Properties of Delay-Period Neuronal Activity in the Monkey Dorsolateral Prefrontal Cortex During a Spatial Delayed Matching-to-Sample Task

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Sawaguchi, T., and Yamane, I. Properties of delay-period neuronal activity in the monkey dorsolateral prefrontal cortex during a spatial delayed matching-to-sample task. J. Neurophysiol. 82: 2070–2080, 1999. The dorsolateral prefrontal cortex (PFC) has been implicated in visuospatial memory, and its cellular basis has been extensively studied with the delayed-response paradigm in monkeys. However, using this paradigm, it is difficult to dissociate neuronal activities related to visuospatial memory from those related to motor preparation, and few studies have provided evidence for the involvement of PFC neurons in visuospatial memory of a sensory cue, rather than in motor preparation. To extend this finding, we examined neuronal activities in the dorsolateral PFC while a rhesus monkey performed a spatial delayed matching-to-sample (SDMTS) task, which allows us to adequately access visuospatial memory independent of any sensorimotor components. The SDMTS task required the subject to make a lever-holding NOGO response or a lever-releasing GO response when a visuospatial matching cue (white spot, one of four peripheral locations, 15° in eccentricity) matched or did not match a sample cue (physically the same as the matching cue) that had been presented prior to a delay period (3 s). Thus, the SDMTS task requires the subject to remember visuospatial information regarding the sample cue location during the delay period and is suitable for accessing visuospatial memory independent of any sensorimotor components, such as motor preparation, for directed movements. Of a total of 385 task-related neurons, 184 showed a sustained increase in activity during the delay period (“delay-period activity”). Most of these neurons (n = 165/184, 90%) showed positional delay-period activity, i.e., delay-period activity where the magnitude differed significantly with the position of the sample cue. This activity appears to be involved in visuospatial memory and to form a “memory field.” To quantitatively examine the properties of positional delay-period activity, we introduced a tuning index (TI) and a discriminative index (DI), which represent the sharpness of tuning and the discriminative ability, respectively, of positional delay-period activity. Both TI and DI varied among neurons with positional delay-period activity and were closely related to the time from the onset of the sample cue to the onset of positional delay-period activity; positional delay-period activity with sharper tuning and a greater discriminative ability had a slower onset. Furthermore, at the population level, both TI and DI were increased during the delay period in the neuronal population with a high DI value. These results extend previous findings to suggest that integrative, convergent processes of neuronal activities for increasing the accuracy of visuospatial memory may occur in the dorsolateral PFC. Thus, a critical role of the dorsolateral PFC in visuospatial memory may be to sharpen it to guide behaviors/decisions requiring accurate visuospatial memory.

INTRODUCTION

In primates, dorsolateral areas of the prefrontal cortex (PFC) have been implicated in visuospatial short-term (or working) memory, and its cellular basis has been studied over the three decades since the original report by Fuster and Alexander (1971) (for reviews, see Funahashi and Kubota 1994; Fuster 1997; Goldman-Rakic 1995). Most of these studies have used delayed-response paradigms in which the subjects (usually monkeys) are required to direct their gaze or hand to a visuospatial, remembered target location that has been cued prior to a brief delay period (Chafee and Goldman-Rakic 1998; Funahashi et al. 1989; Fuster 1973; Kojima and Goldman-Rakic 1982, 1984; Kubota et al. 1974; Niki 1974; Niki and Watanabe 1976; Rao et al. 1997; Sawaguchi et al. 1990). A subset of neurons in the dorsolateral PFC shows a sustained change in activity during the delay period, the magnitude of which differs with the direction of the cue/response. Such “directional” delay-period activity has been considered to represent visuospatial memory (Funahashi and Kubota 1994; Fuster 1997; Goldman-Rakic 1995).

However, because the conventional delayed-response paradigm does not adequately dissociate the cue location from the remembered target location, it is difficult to dissociate neuronal activities related to memory for visuospatial information from those related to motor preparation for directed movement. It is possible that directional delay-period activity is involved in motor preparation for forthcoming directed movement, rather than visuospatial memory of the cue location. Few studies, particularly those by Wise and his colleagues (Boussaoud and Wise 1993; Di Pellegrino and Wise 1993) and those by Goldman-Rakic and colleagues (Funahashi et al. 1993), have provided evidence that at least some directional delay-period activities of the dorsolateral PFC are involved in visuospatial memory for cue location, rather than motor preparation for directed movements. Therefore, this problem may need to be addressed further. In particular, the properties, such as tuning and temporal properties, of neuronal activities for visuospatial memory, which is not associated with any sensorimotor components for directed movements, still remain to be examined, so that we can improve our understanding of the role of the dorsolateral PFC in visuospatial memory.

In the present study, to better control the problem inherent in the conventional delayed-response paradigm and to better examine the properties of neuronal activities for visuospatial memory, we introduced a spatial delayed matching-to-sample
paradigm (SDMTS) for monkeys, which allows us to adequately access visuospatial memory independent of any sensorimotor components, such as motor preparation, for directed movements. We report here that a subset of neurons in the dorsolateral PFC show activities for visuospatial memory during SDMTS task performance and provide evidence that neuronal processes for increasing the accuracy of visuospatial memory may occur in the dorsolateral PFC.

**Methods**

**Subject and behavioral task**

A male rhesus monkey (Macaca mulatta, \( \sim 4.5 \text{ kg} \)) was trained to perform an SDMTS task that was introduced to access visuospatial memory (we tried to train another monkey for \( \sim 1 \text{ yr} \), but failed; this could be because of the difficulty of the present task and/or this particular monkey's character/ability). Throughout the experiment, the subject was treated in accordance with the Guide for Care and Use of Laboratory Animals (National Institutes of Health) and the Guide for Care and Use of Laboratory Primates (Primate Research Institute, Kyoto University, Japan).

Before training, the monkey was habituated to a monkey chair, and preliminary surgery was then performed under deep anesthesia with sodium pentobarbital (\( \sim 25 \text{ mg/kg iv} \)) and under aseptic conditions. Two hollow rods (8 mm id), for restraining the head of the monkey, were implanted on the anterior and posterior portions of the skull with dental acrylic. Small stainless steel bolts (3 mm diam), for grounding, were anchored to the marginal portions of the skull and fixed with dental acrylic. To prevent infection, antibiotics were injected intramuscularly on the day of surgery and daily for 1 wk after surgery.

During daily training and recording sessions, the monkey sat in the monkey chair and faced a multiscan 21-in. cathode ray tube (CRT) monitor (PCTV471, NEC, Tokyo) placed \( \sim 60 \text{ cm} \) in front of him. The monkey's head was rigidly fixed by two stainless steel bars (8 mm diam) to a stereotaxic frame located at the top of the monkey chair, and a water spout was positioned close to the monkey's mouth. The task and the recordings were controlled by a system consisting of an infrared eye-camera system (R-21-C-A, RMS, Hiroaki, Japan), a hold lever, two personal computers (PC9801 FE and PC9801 BX, NEC) that were networked by RS232C and parallel I/O, and other associated peripherals. The eye-camera system was connected to the computers via A/D converters (AB98-05A/4, ADTEK, Yokohama, Japan) and was used for monitoring and sampling eye positions (sampling rate, 4 ms). The hold lever was made of aluminum, and touching and releasing of the lever by the subject was detected electronically by a self-made electronic device for analysis by the computer (sampling rate, 1 ms). One of the personal computers (PC9801 FE) controlled the task and generated visual stimuli on the CRT monitor, while the other computer (PC9801 BX) monitored and sampled neuronal activities, eye positions, and task events. The computer programs were written in C and partially in assembly language.

The phases and time course of the SDMTS task are illustrated in Fig. 1A. The SDMTS task was begun when the subject touched the hold lever located at waist level and fixated on a central spot (a green square, \( 0.5^\circ \times 0.5^\circ \)) on the monitor. One second later, a sample cue (a white square, \( 2^\circ \times 2^\circ \)) was presented for 0.5 s, and this was followed by the first delay period. The sample cue was presented randomly at one of four peripheral locations (upper right, 45°; upper left, 135°; lower left, 225°; lower right, 315°), with an eccentricity of 15°. After the first delay period of 3 s, a matching cue appeared at one of the four peripheral locations for 0.5 s, and this was followed by the second delay period. The matching cue was physically the same as the sample cue. After the second delay period of 3 s, the color of the fixation spot changed from green to red ("go" signal), which instructed the monkey to make a lever-releasing GO response within 0.7 s after the go signal or a lever-holding NOGO-response for over 2.0 s. Selection of the GO and NOGO responses was based on the spatial location of the matching cue; NOGO and GO responses were required when the matching cue had and had not matched the sample cue, respectively. A correct response was rewarded by a drop of water 0.2 s after the response. During each trial, the monkey was required to maintain fixation on the central fixation spot. The monkey performed 700–1500 trials during daily training or recording sessions at a correct-response rate of more than 90%.

**Recordings and intracortical microstimulation**

After training was completed, surgery for recording was performed under aseptic conditions. The monkey was anesthetized with sodium pentobarbital (\( \sim 25 \text{ mg/kg iv} \)), and an oval opening was made in the skull to expose the dura over the frontal cortex. An oval cylinder (\( 18 \times 36 \text{ mm id} \)) was then positioned over the opening and fitted in place with dental acrylic. Prophylactic antibiotics were injected intramuscularly on the day of the surgery and daily for 1 wk after surgery.

The activities of single neurons in the dorsolateral PFC contralateral to the hand used for task performance were recorded extracellularly with glass-insulated elgiloy microelectrodes (impedance, \( \sim 0.5–2 \text{ M\Omega} \)). The microelectrode was positioned using a pulse motor-driven micromanipulator (MO-81, Narishige, Tokyo) and a plastic grid with numerous small holes (0.7 mm id, 1.5 mm apart from each other) attached to the cylinder. The microelectrode was advanced by the micromanipulator in 5-\( \mu \text{m} \) steps to allow monitoring of the extracellular activity of single neurons while the monkey was performing the SDMTS task. When a task-related neuron was located while the electrode was advanced into the cortex, its activity was recorded for more than 60 successive trials. In each recording session, only one penetration was made, and the activities of more than four neurons were recorded.

At the end of each recording session, intracortical microstimulation (ICMS; a train of 22 cathodal pulses of 0.2-ms duration at 333 Hz) was applied through the tip of the microelectrode to examine whether or not the recording site was in the frontal eye field (FEF). When ICMS at a low current intensity (\( \sim 40 \text{ \mu A} \)) induced eye movements while the monkey fixated on the central spot, the recording site was considered to be located in the FEF (cf. Bruce et al. 1985). Data obtained at such sites were excluded from the present study, since our target was neurons in the dorsolateral PFC rostral to the FEF. Furthermore, at selected recording sites, a DC current (15 \( \mu \text{A} \)) was passed through the tip of the microelectrode for 10 s (tip negative) to make a mark to reconstruct the recording sites in a histological examination.

**Data analysis**

In the on-line analysis during the recording sessions, data for neuronal activity were digitized with a window discriminator (DIS-1; BAK Electronics, Germantown, MD) for analysis by the personal computer (sampling rate, 1 ms), which generated histograms and raster displays of neuronal activity. The data for task events and eye positions were also digitized by an A/D converter (AB98–05A/4; ADTEK, Yokohama, Japan) to be sampled by the computer. These digitized data were recorded on-line on the RAM disk of the computer and eventually were transferred to a magneto-optical diskette at the end of daily recording sessions for off-line analyses. Furthermore, all of the analogue data (i.e., neuronal activities, eye positions, and task sequences) during each recording session were recorded on digital audio tape (DAT) using an eight-channel DAT recorder (PC-208 M, Sony, Tokyo).

Off-line analysis was carried out with a personal computer (PC9821 Ra266, NEC) and Visual Basic for Windows (Microsoft Japan, Tokyo). The digitized data were analyzed, and raster displays and averaged histograms of neuronal activities were generated (usually 25
ms/bin). Data from successive task trials were averaged, with respect to the onset of the different events during the task (e.g., onset of the fixation period, the sample cue period, the first delay period, the matching cue period, the second delay period, the go signal, lever-release, and delivery of the reward). For the statistical analysis, the discharge rate (spikes/s) of each neuron during the 1-s period prior to the onset of the sample cue (i.e., fixation period) was examined trial-by-trial, and the data were pooled for all successive task trials and taken as a control “baseline” activity for the statistical comparison. The discharge rate (spikes/s) during each period of the task was also calculated trial-by-trial. When the discharge rate of a neuron during at least one task period differed significantly from the control discharge rate (Mann-Whitney’s U test, \( P < 0.05 \)), the neuron was considered to be “task-related.”

Among the task-related neurons, we focused here on neurons whose activities were related to the first delay period, since our aim was to examine neuronal processes for visuospatial memory, and the subject was required to remember visuospatial data during the first delay period. When the discharge rate of a neuron during at least one task period differed significantly from the control discharge rate (Mann-Whitney’s U test, \( P < 0.05 \)), the neuron was considered to be “task-related.”

The onset of such activity was calculated in the averaged histogram (10 ms/bin) for the “preferred” position, which was associated with the maximal delay-period activity. The onset of this activity was defined as the end of the first bin in which the discharge rate differed from the averaged discharge rate by \( > 2 \) SDs during the control period; similar methods for estimating the onset of neuronal activities of the dorsolateral PFC have been used in our previous studies (e.g., Hasegawa et al. 1998; Sawaguchi 1987).

**Histology**

After the experiments were complete, the monkey was deeply anesthetized with an overdose of sodium pentobarbital and perfused with 0.9% saline (\( \sim 200 \) ml), followed by 10% formalin (\( \sim 500 \) ml). The cortical surface was examined to detect the points of penetration. Figure 1B shows the approximate sites of penetration (\( n = 30 \)) on the surface of the left hemisphere, at which the present data were obtained. The points were scattered throughout the caudal half of the periprincipal sulcal area and the immediately adjacent cortex in the dorsolateral PFC, which were mostly located in the area with cytoarchitectural features of Walker’s area 46 (Walker 1940). Furthermore, ICMS at a current intensity of up to 40 \( \mu A \) during the recording sessions did not induce eye movements for any of these penetrations, which confirmed physiologically that the penetration sites were outside the FEF (cf. Bruce et al. 1985).
RESULTS

Positional delay-period activity

We recorded the activities of a total of 385 task-related neurons from the dorsolateral PFC during performance of the SDMTS task. Of these neurons, 184 showed a sustained increase in activity during the first delay period (delay-period activity). Most of these neurons (n = 165/184, 90%) showed positional delay-period activity, i.e., delay-period activity where the magnitude differed significantly with the position of the sample cue (one-way ANOVA, P < 0.05).

An example of these neurons is shown in Fig. 2. In this figure, raster displays and averaged histograms of neuronal activity are illustrated separately for the four different locations of the sample cue. This neuron showed a sustained increase in activity during the first delay period, particularly for lower-right trials. The discharge rate during the first delay period differed significantly with the sample cue location (mean ± SD spikes/s: 7.4 ± 1.4 for upper-right trials, 7.0 ± 1.3 for upper-left trials, 8.3 ± 1.7 for lower-left trials, 15.5 ± 2.9 for lower-right trials; ANOVA, P < 0.001). The lower-right position was associated with the maximal delay-period activity, and the opposite position (upper-left) was associated with the minimal activity, as shown in the polar plot in the inset in Fig. 2, where the percent change in delay-period activity, compared with the baseline activity, is illustrated for the four different positions.

Tuning of positional delay-period activity

To quantitatively examine the properties of positional delay-period activity, we calculated a tuning index (TI) as follows:

\[ TI = \frac{\text{preferred} - \text{unpreferred}}{\text{preferred} + \text{unpreferred}} \]

where preferred is the average discharge rate during the first delay period for the preferred position associated with the maximal delay-period activity and unpreferred is that for the unpreferred position (usually opposite the preferred position) associated with the minimal delay-period activity. Thus, TI quantitatively represents the sharpness of the tuning of positional delay-period activity; it ranges from 0 to 1, and larger values indicate greater sharpness of such tuning. For the neuronal activity shown in Fig. 2, the preferred position was the lower right, the unpreferred position was the upper left, and TI was 0.38 (inset in Fig. 2).

The characteristics of tuning (TI values and preferred positions) were examined for the 165 neurons with positional delay-period activity. An example of the tuning of positional delay-period activity for three different neurons is shown as a polar plot in Fig. 3, in which the percent change in delay-period activity, compared with the baseline activity, is illustrated for the four different positions.

The positional delay-period activities of each of these particular neurons showed a preference for the upper-right position, and they were tuned to various degrees; the TI values were 0.12, 0.32, and 0.52, respectively. Figure 4A summarizes

FIG. 2. Prefrontal cortical neuron showing a sustained increase in activity during the first delay period of the SDMTS task, the magnitude of which differed significantly with the location of the sample cue (positional delay-period activity). Raster displays and averaged histograms (25 ms/bin) of neuronal activity are illustrated separately for the four different locations of the sample. F, fixation period; SC, sample cue period; D1, first delay period; MC, matching cue period. Inset: percent change in delay-period activity (solid line), compared with the baseline activity, is illustrated for the four different positions. Dashed lines: baseline activity (i.e., 100%). TI, tuning index; DI, discriminative index.
the distribution of TI for the 165 neurons. The TI value ranged from 0.07 to 0.73 (mean ± SD 0.24 ± 0.14) with a median of 0.21, indicating that the sharpness of tuning varied among the neurons; some were broadly tuned and others were sharply tuned, as in the example in Fig. 3, and there was no clear boundary or division for the sharpness of tuning. Furthermore, the preferred position of positional delay-period activity was biased toward the contralateral visual field, as shown in Fig. 4B. In Fig. 4B, the number of neurons is plotted for each of the preferred positions. As shown, more than two-thirds of the neurons (n = 114/165, 69%) showed a preferred position contralateral to the recording site; this bias was statistically significant (chi-square test, $\chi^2 = 22.55$, df = 1, $P < 0.001$). Thus, the sharpness of the tuning of positional delay-period activity was varied and continuous across the neurons, and the preferred position was biased toward the contralateral visual field.

### Discriminative ability of positional delay-period activity

To correctly perform the SDMTS task, the position of the sample cue must be discriminated to be memorized, and positional delay-period activity may be related to such discrimination. To examine this point quantitatively, we introduced a discriminative index (DI) for positional delay-period activity, i.e., the number of sample cue positions for which the magnitude of the delay-period activity was significantly less than that of the maximal delay-period activity at a certain (i.e., preferred) position (Student’s $t$-test, $P < 0.05$). Although there are only four possible DI values (0, 1, 2, or 3), this index quantitatively represents the discriminative ability of positional delay-period activity for the sample cue position. For the neuronal activity shown in Fig. 2, the DI value was 3; the maximal delay-period activity for the preferred position (lower-right; mean ± SD spikes/s; 15.5 ± 2.9) was significantly greater than those for all of the other three positions (7.4 ± 1.4 for upper-right trials, $t$-test, $P < 0.001$; 7.0 ± 1.3 for upper-left trials, $P < 0.001$; 8.3 ± 1.7 for lower-left trials, $P < 0.001$).

Figure 5 shows the distribution of DI values for the 165 neurons with positional delay-period activity. As shown, DI ranged from 1 to 3, and more than half of the neurons (n = 90/165, 55%) showed a DI value of 1, followed by neurons with a DI value of 2 (50/165, 30%). Few neurons had a DI value of 3 (25/165, 15%). This biased distribution was statistically significant (chi-square test, $\chi^2 = 39.09$, df = 2, $P < 0.001$). Thus, most of the neurons with positional delay-period activity could not discriminate a particular sample cue location from others.
Onset time of positional delay-period activity and its relationship to TI and DI

In neurons with positional delay-period activity, the time from the onset of the sample cue to the onset of such activity was calculated in the averaged histogram (10 ms/bin) for the preferred position, and the relationships between this onset time and both TI and DI were examined. Figure 6 shows the distribution of the onset time for these neurons (n = 165). The onset time of positional delay-period activity was varied and continuous across the neurons, ranging from 40 to 1500 ms (mean ± SD, 367 ± 323 ms) with a median of 260 ms.

Figure 7A illustrates the relationship between the onset time and the TI, where TI is plotted against the onset time for each of the neurons with positional delay-period activity. As shown in Fig. 7A, the onset time was positively and significantly correlated with the TI value; the correlation coefficient (r) was 0.80 with a high level of significance (t-test, t = 16.75, df = 163, P < 0.001). This indicates that more sharply tuned positional delay-period activity had a slower onset after the onset of the sample cue. Furthermore, positional delay-period activity with a greater discriminative ability had a slower onset, as shown in Fig. 7B, which presents the relationship between the onset time and the DI value. Neurons with a DI value of 1 had the shortest onset time (mean ± SD, 186 ± 140 ms, n = 90), followed by those with a DI value of 2 (433 ± 271 ms, n = 50). Neurons with a DI value of 3 had the longest onset time (842 ± 354 ms, n = 25). These differences were statistically significant (neurons with a DI value of 1 versus those with a DI value of 2, U test, P < 0.01; neurons with a DI value of 2 versus those with a DI value of 3, P < 0.01).

Temporal properties of positional delay-period activity at the population level

To better examine the properties of positional delay-period activity, the temporal properties of positional delay-period activity were analyzed at the population level. The neurons with positional delay-period activity were divided into three distinct groups based on the DI value: neurons with a DI value of 1 (DI-1 neurons, n = 90), those with a DI value of 2 (DI-2 neurons, n = 50), and those with a DI value of 3 (DI-3 neurons, n = 25). Therefore, we summed neuronal activity at the preferred position for these three groups of neurons and made population histograms (Fig. 8A). As shown in Fig. 8A, the temporal profiles of these groups differed. The DI-1 neuronal population showed a sharp, phasic change in activity during the sample cue period, followed by a sustained activity that continued throughout the first delay period. The DI-2 and DI-3 neuronal populations appeared to lack such a phasic change in activity, and the onset of sustained activity was not as sharp for either of these populations. Positional delay-period activity was sustained during the first delay period for both the DI-2 and DI-3 populations, and its onset was slower for the DI-3 population than for the DI-2 population, as expected from the above results. The temporal changes in TI and DI also varied in these different populations of neurons. In Fig. 8B, the mean TI and DI values are plotted for the sample cue period (500 ms) and each 500-ms period of the first delay period (i.e., D1-1–D1-6). For the DI-1 population, both TI and DI were maximal in the sample cue period and gradually decreased during the delay period, whereas for the DI-2 population, both of these values were maximal in the early delay period. In contrast, for the DI-3 population, both TI and DI increased during the delay period and were maximal in its later portion.
Positional delay-period activity during error trials

To examine how positional delay-period activity is related to behavioral performance, we analyzed the activity during error trials. Although errors rarely occurred and we could not perform sufficient statistical analyses, positional delay-period activity always disappeared or was less apparent when the subject made an error response, as shown in the example in Fig. 9. This neuron showed positional delay-period activity with a preferred position in the upper right. The activities during four subsequent correct \((n = 2)\) and error-response trials \((n = 2)\) with the upper-right cue are illustrated in Fig. 9. As shown, positional delay-period activity, which was apparent during

![Diagram of Positional Delay-Period Activity](image_url)
correct trials, did not appear during the error trials. Indeed, whereas the discharge rate during the first delay period was larger than the baseline discharge rate during the fixation period for the two correct trials (mean ± SD spikes/s; 20.3 ± 15.1 versus 9.0 ± 12.2), the discharge rate during the first delay period was similar to the baseline discharge rate for the two error trials (9.8 ± 10.8 versus 9.0 ± 11.4).

Activity during the second delay period

In the present SDMTS task, a second delay period, which was as long as the first delay period, was introduced between the matching cue period and the response period. The matching cue was physically the same as the sample cue, but visuospatial memory during the second delay period was not required to perform the task; instead, some preparatory processes for the GO/NOGO response might take place during this period. Therefore, we analyzed the activity during the second delay period as with the “first delay-period activity” for neurons with positional delay-period activity. We also analyzed whether or not this activity was significantly different (i.e., “differential”) between GO and NOGO trials; differential neuronal activities of the PFC between GO and NOGO responses have been demonstrated in previous studies with the GO/NOGO-response paradigm in monkeys (Komatsu 1982; Kubota and Komatsu 1985; Watanabe 1986a,b).

Overall, only one-third of the neurons with positional delay-period activity (n = 55/165, 33%) showed “second delay-period activity,” i.e., a significant increase (n = 29) or decrease (n = 26) in activity, compared with the baseline activity, during the second delay period. An example of such neurons is shown in Fig. 10, in which raster displays and averaged histograms of activity are illustrated separately for the four different locations of the sample cue (Fig. 10A) and the matching cue (Fig. 10B), and for GO and NOGO trials (Fig. 10D). A polar plot of the first delay-period activity and second delay-period activity is illustrated in Fig. 10C. This neuron showed positional delay-period activity during the first delay period, as shown in Fig. 10A. The discharge rate during the first delay period was relatively large for trials with the sample cue in the upper-right and upper-left positions and varied significantly with the sample cue location (mean ± SD spikes/s; 19.5 ± 3.3 for upper-right trials, 18.2 ± 3.0 for upper-left trials, 12.1 ± 10.2)

![FIG. 10. A neuron showing both positional delay-period activity during the first and second delay-period activity. A: raster displays and averaged histograms (25 ms/bin) of neuronal activity, which are aligned at the fixation (F), the sample cue (SC), the first delay (D1), and the matching cue (MC) periods and are illustrated separately for the four different locations of the sample cue. Inset: sample cue positions and the central fixation spot. B: raster displays and averaged histograms of the neuronal activity, which are aligned at the matching cue period (MC), the second delay period (D2), and the onset of the go signal (GS) and are illustrated separately for the four different locations of the matching cue. Inset: matching cue positions and the central fixation spot. C: tuning of delay-period activity during the first (D1) and second (D2) delay period. Percent change in delay-period activity (solid line), compared with baseline activity, is illustrated for the four different positions of the sample cue (for D1) or the matching cue (for D2) as a polar plot. Dashed lines: baseline activity (i.e., 100%). TI, tuning index; DI, discriminative index. D: raster displays and averaged histograms of the neuronal activity for GO and NOGO trials. Activity in GO responses is for selected correct trials for illustrative purposes. Conventions are the same as in B.](http://jn.physiology.org/doi/pdf/10.220.32.247)
4.3 for lower-left trials, 13.3 ± 4.7 for lower-right trials; ANOVA, P < 0.001). The upper-right position was associated with the maximal delay-period activity, whereas the opposite position (lower-left) was associated with the minimal activity, although the tuning of positional delay-period activity was not very sharp (Fig. 10C); TI and DI were 0.23 and 2, respectively. In addition to positional delay-period activity during the first delay period, this neuron also showed second delay-period activity for all of the locations of the matching cue (Fig. 10B); the discharge rate during the second delay period was significantly greater than the baseline discharge rate (9.7 ± 4.8) for all four locations of the matching cue (12.6 ± 4.7 for upper-right trials, U test, P < 0.01; 13.6 ± 2.6 for upper-left trials, P < 0.05; 12.7 ± 3.7 for lower-left trials, P < 0.01; 13.7 ± 3.5 for lower-right trials, P < 0.05). However, the second delay-period activity did not differ significantly with the matching cue location (ANOVA, P > 0.05, not significant [NS]), i.e., the second delay-period activity was not “positional” for the matching cue location. Indeed, the tuning of the second delay-period activity was very broad (Fig. 10C). When TI and DI were calculated as with the first delay-period activity, TI was small (0.04) and DI was 0 for the second delay-period activity. Furthermore, when the second delay-period activity was examined separately for GO and NOGO trials (Fig. 10D), no significant difference in the magnitude was observed (12.3 ± 3.4 for GO trials, 13.6 ± 4.1 for NOGO trials; t-test, P > 0.05, NS). Overall, most of the neurons with positional delay-period activity during the first delay period did not show positional second delay-period activity for the matching cue location (n = 135/165, 82%) or differential second delay-period activity between GO and NOGO trials (n = 136/165, 82%) during the second delay period.

DISCUSSION

The present study demonstrated that a subset of neurons in the monkey dorsolateral PFC showed positional delay-period activity during performance of a SDMTS task. This activity is considered to represent visuospatial memory independent of sensorimotor components and to form a “memory field.” Furthermore, positional delay-period activity with sharper tuning and a greater discriminative ability had a slower onset from the onset of the sample cue, whose location was to be memorized. At the population level, both tuning and discriminative ability increased during the delay period for the neuronal population with a high discriminative ability. These findings suggest that neuronal processes for increasing the accuracy of visuospatial memory (i.e., sharpening) may occur in the dorsolateral PFC.

Positional delay-period activity representing visuospatial memory for cue location

Positional delay-period activity is a sustained increase in activity during the first delay period of the SDMTS task, the magnitude of which differs significantly with the position of the visuospatial sample cue to be memorized. This activity appears to be involved in visuospatial short-term memory, which is not associated with any sensorimotor components for directed movements, since the first delay period required the subject to remember visuospatial information regarding the sample cue location over a temporal interval until the appearance of the matching cue and was not associated with motor preparation or any other sensorimotor components for directed movements. An analysis of error trials supported this notion, i.e., positional delay-period activity disappeared or was less apparent when the subject made errors, indicating that this activity is associated with visuospatial memory that is required for correct performance of the SDMTS task. This is further supported by the fact that most of the neurons with positional delay-period activity did not show positional second delay-period activity during the second delay period after the matching cue period; the matching cue was physically the same as the sample cue, but visuospatial memory of the matching cue location during the second delay period was not required to perform the task. Although we used only four spatial locations as the sample cue location, this is not a critical problem, since even under these conditions a considerable number of neurons showed positional delay-period activity, and its tuning and discriminative ability varied across the neurons, which allowed us to make quantitative analyses and comparisons.

Most previous studies of the cellular basis of visuospatial memory in the dorsolateral PFC of monkeys have used delayed-response paradigms in which the subjects are required to direct their gaze or hand to a visuospatial, remembered target location that has been cued prior to a brief delay period (Chafee and Goldman-Rakic 1998; Funahashi et al. 1989, 1993; Fuster 1973; Kojima and Goldman-Rakic 1982, 1984; Kubota et al. 1974; Niki 1974; Niki and Watanabe 1976; Rao et al. 1997; Sawaguchi et al. 1990). Some of these studies have suggested that a subset of neurons have a memory field for representing visuospatial memory (Funahashi et al. 1989). However, as described earlier in this article, the conventional delayed-response paradigm does not adequately dissociate the cue location from the remembered target location, so that it is difficult to dissociate neuronal activities related to visuospatial memory from those related to motor preparation for directed movements that are required as a response. Only some studies, particularly those by Wise and his colleagues (Boussaoud and Wise 1993; Di Pellegrino and Wise 1993) and those by Goldman-Rakic and colleagues (Funahashi et al. 1993), have tried to dissociate these possible neuronal activities and provided evidence that several neurons of the dorsolateral PFC are involved in visuospatial memory for cue location, rather than motor preparation for directed movements. The present study confirms and extends these findings, i.e., a subset of neurons in the dorsolateral PFC are actually involved in visuospatial memory for cue location and form a memory field for visuospatial information, but not for motor preparation associated with directed movements.

Tuning of the memory field

Although the delayed-response paradigm involves the above-mentioned problem, the characteristics of the memory field of positional delay-period activity are similar to those demonstrated in studies with oculomotor delayed-response (ODR) tasks (Funahashi et al. 1989). In studies with the ODR paradigm, directional delay-period activity has been considered to represent a memory field. The preferred direction of such directional delay-period activity of the dorsolateral PFC is biased toward the contralateral visual field, similar to the present finding. Further, as with the present findings regarding
Prefrontal neuronal processes for increasing the accuracy of visuospatial memory

The major findings of the present study involve the characteristics of tuning and the discriminative ability of neuronal activity in the dorsolateral PFC. At the behavioral level, highly accurate visuospatial memory is usually required for the correct performance of visuospatial memory tasks, such as the present task. However, both the tuning and discriminative ability of positional delay-period activity varied among the neurons, i.e., the memory field of neurons in the dorsolateral PFC varies with regard to tuning and discriminative ability. The discriminative ability of most of the neurons is too poor to be able to discriminate a particular position of the sample cue from others under the present conditions. Therefore, more accurate visuospatial memory may be achieved by some processes involving populations of neurons with memory fields with various degrees of tuning and discriminative ability.

Regarding this problem, it is noteworthy that the value of the TI was positively and significantly correlated with the time from the onset of the sample cue to the onset of positional delay-period activity. In addition, positional delay-period activity with a greater DI had a significantly slower onset. Thus, positional delay-period activity with sharper tuning and a greater discriminative ability had a slower onset from the onset of the sample cue. Furthermore, fewer neurons showed positional delay-period activity with sharper tuning and greater discriminative ability, and the distribution of the sharpness of tuning was continuous/gradual. In addition, the onset time of positional delay-period activity varied among the neurons and its distribution was also continuous/gradual. These findings suggest that there may be integrative, convergent processes from neurons with memory fields with broader tuning and poor discriminative abilities to those with memory fields with sharper tuning and greater discriminative abilities in the dorsolateral PFC.

At the population level, neurons with a high DI value (i.e., 3) showed positional delay-period activity, with a slow onset and with TI and DI values that increased as the delay progressed, and this group of neurons may serve to increase the accuracy of visuospatial memory and to retain this accurate visuospatial memory. In contrast, neurons with a low DI value (i.e., 1) showed a phasic, early change in activity during the sample cue period, and the TI and DI values were the largest in this period. Previous studies with ODR tasks have demonstrated a similar phasic activity in summed directional delay-period activities of several neurons in the monkey PFC (Chafee and Goldman-Rakic 1998; Funahashi et al. 1989). This group of neurons may be related to sensory aspects of the cue more strongly than other groups and may play a role in coding/discriminating visuospatial sensory cues. Neurons with an intermediate DI value (i.e., 2) showed profiles intermediate between those of these two groups; the onset of activity was intermediate, and its TI and DI values were largest in the early period of the delay. Previous studies with the delayed-response paradigm have demonstrated that the neuronal activity of the PFC in the early period of the delay is involved in encoding processes of visuospatial memory (Kojima and Goldman-Rakic 1982, 1984; Stamm 1969), and this group of neurons may be involved in such processes.

Thus, there appear to be integrative, convergent processes from neurons with memory fields with broader tuning and poor discriminative abilities to those with memory fields with sharper tuning and greater discriminative abilities in the dorsolateral PFC, thereby increasing the accuracy of visuospatial memory to guide behaviors/decisions requiring accurate visuospatial memory. The coding and encoding of visuospatial information may occur in early phases of these processes, and the process of sharpening visuospatial memory may then progress.

A possible role of the dorsolateral PFC in visuospatial memory

The present findings confirm that a subset of neurons in the primate dorsolateral PFC are involved in visuospatial memory for cue location and form a memory field to represent it. Furthermore, the present study provides substantial evidence that neuronal processes for increasing the accuracy of visuospatial memory may occur in the dorsolateral PFC; these processes appear to follow the coding and encoding processes of visuospatial information within this area.

Although the dorsolateral PFC has long been considered to play a “major” role in visuospatial memory (cf. Goldman-Rakic 1987, 1995), some brain areas other than the dorsolateral PFC, in particular posterior parietal cortical areas (e.g., areas LIP and 7a), also are involved in visuospatial memory (for a review, see Goldman-Rakic 1988). For example, Constantinidis and Steinmetz (1996) demonstrated that a population of neurons in area 7a showed a sustained change in activity during a delay period of a visuospatial memory task similar to the present SDMTS task; this activity appears to be similar to the present positional delay-period activity. Their findings are interesting because they used a behavioral paradigm similar to the present SDMTS task, but, unfortunately, they did not adequately analyze the tuning or discriminative ability or their relationships with the temporal properties of delay-period activity. More recently, Chafee and Goldman-Rakic (1998) demonstrated that neurons in area 7a showed activities very similar to those in the dorsolateral PFC during performance of an ODR task, and they failed to detect, at the cellular level, a critical/specific role of the dorsolateral PFC in visuospatial memory. Thus, both the dorsolateral PFC and the posterior parietal cortex are involved in visuospatial memory, and the critical/specific role of the dorsolateral PFC in visuospatial memory is unclear. Extending the previous studies, the present findings allow us to hypothesize that a critical role of the dorsolateral PFC in visuospatial memory is to increase its accuracy by integrative,
convergent processes of populations of neurons with memory fields with various degrees of tuning and discriminative ability, thereby guiding behaviors/decisions requiring accurate visuospatial memory. This hypothesis emphasizes the “sharpening” role of dorsolateral PFC neurons for visuospatial information/memory and should be original and conceptually novel. However, as far as we know, analyses similar to those in the present study have not been performed for delay-period activities of other brain areas, so that it is unclear whether or not this sharpening role is unique/specific to the dorsolateral PFC. Therefore, further studies are required to confirm and develop this hypothesis. In particular, studies with analyses and a behavioral paradigm similar to those reported here should be performed for neuronal activities of other brain regions, particularly the posterior parietal cortex, to clarify the specific/critical role of the primate dorsolateral PFC in visuospatial memory.

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REFERENCES


