (Gaffan and Parker 2000; Isseroff et al. 1982; Parker et al. 1997; Schulman 1964; Stokes and Best 1988, 1990a,b; Winocur 1985), many of which are also impaired by DLPFC lesions (Fuster 1997; Goldman-Rakic 1987). Furthermore, neurophysiological studies using primates have revealed that many MD neurons exhibit delay-period activity during delayed-response performance (Fuster and Alexander 1973; Tanibuchi and Goldman-Rakic 2003; Watanabe and Funahashi 2004). Delay-period activity has been observed in many DLPFC neurons and is considered to be a neuronal correlate of a process for the temporary storage of working memory (Funahashi and Takeda 2002; Fuster 1997; Goldman-Rakic 1987). These results indicate close functional interactions between the MD and DLPFC and suggest that the MD also participates in cognitive processes such as working memory.

In our previous study (Watanabe and Funahashi 2004), we examined the characteristics of task-related activity observed in MD neurons while monkeys performed an oculomotor delayed-response (ODR) task. We compared these characteristics between the MD and DLPFC and found both similarities and differences. For example, the proportion of neurons with cue-period activity, the proportion of neurons with delay-period activity, and the proportion of neurons that showed directional selectivity in these activities were similar between the two structures. However, more MD neurons exhibited saccade-related activity than DLPFC neurons, and most MD neurons exhibited this activity presaccadically. These differences suggest that there is a difference in how the MD and DLPFC participate in spatial working memory processes. To further clarify the functional similarities and differences between the MD and DLPFC, it is important to identify the information represented by each task-related activity while monkeys perform spatial working memory tasks. Such studies have been performed in the DLPFC (Funahashi et al. 1993; Niki and Watanabe 1976; Takeda and Funahashi 2002). For example, Takeda and Funahashi (2002) found that cue-period activity and most delay-period activity represented retrospective (sensory) information, whereas most response-period activity represented prospective (motor) information. On the other hand, the information represented by task-related activity in the MD during ODR performance is unknown. Therefore it is important to examine these characteristics in the MD and to compare these findings with those in the DLPFC to understand
how the MD participates in cognitive processes, such as spatial working memory processes.

In the present study, we used two ODR tasks, which were used in the experiment in the DLPFC by Takeda and Funahashi (2002). In the ordinary ODR task, monkeys were required to make a memory-guided saccade to the cue location after a delay, whereas in the rotatory ODR (R-ODR) task, they were required to make a memory-guided saccade 90° clockwise from the cue direction. By comparing the directional selectivity of the same task-related activity between these two tasks, we determined whether this activity represented the cue location or the saccade direction. Preliminary results have been published in abstract form (Watanabe and Funahashi 2003).

This study was conducted as part of the Cooperation Research Program of the Primate Research Institute, Kyoto University (2000–2002).

METH O D S

The subjects, apparatus, and surgical and recording procedures used in this experiment were identical to those in our previous report (Watanabe and Funahashi 2004). Briefly, we used two rhesus monkeys (monkeys P and Q). All experiments were conducted in accordance with 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.

Behavioral tasks

Because we wished to compare the results obtained in the MD with those obtained in the DLPFC by Takeda and Funahashi (2002), we used the same two ODR tasks (ODR and R-ODR tasks) under the same behavioral conditions as were used in the DLPFC. As Takeda and Funahashi (2002) did in their DLPFC experiments, we determined whether task-related MD activity represented the location of the visual cue or the direction of the saccade by comparing the best directions of the same task-related activity between these two tasks.

ODR task

In this task, the monkey was required to make a memory-guided saccade to the location where a visual cue had been presented. The temporal sequence of this task is illustrated in Fig. 1A (top). After a 5-s intertrial interval, a fixation point (FP; a white circle, 0.5° diam in visual angle) was presented at the center of the television monitor. If the monkey continued to look at the FP for 1 s (fixation period), a visual cue (a white circle, 1° diam in visual angle) was presented for 0.5 s (cue period) at one of eight predetermined locations around the FP (Fig. 1B). The monkey was required to maintain fixation at the FP throughout the 0.5-s cue period and the 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 0.4 s (response period) to the location where the visual cue had been presented. If the monkey made a correct saccade, a drop (~0.2 ml) of water was given as a reward. To determine whether or not the monkey made a correct saccade, we set a square window (4°–7° in visual angle) around the target location and judged that the monkey had performed a correct saccade if its eye position fell within this window. If the monkey broke fixation during the cue period or delay period or failed to perform a saccade within the 0.4-s response period or if the saccade did not fall within the correct window, the trial was aborted immediately without a reward and the next trial began. The visual cue was presented randomly at one of eight predetermined peripheral locations (Fig. 1B). The eccentricity of the cue location was 17°, which was the same condition used in the DLPFC by Takeda and Funahashi (2002).

R-ODR task

In this task, the monkey was required to make a saccade 90° clockwise from the location where a visual cue had been presented. Figure 1A (bottom) shows the temporal sequence of this task. After a 5-s intertrial interval, the FP [a white plus (+) mark, 0.5° in visual angle] was presented at the center of the television monitor. If the monkey continued to look at the FP for 1 s (fixation period), a visual cue (a white circle, 1° diam in visual angle) was presented for 0.5 s (cue period) at one of four predetermined locations around the FP. The monkey was required to maintain fixation at the FP throughout the 0.5-s cue period and the 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 0.4 s (response period) to the location 90° clockwise from the direction where the visual cue had been presented. If the monkey made a correct saccade, a drop (~0.2 ml) of water was given as a reward. We used the same square window around the target location and the same criterion to determine whether or not the monkey performed a correct saccade as was used in the ODR task. The visual cue was presented randomly at one of four predetermined peripheral locations (Fig. 1B). The eccentricity of the cue location was 17°. The numbers and eccentricity of cue locations

FIG. 1. A: diagrams of 2 oculomotor-delayed response (ODR) tasks. Top: an ordinary ODR task. The monkey was required to make a saccade to the location at which a visual cue had been presented. Bottom: a rotatory ODR (R-ODR) task. The monkey was required to make a saccade 90° clockwise from the location at which a visual cue had been presented. B: arrangements of visual cue locations in both tasks. FP, fixation point. The eccentricity of the cue locations was 17°. J Neurophysiol • VOL 92 • SEPTEMBER 2004 • www.jn.org
were the same as those used in the DLPFC by Takeda and Funahashi (2002).

Analyzing single-neuron activity

We used an epoxy-coated tungsten microelectrode to record single-neuron activity from the MD. We first visually inspected whether or not the recorded neuron exhibited task-related activity in relation to any task events by looking at rasters and histograms aligned at several task events. To confirm our observations, we then conducted a statistical analysis. First, to obtain the neuron's baseline discharge rate, we calculated the mean discharge rate during the last 500 ms of the fixation period for each cue condition. For cue-period activity, we calculated the mean discharge rate during the 300 ms period (from 50 to 350 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 baseline discharge rate by the Mann-Whitney U test (P < 0.05), we considered that this neuron exhibited cue-period activity. For delay-period activity, we calculated the mean discharge rate during the 3-s delay period for each cue condition. If the mean discharge rate during the delay period differed significantly from the baseline discharge rate by the Mann-Whitney U test (P < 0.05), we considered that the neuron exhibited delay-period activity. Similarly, for response-period activity, we calculated the mean discharge rate during the 300 ms response period (150 ms before and after the period when peak activity was observed) for each cue condition. If the mean discharge rate during this response period differed significantly from the baseline discharge rate by the Mann-Whitney U test (P < 0.05), we considered that the neuron exhibited response-period activity. In addition, we classified response-period activity into two groups (pre- or postsaccadic) based on whether or not the initiation of response-period activity preceded the initiation of saccadic eye movements by aligning this activity at saccadic initiation.

Identification of information represented by task-related activity

Using the same criteria that were used by Takeda and Funahashi (2002), we determined whether task-related activity represented the location of the visual cue or the direction of the saccade. We first constructed tuning curves of task-related activity under the two task conditions. To examine whether task-related activity exhibited directional selectivity, we examined differences in the mean discharge rates across all cue conditions for each task-related activity by one-way ANOVA. We considered that task-related activity had directional selectivity if there were significant differences in the mean discharge rates across all cue conditions (P < 0.05). For neurons that exhibited directionally selective activity, we constructed tuning curves to determine the best direction of task-related activity. Tuning curves were constructed using the mean discharge rates of task-related activity for all cue conditions by their best fit to the Gaussian function

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

where \( f(d) \) is the discharge rate as a function of \( d \), which is the visual cue location. The constants can be interpreted as follows: \( B \) is the baseline discharge rate, \( R \) is the discharge rate above the baseline at the best direction, \( D \) represents the best direction, and \( Td \) is an index of the tuning width. From these tuning curves, we obtained the best direction of task-related activity in the ODR task (\( D_{ODR} \)) and the best direction of the same activity in the R-ODR task (\( D_{R-ODR} \)).

In this study, we used the location of the visual cue to describe trial conditions in both tasks and directional preferences of task-related activity. Therefore we use the term “cue condition” to describe the trial condition in the ODR and R-ODR tasks. For example, the 0° cue condition indicates a trial in which the visual cue was presented at the 0° location in both tasks. In the 0° cue condition, the direction of the saccade was 0° in the ODR task but 270° in the R-ODR task.

To determine whether task-related activity represented the location of the visual cue or the direction of the saccade, we compared \( D_{ODR} \) and \( D_{R-ODR} \) for the same task-related activity. 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 difference between the best directions in the two tasks (\( D_{R-ODR} - D_{ODR} \)) was <45°, we considered that this task-related activity represented the location of the visual cue. On the other hand, if this difference (\( D_{R-ODR} - D_{ODR} \)) was >45° and <135°, we considered that this task-related activity represented the direction of the saccade. For some neurons, this difference (\( D_{R-ODR} - D_{ODR} \)) was >135°. In these neurons, we could not determine whether this activity represented the location of the visual cue or the direction of the saccade for these neurons. Therefore we excluded these neurons from the analysis.

RESULTS

Neural database

We recorded the activities of 238 neurons from the MD in two monkeys (monkey \( P, n = 201; \) monkey \( Q, n = 37; \) Table 1). The methods used for histological identification of the recorded neurons have been described previously (Watanabe and Funahashi 2004). Among the 238 neurons, 153 were recorded in both tasks. Of these, 120 exhibited task-related activity in relation to at least one task event, 98 exhibited task-related activity during the same task event in both tasks, and the remaining 22 exhibited task-related activity only in the ODR task (\( n = 17 \)) or only in the R-ODR task (\( n = 5 \)). In the present study, because we tried to understand the information that was represented by each task-related activity during ODR performance, we needed to compare the best directions of the same task-related activity between the ODR and R-ODR tasks in the same neuron. Therefore we analyzed 98 neurons that exhibited directional task-related activity in the same task event in both tasks in detail.

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>37</td>
<td>27</td>
</tr>
<tr>
<td>Directional</td>
<td>37</td>
<td>24</td>
</tr>
<tr>
<td>Omni-directional</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Delay-period activity</td>
<td>75</td>
<td>56</td>
</tr>
<tr>
<td>Directional</td>
<td>57</td>
<td>39</td>
</tr>
<tr>
<td>Omni-directional</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Response-period activity</td>
<td>118</td>
<td>94</td>
</tr>
<tr>
<td>Pre-saccadic activity</td>
<td>87</td>
<td>77</td>
</tr>
<tr>
<td>Directional</td>
<td>68</td>
<td>66</td>
</tr>
<tr>
<td>Omni-directional</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Post-saccadic activity</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>Directional</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Omni-directional</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>No task-related activity</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>Total</td>
<td>210</td>
<td>181</td>
</tr>
</tbody>
</table>

Because many neurons exhibited task-related activity for more than one task event, the sum of the number of neurons with each task-related activity exceeds the total number of neurons. ODR, oculomotor-delayed response; R-ODR, rotary ODR.
Comparison of baseline discharge rates between the ODR and R-ODR tasks

Because rule-dependent activity has been observed in the DLPFC (Wallis and Miller 2003; White and Wise 1999), one might expect that similar modulation depending on a behavioral rule can be observed in MD neurons. Therefore to test whether the difference between the tasks affected the baseline discharge rates of MD neurons, we first compared the baseline discharge rates in the ODR and R-ODR tasks. We used the mean discharge rates during the last 500 ms of the fixation period as baseline discharge rates because the monkey’s behavior was exactly the same during this period in these two tasks. Figure 2 shows a scattergram using baseline discharge rates of 153 neurons recorded in both tasks. The baseline discharge rates in both tasks were significantly correlated. The correlation coefficient was 0.93. The mean discharge rate was 13.1 + 12 spikes/s for the ODR task and 13.3 + 13 spikes/s for the R-ODR task. These values were not significantly different (Wilcoxon signed-rank test, P > 0.1). Therefore these results indicate that there was no task-dependent difference in the baseline discharge rates.

Cue-period activity

Twenty-two MD neurons exhibited cue-period activity in both tasks. Among these, 19 exhibited directional cue-period activity in both tasks and the remaining 3 exhibited directional activity in one task and omni-directional activity in the other task. Figure 3 shows an example of directional cue-period activity. In the ODR task, this neuron exhibited significant cue-period activity when visual cues were presented in the left visual field (90°, z = -1.99, P < 0.05; 135°, z = -3.38, P < 0.001; 180°, z = -3.76, P < 0.001; Fig. 3A). In the R-ODR task, significant cue-period activity was also observed when the visual cues were presented at the 180° location (z = -3.50, P < 0.001; Fig. 3B). The best direction based on the tuning curve was 159.7° in the ODR task and 143.8° in the R-ODR task. The difference between the best directions was only 15.9°. Because the directions of saccades in the same cue condition were different in these two tasks, these results indicate that this neuron’s directional cue-period activity represents the location of the visual cue.

Figure 4 shows tuning curves of two other neurons that exhibited directional cue-period activity. For neuron P178 (Fig. 4A), the best direction of cue-period activity was 170.8° in the ODR task and 167.9° in the R-ODR task. For neuron P044 (Fig. 4B), the best direction was 194.1° in the ODR task and 187.0° in the R-ODR task. For both neurons, the best directions of cue-period activity were almost identical in the two tasks. Figure 10A shows the distribution of the differences in the best directions between the two tasks (D_{R-ODR} - D_{ODR}) for all neurons that exhibited directional cue-period activity. These differences were distributed between −45 and 45°. The mean difference in the best directions was 2.8 ± 17.9° (mean ± SD). Therefore these results indicate that directional cue-period activity represents the location of the visual cue for all recorded MD neurons that exhibited this activity.

Delay-period activity

Forty-three MD neurons exhibited delay-period activity in both tasks. Among these, 27 (62%) exhibited directional delay-period activity in both tasks. For these 27 neurons, we compared the best directions of delay-period activity between the two tasks. One neuron was excluded from this analysis because the best direction in the R-ODR task was >135° counterclockwise from the best direction in the ODR task. We found that directional delay-period activity can be classified into two groups: one that represents the location of the visual cue and another that represents the direction of the saccade.

Among the 26 neurons analyzed, 15 (58%) had delay-period activity that represented the location of the visual cue. Figure 5 illustrates an example of this activity. In the ODR task, this neuron exhibited significant delay-period activity when visual cues were presented in the left visual field (90°, z = -2.31, P < 0.05; 135°, z = -3.04, P < 0.005; 180°, z = -3.06, P < 0.005; 225°, z = -2.96, P < 0.005; Fig. 5A). In the R-ODR task, significant delay-period activity was observed when visual cues were presented at the 180° location (z = -3.19, P < 0.005; Fig. 5B). The best direction was 169.9° in the ODR task and 143.5° in the R-ODR task. The difference was only 26.4°. Because the directions of the saccades in the same cue condition were different in these two tasks, these results indicate that this neuron’s directional delay-period activity represents the location of the visual cue.

On the other hand, 11 neurons (42%) had delay-period activity that represented the direction of saccadic eye movements. Figure 6 shows an example of this activity. In the ODR task, this neuron exhibited significant delay-period activity when visual cues were presented in the left visual field (135°, z = -2.89, P < 0.005; 180°, z = -2.57, P < 0.05; 225°, z = -2.01, P < 0.05; Fig. 6A). In the R-ODR task, significant delay-period activity was observed...
mainly when visual cues were presented in the lower visual field (270°, z = −2.27, P < 0.05; Fig. 6B). The best direction based on the tuning curve was 156.4° in the ODR task, and 240.5° in the R-ODR task (Fig. 7B). The difference between these two directions was 84.1°. Because the directions of the saccades in the same cue condition in these two tasks differed by 90°, these results indicate that directional delay-period activity of this neuron represents the direction of the saccade. Figure 7C shows a tuning curve for a different MD neuron’s delay-period activity. The difference between the best direction in these two tasks was 85° (217.4° in the ODR task and 302.4° in the R-ODR task). Therefore the results also indicate that this neuron’s delay-period activity represents the direction of the saccade.

Figure 10B shows the distribution of the differences in best directions between the two tasks. The differences in the best directions (D_{R-ODR} − D_{ODR}) were distributed between −45 and 135°. In 15 neurons, the differences between the best directions were distributed between −45 and 45°, indicating that these neurons’ delay-period activity represents the location of the visual cue. However, in 11 neurons, the differences in the best directions were >45°, indicating that the delay-period activity of these neurons represents the direction of the saccade. Therefore we could conclude that for about half of the

FIG. 3. Directional cue-period activity encoding the location of the visual cue. The center diagram shows a polar plot of the magnitude of cue-period activity where the average discharge rate is depicted as the radial eccentricity in that direction. The arrow indicates the best direction of the activity. The baseline discharge rates are shown as dotted lines. Asterisks indicate cue conditions with statistically significant cue-period activity. A: activity during ODR performance. Significant cue-period activity was present in 90, 135, and 180° trials. B: activity during R-ODR performance. Significant cue-period activity was present for the 180° location. Delay length was 3 s. Histogram bin width was 30 ms. C, cue period; D, delay period; R, response period.
MD neurons with directional delay-period activity, such activity represents the location of the visual cue, whereas in the other half such activity represents the direction of the saccade.

**Response-period activity**

Of the 98 MD neurons with task-related activity, 78 (80%) exhibited response-period activity in both tasks. For the 53 neurons that exhibited directional response-period activity in both tasks (51 had presaccadic activity and 2 had only postsaccadic activity), we compared the best directions of response-period activity between the two tasks. One neuron with presaccadic activity was excluded from this analysis because the best direction in the R-ODR task was >135° counterclockwise from the best direction in the ODR task. We found that almost all directional response-period activity (50 presaccadic activity and 1 postsaccadic activity) represented the direction of the saccade and that only one postsaccadic activity represented the location of the visual cue.

Among the 52 neurons examined, 51 (98%) showed response-period activity that represented the direction of the saccade. Figure 8 shows an example of this activity. In the ODR task, this neuron exhibited significant response-period activity when visual cues were presented in the left visual field (90°, z = -2.88, P < 0.005; 135°, z = -3.89, P < 0.001; 180°, z = -3.82, P < 0.001; 225°, z = -3.73, P < 0.001; 270°, z = -2.87, P < 0.005; 315°, z = -2.15, P < 0.05; Fig. 8A). In the R-ODR task, the maximum response-period activity was observed when visual cues were presented at the 270° direction (z = -2.84, P < 0.005; Fig. 8B), although significant response-period activity was observed for all cue conditions. The best direction based on tuning curves (Fig. 9A) was 183.4° in the ODR task and 265.8° in the R-ODR task. The difference between the best directions was 82.4°. Because the directions of the saccades in the same cue condition differed by 90° in these two tasks, these results indicate that this neuron’s directional response-period activity represents the direction of the saccade. Figure 9, B and C, shows two other examples of response-period activity. For neuron P257, the best direction was 266.8° in the ODR task and 359.3° in the R-ODR task (Fig. 9B), and for neuron P307, it was 322.3° in the ODR task and 50.8° in the R-ODR task (Fig. 9C). The difference between the best directions was 92.5° for neuron P257 and 88.5° for neuron P307. These results indicate that directional response-period activity of these neurons also represents the direction of the saccade. Figure 10C shows the distribution of differences in best directions for directional response-period activity between the two tasks. The differences in the best directions (D<sub>R-ODR</sub> - D<sub>ODR</sub>) were distributed between 45 and 135° in almost all neurons with directional response-period activity. Therefore we conclude that almost all response-period activity observed in the MD represents the direction of the saccade.

**Comparison of information represented by delay-period activity and other task-related activity**

Among 27 neurons with directional delay-period activity in both tasks, 23 (85%) also exhibited task-related activity in relation to other task events; 1 had cue-period activity, 9 had response-period activity, and 13 had both cue- and response-period activity. To understand the functional relationships between delay-period activity and other task-related activities, we compared the information represented by the activity for a single neuron’s different task-related activities. Fourteen neurons had both cue- and delay-period activity. As we described previously, all cue-period activity represented the location of the visual cue. In 10 neurons (71%), delay-period activity also represented the location of the visual cue. One possible explanation for these results is that most delay-period activity may be a continuation of cue-period activity in MD neurons with both activities. Another possibility is that visuospatial input from a single source causes both cue- and delay-period activities in these neurons. On the other hand, in four neurons (29%), delay-period activity represented the direction of the saccade. Because sensory-to-motor information processing is necessary to perform both ODR and R-ODR tasks, this result suggests that these neurons participate in this information processing.

Among 22 MD neurons with both delay- and response-period activity, the delay-period activity of 14 neurons (64%) represented the location of the visual cue, whereas the delay-period activity of 8 neurons (36%) represented the direction of the saccade. Because almost all response-period activity represented the direction of the saccade, these results indicate that delay-period activity is functionally independent of response-period activity, suggesting that delay-period activity and response-period activity are independently affected by inputs from different structures; e.g., delay-period activity in the MD may be affected mainly by inputs from the DLPFC, whereas response-period activity may be affected mainly by inputs from the superior colliculus, the frontal eye field, or the substantia nigra pars reticulata.
Comparison of the temporal patterns of delay-period activity representing different information

Takeda and Funahashi (2002) constructed population-averaged histograms using a population of delay-period activity representing different information in DLPFC neurons and compared the temporal patterns of these histograms. They found that delay-period activity that represented the location of the visual cue showed tonically sustained activation during the delay period, whereas delay-period activity that represented the direction of the saccade showed gradually increasing activation during the delay period. To compare the temporal patterns of delay-period activity between DLPFC and MD neurons, we constructed population-averaged histograms using a population of delay-period activity that represented the location of the visual cue (n = 15) and a population of delay-period activity that represented the direction of the saccade (n = 11; Fig. 11). To construct population-averaged histograms, delay-period activity in the cue condition for which maximum delay-period activity was observed was sampled from the database. Similar to delay-period activity observed in the DLPFC (Takeda and Funahashi 2002), delay-period activity that represented the location of the visual cue showed tonic sustained excitation during the delay-period in both the ODR and R-ODR tasks. Delay-period activity that represented the direction of the

Fig. 5. Directional delay-period activity encoding the location of the visual cue. A: activity during ODR performance. Significant delay-period activity was present in 90, 135, 180°, and 225° trials. B: activity during R-ODR performance. Significant delay-period activity was present in the 180° trial. The delay length was 3 s. Histogram bin width was 30 ms.

J Neurophysiol • VOL 92 • SEPTEMBER 2004 • www.jn.org
FIG. 6. Directional delay-period activity encoding the direction of the saccade. A: activity during ODR performance. Significant delay-period activity was present in the 135, 180, 225, and 270 trials. B: activity during R-ODR performance. Significant delay-period activity was present in the 0 and 270° trials. Delay length was 3 s. Histogram bin width was 30 ms.

FIG. 7. Comparison of tuning curves of delay-period activity between the ODR (---) and R-ODR tasks (----). A: neuron P189: the best direction was 272.3° in the ODR task and 257.3° in the R-ODR task. B: neuron P266: the best direction was 156.4° in the ODR task and 240.5° in the R-ODR task. C: neuron P096: the best direction was 217.4° in the ODR task and 302.4° in the R-ODR task.
FIG. 8. Directional response-period activity encoding the direction of the saccade. A: activity during ODR performance. Significant response-period activity was present in 90, 135, 180, 225, 270, and 315° trials. B: activity during R-ODR performance. The maximum response-period activity was present in 270° trials. The delay length was 3 s, and the histogram bin width was 30 ms.

FIG. 9. Comparison of tuning curves of response-period activity between the ODR (—) and R-ODR tasks (— —). A: neuron Q063: the best direction was 183.4° in the ODR task and 265.8° in the R-ODR task. B: neuron P257: the best direction was 266.8° in the ODR task and 359.3° in the R-ODR task. C: neuron P307: the best direction was 322.3° in the ODR task and 50.8° in the R-ODR task.
saccade showed tonic sustained activation during the delay period in the ODR task but gradually increasing activation during the delay period in the R-ODR task (15 spikes/s at the beginning of the delay period and 21 spikes/s at the end of the delay period). In addition, the degree of the increase in the R-ODR task was similar between MD neurons and DLPFC neurons (12 spikes/s at the beginning of the delay period and 22 spikes/s at the end of the delay period) (Takeda and Funahashi 2002).

**DISCUSSION**

In the present study, we examined the information that was represented by task-related activity in MD neurons by comparing the best direction of this activity between two oculomotor delayed-response tasks (ODR and R-ODR tasks). We found that all cue-period activity represented the location of the visual cue, 56% of directional delay-period activity represented the location of the visual cue, whereas 41% represented the direction of the saccade, and almost all directional response-period activity (98%) represented the direction of the saccade. These results indicate that task-related activity observed in MD neurons represents either visual (retrospective) or motor (prospective) information during spatial working memory performance and suggest that the MD participates in sensory-to-motor information processing in relation to spatial working memory tasks.

**FIG. 10.** Distribution of the differences between the best directions in the ODR and R-ODR tasks \((D_{\text{R-ODR}} - D_{\text{ODR}})\) for each task-related activity. \(A\): cue-period activity, \(B\): delay-period activity, \(C\): response-period activity. ■ and □, presaccadic activity and postsaccadic activity, respectively.

**FIG. 11.** Population histograms constructed using a population of delay-period activity that encoded either the location of the visual cue (ODRcue and R-ODRcue) or the direction of the saccade (ODRsac and R-ODRsac) in each task.
Cue-period activity represents the location of the visual cue

Visual responses in MD neurons have been observed in previous studies (Fuster and Alexander 1973; Tanibuchi and Goldman-Rakic 2003; Watanabe and Funahashi 2004). Fuster and Alexander (1973) collected 159 single-neuron activities from the MD and found that 26% of these had excitatory visual responses. Tanibuchi and Goldman-Rakic (2003) showed that MD neurons responded exclusively to pictures of human faces or natural objects. Wyder et al. (2003) and Sommer and Wurtz (2004) examined the characteristics of visual responses in the oculomotor thalamus (including the lateral border of the MD) and the lateral part of the MD during oculomotor performance, respectively. These results indicate that the MD contains neurons that respond to visual stimuli, and their response characteristics are similar to those observed in the DLPFC. Watanabe and Funahashi (2004) examined cue-period activity while monkeys performed the ODR task and compared the characteristics of this activity between the MD and DLPFC. They found a strong similarity in the directional preference and tuning characteristics of cue-period activity between the MD and DLPFC. In the present experiment, we compared the best directions of cue-period activity between the ODR and R-ODR tasks. In trials under the same cue conditions, although visual cues were presented in the same location, the directions of the saccades were different in these tasks. Therefore we could determine whether cue-period activity represented the location of the visual cue or the direction of the saccade by comparing the best directions between the two task conditions. As a result, for all MD neurons with directional cue-period activity, the best directions obtained from tuning curves were almost identical for the two tasks. Therefore all directional cue-period activities observed in MD neurons are considered to represent the location of the visual cue (retrospective information). Takeda and Funahashi (2002) performed the same analysis in DLPFC neurons and found that all directional cue-period activity represented the location of the visual cue. As shown in Fig. 12, the present results in the MD agree with those in the DLPFC. Because dense reciprocal connections are present between the MD and DLPFC (Giguere and Goldman-Rakic 1988; Goldman-Rakic and Porrino 1985; Kievit and Kuypers 1977; Ray and Price 1993), the similarity in characteristics of cue-period activity between the MD and DLPFC indicates strong functional interactions between these two structures through their anatomical connections. However, inputs from the superior colliculus and the substantia nigra may also affect cue-period activity in the MD.

Delay-period activity represents either the location of the visual cue or the direction of the saccade

Neurophysiological studies using spatial working memory tasks such as delayed-response tasks have revealed that many DLPFC neurons show delay-period activity. The characteristics of delay-period activity have been described in detail (e.g., see a review by Funahashi and Takeda 2002). Directional delay-period activity observed in the DLPFC is a sustained activation during the delay period when the visual cues are presented within the neuron’s memory field. This activity is observed when the subject performs a correct response. Therefore directional delay-period activity observed in the DLPFC has been considered to be the neural correlate of a mechanism for the temporary storage of information (Funahashi and Kubota 1994; Fuster 1997; Goldman-Rakic 1987; Takeda and Funahashi 2002). In our previous study (Watanabe and Funahashi 2004), we found that the characteristics of directional delay-period activity observed in the MD were similar to those in the DLPFC. Therefore directional delay-period activity observed in the MD can also be considered a neuronal activity related to a mechanism for the temporary storage of information.

By comparing the directional selectivity of delay-period activity observed in the same MD neuron between the ODR and R-ODR tasks, directional delay-period activity can be classified into two groups according to the information it represents. In one group (56%), delay-period activity represents the location of the visual cue (retrospective information), whereas in the other group (41%), delay-period activity represents the direction of the saccade (prospective information). Thus these results show that MD neurons can retain either retrospective or prospective information during the delay period as directional delay-period activity and that the proportion of delay-period activity that represents retrospective information is similar to the proportion of delay-period activity that represents prospective information in the MD.

The same analysis has been performed in the DLPFC by Takeda and Funahashi (2002) using the same ODR and R-ODR tasks. As shown in Fig. 12, they found that 86% of directional delay-period activity represented the location of the visual cue, whereas only 13% represented the direction of the saccade in DLPFC neurons. The fact that most delay-period activity in the DLPFC during spatial delayed-response performance represented the location of the visual cue was also noted by Niki and Watanabe (1976) and Funahashi et al. (1993). For example, Niki and Watanabe (1976) examined delay-period activity of the same neuron under three different task condi-
nearly all of the neurons with response-period activity showed a delay-period activity represented the location of the visual cue, whereas 22% represented the direction of the response. Funahashi et al. (1993) also examined the same neuron’s delay-period activity in a delayed pro-saccade task and a delayed anti-saccade task and found that 70% of directional delay-period activity represented the location of the visual cue, whereas 30% represented the direction of the saccade. Furthermore, in tasks that require nonspatial information processing such as a delayed matching-to-sample task and a delayed paired associate task, more delay-period activity in the DLPFC has been shown to represent retrospective information such as the sample stimuli, although delay-period activity can represent either retrospective or prospective information (Quintana and Fuster 1999; Rainer and Miller 2002; Rainer et al. 1999). These results indicate that, in general, more DLPFC neurons retain retrospective information such as sample or cue stimuli than prospective information as such as response directions. As shown in Fig. 12, the results obtained in the DLPFC differ from those obtained in the MD in that the proportion of delay-period activity in the MD that represented prospective information was similar to the proportion of delay-period activity that represented prospective information. These results indicate that although both MD and DLPFC neurons participate in either retro- or prospective information processing, a greater percentage of MD neurons participate in prospective information processing. Therefore although the MD and DLPFC have strong reciprocal connections (Giguere and Goldman-Rakic 1988; Goldman-Rakic and Porrino 1985; Kievit and Kuypers 1977; Ray and Price 1993), these results suggest that information processing that occurs in the MD is not the same as that in the DLPFC.

Most response-period activity represents the direction of the saccade

In the present study, the best direction in the ODR task was observed at -90° clockwise from the best direction in the R-ODR task for almost all (98%) MD neurons with response-period activity. Because the direction of the saccade was 90° clockwise from the direction of the visual cue in the R-ODR task, these directional response-period activities are considered to represent the direction of the saccade. In the MD, 84% of neurons with task-related activity exhibited response-period activity, and most (74%) of these neurons showed presaccadic activity. In addition, because most (74%) of the neurons with postsaccadic activity showed short-directional selectivity (Watanabe and Funahashi 2004), almost all neurons with directional selectivity were classified as having presaccadic activity. Thus in the MD, most of the neurons with directional selectivity showed presaccadic activity, and the presaccadic activity of these neurons represented information regarding the direction of the saccade.

As shown in Fig. 12, the present results in the MD are in sharp contrast to those obtained in the DLPFC. In the DLPFC, nearly all of the neurons with response-period activity showed directional selectivity, but most (78%) of this was postsaccadic (Funahashi et al. 1991). Takeda and Funahashi (2002) reported that 58% of directional response-period activity in the DLPFC represented the direction of the saccade, whereas 35% represented the location of the visual cue (Fig. 12, bottom right). In addition, they showed that a large proportion of postsaccadic activity represented the location of the visual cue, whereas presaccadic activity often represented the direction of the saccade. In the DLPFC, many postsaccadic activities and even presaccadic activities represented the location of the visual cue. Therefore Takeda and Funahashi (2002) suggested that both postsaccadic activity and presaccadic activity each function not as a signal to control saccadic eye movements but also as a signal to modulate task-related activities in the DLPFC. In contrast, most MD neurons with directional response-period activity showed presaccadic activity, and such presaccadic activity of these MD neurons represented information regarding the direction of the saccade. Therefore presaccadic activity observed in MD neurons apparently functions as a signal to control saccadic eye movements. Thus although both the MD and DLPFC participate in cognitive processes such as working memory processes, the role of the MD in these processes is different from that of the DLPFC.

Twenty-two MD neurons exhibited both directional delay- and directional response-period activity. Directional response-period activity represented the direction of the saccade. However, in these neurons, 36% of delay-period activity represented the direction of the saccade and 64% represented the location of the visual cue. In addition, we compared the best directions for delay- and response-period activities in MD neurons with both activities and found that there are two populations of MD neurons; in one group, the best directions in the two activities were similar and in the other, the best directions in the two activities were opposite (Watanabe and Funahashi 2004). These results indicate that most delay-period activity is functionally independent of response-period activity. Delay-period activity and response-period activity might be affected independently by inputs from different sources; e.g., delay-period activity might be affected by inputs from the DLPFC, whereas response-period activity might be affected by inputs from the superior colliculus, the frontal eye field, or the substantia nigra pars reticulata.

Information processing in the MD

Population-averaged histograms constructed using a population of delay-period activity that represented the location of the visual cue showed tonic sustained activation during the delay period in both the ODR and R-ODR tasks. The same histograms constructed using a population of delay-period activity that represented the direction of the saccade showed tonic sustained activation during the delay period in the ODR task, but showed gradually increasing activation in the R-ODR task. In the DLPFC (Takeda and Funahashi 2002), similar temporal patterns were observed in population-averaged histograms constructed using a population of delay-period activity that represented the location of the visual cue. However, the histograms constructed using delay-period activity that represented the direction of the saccade showed gradually increasing activation in both the ODR and R-ODR tasks. The difference in the temporal pattern of population-averaged histograms between the MD and DLPFC may be due to our method for sampling MD activities. In the present study, we collected neuronal activity throughout the entire MD, whereas Takeda

J Neurophysiol • VOL. 92 • SEPTEMBER 2004 • www.jn.org
and Funahashi (2002) collected neuronal activity only from the DLPFC, which has anatomical connections with only a limited region of the MD (the parvocellular area of the MD). However, gradually increasing activation was clearly observed in the MD during the delay period in the R-ODR task. The increase in delay-period activity in the DLPFC in the R-ODR task was greater than that in the ODR task. Therefore at the population level, neuronal activity that represents retrospective information shows sustained activation during the delay period, whereas neuronal activity that represents prospective information develops gradually during the delay period. Constantinidis et al. (2001) reported similar temporal patterns in delay-period activity that represented retro- or prospective information in DLPFC neurons. In addition, Quintana and Fuster (1999) showed that the discharge of prefrontal neurons attuned to response directions tended to accelerate during the delay. These results indicate that, in general, neuronal activity that represents prospective information develops gradually during the delay period. However, neuronal activity that represents retrospective information tends either to be maintained during the delay period, as seen in the MD and DLPFC (Constantinidis et al. 2001; Takeda and Funahashi 2002), or gradually diminishes during the delay period, as seen in the DLPFC (Quintana and Fuster 1999; Rainer and Miller 2002).

In the MD, gradually increasing activation was observed in population-averaged histograms that represented the direction of the saccade only during the R-ODR task. In the ODR task, the location of the visual cue and the direction of the saccade are the same, whereas in the ODR task the direction of the saccade is 90° clockwise from the direction of the visual cue. Therefore information processes from visual input to motor output are more significant for correct performance in the delay-period activity in the MD. The authors also thank Drs. M. Kimura and N. Matsumoto for providing valuable advice on recording neuronal activity from the thalamus.

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