Neuronal Activity Throughout the Primate Mediodorsal Nucleus of the Thalamus During Oculomotor Delayed-Responses. I. Cue-, Delay-, and Response-Period Activity

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. I. Cue-, delay-, and response-period activity. J Neurophysiol 92: 1738–1755, 2004. First published May 12, 2004; 10.1152/jn.00994.2003. The thalamic mediodorsal nucleus (MD) has strong reciprocal connections with the dorsolateral prefrontal cortex (DLPFC), suggesting that the MD, like the DLPFC, participates in higher cognitive functions. To examine MD’s participation in cognitive functions, we analyzed the characteristics of task-related activities sampled homogeneously from the MD while two monkeys performed a spatial working memory task using oculomotor responses. Of 141 task-related MD neurons, 26, 53, and 84% exhibited cue-, delay-, and response-period activity, respectively. Most of cue- and response-period activities showed phasic excitation, and most of delay-period activity showed tonic sustained activation. Among neurons with response-period activity, 74% exhibited presaccadic activity. Of 173 neurons with cue-period and presaccadic activities were directional, whereas most postsaccadic activity was omni-directional. A significant contralateral bias in the best directions was present in cue-period and presaccadic activity. However, such bias was not present in delay-period activity, although most neurons had a best direction toward the contralateral visual field. We compared these characteristics with those observed in DLPFC neurons. Response-period activity was more frequently observed in the MD (84%) than in the DLPFC (56%). The directional selectivity and bias of task-related activities and the ratios of pre- and postsaccadic activities were different between MD and DLPFC. These results indicate that the MD participates in higher cognitive functions such as spatial working memory. However, the manner in which these two structures participate in these processes differs, in that the MD participates more in motor control aspects compared with the DLPFC.

INTRODUCTION

The thalamic mediodorsal nucleus (MD) is a major source of efferents to the prefrontal cortex and is a major target of efferents from the prefrontal cortex (Giguere and Goldman-Rakic 1988; Goldman-Rakic and Porrino 1985; Kievit and Kuypers 1977; Rouiller et al. 1999). The MD is also a key structure in the cortico-basal ganglia-thalamo-cortical loop that originates from and terminates in the prefrontal cortex (Alexander et al. 1986). The thalamus is often considered a variable gate that regulates the flow of information to the cerebral cortex. However, the fact that the MD receives direct prefrontal efferents and inputs from the basal ganglia and limbic structures suggests that the MD not only plays a role in the gating function of the information flow to the cerebral cortex but also plays an important role in cognitive processes.

Several lines of evidence from lesion and recording studies further indicate that the MD plays a cognitive role. In humans, it is widely known that damage to the medial thalamus, including the MD, causes symptoms of dysexecutive or “prefrontal” syndromes, alone or in combination with amnesia (Van der Werf et al. 2000). Recent imaging studies in humans have shown MD activation in delayed matching- or non-matching-to-sample tasks (de Zubicaray et al. 2001; Elliott and Dolan 1999) and in Wisconsin card-sorting performance (Monchi et al. 2001). Lesions to the MD in monkeys have been shown to produce severe deficits in the performance of cognitive tasks, including delayed matching-to-sample tasks (Parker et al. 1997), scene memory and object-reward association tasks (Gaffan and Parker 2000), and delayed-response tasks (Isseroff et al. 1982). In addition, neurophysiological studies have shown that monkey MD neurons exhibit sustained activation during the delay period while the monkey performs delayed-response tasks (Fuster and Alexander 1971, 1973; Tanibuchi and Goldman-Rakic 2003), suggesting that the MD participates in spatial working memory processes. Recently Tanibuchi and Goldman-Rakic (2003) reported neurons that exhibited spatially selective activity in the MD while monkeys performed an oculomotor delayed-response (ODR) task. These results indicate that the MD is an important structure for understanding the neural mechanisms of many cognitive functions, including working memory.

Behavioral and neurophysiological properties of the prefrontal cortex have been extensively examined using a variety of behavioral tasks in monkeys (see reviews by Fuster 1997; Stuss and Knight 2001). However, little is known about the physiological and behavioral properties of the MD. Recently, several neurophysiological studies in the MD using oculomotor tasks have been published (Sommer and Wurtz 2004; Tanibuchi and Goldman-Rakic 2003; Wyder et al. 2003, 2004). However, these studies only examined a restricted part of the MD. For example, Tanibuchi and Goldman-Rakic (2003) made patchy and clustered penetrations mainly in the lateral part of the MD. Wyder et al. (2003, 2004) focused on the functions of the oculomotor thalamus and examined neurons only at the lateral edge of the MD. Sommer and Wurtz (2004) examined only...
identified relay neurons in the MD that transmit information from the superior colliculus to the frontal eye field. In contrast to these studies, we sought to sample homogeneously across the MD, compare neuronal activity quantitatively between the MD and the dorsolateral prefrontal cortex (DLPFC), and determine the similarities and differences between the properties of these two structures. The functional characteristics of task-related activity recorded from the DLPFC have been fully analyzed while monkeys performed the ODR task (Funahashi et al. 1989–1991, 1993; Takeda and Funahashi 2002). Therefore in the present experiment, we used the ODR task to examine MD activity and compared the characteristics of task-related MD activity to those obtained from the DLPFC. A part of this experiment was published in abstract form (Watanabe and Funahashi 2000; Watanabe et al. 2000).

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METHODS

Subjects and apparatus

Two rhesus monkeys (monkey P, 4.0 kg; monkey Q, 3.5 kg) were used in this experiment. Each monkey was housed individually in a home cage. Water intake was restricted in their home cages. However, their daily requirement of water was given in the laboratory as a reward. In addition, fruit and vegetables were given in their home cages. To ensure that each monkey stayed in good physical condition, we measured each monkey’s body weight and water intake daily. During training and recording sessions, the monkey sat quietly in a primate chair in a dark sound-attenuated room, and its head movement was restricted painlessly by a stainless steel rod fixed to the skull. The monkey faced a 21-in color TV monitor (PC-TV471, NEC, Japan) on which a fixation point and visual cues were presented. The TV 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-486HX, Epson) controlled the monkey’s behavior, presented visual stimuli on the monitor, recorded neuronal activity, and monitored eye movements. 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 at the Faculty of Integrated Human Studies, Kyoto University.

Surgical procedure

We first performed surgery under aseptic conditions to implant an eye coil for monitoring eye movements and a stainless steel rod for restricting the monkey’s head movements during the experiments. The monkeys were anesthetized by pentobarbital sodium (25 mg/kg). The eye coil was implanted in one eye using the technique described by Judge et al. (1980). To painlessly prevent the monkey from moving its head during the experiment, a rod made of stainless steel was fixed to the skull. To reinforce the fixation of the rod, stainless steel bolts were used. The connector for the eye coil, the rod, and the stainless steel bolts were fixed to the skull with dental acrylic. After the monkey fully recovered from the surgery, we began the monkey’s training.

After the correct performance rate in the ODR task exceeded 80% for 1 wk, we performed a second surgery to fix a recording cylinder using the same procedure as in the first surgery. We set the monkey’s head in a stereotaxic apparatus, made a small hole in the skull using a trephine, and attached a stainless steel recording cylinder (20 mm in diameter) vertically on this hole. The center of the hole was adjusted at the stereotaxic location of the MD (0 mm lateral and 5 mm anterior from the interaural plane for both monkeys) based on Olszewski’s stereotaxic atlas (Olszewski 1952). After each surgery, the monkeys were given antibiotics (Cephalosporin, Fujisawa) for a few days and a full amount of food and water until they had fully recovered from the surgery.

Behavioral task

In the present experiment, our goal was to characterize task-related activity in the MD using methods comparable to those used by Funahashi et al. (1989–1991) to study the DLPFC. Therefore we tested neurons with the same ODR task used in those prior studies. In the ODR task, the monkey was required to make a memory-guided saccade to the location where the visual cue had been presented. The temporal sequence of this task is illustrated in Fig. 1A. 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 TV 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. 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 0.4 s (response period) to the location where the visual cue had been presented. If the monkey performed the correct eye movement, a drop (≈0.2 ml) of water was given as a reward. To determine whether or not the monkey made a correct eye movement, we set a square window (4° × 7° in visual angle) around the target location and judged that the monkey performed a correct saccade if its eye position fell within this window. If the monkey broke fixation during the cue period or the delay period, if it failed to perform a saccade within the 0.4-s response period, or if its eye movement 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 the eight predetermined peripheral locations shown in Fig. 1B. In the present experiment, we used a single eccentricity (17°) to examine the characteristics of MD neuron activity to match the method used in prior DLPFC studies that used single eccentricities (13° in Funahashi et al. 1989–1991 and 17° in Takeda and Funahashi 2002). Because the characteristics of task-related activities obtained under the 13° eccentricity condition by Funahashi et al. (1989–1991) were not significantly different from those obtained under the 17° condition by Takeda and Funahashi (2002), we decided to use 17° in the present experiment. In the DLPFC, visual receptive fields have been shown to be large and usually extend to the peripheral visual field (Mikami et al. 1982; Suzuki and Azuma 1983). Similarly, the memory fields of these two structures have been shown to be large and usually extend to the peripheral visual field (Mikami et al. 1982; Suzuki and Azuma 1983). Similarly, the memory fields of these two structures have been shown to be large and usually extend to the peripheral visual field (Mikami et al. 1982; Suzuki and Azuma 1983).
DLPFC neurons have also been shown to be as large as their visual receptive fields (Rainer et al. 1998). Because the MD has strong reciprocal connections with the prefrontal cortex, it is expected that the characteristics of the visual receptive fields, memory fields, and movement fields of MD neurons are similar to those of DLPFC neurons. In addition, a recent study by Sommer and Wurtz (2004) showed that the best eccentricities for the visual receptive fields and movement fields of MD neurons are ~20 and 15°, respectively. Therefore although we used only one eccentricity (17°), the value we used is near-optimal for examining visual-, mnemonic-, and saccade-related activities in the MD.

Recording single-neuron activity

After the monkey fully recovered from the second surgery, we started recording single-neuron activity from the MD. An epoxy-coated tungsten microelectrode (25-10-2L, Frederic Hair) was used to record single-neuron activity. The impedance of the microelectrode was 0.3–1.5 MΩ at 1 kHz. A microelectrode was set in a micromanipulator (MO-95, Narishige) with a guide tube (22 gauge stainless steel hypodermic needle, 60 mm long). First, we manually lowered the guide tube until its tip was 10 mm below the bottom edge of the recording cylinder and then lowered the microelectrode vertically through the guide tube using the micromanipulator. To identify the thalamus during recording sessions, we monitored the characteristics of spontaneous neuronal discharges observed during lowering of the electrode. We usually first encountered activities recorded from the dorsal bank of the cingulate sulcus and then, after a brief pause, encountered activities recorded from the ventral bank of the cingulate sulcus. After no activity was observed for 2–4 mm, we often observed spike discharges of short-duration for a short distance; this suggested that the tip of the electrode was in the corpus callosum. After a brief silent period, we then encountered single-neuron activities, often associated with some sort of mechanical noise. Because the lateral ventricle is located between the corpus callosum and the dorsal thalamus, we considered that this silent zone corresponds to the lateral ventricle. Thalamic single-neuron activity was observed between 22 and 30 mm from the bottom edge of the recording cylinder. The path of the microelectrode was confirmed by taking X-ray photographs.

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 transferred to a computer (PC-486HX, Epson) and stored together with task events on magnetic media. We also stored raw neuron activity, task events, and horizontal and vertical eye movements on magnetic tape using a data recorder (PC-108 M, Sony Precision Technology).

Data analysis

To examine whether a recorded neuron exhibited significant activity in relation to any task event, we made rasters and histograms aligned at several task events (e.g., the onset of the cue period, the end of the delay period, the onset of reward delivery) for each cue condition in the ODR task. Using these rasters and histograms, we first visually inspected whether or not the neuron had task-related activity. We then conducted statistical analyses to determine the characteristics of such task-related activity. 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. Because some neurons had phasic responses to FP presentation, we only used the last 500 ms of the fixation period to exclude these responses. 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 the 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 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. For response-period activity, we first searched for the trial condition for which the maximum response-period activity was observed and determined the period when the peak activity was observed using histograms aligned at the initiation of the saccade by visual inspection. We then calculated the mean discharge rate during the 300-ms response period (150 ms before and 150 ms after the period when the peak activity was observed) for each cue condition. If the mean discharge rate differed significantly from the baseline discharge rate by the Mann-Whitney U test (P < 0.05), we determined that the neuron exhibited response-period activity. In addition, we also classified response-period activity into two groups (pre- and post-saccadic activity). This classification was based on whether or not the initiation of response-period activity preceded the initiation of saccadic eye movements. To classify response-period activity, we examined neuronal activities aligned at the initiation of the saccade.

Most DLPFC neurons exhibited directionally selective activity, which was characterized by constructing a tuning curve of this activity (Funahashi et al. 1989–1991; Takeda and Funahashi 2002). To compare the directional characteristics of task-related activity between the DLPFC and MD, we used the same method to analyze the directional characteristics of MD neurons as was used for DLPFC neurons. To examine whether cue-, delay-, or response-period activity exhibited directional selectivity, we first examined the difference in the mean discharge rate across all cue conditions for each task-related activity by one-way ANOVA. We considered that task-related activity had directional selectivity if this difference was significant (P < 0.05). However, if significant task-related activity was observed for all cue conditions and if the mean discharge rate was not significantly different across all cue conditions by one-way ANOVA, we considered that this task-related activity was omni-directional.

For directionally selective task-related activity, we constructed a tuning curve to determine the best direction and the tuning width of this activity. The tuning curve was created from the mean discharge rate of task-related activity under each cue condition by its best fit to the Gaussian function

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

where \( f(d) \) is the discharge rate as a function of the visual cue location \( d \). The constants can be interpreted as follows: \( B \) is the baseline discharge rate (the mean discharge rate during the last 500 ms of the fixation period), \( R \) is the discharge rate above the baseline at the best direction, \( D \) is the best direction where the maximum task-related activity was observed, and \( T_d \) is an index of the tuning width. We determined \( D \) and \( T_d \) for each directional task-related activity.

Histological examinations

Just before the end of the experiment, we inserted glass-coated elgiloy microelectrodes at four selected locations within the recording area and made electrolytic lesions by passing a positive current (3 μA for 15–20 s) through the electrode (Suzuki and Azuma 1987). During perfusion, the monkeys were killed by intravenously injecting an overdose of pentobarbital sodium (45–50 mg/kg). For monkey \( Q \), perfusion was performed from the common carotid artery first with saline, followed by 10% formalin solution containing 2% potassium ferrocyanide, then 10% formalin solution containing 5% sucrose, and finally 10% formalin solution containing 10% sucrose. The brain was then removed from the skull and stored in 10% formalin solution containing 30% sucrose at 4°C for several days. For monkey \( P \),
perfusion was done transcardially first with 0.1 M heparinized phosphate-buffered saline (pH 7.4), followed by 10% formalin solution in 0.1 M phosphate buffer containing 2% potassium ferrocyanide, then 0.1 M phosphate buffer containing 10% sucrose, and finally 0.1 M phosphate buffer containing 30% sucrose. The brain was also removed from the skull and stored in 0.1 M phosphate buffer containing 30% sucrose at 4°C for several days. Each brain was then cut into 50-μm-thick coronal sections using a freezing microtome. To identify the thalamic nuclei, especially the MD, every other section of monkey P’s brain was stained using the Nissl method (0.2% cresyl violet solution), and some sections were stained using the thiocholine method to demonstrate acetylcholinesterase (AChE) activity (Koelle and Friedenwald 1949; Lewis 1961), which very effectively labels the internally medullary laminae (Fitzpatrick et al. 1989). For monkey Q, every other section was stained using the Nissl method and some sections were stained with 0.1% luxol fast blue to stain myelin (Kluver and Barrera 1953).

**RESULTS**

**Identification of MD**

During recording sessions, microelectrodes were advanced vertically toward the thalamus. Changes in spontaneous activity recorded by the electrode were used to identify the boundary between the lateral ventricle and the dorsal surface of the thalamus during recording. Landmarks, such as the depth of the ventral bank of the cingulate sulcus, the lateral ventricle, and the dorsal surface of the thalamus, were determined at each penetration. These landmarks together with electrolytic lesions were used to determine the region in the thalamus where single-neuron activity was recorded at the postmortem histological reconstruction. These landmarks were also used to determine the percentage of tissue shrinkage during histological procedures. The MD was identified histologically using Nissl-stained sections for each monkey (Fig. 2A). In addition, sections stained with the thiocholine method (Fig. 2B; monkey P) and sections stained with 0.1% luxol fast blue (monkey Q) were used to identify the location and the extent of the MD because, using these two methods, we could easily identify the location of the internal medullary lamina, which is located at the lateral and ventral side of the MD. The proportion of tissue shrinkage was 15% for monkey P and 9% for monkey Q.

**Neuronal data base**

Histological examinations revealed that 210 single-neuron activities were recorded from the MD (monkey P, N = 177; monkey Q, N = 33) while the two monkeys performed the ODR task. The mean baseline discharge rate of these MD neurons was 12.4 ± 11.7 (SD) spikes/s for monkey P and 14.9 ± 15.7 spikes/s for monkey Q. The median of the baseline discharge rate was 9.7 spikes/s for monkey P and 9.8 spikes/s for monkey Q. Most neurons (N = 170, 81%) had a baseline discharge rate of <20 spikes/s. These results were in accordance with the previous observation made by Fuster and Alexander (1973).

Among the 210 neurons recorded from the MD, 141 (67%) modulated their firing rates significantly (P < 0.05, Mann-Whitney U test) in relation to one or more task events of the ODR task. Therefore these were classified as having task-related activity. Of these 141 task-related MD neurons, 37 (26%) showed cue-period activity, 75 (53%) showed delay-period activity, and 118 (84%) showed response-period activity (Table 1). In addition, among these 141 neurons, 5 had only cue-period activity, 16 had only delay-period activity, and 54 had only response-period activity. The remaining 66 (47%) exhibited task-related activity during two or more task periods; 2 had cue- and delay-period activity, 34 had delay- and response-period activity, 7 had cue- and response-period activity, and 23 had cue-, delay-, and response-period activity.

**Delay-period activity**

Seventy-five neurons (53% of task-related MD neurons) showed delay-period activity. By comparing the mean discharge rate during the delay period with the baseline discharge rate during the fixation period, 63 (84%) were classified as having excitatory delay-period activity (Fig. 3, A–C) and 12 (16%) were classified as having inhibitory delay-period activity (D). The neurons with excitatory delay-period activity were further classified into three types based on the difference in the temporal pattern of delay-period activity by visual inspection. Among these 63 neurons, 35 showed tonic sustained excitation (Fig. 3A), 13 showed gradually increasing activity (Fig. 3B), and 5 showed gradually decreasing activity (Fig. 3C). The remaining 10 neurons also exhibited excitatory delay-period activity; however, these activities could not be classified into...
Because many neurons exhibited task-related activity in more than one task event, the sum of the numbers of neurons with each task-related activity exceeds the total number of neurons.

one of these three types because these neurons showed occasional burst activities or no monotonic increasing or decreasing activity.

**Directional selectivity of delay-period activity**

Among the 75 neurons with delay-period activity, 57 (76%) exhibited directional selectivity; 46 (81%) exhibited excitatory activity and 11 (19%) exhibited inhibitory activity. Figure 4A shows an example of directional delay-period activity. In this example, the strongest excitatory delay-period activity was observed when the visual cue was presented at the upper right quadrant of the visual field [1-way ANOVA, $F = 16.5, df = (7, 79); P < 0.01$]. Among the 46 neurons with excitatory directional delay-period activity, 5 showed significant inhibition during the delay period at the cue direction roughly opposite the direction where the maximum excitatory delay-period activity was observed. Figure 4B shows an example of this activity [1-way ANOVA, $F = 16.84, df = (7, 79); P < 0.01$]. In this example, significant excitatory delay-period activity was observed when the visual cue was presented at the 45° location ($z = -2.8, P < 0.01$, Fig. 4C). Significant inhibition was observed during the delay period when the visual cue was presented at the lower left quadrant of the visual field (180°, $z = 2.28, P < 0.05$; 225°, $z = 1.97, P < 0.05$; 270°, $z = 2.01, P < 0.05$; Fig. 4D).

Of the 75 neurons with significant delay-period activity, 18 (24%) were classified as having omni-directional delay-period activity. In these neurons, the mean discharge rate of delay-period activity was not significantly different across all cue conditions by ANOVA ($P > 0.05$), although the magnitude of delay-period activity was significantly different ($P < 0.05$) from the baseline discharge rate for all cue conditions. Among the 18 neurons with omni-directional delay-period activity, 17 (94%) had excitatory delay-period activity and one had inhibitory delay-period activity.

**Best directions and tuning indices of delay-period activity**

To quantify the directional selectivity of delay-period activity, we constructed tuning curves of this activity by finding the best fit to the Gaussian function for all 57 MD neurons that showed directional delay-period activity. We discarded three neurons from this analysis because their delay-period activity showed poor Gaussian fitting. Using these tuning curves, we obtained the best direction ($D$) and the index of the tuning width (tuning index, $Td$) of delay-period activity. Examples of tuning curves are shown in Fig. 5A. Figure 5A, 1 and 2, shows the tuning curves of the excitatory delay-period activity of two MD neurons (neuron $P30702$, $D = 144°$, $Td = 34°$; neuron $P04902$, $D = 46°$, $Td = 62°$). Figure 5A3 shows an example of the tuning curve of inhibitory delay-period activity (neuron $P30401$, $D = 6°$, $Td = 62°$).

Figure 5B shows polar plots of best directions for 54 MD neurons with directional delay-period activity. In this figure, the best directions of neurons recorded from the right thalamus were transformed into mirror-image directions as if all neurons were recorded from the left thalamus. The best directions were distributed among nearly all of the directions around the FP. Among the 44 neurons with excitatory delay-period activity, the best directions of 25 neurons (57%) were directed toward the visual field contralateral to the recording hemisphere ($−80°–80°$). The best directions of 17 neurons (39%) were directed toward the visual field ipsilateral to the recording hemisphere ($100°–260°$). The remaining two neurons had the best directions along the vertical meridian ($90° ± 10°$). No significant contralateral bias was observed ($\chi^2 = 2.476, df = 1, P > 0.1$), although most of the excitatory directional delay-period activities had best directions toward the contralateral visual field.

Polar plots of the best directions for the 10 neurons with inhibitory delay-period activity are shown with dashed lines in Fig. 5B. The best directions of six neurons were directed toward the visual field contralateral to the recording hemisphere, whereas the best directions of three neurons were directed toward the visual field ipsilateral to the recording hemisphere. The remaining neuron had its best direction along the vertical meridian ($270° ± 10°$). No significant contralateral bias was observed ($\chi^2 = 2.01, df = 1, P > 0.1$).

The distribution of tuning indices for the 54 MD neurons with delay-period activity is shown in Fig. 5C. The tuning indices of excitatory delay-period activity ($\bullet$, $n = 44$) were distributed from 8 to 127°. The median was 54° and the mean was 59 ± 31°. The tuning indices of inhibitory delay-period activity
activity (□, \( n = 10 \)) were distributed from 43 to 177°. The median was 66° and the mean was 78 ± 40°. There was no significant difference in tuning indices between these two types of delay-period activity (\( t = 1.668; \) df = 52; \( P = 0.101 \)).

**Cue-period activity**

Of the 141 task-related MD neurons, 37 (26%) showed cue-period activity (Fig. 6, A and B). Among these 37 neurons, 35 (95%) showed excitatory cue-period activity and the remaining 2 (5%) showed inhibitory cue-period activity. The latency of cue-period activity was measured by making a cumulative histogram aligned at the presentation of the visual cue at the condition where a neuron showed the greatest cue-period activity. Figure 6D shows the distribution of the latencies of cue-period activity. Latencies were distributed from 30 to 190 ms; the mean was 119.2 ± 43 (SD) ms and the median was 110 ms.

All cue-period activities showed directional selectivity. Figure 6A shows an example of directional cue-period activity. In this neuron, significant cue-period activity was observed when visual cues were presented at the 90, 135, and 180° locations (90°, \( z = -1.99, P < 0.05 \); 135°, \( z = -3.38, P < 0.001 \); 180°, \( z = -3.76, P < 0.001 \)). The greatest activity was observed when the visual cue was presented at the 135° location (Fig. 6B), whereas no significant activity was observed when the visual cue was presented at the 315° location (Fig. 6C). However, among the 35 neurons with excitatory directional cue-period activity, 9 exhibited significant inhibition during the cue period when the visual cue was presented at the position roughly opposite to where the maximum excitatory cue-period activity was observed.

To quantify the directional selectivity of cue-period activity, we constructed tuning curves of this activity. Figure 7A shows tuning curves of the cue-period activity of two MD neurons (neuron P15302, \( D = 29°, Td = 44° \); neuron P28801, \( D = 225° \)).

**FIG. 4.** A: an example of directional delay-period activity while a monkey performed the ODR task. This neuron exhibited significant delay-period activity when the visual cues were presented at the upper right quadrant of the visual field. The central diagram shows a polar plot of this delay-period activity. The average discharge rate during the delay period for each cue location is depicted as the radial eccentricity of the plot in that direction. The baseline discharge rate is shown by dotted lines. Asterisks indicate cue directions with statistically significant delay-period activity. The delay length was 3 s. The histogram bin width was 30 ms. B–D: another example of directional delay-period activity. This neuron had significant delay-period activity only when the cue was presented at the 45° location and was suppressed during the delay period when the cue was presented at a roughly opposite location. B: a polar plot of the delay-period activity. C: this neuron’s activity at the 45° location. D: this neuron’s activity at the 225° location. The histogram bin width was 30 ms.
172°, Td = 67°). Figure 7B shows polar plots of the best directions for 37 MD neurons with cue-period activity. The best directions were distributed to nearly all directions around the FP. Among the 35 neurons with excitatory cue-period activity, the best directions of 22 neurons (63%) were directed toward the visual field contralateral to the recording hemisphere (80–260°), whereas the best directions of 8 (23%) were directed toward the visual field ipsilateral to the recording hemisphere (100–260°). A significant contralateral bias was observed (χ² = 6.53, df = 1, P < 0.05). The remaining five neurons had their best directions along the vertical meridian; three had best directions along the upper meridian (90 ± 10°) and two had best directions along the lower meridian (270 ± 10°). For two neurons with inhibitory cue-period activity, one had a best direction toward the contralateral visual field and the other had a best direction toward the ipsilateral visual field. The distribution of tuning indices is shown in Fig. 7C. The tuning indices of the 35 MD neurons with excitatory cue-period activity were distributed from 7 to 161°. The median was 41° and the mean was 48 ± 36°. The tuning indices of the two MD neurons with inhibitory cue-period activity were 21 and 38°.

Response-period activity

Among the 141 task-related MD neurons, 118 (83%) showed response-period activity (Fig. 8, A and B). The latencies of response-period activity were calculated by constructing cumulative histograms of response-period activity aligned at the initiation of eye movement. Latency was defined as the time from the initiation of saccadic eye movement to the start of response-period activity. Figure 8C shows the distribution of these latencies. Latencies of response-period activity were distributed from −170 to 370 ms; the mean was −23.5 ± 74.3 ms and the median was −39 ms. Using these values, response-period activity was classified into two groups (pre- or postsaccadic activity) based on whether response-period activity was initiated before or after the initiation of the saccade. Examples of pre- and postsaccadic activity are shown in Fig. 8, A and B, respectively. Among the 118 MD neurons with response-period activity, 87 (74%) had presaccadic activity, and 31 (26%) had only postsaccadic activity.
Exhibited directional selectivity. Figure 9A
remaining 21 had both pre- and postsaccadic activity.
A2: excitatory cue-period activity with a best direction at 172° and
T_d = 67°. B: polar plots of best directions of 37 MD neurons with cue-period activity. A significant contralateral bias was observed. C: distribution of tuning indices of 37 MD neurons with cue-period activity. ■, neurons with excitatory activity; □, neurons with inhibitory activity.

Presaccadic activity

Among the 87 neurons with presaccadic activity, 68 (78%) exhibited directional presaccadic activity and the remaining 19 exhibited omni-directional presaccadic activity. The presaccadic activity was all excitatory. Of the 87 neurons with presaccadic activity, 21 exhibited omni-directional presaccadic activity. The remaining 66 neurons had only presaccadic activity, the remaining 19 neurons were classified as having omni-directional activity. An example of omni-directional presaccadic activity is shown in Fig. 9G. In this neuron, the mean discharge rate of presaccadic activity was not significantly different across all cue conditions by ANOVA (P > 0.05), although significant response-period activity was observed in all cue conditions (e.g., Fig. 9H).

Of the 66 neurons with only presaccadic activity, the remaining 19 neurons were classified as having omni-directional activity. Twelve of these latter exhibited postsaccadic activity when the monkey made saccades to the directions approximately opposite the directions for which presaccadic activity was observed. The remaining nine neurons showed omni-directional postsaccadic activity. Figure 10A shows an example of the former neuron. Presaccadic activity was observed when the monkey made saccades upward (90°, z = –3.45, P < 0.001; Fig. 10B), while postsaccadic activity was observed when the monkey made saccades downward (270°, z = –2.70, P < 0.01; Fig. 10C). Figure 10D shows an example of the latter neurons. In this


FIG. 8. A: presaccadic activity aligned at the initiation of eye movement. B: postsaccadic activity aligned at the initiation of eye movement. C: distribution of latencies of response-period activity. Latencies were distributed from –170 to 370 ms; the mean was –23.5 ± 74.3 (SD) ms.
example, the largest presaccadic activity was observed when the monkey made saccades to the upper right (0°, $z = -3.75, P < 0.001$; $45^\circ, z = -3.80, P < 0.001$; $90^\circ, z = -3.82, P < 0.001$; $135^\circ, z = -3.96, P < 0.001$). The maximum activity was observed when the monkey made saccades to the $45^\circ$ direction (Fig. 11B). Response-period activity was initiated $30$ ms after initiation of the saccade. No significant activity was observed when the monkey made saccades to the $225^\circ$ direction (Fig. 11C). On the other hand, the remaining 23 (74%) neurons exhibited omni-directional postsaccadic activity (Fig. 11D); 21 showed excitation and 2 showed inhibition.

Post-saccadic activity

Of the 118 neurons with response-period activity, 31 (26%) were classified as having only post-saccadic activity. Among them, only eight (26%) exhibited a phasic excitatory response and directional selectivity. Figure 11A shows an example of directional post-saccadic activity. In this neuron, significant post-saccadic activity was observed when the monkey made saccades to the upper right (0°, $z = -3.92, P < 0.001$; $45^\circ, z = -2.19, P < 0.05$; $90^\circ, z = -2.05, P < 0.05$; $135^\circ, z = -3.96, P < 0.001$). The maximum activity was observed when the monkey made saccades to the $45^\circ$ direction (Fig. 11B). Postsaccadic activity was initiated $30$ ms after initiation of the saccade. No significant activity was observed when the monkey made saccades to the $225^\circ$ direction (Fig. 11C). On the other hand, the remaining 23 (74%) neurons exhibited omni-directional post-saccadic activity (Fig. 11D); 21 showed excitation and 2 showed inhibition.
Directional characteristics of response-period activity

To quantify the directional selectivity of response-period activity, we constructed tuning curves of this activity for the 76 MD neurons with directional response-period activity. Figure 12A shows the tuning curves of response-period activity of two MD neurons (neuron P09002, $D = -15^\circ$, $T_d = 35^\circ$; neuron P09302, $D = 88^\circ$, $T_d = 70^\circ$). Figure 12B shows polar plots of the best directions for these 76 MD neurons. Best directions were distributed at nearly all directions around the FP. Among the 68 neurons with presaccadic activity, the best directions of 40 neurons (59%) were directed toward the visual field contralateral to the recording hemisphere, whereas the best directions of 18 neurons (26%) were directed ipsilateral to the recording hemisphere. A significant contralateral bias was observed ($\chi^2 = 8.34$, df = 1, $P < 0.005$). The remaining neurons had best directions along the vertical meridian; three neurons had best directions along the upper meridian ($90 \pm 10^\circ$) and seven had best directions along the lower meridian ($270 \pm 10^\circ$). Among the eight neurons with only postsaccadic activity, the best directions of four were directed to the visual field contralateral to the recording hemisphere, whereas the best directions of three were directed ipsilateral to the recording hemisphere. No significant contralateral bias was observed ($\chi^2 = 0.14$, df = 1, $P > 0.05$). The remaining neuron had a best direction along the lower meridian ($270 \pm 10^\circ$). The distribution of tuning indices for the 76 MD neurons is shown in Fig. 12C. The tuning indices were distributed from 12 to 117°. The median was 53° and the mean was $55 \pm 20^\circ$ for presaccadic neurons. The tuning indices of the eight neurons with only postsaccadic activity were distributed from 11 to 156°, with a median of 62° and a mean of $61 \pm 45^\circ$. There was no significant difference in the tuning indices of pre- and postsaccadic activity ($t$-test, $P = 0.445$).

Functional relations between delay-period activity and other task-related activity

Among the 75 neurons with delay-period activity, 59 (79%) exhibited other task-related activities; 2 had cue-period activity, 34 had response-period activity, and 23 had both cue- and response-period activity. Most of these neurons ($n = 50, 85\%$) showed directional selectivity. To understand the functional relationships between cue- and delay-period activities, we compared the directional selectivities of these two activities in the same neuron. An example is shown in Fig. 13A. The best direction was $159.7^\circ$ for cue-period activity and $159.3^\circ$ for delay-period activity. The best directions of these two activities
Differences between the best directions of cue- and delay-period activity. In addition, the distribution of the best directions of these two activities was 166.6°. We constructed tuning curves for the 32 MD neurons with both directional delay- and response-period activities. Figure 13E shows a scattergram of the relationship between the best directions of these two activities. A positive but nonsignificant correlation (r = 0.12) was observed. In Fig. 13E the dots near the solid line represent data in which the best directions of delay-period and response-period activity were similar, whereas the dots near the dotted lines represent data in which the best directions of delay-period and response-period activity were opposite. The scattergram shown in Fig. 13E indicates that there are two populations of MD neurons with both delay- and response-period activity; for one group of MD neurons, the best directions for the two activities are similar, whereas for the other group, the best directions for the two activities are opposite. This was confirmed by examining the distribution of the differences between the best directions of delay- and response-period activities (Dresponse - Ddelay; Fig. 13F). The values were distributed between 0 and 177° (mean: 92.4 ± 65°; median: 91°). The distribution had two peaks (one located close to 0° and the other near 180°), indicating that for some neurons the best directions for delay- and response-period activities were similar, whereas for others, these best directions were opposite. These results suggest that for the latter neurons, response-period activity is not a simple prolongation of delay-period activity but rather an independent functional component different from delay-period activity.

Distribution of neurons with task-related activity in the MD

We examined the spatial distribution of neurons with each task-related activity within the MD. Because most task-related activities were collected from monkey P, we analyzed the spatial distribution of these neurons in more detail. Figure 14 shows the locations of MD neurons exhibiting cue-, delay-, or response-period activity in monkey P. We observed every task-related activity throughout the recording area in the MD. However, there was some bias in the distribution of each task-related activity within the MD. For example, more neurons with directional delay-period activity and more neurons with directional response-period activity were located in the lateral part of the MD. However, neurons with omni-directional delay-period activity and those with omni-directional response-period activity were more frequently observed in the medial part of the MD. To examine the statistical significance of these observations, we divided recorded MD neurons into three groups depending on their location in the mediolateral axis of the MD and compared the percentages of neurons with task-related activities among these three groups. As shown in Fig. 15, neurons with directional delay- and response-period activity were predominantly located in the lateral part of the MD (delay-period activity, χ² = 17.6, df = 2, P < 0.001;
FIG. 14. Recording sites of MD neurons with task-related activity were plotted in coronal sections of monkey P’s brain. Small dots indicate recording sites of nontask-related MD neurons. Numbers indicate the distance from the interaural plane (mm). Pc, paracentral nucleus; Cs, centrosuperior nucleus; Cif, centroinferior nucleus; Hl, lateral habenular nucleus.

FIG. 15. Distributions of task-related activity in the mediolateral axis of the MD. The recorded MD neurons were divided into three groups based on where they were recorded in the mediolateral axis of the MD. Each histogram corresponds to the percentage of neurons exhibiting either directional or omnidirectional selectivity.
response-period activity; \( \chi^2 = 11.6, \text{df} = 2, P < 0.001 \)), whereas those with omni-directional activity were predominantly observed in the medial part of the MD (delay-period activity, \( \chi^2 = 12.2, \text{df} = 2, P < 0.005 \); response-period activity; \( \chi^2 = 21.7, \text{df} = 2, P < 0.001 \)). A similar tendency was observed in monkey Q.

We also examined the proportion of neurons with each task-related activity in the anterior-posterior axis and in the dorsal-ventral axis and found a bias in response-period activity in the anterior-posterior axis. In monkey P, directional response-period activity was more frequently observed in the posterior half of the MD (\( \chi^2 = 4.9, \text{df} = 1, P < 0.05 \)), whereas omni-directional response-period activity was predominantly observed in the anterior half of the MD (\( \chi^2 = 8.67, \text{df} = 1, P < 0.005 \)). In monkey Q, although directional response-period activity was distributed evenly along the anterior-posterior axis, omni-directional response-period activity was predominantly observed in the anterior half of the MD. We found no significant biases in the distribution of neurons with task-related activity in the dorsal-ventral axis. We also examined the spatial distributions of the best directions and tuning indices of neurons within the MD. However, we found no biases in the spatial distributions of these parameters within the MD.

**DISCUSSION**

The aim of this experiment was to characterize task-related activity observed in the MD using methods comparable to those used by Funahashi et al. (1989–1991) to study the DLPFC. We observed the same task-related activities that were seen in the DLPFC. However, several unique characteristics were observed in MD activity. For example, among neurons with response-period activity, 74% showed presaccadic activity. A significant contralateral bias in best directions was observed for cue-period activity and presaccadic activity but not for delay-period activity. These findings are summarized in Fig. 16. In the following sections, we compare our current results obtained in the MD to those obtained in the DLPFC by Funahashi et al. (1989–1991) and discuss the participation of the MD in cognitive functions.

**Delay-period activity in the MD**

We collected task-related activities homogeneously from the whole MD while two monkeys performed an ODR task. Of 141 task-related MD neurons, 53% exhibited delay-period activity (Fig. 16A). Among them, 84% showed excitatory delay-period activity, whereas 16% showed inhibitory delay-period activity. Among the MD neurons with delay-period activity, 76% were directional and 24% were omni-directional (Fig. 16C). Delay-period activity was observed throughout the MD. However, directional delay-period activity was more frequently observed in the lateral part of the MD, whereas omni-directional delay-period activity was more frequently observed in the medial part of the MD. Delay-period activity observed in the MD was mostly tonic sustained activation during the delay period, but some was gradually increasing or decreasing activation. Although Fuster and Alexander (1973) did not find directional delay-period activity in the MD, the percentage of neurons with delay-period activity (51%) among all neurons with task-related activity was comparable to our result (53%).

In the DLPFC, 51% of task-related neurons exhibited delay-period activity (Fig. 16A), and among them 79% were directional and 21% were omni-directional (Fig. 16C) (Funahashi et al. 1989). In another study, 47% of task-related neurons exhibited delay-period activity and among them 93% were directional (Takeda and Funahashi 2002). Therefore the percentage of neurons with delay-period activity among all neurons that showed task-related activity and the percentages of neurons with either directional or omni-directional delay-period activity

![Fig. 16. Comparison of the characteristics of task-related activity between MD neurons and DLPFC neurons. The data regarding DLPFC neurons are based on data obtained by Funahashi et al. (1989–1991). A: a comparison of the proportion of pre- and postsaccadic activity between the MD and DLPFC. B: a comparison of the proportion of pre- and postsaccadic activity between the MD and DLPFC. C: a comparison of the directional selectivity of each task-related activity between the MD and DLPFC.](http://jn.physiology.org/Downloaded from 10.220.33.1 on October 28, 2016)
are similar between the MD and DLPFC. In addition, the temporal patterns of delay-period activity we observed in the MD (tonic sustained excitation, gradual increase, gradual decrease, and inhibition) were the same as those observed in the DLPFC (Chafee and Goldman-Rakic 1998; Funahashi et al. 1989). Thus we found a great similarity in the characteristics of delay-period activity between the MD and DLPFC. This similarity could be due to strong anatomical connections between these two structures (Goldman-Rakic and Porrino 1985; Kievit and Kuypers 1977; Rouiller et al. 1999). This notion is supported by our observation that directional delay-period activity was observed more frequently in the lateral part of the MD, which mainly connects to the DLPFC and the frontal eye field (Giguere and Goldman-Rakic 1988; Goldman-Rakic and Por- 

rino 1985). This observation agrees with the result of Tanibuchi and Goldman-Rakic (2003).

The characteristics of delay-period activity observed in the DLPFC have been described in detail in many reports (e.g., see a review by Funahashi and Takeda 2002). Directional delay-period activity observed in the DLPFC was mainly a sustained activation during the delay period when the visual cue was presented within the neuron’s memory field (Funahashi et al. 1989). This activity was observed only when the monkey performed saccadic eye movements to memorized correct targets (Funahashi et al. 1989). Therefore directional delay-period activity observed in the DLPFC has been considered to be a neural correlate of a mechanism for the temporary storage of information (Funahashi and Kubota 1994; Funahashi and Takeda 2002; Fuster 1997; Goldman-Rakic 1987). In the present study, we observed similar characteristics for directional delay-period activity in the MD. Therefore directional delay-period activity observed in the MD can also be considered a neuronal activity that represents a mechanism for the temporary storage of information.

However, several differences were also found in the characteristics of delay-period activity between the MD and DLPFC. First, as shown in Table 2, the distributions of the best directions were different between the MD and DLPFC. In both areas, the best directions of delay-period activity were distributed in all directions around the FP. A significant contralateral bias of the best directions was observed in the DLPFC (Funahashi et al. 1989). In contrast, a contralateral bias was not observed in the MD, although most of the best directions were directed toward the contralateral visual field. Second, the mean tuning indices were different between the MD and DLPFC (Table 3). The mean tuning index of both excitatory and inhibitory activity was broader in the MD (59° for excitatory activity and 78° for inhibitory activity) than in the DLPFC (27° for excitatory activity and 48° for inhibitory activity) (Funahashi et al. 1989). Wyder et al. (2003) reported similar tuning characteristics of delay-period activity in the “oculomo-

TABLE 2. Comparison of the directional bias of task-related activity

<table>
<thead>
<tr>
<th>Delay</th>
<th>Excitatory</th>
<th>Inhibitory</th>
<th>Pre-saccadic</th>
<th>Post-saccadic</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>O (P &lt; 0.05)</td>
<td>X</td>
<td>X</td>
<td>O (P &lt; 0.005)</td>
</tr>
<tr>
<td>DLPFC</td>
<td>O (P &lt; 0.001)</td>
<td>O (P &lt; 0.01)</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

“O” indicates the presence of significant contralateral bias, whereas “X” indicates the absence of significant contralateral bias. The data regarding the DLPFC are those obtained by Funahashi et al. (1989–1991). MD, mediodorsal nucleus; DLPFC, dorsolateral prefrontal cortex.

The present results indicate that although delay-period activity is very similar in MD and DLPFC with respect to its temporal pattern, its frequency of occurrence, and its tendency to be directional, nevertheless it is not identical in the two structures. The differences in contralaterality and tuning width of delay-period activity suggest that there are some differences in how these two structures participate in cognitive processes, such as spatial working memory. Thus further studies are...
needed to identify the specific function of the MD: for example, what information does MD delay-period activity represent? Such studies have been performed in the DLPFC (Funahashi et al. 1993; Niki and Watanabe 1976; Takeda and Funahashi 2002), and these have shown that a great majority of DLFP delay-period activity encodes retrospective (sensory) information, whereas a minority of delay-period activity encodes prospective (motor) information. However, the kind of information encoded by MD delay-period activity is still not clear. We need to carefully examine the characteristics of delay-period activity in MD neurons to better understand the specific roles of the MD in cognitive processes. In an accompanying paper (Watanabe and Funahashi 2004), we examined the information represented by MD neuron’s task-related activity using two different ODR tasks and compared the results between the MD and DLPFC.

Response-period activity observed in the MD

In the present study, we found that 84% of task-related MD neurons exhibited response-period activity (Fig. 16A). Most of these (74%) showed presaccadic activity, and only 26% showed postsaccadic activity (Fig. 16B). The response latencies were distributed between −170 and 370 ms. Among neurons with presaccadic activity, 78% showed directional activity and the remaining 22% showed omni-directional activity (Fig. 16C). On the other hand, among neurons with postsaccadic activity, 74% showed omni-directional activity and only 26% showed directional activity (Fig. 16C). A significant contralateral bias in the distribution of the best directions was observed in presaccadic activity but not in postsaccadic activity. Recently, saccade-related MD activity has been reported by several researchers. For example, Sommer and Wurtz (2002, 2004) found that 74% of the recorded neurons exhibited excitatory presaccadic activity, with an average latency of −66 ms, 82% of these were spatially tuned, and the best direction was contraversive for all directionally tuned neurons. Tanibuchi and Goldman-Rakic (2003) also found directionally tuned saccade-related MD activity and reported that 73% of the neurons exhibited presaccadic activity. Our present results agree with these results.

The distributions of the best directions and tuning indices and temporal patterns of presaccadic activity were similar to those of presaccadic activity observed in other structures such as the superior colliculus (SC) (Munoz and Wurtz 1995), the frontal eye field (Bruce and Goldberg 1985; Sommer and Wurtz 2000, 2001), and the DLPFC (Boch and Goldberg 1989; Funahashi et al. 1991), suggesting that presaccadic activity observed in the MD is related to the execution or control of saccadic eye movements. The MD receives anatomical projections from both the SC (Lynch et al. 1994) and the frontal eye field (Giguere and Goldman-Rakic 1988; Rouiller et al. 1999). A recent neurophysiological study by Sommer and Wurtz (2002, 2004) showed that MD neurons were activated orthodromically by electrical stimulation in the SC at short latency and that these MD neurons exhibited saccade-related activity. In addition, the MD receives anatomical projections from the SNr (Ilinsky et al. 1985) and SNr neurons exhibit presaccadic suppression (Hikosaka and Wurtz 1983). Because the MD receives inhibitory inputs from the SNr, presaccadic suppression in the SNr could disinhibit MD neurons. Such presaccadic disinhibition may also cause presaccadic activation in MD neurons. These results suggest that the presaccadic activity of MD neurons may be caused by inputs from the DLPFC, the frontal eye field, the SC, and the SNr.

We observed striking differences when we compared the characteristics of response-period activity between the MD and DLPFC. In the MD, 84% of task-related neurons exhibited response-period activity, whereas in the DLPFC, only 56% (Funahashi et al. 1991) or 61% (Takeda and Funahashi 2002) of task-related neurons exhibited response-period activity (Fig. 16A). The proportion of neurons with response-period activity among neurons with task-related activity was significantly lower in the DLPFC than in the MD. Further, in the MD, 74% of response-period activity was presaccadic, whereas in the DLPFC, 78% (Funahashi et al. 1991) or 85% (Takeda and Funahashi 2002) of response-period activity was postsaccadic (Fig. 16B). In addition, in the MD, 78% of presaccadic activity and only 26% of postsaccadic activity showed directional selectivity (Fig. 16C), whereas in the DLPFC, 97% of presaccadic activity and 92% of postsaccadic activity showed directional selectivity (Funahashi et al. 1991) (Fig. 16C). Thus more neurons in the MD exhibited presaccadic activity than in the DLPFC, and more presaccadic neurons in the MD exhibited omni-directional activity. These results indicate that the participation of the MD in ODR task performance is different from that of the DLPFC, especially with regard to the control and execution of motor responses, and suggest that the MD participates in the control and execution of saccadic eye movements more directly than the DLPFC. On the other hand, although some DLPFC neurons exhibited presaccadic activity, most saccade-related DLPFC activity was postsaccadic, and hence, this postsaccadic activity is considered to be a feedback signal from oculomotor structures for manipulating task-related activity, especially delay-period activity (Funahashi and Kubota 1994; Funahashi and Takeda 2002; Goldman-Rakic et al. 1990). Sommer and Wurtz (2002, 2004) indicated that presaccadic activity observed in the MD is a corollary discharge for internal monitoring of saccadic eye movement, which is transmitted from the SC to the frontal eye field. Wyder et al. (2003) partially supported this conclusion. The presaccadic MD activity observed in the present study may be a corollary discharge from the SC and may also play a role in controlling or modulating delay-period activity in the DLPFC through thalamo-cortical afferent projections. The fact that a rather large population of presaccadic activity (22%) exhibited omni-directional selectivity may also support the latter notion because omni-directional presaccadic activity does not seem to directly participate in the execution of eye movement toward any particular direction.

Cue-period activity observed in the MD

In the present study, 26% of task-related MD neurons exhibited cue-period activity. All showed directional selectivity. The best directions were biased contralaterally, and the mean response latency was 119.2 ms. Recently, Tanibuchi and Goldman-Rakic (2003) reported that 14% of MD neurons responded exclusively to picture stimuli (human faces or natural objects) and that the mean response latency was 196.9 ms. Wyder et al. (2003) observed visual responses in half of the recorded neurons during visually guided delayed saccade per-
formance in the “oculomotor thalamus” and found that the mean onset latency was 141 ms. They also found a significant contralateral bias in the directional selectivity of visual responses. Although the basic characteristics of visual responses were similar between our present study and Wyder et al. (2003), the proportions of visually responded neurons were different. This discrepancy might be caused partly by the fact that the neural population studied by Wyder et al. (2003) was different from our neural population in that Wyder et al. (2003) examined a neural population in the “oculomotor thalamus,” which corresponds to the internal medullary lamina, whereas we examined a neural population in the MD.

A comparison of the characteristics of cue-period activity between the MD and DLPFC reveals functional similarities between these two structures (Fig. 16). In the DLPFC, 28% (Funahashi et al. 1990) or 38% (Takeda and Funahashi 2002) of the task-related neurons exhibited cue-period activity during ODR task performance. Almost all of the neurons (96 or 100%) exhibited directional selectivity, and the best directions were contralaterally biased (Funahashi et al. 1990; Takeda and Funahashi 2002). Possible sources of visual inputs to the MD would be the DLPFC (Goldman-Rakic and Porrino 1985), the SC (Lynch et al. 1994), and the SNr (Ilinsky et al. 1985). However, the DLPFC and MD have strong reciprocal connections, and the characteristics of cue-period activity are very similar between these structures. Therefore cue-period activity observed in the MD may be a product of tight functional connections between the MD and DLPFC. This idea is supported by the finding that directional preferences between cue- and delay-period activities are almost identical in neurons with both activities in both structures.

Issues regarding the methodology

The goal of our present experiment was to characterize task-related activity in the MD using methods comparable to those used by Funahashi et al. (1989–1991) to study the DLPFC. For this purpose, we tested neurons using the same ODR task that was used in those prior studies. However, our current experiment raises two issues.

The first issue is related to the fact that we used a single eccentricity (17°) to examine the characteristics of MD neuron activity. Because prior DLPFC studies used single eccentricities (13° in Funahashi et al. 1989–1991 and 17° in Takeda and Funahashi 2002), we tried to match the method used in those prior studies. In addition, the characteristics of task-related activities obtained under the 13° eccentricity condition by Funahashi et al. (1989–1991) were not significantly different from those obtained under the 17° condition by Takeda and Funahashi (2002) in the DLPFC, which led to our decision to use 17° in the present experiment. A recent study by Sommer and Wurtz (2004) showed that the best eccentricities of MD neurons’ visual receptive fields and movement fields are distributed between 5 and 35° and between 2 and 35°, respectively, and that their mean values are ~20 and 15°, respectively. Therefore although we used only one eccentricity, the 17° eccentricity we used should be an optimal value for examining visual-, mnemonic-, and saccade-related activities in the MD. However, in the DLPFC, visual receptive fields have been shown to be large and usually extend to the peripheral visual field (Mikami et al. 1982; Suzuki and Azuma 1983).

Similarly, the memory fields of DLPFC neurons have also been shown to be as large as the visual receptive fields of DLPFC neurons (Rainer et al. 1998). Because the MD has strong reciprocal connections with the prefrontal cortex, it is expected that the characteristics of the visual receptive fields, memory fields, and movement fields of MD neurons would be similar to those of DLPFC neurons. Sommer and Wurtz (2004) showed that eccentricity ranges of visual fields and movement fields of MD neurons were between 15 and 55° and between 5 and 35°, respectively. In the present experiment, we did not determine the best eccentricity and eccentricity range for each task-related activity. Therefore some of the characteristics we reported (e.g., the proportion of task-related activities, the proportion of directionally selective activity) might be underestimated.

The second issue is related to the anatomical relationship between the MD and DLPFC. In the present experiment, we compared the characteristics of task-related activities between MD neurons and DLPFC neurons recorded while monkeys performed the same behavioral task. We sampled single-neuron activity throughout the MD, whereas Funahashi et al. (1989–1991) and Takeda and Funahashi (2002) sampled single-neuron activity only from the dorsolateral part of the lateral prefrontal cortex (DLPFC, the cortex within and surrounding the principal sulcus). The DLPFC has anatomical connections only with the intermediate (parvocellular) part of the MD, whereas the MD has connections with the entire prefrontal cortex, including the orbital surface and the medial part of the prefrontal cortex (Giguere and Goldman-Rakic 1988; Goldman-Rakic and Porrino 1985; Kivel and Kuypers 1977). Therefore our current results obtained in the MD might not entirely agree with those obtained in the DLPFC by Funahashi et al. (1989–1991). However, directionally selective task-related activity was more frequently observed in the lateral part of the MD whereas omni-directional task-related activity was more frequently observed in the medial part of the MD, as shown in Fig. 15. This tendency agrees with the anatomical relations between the MD and the prefrontal cortex.

Conclusions

The present results indicate that although the temporal patterns and the proportions of task-related activity and directionally selective activity are similar between the MD and DLPFC, the characteristics of task-related activity were not identical. These results suggest that there are some differences in how these two structures participate in cognitive processes. Thus further studies are needed to identify the specific function of the MD. An important issue is to identify the information represented by MD task-related activity. In our accompanying paper (Watanabe and Funahashi 2004), we examined this issue using two different ODR tasks and compared the results between the MD and DLPFC.

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